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Enzymatic Ring-Opening Polymerization (ROP) of Polylactones: Roles of Non-Aqueous Solvents

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Abstract

Aliphatic polyesters such as polylactides (PLAs) and other polylactones are thermoplastic, renewable and biocompatible polymers with high potentials to replace petro-chemical-based synthetic polymers. A benign route for synthesizing these polyesters is through the enzyme-catalyzed ring-opening polymerization (ROP) reaction; this type of enzymatic process is very sensitive to reaction conditions such as solvents, water content and temperature. This review systematically discusses the crucial roles of different solvents (such as solvent-free or in bulk, organic solvents, supercritical fluids, ionic liquids, and aqueous biphasic systems) on the degree of polymerization and polydispersity. In general, many studies suggest that hydrophobic organic solvents with minimum water contents lead to efficient enzymatic polymerization and subsequently high molecular weights of polyesters; the selection of solvents is also limited by the reaction temperature, e.g. the ROP of lactide is often conducted at above 100 °C, therefore, the solvent typically needs to have its boiling point above this temperature. The use of supercritical fluids could be limited by its scaling-up potential, while ionic liquids have exhibited many advantages include their low-volatility, high thermal stability, controllable enzyme-compatibility, and a wide range of choices. However, the fundamental and mechanistic understanding of the specific roles of ionic liquids in enzymatic ROP reactions is still lacking. Furthermore, the lipase specificity towards L- and D-lactide is also surveyed, followed by the discussion of engineered lipases with improved enantioselectivity and thermal stability. In addition, the preparation of polyester-derived materials such as polyester-grafted cellulose by the enzymatic ROP method is briefly reviewed.

Keywords

ring-opening polymerization; polyester; polylactide; polylactone; biopolymer; ionic liquid; supercritical fluids

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INTRODUCTION

The scientific and lay community's increasing concerns related to the environmental impacts and non-renewable supply of petro-chemical-based synthetic polymers have driven the search to find biodegradable materials from renewable sources. Aliphatic polyesters, particularly polylactides (PLAs) and other polylactones as well as their derivatives, play a leading role in biodegradable materials. These biodegradable polyesters are thermoplastic, renewable and biocompatible polymers with mechanical properties being similar to those of polystyrene or polyethylene terephthalate (PET or PETE).¹ In addition to their uses in packaging and horticultural materials,² polyesters (with an average molecular weight > 60,000 g/mol)³ have advantageous applications in biomedical fields (due to their high biocompatibility and lack of toxicity) including controlled drug delivery carriers (such as for Camptothecin, Doxorubicin, Amphotericin B, and Vancomycin, etc.,⁴ for therapeutic peptides/proteins and for gene delivery⁵), tissue engineering scaffolds, surgical suture and bone fixation materials.⁶⁻⁹ Aliphatic polyesters can be synthesized by two common methods, i.e. polycondensation and ring-opening polymerization (ROP); both processes can be catalyzed by classic anionic, cationic or metallic catalysts (such as metal complexes based on Al, Mg, Zn, Ca, Sn and Zr).¹⁰⁻¹² Due to the increasing use of polyesters in pharmaceuticals (such as in drug delivery), tissue engineering, orthopedics and food packaging, there is a strong interest in producing these polymers without the use of metal catalysts because some of them (such as the common tin-based catalyst tin(II) 2-ethylhexanoate, also known as stannous octoate, Sn(Oct)₂) have shown some toxicity.^{13, 14} FDA approves[†] that stannous octoate could be added at 1 wt% concentration of the resin that are used as polymeric coatings in contact with food under certain conditions. In addition, stannous chloride is usually considered as safe for use at a level 0.0015% calculated as tin.[‡] On the other hand, stannous octoate has exhibited a moderate to severe inhibition of cell growth, and its IC₅₀ values are 125.9 ppm and 26.1 ppm for inhibiting the growth of human endothelial cells and mouse Swiss 3T3 fibroblasts, respectively.¹⁴ Therefore, biocatalysts such as lipases and esterases, have gained growing attention in the enzymatic synthesis of aliphatic polyesters via polycondensation or ROP; in particular, the ROP reactions of lactides and lactones have been extensively examined by using enzymatic systems.^{6, 10, 15-19}

Polylactide (PLA), also known as poly(lactic acid) is a sustainable polymer since it can be prepared from renewable lactic acid or lactide (cyclic dimer of lactic acid). Lactic acid is typically produced from the microbial fermentation of agricultural by-products including carbohydrate-rich substances.⁶ Lactide (LA), as a special type of lactone, has two chiral centers, and thus LA has three stereoisomers L,L-lactide (L-LA), D,D-lactide (D-LA), and meso-lactide (or DL-LA) (see Scheme 1), whose corresponding polymers are known as PLLA, PDLA, and PDLLA respectively. Upon blending PLLA and PDLA, or synthesizing the stereo block copolymer containing PLLA and PDLA segments, a PLA stereocomplex

[†]See Code of Federal Regulations Title 21, Chapter I, Subchapter B, Part 175, Subpart C, Sec. 175.300 Resinous and polymeric coatings, Revised as of April 1, 2016.

[‡]See Code of Federal Regulations Title 21, Chapter I, Subchapter E, Part 582, Subpart D, Sec. 582.3845 Stannous chloride, Revised as of April 1, 2016.

could be formed which has an improved thermal and hydrolytical stability, mechanical properties and gas barrier properties.²⁰ Some lactones are naturally occurring saturated or unsaturated γ - and δ -lactones, which are cyclic esters of the corresponding hydroxy fatty acids. But more lactones are synthetically produced, such as ϵ -caprolactone being prepared from the oxidation of cyclohexanone by peracetic acid.¹² There are several common methods for synthesizing PLA and other polylactones each of which has some drawbacks: (a) A direct polycondensation polymerization often leads to a low-molecular-weight PLA with poor mechanical properties; (b) Azeotropic condensation polymerization can produce high-molecular-weight PLA (M_n up to 300,000 g/mol),²¹ but this approach suffers from several issues including the need of high temperature, the continuous removal of byproducts (mostly water), and a long reaction time; (c) Solid state polymerization (SSP) operates at a temperature above the glass transition temperature but below the melting temperature,²² and has the advantage of producing high molecular weight and good control of side reactions but requires a much longer reaction time than in melt state or solutions; (d) On the other hand, ring-opening polymerization (ROP) of lactide (LA) through the coordination polymerization with metal derivatives such as tin(II) octoate ($\text{Sn}(\text{Oct})_2$) or tin(II) butoxide (PLA M_n up to $\sim 10^6$ g/mol),²³ anionic polymerization (such as strong bases with alcohols) or cationic polymerization is industrially preferred to achieve high molecular-weight PLA in bulk (in the melt/absence of solvent);^{6, 24} however, the drawback from this route is the possible residues of metal catalysts in polyesters; this could be disadvantageous for medical and electronic applications although 10 ppm $\text{Sn}(\text{Oct})_2$ residue in PLA is generally considered to be safe.²⁴ The present review focuses on the enzymatic approach to the ROP reactions of lactides and other lactones (Schemes 2 and 3),²⁵ with an emphasis on the reaction media.

ENZYMATIC ROP IN BULK

Early studies of enzymatic ROP reactions of lactides and lactones were mainly performed under solvent-free conditions (so called 'in bulk'). In the case of lactides, the solvent-free condition usually requires a high reaction temperature (above the melting point of lactides: L-, 96 °C, and DL-, 126 °C)²⁶. The polymerization of other lactones is usually carried out at lower temperatures (mostly 45–80 °C)^{17, 27} since most lactones are liquid at room temperature. The enzymatic ROP under the bulk condition has been extensively discussed in several review articles;^{10, 17, 19, 27, 28} therefore, we only highlight a few representative examples for comparison purpose. The foreseeable disadvantage of solvent-free polymerization is that at the early stage of reaction, the formation of oligomers turns the reaction mixture into solid, which causes the uneven polymerization across different areas of the reactor.

In the absence of solvent, Matsumura et al.²⁹ conducted the ROP of D,L-lactide catalyzed by *Pseudomonas cepacia* lipase PS and obtained the polyester with weight-average molecular weights (M_w) up to 126,000 g/mol and 16% yield at 130 °C under optimum conditions. This group further studied the same ROP catalyzed by lipase PS at 130 °C and obtained PDLA with M_w 270,000 g/mol, 1.1 polydispersity index (PDI), and 16% yield;³⁰ the same group³¹ also reported that porcine pancreatic lipase (PPL) exhibited high activities towards the ROP of lactides in bulk, resulting in PLLA (M_w 17,600 g/mol and PDI 1.9), PDLA (27,000 g/mol and 1.4) and PDLA (26,600 g/mol and 2.1). The Albertsson group³² reported that PLLA

with M_n up to 78,100 g/mol (PDI 1.4) was obtained from the lipase PS-catalyzed ROP in bulk at 125 °C for 7 days. When the same reaction in bulk was catalyzed by Novozym 435 (immobilized *Candida antarctica* lipase B (CALB)) at 100 °C, PLLA was obtained with M_w 2,440 g/mol, PDI 2.6 and yield 91%.³³ The Yoshizawa-Fujita group³⁴ evaluated the free CALB-catalyzed ROP of L-lactide at 130 °C, and produced the polyester with M_w 40,000 g/mol, PDI 1.13 and yield 54.1%.

A number of studies have examined the enzymatic ROP of other lactones. Matsumura et al.³⁵ examined the ROP of β -propiolactone in bulk catalyzed by *Candida cylindracea* lipase or porcine pancreatic lipase (PPL) and obtained polyesters with M_w up to >50,000 g/mol; interestingly, this group noted that the molecular weight of the polyester was inversely proportional to the lipase concentration while the molecular weight and reaction rate increased with the reaction temperature from 40 to 60 °C. Uyama et al.³⁶ evaluated the ROP reactions of ϵ -caprolactone (CL), 11-undecanolide (UDL), and 12-dodecanolide (DDL) in bulk at 60 °C catalyzed by Novozym 435, and observed M_n 4,300 g/mol for poly(caprolactone) (known as PCL, 99% yield and 2.7 PDI), 4,900 g/mol for poly(UDL) (88% yield and 3.7 PDI), and 2,800 g/mol for poly(DDL) (59% yield and 3.4 PDI). The addition of 1-octanol as the initiator increased the reaction rate but decreased the polyester molecular weight. Dong et al.³⁷ evaluated the ROP reactions of six lactones and condensation polymerization of six linear hydroxyesters in bulk catalyzed by lipase from *Pseudomonas* sp. at 45 °C for 20 days, found that the ROP reactions of lactones (except γ -butyrolactone) usually afforded higher molecular weights (M_n up to 8,800 g/mol) and higher conversions (up to 100%) than the condensation of corresponding linear hydroxyesters. The Kobayashi and Duda groups^{15, 38–40} compared the chemical and enzymatic ROP reaction rates of different sizes of lactones, and suggested that the chemical polymerization rates (using the zinc 2-ethylhexanoate/butyl alcohol system) are 2500:330:21:0.9:1.0:0.9:1.0 for the 6-, 7-, 9-, 12-, 13-, 16-, and 17-membered lactones respectively, while the lipase-catalyzed polymerization rates are in an inverse order of 0.10:0.13:0.19:0.74:1.0 for the 7-, 12-, 13-, 16-, and 17-membered lactones respectively. They argued that the higher ring strain of smaller rings is partly relieved in the transition state of the polyester chain growth resulting in faster propagation in chemical polymerization, while in the enzymatic polymerization, larger lactone rings with higher hydrophobicity promote the formation of the lactone-lipase complex.⁴¹ The Gross group⁴² studied the ROP of ϵ -caprolactone catalyzed by Novozym 545 in bulk, and observed that the molecular weight (M_n) increased with the monomer conversion, but decreased with the increasing lipase concentration at the same monomer conversion level. The Bisht group⁴³ synthesized (*S*)-enriched substituted poly(ϵ -caprolactone)s from 4-methyl- ϵ -caprolactone and 4-ethyl- ϵ -caprolactone catalyzed by Novozym-435 in bulk, resulting in poly(4-methyl- ϵ -caprolactone) ($ee_p > 0.95$, $M_n = 5,400$ g/mol) and poly(4-ethyl- ϵ -caprolactone) ($ee_p > 0.98$, $M_n = 4,000$ g/mol). Sobczak⁴⁴ evaluated the CALB-catalyzed ROP of ϵ -caprolactone at different initiator (PEG 400) concentrations, and suggested that a lower initiator concentration (e.g. ϵ -caprolactone/PEG molar ratio 100:1) favored a higher PCL molecular weight (M_n up to 5,200 g/mol). Both the kinetic model and experimental data by the Beers group⁴⁵ suggest that the removal of water from enzymatic ROP of ϵ -caprolactone induced no appreciable changes in polymerization rates, but led to higher-molecular-weight polyesters. Matos et al.⁴⁶ systematically studied the

effect of microwave irradiation on the enzymatic ROP of ϵ -caprolactone catalyzed by Novozym 435, and concluded that the reaction temperature had a major impact on the polymerization reaction while a high microwave intensity was not desirable. Under optimal conditions (90 °C, 240 min, and 50 W), PCL with M_n of ~20,600 g/mol and PDI of 1.2 was synthesized.

ENZYMATIC ROP IN ORGANIC SOLVENTS

The use of enzymes (mainly lipases) for ROP of lactides and other lactones has been actively pursued in organic solvents.^{27, 28} When solvents are used in the synthesis of these polyesters, the common organic solvents are toluene and heptane, which are hazardous, toxic and flammable; lactides are poorly soluble in common organic solvents while melted lactides at high temperatures are polar/hydrophilic and inhibitory to the enzymatic propagation.^{4, 47} Additionally, lipases typically show moderate activities in these media, especially towards L-lactide and DL-lactide.^{48, 49} Under optimum conditions in toluene at 60 °C, PDLA was obtained with M_n = 12,000 g/mol and PDI = 1.1.⁴⁹ Yoshizawa-Fujita et al.³⁴ obtained PLA with M_n = 44,100 g/mol, PDI = 1.15 and yield = 26.9% when the ROP reaction in toluene was catalyzed by free CALB at 100 °C for 24 h. Sobczak⁴⁴ conducted the CALB-catalyzed ROP of lactide (2.52g) in 5.0 mL toluene at 60–80 °C using PEG 400 as the initiator, and found that a lower initiator concentration (e.g. lactide/PEG molar ratio 100:1) lead to a higher molecular weight (M_n up to 4,700 g/mol). Omay et al.⁵⁰ performed the polymerization of D,L-lactide in dry toluene at 80 °C, and reported M_n of 26,000 g/mol and 21,000 g/mol respectively for Novozym 435 and free CALB. Duchiron et al.⁵¹ suggested that lipases could be activated by the mixture of toluene and triethylamine (2:1 ratio), resulting in up to 4,900 g/mol M_n and 89% yield for Novozym 435-catalyzed ROP of D-lactide, and 1,800 g/mol M_n and 80% yield for lipase PS-catalyzed ROP of L-lactide.

Many groups focused on the polymerization of other lactones. Knani et al.⁵² carried out the ROP of ϵ -caprolactone with methanol catalyzed by porcine pancreatic lipase (PPL) in *n*-hexane at 40 °C, achieving a degree of polymerization (DP) up to 35. The Marchessault group⁵³ used PPL and lipase from *Pseudomonas cepacia* (PCL) in the ROP reactions of β -butyrolactone, β -propiolactone, γ -butyrolactone and ϵ -caprolactone in bulk or in organic solvents (such as *n*-hexane and isooctane), resulting in the highest M_w values for respective polyesters of 1045 g/mol (33% yield, PPL in bulk at room temperature for 500 h), 2323 g/mol (44% yield, PPL in *n*-hexane at 60 °C for 430 h), 932 g/mol (25% yield, PPL in *n*-hexane at 60 °C for 430 h), and 2,902 g/mol (45% yield, PPL in bulk at room temperature for 1,100 h). Xie et al.⁵⁴ conducted the ROP of β -butyrolactone catalyzed by thermophilic lipases from the ESL-001 ClonZyme library, and found the polymerization in isooctane led to higher stereoselectivity than that in bulk (37% ee vs 27% ee at 80 °C), but the molecular weight (M_w) in bulk was higher than that in isooctane (3,900 vs 2,800 g/mol at 80 °C). Kobayashi and co-workers⁵⁵ screened a number of lipases for the ROP reactions in bulk and suggested that *Pseudomonas fluorescens* lipase enabled the highest molecular weights for PCL (M_n 12,000 g/mol, PDI 2.3, conversion 99% at 75 °C for 20 days) and poly(δ -valerolactone) (M_n 2,100 g/mol, PDI 3.1, conversion 94% at 75 °C for 10 days). They further evaluated several organic solvents in the enzymatic ROP processes, and found solvents with higher log P values led to a higher molecular weight and higher conversion.

One of the best solvents identified was isooctane, which produced PCL with M_n 3,700 g/mol, PDI 2.4 and conversion 100% (at 45 °C for 20 days) and poly(δ -valerolactone) with M_n 3,200 g/mol, PDI 1.9 and conversion 98% (at 45 °C for 15 days). The Gross group⁵⁶ examined the effect of different initiators on the PPL-catalyzed ROP of ϵ -caprolactone in heptane at 65 °C, found the rate of initiation by butylamine is much higher than that by butanol or water; however, a higher M_n (up to 7,600 g/mol) was observed in the presence of water as the initiator at 85% conversion, and lower M_n values (1,900 and 1,200 g/mol) were obtained in butanol and butylamine respectively both at 100% conversion. The same group⁵⁷ further investigated the ROP of ϵ -caprolactone in various organic solvents catalyzed by Novozym 435 at 70 °C, and observed that water-miscible solvents (such as dioxane, acetonitrile and tetrahydrofuran) led to low propagation rates (below 30% substrate conversion in 4 h) and low molecular weight (M_n below 5,200 g/mol), while hydrophobic solvents (e.g. isopropyl ether, toluene, butyl ether and isooctane) enabled high propagation rates and high molecular weight (M_n up to 11,500–17,000 g/mol). In particular, the ROP reaction conducted in toluene (1:2 wt/vol, substrate/toluene ratio) at 70 °C for 4 h afforded 85% monomer conversion and M_n 17,000 g/mol (PDI 1.8); the scaling up from 0.3 mL ϵ -caprolactone to 10 mL even increased M_n to 44,800 g/mol (PDI 1.7) while the isolated yield (86%) remained high. Similar results were reported by the Li group⁵⁸ that more hydrophobic solvents (such as toluene, cyclohexane and *n*-hexane) led to high M_n (up to ~18,900 g/mol) of poly(ϵ -caprolactone) from the enzymatic ROP catalyzed by Novozym 435, whilst less hydrophobic ones (e.g. 1,4-dioxane, acetone, THF, and chloroform) yielded lower molecular weights (2,800–4,200 g/mol). The scaled-up reaction in toluene (45 °C for 24 h) increased the PCL molecular weight (M_n) to ~41,500 g/mol with 78% isolated yield and 1.69 PDI. Panova and Kaplan⁵⁹ examined the effect of different ϵ -caprolactone concentrations (0.065–7.8 M) on the Novozym 435-catalyzed ROP in toluene at 70 °C, and suggested that both the monomer conversion and the degree of polymerization increased with the monomer concentration (up to certain concentrations) and then decreased with a further increase in the monomer concentration. The decreased monomer conversion in concentrated monomer solutions is likely due to the poorer partitioning of PCL between toluene and the lipase, which could lead to the enzyme inhibition by the reaction product and/or slow diffusion of monomer to the enzyme active site. Barrera-Rivera et al.⁶⁰ evaluated a new lipase from *Yarrowia lipolytica* in the ROP of ϵ -caprolactone in *n*-heptane at 50–70 °C, producing PCL with the highest M_n of 977 g/mol at 55 °C for 360 h along with a complete monomer conversion.

The Gross group⁶¹ found that immobilized *Humicola insolens* cutinase was comparable with Novozym 435 in the polymerization of ϵ -caprolactone (M_n 24,900 g/mol vs 29,400 g/mol) and ω -pentadecalactone (M_n 44,600 g/mol vs 43,100 g/mol) in toluene [lactone/toluene (w/v) = 1/2] at 70 °C for 24 h. Cao et al.⁶² performed the ROP of δ -valerolactone catalyzed by a thermophilic esterase from the archaeon *Archaeoglobus fulgidus* at 70 °C for 72 h in various organic solvents, and found that the enzyme was more active in hydrophobic media (e.g. toluene, cyclohexane and *n*-hexane) than in hydrophilic or less hydrophobic ones (such as 1,4-dioxane, acetone, THF, dichloromethane and chloroform); the best solvent reported was toluene, which led to a monomer conversion of 97% and the highest M_n of 2,225 g/mol (PDI 1.37). Ozsagiroglu et al.⁶³ compared the effect of several organic solvents on the

enzymatic ROP of ϵ -caprolactone, and reported that the highest molecular weights were usually obtained in toluene, followed by diisopropyl ether and then *n*-hexane. Wang et al.⁶⁴ also observed that immobilized thermophilic esterase from *Archaeoglobus fulgidus* exhibited higher activities in more hydrophobic solvents (such as toluene, cyclohexane and *n*-hexane) than in the hydrophilic type (such as 1,4-dioxane, acetone and THF) towards the enzymatic ROP of ϵ -caprolactone, although the overall M_n values were relatively low (up to 1,070 g/mol). Poojari et al.⁶⁵ carried out the ROP of ϵ -caprolactone catalyzed by Novozym 435 in toluene at 70 °C for 4 h per cycle for up to 10 reaction cycles, which consistently produced polyesters with M_w ~50,000 g/mol and PDI ~1.4 although the product yields were not reported. The Möller group⁶⁶ examined the effect of water content in toluene on the ROP of ϵ -caprolactone, and observed that 359 ppm water led to the highest M_n of 7,700 g/mol when the reaction was catalyzed by Novozym 435. The Mecking group⁶⁷ conducted the entropy-driven ROP of nonadecalactone (C₁₉) and tricosalactone (C₂₃) catalyzed by Novozym 435 and obtained M_n up to 68,200 and 57,800 g/mol respectively; the high crystallinity polymers could have the Young's moduli on the order of 600 MPa which resembles polyethylene; they also pointed out that the residual lipase in the polyester could cause further polymer degradation during the size exclusion chromatography (SEC) analysis.

In general, the enzymatic ROP reactions are efficient in hydrophobic organic solvents. But the choice of organic solvents is further limited by the reaction temperature; for example, the ROP of lactides is often held at above 100 °C, therefore, the solvent needs to have its boiling point above this temperature. In addition, the volatility and toxicity could be the other concerns that need to be addressed.

ENZYMATIC ROP IN scCO₂

As an alternative green solvent, supercritical carbon dioxide (scCO₂) has been used in the enzymatic polymerization synthesis of poly(ϵ -caprolactone) producing M_n up to 50,000–80,000 g/mol, but a poor molecular weight control was observed (PDI ~2).⁴⁷ The Kobayashi group⁶⁸ reported the ROP of ϵ -caprolactone in scCO₂ catalyzed by *Candida antarctica* lipase at 60 °C for 24 h under 10 MPa, achieving M_n 17,000 g/mol, 85% conversion and PDI 4.0. The Howdle group⁶⁹ conducted the ROP reaction of ϵ -caprolactone in scCO₂ catalyzed by Novozym 435 at 35–65 °C and under 1180–3200 psi, obtaining M_n up to 37,000 g/mol, typical PDI = 1.4–1.6, and typical product yields 95–98%. The enzyme catalyst could be recycled and reused with high catalytic activities. The Howdle group⁷⁰ examined the kinetics of Novozym 435-catalyzed ROP of ϵ -caprolactone in scCO₂, and obtained high M_n up to 50,000 g/mol and polydispersity in the range of 2. Polloni et al.⁷¹ found that the enzymatic ROP of ϵ -pentadecalactone catalyzed by Novozym 435 in scCO₂ led to M_n up to 33,000 g/mol and PDI 3.8, but the addition of co-solvent (such as dichloromethane or chloroform) increased M_n up to 52,400 g/mol. Santos et al.⁷² use the fractional factorial design to evaluate the reaction conditions of enzymatic polymerization of ϵ -caprolactone in scCO₂ and reported the highest M_n of 7420 g/mol (PDI 1.96). The Ferreira group⁷³ conducted the enzymatic ROP of ϵ -caprolactone in scCO₂ and obtained PCL with M_n up to 13,700 g/mol (90% yield, PDI 1.2–1.7); they also noted that the solvent/monomer ratio is a critical factor in controlling the molecular weight (1:2 ratio gave the highest molecular

weights). The Oliveira group³ performed the enzymatic polymerization of ϵ -caprolactone in liquified petroleum gas (LPG) and scCO_2 catalyzed by Novozym 435, and observed that the batch reaction in LPG gave PCL with M_n up to 11,800 g/mol (68% yield and PDI 1.6) while in scCO_2 , the batch reaction afforded M_n up to 15,000 g/mol (81% yield, PDI 1.2–1.7) and the Packed-Bed Reactor produced M_n up to 21,700 g/mol (60.1% yield, PDI 1.7–2.1). Their results suggest that the pressure has no major impact on the reaction outcomes but the solvent/monomer ratio and the enzyme amount play a major role on the reaction yield. In the place of scCO_2 , 1,1,1,2-tetrafluoroethane (also known as known as R-134a) was considered by García-Arrazola et al.⁷⁴ as a solvent for the enzymatic ROP reaction because R-134a becomes liquid at a relatively low pressure (< 2 MPa, room temperature); the highest M_w of PCL obtained in this solvent was 37,600 g/mol (PDI = 1.7 and yield = 75.0%) when the reaction was conducted at 65 °C for 48 h.

Not many enzymatic ROP reactions of lactide have been reported in scCO_2 . Using the biphasic system of scCO_2 and melted L-lactide, only up to M_w 12,900 g/mol of polylactide was obtained when the ROP was catalyzed by Novozym 435 (immobilized CALB) under a low initial water activity ($a_w < 0.16$) at 65 °C.⁷⁵ Overall, there have been issues associated with the scaling-up of supercritical fluid reactors. Therefore, there is a strong need for unconventional solvents that are more benign than volatile solvents, are enzyme-compatible, and enable a high degree of polymerization and a controlled polydispersity.

ENZYMATIC ROP IN IONIC LIQUIDS

As a new generation of non-aqueous solvents, ionic liquids consist of ions and remain liquid at temperatures lower than 100 °C.^{79, 80} Ionic liquids have many favorable properties such as extremely low vapor pressure, a wide liquid range, low flammability, high ionic conductivity, high thermal conductivity, high dissolution capability for many substrates, high thermal and chemical stability, and a wide electrochemical potential window.⁸¹ More importantly, the physical properties of ionic liquids can be finely tuned through the judicious selection of cations and anions; therefore, a number of enzymatic reactions have been reported in different types of ionic liquids^{82–85} including the work of our group in functionalized ionic liquids.^{86–88} As illustrated in Table 1, several common ionic liquids have been examined in the enzymatic polymerization of lactides, and are compared with solvent-free, organic solvents and scCO_2 . The Yoshizawa-Fujita group³⁴ carried out CALB-catalyzed ROP of L-lactide in 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF₄]) at 110 °C, achieving M_n 54,600 g/mol, 1.25 polydispersity and 24.3% yield; in comparison, the solvent-free condition at 130 °C resulted in M_n 40,000 g/mol, and 54.1% yield while toluene as the solvent at 120 °C led to M_n 42,600 g/mol and 17.3% yield. This group also compared the lipase activity during the polymerization reaction that was decreasing with different ionic liquids [BMIM][BF₄] > [BMIM][Tf₂N] > [BMIM][PF₆] > [BMIM][dca] (Tf₂N[−] = bis(trifluoromethylsulfonyl)imide, and dca[−] = dicyanamide). Several other studies also reported a lower degree polymerization of lactide in [BMIM][PF₆], such as M_n 581 g/mol and 29.5% yield at 65 °C,⁷⁶ and M_n 19,600 g/mol at 90 °C; however, a higher molecular weight M_n of 37,800 g/mol and a higher yield of 63.2% was achieved in [HMIM][PF₆] at 90 °C.⁷⁸ Although some encouraging results were obtained when using ionic liquids, there are still concerns of low molecular weights and yields.

Several groups focused on the enzymatic ROP of other lactones in ionic liquids. The Kobayashi group⁸⁹ performed the ROP of ϵ -caprolactone in [BMIM][BF₄] catalyzed by CALB at 60 °C for 168 h resulting in M_n 4,200 g/mol and PDI 2.7, which is superior than that in [BMIM][PF₆]. The Heise group⁹⁰ carried out the ROP of ϵ -caprolactone in ionic liquids at 60 °C for 24 h catalyzed by Novozym 435, and found a distinct polymer layer formed on the top of [BMIM][PF₆] or [BMIM][BF₄] while the polymer PCL was soluble in [BMIM][Tf₂N]. The number average molecular weight (M_n) of 7,000–9,500 g/mol and a PDI below 2.5 were obtained in these ionic liquids, while the same reaction in toluene resulted in a slightly higher M_n (13,000 g/mol). However, the MALDI-ToF spectra of PCL suggested that a lower ratio of cycles to linear polymers was produced in ionic liquids than those synthesized in toluene. The Sreenc group⁹¹ evaluated the ROP of various lactones catalyzed by Novozym 435 in [BMIM][Tf₂N] (containing 0.1 wt% water), and obtained polyesters from β -propiolactone, δ -valerolactone, and ϵ -caprolactone with degrees of polymerization as high as 170, 25, and 85 respectively, and a copolymer of β -propiolactone and β -butyrolactone with a degree of polymerization of 180 (M_n ~13,000 g/mol); they also suggested that reducing the enzyme's water content could significantly increase the molecular weight of the polymer (by as much as 50% for β -propiolactone and ϵ -caprolactone). Barrera-Rivera et al.⁹² obtained PCL with M_n in the range of 300–9,000 g/mol through the ROP in several hydrophilic imidazolium and pyridinium ionic liquids catalyzed by *Yarrowia lipolytica* lipase (YLL), *Candida rugosa* lipase (CRL), and porcine pancreatic lipase (PPL) at 60–150 °C for 24 h. The He group⁹³ reported that a more viscous dicationic ionic liquid [C₄(C₆IM)₂][PF₆]₂ could lead to a higher PCL M_n of 26,200 g/mol and yield of 62% in the ROP reaction catalyzed by Novozym 435 at 90 °C for 48 h, when comparing with a lower M_n of 11,700 and yield of 37% in a less viscous monocationic ionic liquid [C₁₂MIM][PF₆]. The same group⁹⁴ noted that Novozym 435 coated with [C₁₂MIM][Tf₂N] enabled the ROP under solvent-free environment to produce PLC with M_n 35,600 g/mol and 62% yield at 60 °C for 48 h, whilst Novozym 435-catalyzed ROP in [C₁₂MIM][Tf₂N] (as the solvent) led to PCL with M_n 20,300 g/mol and 54% yield. Dong et al.⁹⁵ also suggested that [BMIM][PF₆]-coated Novozym 435 was more reactive than the case when the same amount of ionic liquid was used as the solvent in the ROP of 1,4-dioxan-2-one; the coated lipase produced polyesters with M_w up to 182,100 g/mol after 18 h of reaction at 70 °C. The Piotrowska group⁹⁶ conducted the Novozym 435-catalyzed ROP at 80 °C for 7 days in [BMIM][Tf₂N] and [BMIM][PF₆], yielding PCL with M_n of 4,600 g/mol (PDI 1.52) and 3,000 g/mol (PDI 1.52) respectively; they further indicated that PCL synthesized in [BMIM][Tf₂N] could be hydrolyzed faster than that produced in [BMIM][PF₆] due to a lower degree of crystallinity of the former polyester.

The advantages of using ionic liquids as co-solvents include their high boiling points, low volatility, high thermal stability, tunable enzyme-compatibility, and a wide range of choices. Some potential disadvantages are the high cost of ionic liquids, the hydrophilic nature of ionic liquids making the drying process challenging, and the possible degradation effect of ionic liquids on polyesters at high temperatures.

ENZYMATIC ROP IN AQUEOUS BIPHASIC SYSTEMS

For large (hydrophobic) lactones, it is possible to conduct the enzymatic ROP in water as a biphasic system, although generally low-molecular-weight polyesters are produced. Namekawa et al.⁹⁷ studied the lipase-catalyzed ROP of lactones in water, and found that more hydrophilic lactones (e.g. ϵ -caprolactone and 8-octanolide) could not form emulsion with water and the lipase, and subsequently no polymerization was detected. On the contrary, they observed that large-ring lactones [such as 11-undecanolide (UDL), 12-dodecanolide (DDL), and 15-pentadecanolide (PDL)] formed emulsions with water and the lipase, producing polyesters with M_n up to 2,100 g/mol after 72 h at 60 °C. The Albertsson group³² examined the ROP of hexadecanolide (HDL) catalyzed by lipase PS and AK in mini-emulsion consisting of HDL, hexadecane, and 1.0 wt% Brij 58 solution in water; the highest M_n of 9,330 g/mol (PDI 5.6) was obtained by using lipase PS and the nanoparticles yielded were between 114 and 534 nm in size. Panlawan et al.⁹⁸ formed the biphasic o/w system by dispersing pentadecalactone (ω -PDL) in water, and evaluated the ROP of this system catalyzed by *Burkholderia cepacia* lipase (Lipase PS) or Chirazyme L2 (L2, *Candida antarctica* type B lipase fixed on a macroporous phenolic type carrier). The addition of toluene prevented the solidification of oligo(ω -PDL) chains with a low degree of polymerization; the highest M_n obtained under optimum conditions was ~3,500 g/mol by using Chirazyme L2. Inprakhon et al.⁹⁹ carried out the enzymatic ROP of ϵ -caprolactone in aqueous dispersion, and found that the immobilized lipase (i.e. Novozym 435) afforded a higher number-average degree of polymerization (up to 38) than the free CALB (8 at the maximum).

ENGINEERED LIPASES FOR AN IMPROVED specificity

There have been mixed results on the lipase specificity on L- and D-lactide. Matsumura et al.²⁹ observed no activity of Novozym 435 towards the ROP of D,L-lactide, but a high activity for *Pseudomonas cepacia* lipase PS and a modest activity for *Candida cylindracea* lipase and porcine pancreatic lipase (PPL). Under optimum conditions, lipase PS gave weight-average molecular weights (M_w) up to 126,000 g/mol and 16% yield at 130 °C. This group³¹ further demonstrated that PPL exhibited high activities toward the ROP of lactides in bulk, resulting in PLLA (M_w 17,600 g/mol and PDI 1.9), PDLA (27,000 g/mol and 1.4) and PDLLA (26,600 g/mol and 2.1). Therefore, it was suggested^{51, 100} that *Candida antarctica* lipase B has a better selectivity toward D-lactide than L-isomer, whilst lipase from *Burkholderia cepacia* (known as lipase PS) is more specific toward L-lactide. Duchiron et al.⁵¹ indicated that the addition of triethylamine could activate the lipases, resulting in 4,900 g/mol M_n and 89% yield for Novozym 435-catalyzed ROP of D-lactide, and 1,800 g/mol M_n and 80% yield for lipase PS-catalyzed ROP of L-lactide. On the contrary, a number of studies still reported the synthesis of relatively high molecular weights of polylactide catalyzed by Novozym 435 in organic solvents and ionic liquids. For example, Omay et al.⁵⁰ carried out the polymerization of D,L-lactide in dry toluene at 80 °C, and obtained M_n of 26,000 and 21,000 g/mol respectively by using Novozym 435 and free CALB. In summary, different lipases have different specificities and activities towards L- and D-lactide, which could be further tuned and optimized through protein engineering. For example, Takwa et al.

¹⁰⁰ designed two mutants of CALB, showing 90-fold improved activity, and increased rate and the degree of polymerization of ROP of D-lactide in toluene at 60 °C.

ENZYMATIC ROP SYNTHESIS OF POLYESTER-DERIVED MATERIALS

As the leading biodegradable materials, aliphatic polyesters including polylactides (PLAs) and other polylactones are thermoplastic, biodegradable, renewable and biocompatible polymers with mechanical properties (i.e., high strength and high modulus) similar to that of polystyrene (PS) or polyethylene terephthalate (PET).¹ Properties of PLA depend on several major factors such as the component isomers, processing temperature, annealing time and molecular weight. Optically active PLA, i.e. PLLA and PDLA, are semi-crystalline. PLLA has a crystallinity of ~37%, a glass transition temperature (T_g) of 55–65 °C and a melting temperature (T_m) of 170–200 °C; regular PLA has a T_g of 45–60 °C and a T_m of 150–162 °C; PDLA is amorphous with T_g of 50–60 °C.¹⁰¹ However, PLAs are generally brittle materials (poor toughness) with low impact strength (PLAs: Young's modulus 1–4 GPa^{101, 102}) and other issues (such as low glass transition temperature, high hydrophobicity, low thermal resistance, low heat distortion temperature, and limited crystallinity along with low rate of crystallization), which is similar to PS and PET in some respects.^{103–106} These shortcomings become major drawbacks for these biodegradable and sustainable polymers to be widely used in many areas. To improve the mechanical durability of these polyesters and reduce their costs of production, a number of approaches have been actively pursued. (1) Copolymers: Poly(lactic-glycolic acid) (see Scheme 2) has been approved by the FDA for clinical uses such as controlled drug release. Other popular copolymers include copolymerization of PLA and poly(ϵ -caprolactone) (PCL),^{107, 108} and copolymerization of lactide with diesters and diols.¹⁰⁹ (2) Polymer blends, such as PLA-starch blend, and PLA-poly(ϵ -caprolactone) (PCL) blend;^{110, 111} however, these blends often suffer from poor mechanical properties due to limited miscibility and insufficient adhesion between the phases although the use of cellulose-dissolving ionic liquid 1-butyl-3-methylimidazolium chloride ([BMIM]Cl) could lead to partial miscibility between cellulose and PCL. (3) PLA-based nanocomposites: a variety of nanofillers have been used to construct PLA nanocomposites to enhance the PLA properties; these nanocomposites include clay-based, nanocellulose-based, carbonaceous-based, metal/metallic (hydr)oxide-based, and others.¹¹² Nanofibers or whiskers (2D) have a diameter below 100 nm and are characterized with an aspect ratio of at least 100. Carbon nanotubes and nanocellulose substrates are typical examples of this category.

Among these hybrid materials, nanocellulose-based PLA composites are of particular interest because cellulose is also renewable polymers, and cellulose nanocrystals have a high surface area, unique morphology, and good mechanical response upon stress. Cellulose is the most abundant biomass on earth and can be processed into different forms of nanofillers such as rod-like cellulose nanocrystals and nanofibrillated cellulose.¹¹² However, cellulose tends to be more hydrophilic (due to multiple hydroxyl groups) and thus absorbs water, and is less flexible for processing. Therefore, it is desirable to produce cellulose composites to overcome these bottlenecks. Nevertheless, the challenge becomes the hydrophilic cellulose fibers with polar surfaces being not compatible with the hydrophobic matrix. A physical blending of nanocelluloses into PLA matrix suffers from a poor dispersion because

hydrophilic nanocelluloses are not highly compatible with hydrophobic PLA matrix. Another issue is that, upon drying, irreversible agglomeration of nanocelluloses occurs due to strong hydrogen bonds of hydroxyl groups at their surface. One effective approach is to modify the cellulose surface by grafting with polymer chains (Scheme 4). By using cellulose-grafting-polyester as filler material in a matrix polymer (such as polyesters), reinforced composites can be produced with applications in loading-bearing construction materials and biomedical materials. If the matrix polymer (e.g. polyesters) is also biodegradable, the composites are completely degradable with enhanced mechanical properties. To improve the compatibility of nanocelluloses, several chemical approaches (such as esterification, silanization and polymer grafting) have been attempted to modify the celluloses.¹¹² For example, Li et al.¹¹³ grafted epoxy-terminated copolymers of PLA and glycidyl methacrylate onto the surface of bacterial cellulose nanofibers via the reaction between epoxy groups (from copolymer) and hydroxyl or amine groups (from cellulose or modified cellulose). A more recent development is to covalently link polyester chains onto the surface of nanocelluloses through “grafting from” or “grafting to” ring-opening polymerization (ROP); these ROP modifications of cellulose or its derivatives are often catalyzed by tin(II) 2-ethylhexanoate [Sn(Oct)₂], organic acids (e.g. tartaric acid, citric acid, lactic acid and proline), or even LiCl as heterogeneous or homogeneous processes.^{114–116} The Liu group¹¹⁷ conducted the ROP of L-lactide catalyzed by Sn(Oct)₂ to graft PLLA onto cellulose (cotton linter pulp), achieving the molar substitution up to 1.45, the average degree of polymerization of PLLA-side chain up to 1.70, and the degree of lactyl substitution up to 0.97; the cytotoxicity study indicated a high biocompatibility of cellulose-*g*-PLLA; in aqueous solutions, the copolymer self-assembles into micelles with the hydrophobic PLLA segments at the core and the hydrophilic cellulose segments as the outer shells, which is ideal for drug delivery. Using the “grafting from” method, Lin et al.¹¹⁸ synthesized filaceous cellulose whisker-*graft*-polycaprolactone nanoparticles through surface-grafting rodlike cellulose whiskers with polycaprolactone via microwave-assisted ring-opening polymerization catalyzed by Sn(Oct)₂. Similarly, Goffin et al.¹¹⁹ attached PLA chains on the surface of cellulose nanowhiskers by ring-opening polymerization of L-lactide catalyzed by Sn(Oct)₂; the nanohybrids were further dispersed into PLA using melt-blending to produce PLA-based nanocomposites. The Wu group¹²⁰ (and then the He group¹²¹) grafted PLLA chains onto cellulose via the homogeneous ROP catalyzed by 4-dimethylaminopyridine (DMAP) after dissolving cellulose in 1-allyl-3-methylimidazolium chloride; they could control the amount and length of grafted PLLA in cellulose-*g*-PLLA copolymers with a molar substitution of PLLA between 0.99 and 12.28 by varying the molar ratios of LA monomer to cellulose; they found that the copolymer is amorphous and becomes soft and flowed at the molar substitution of PLLA above 4.40 (DS = 1.74), which is especially desirable for the production of fibers and films via melt spinning and hot compression molding. Purnama and Kim¹²² prepared the bio-stereocomplex–nanocomposite material by grafting PLLA onto acetylated–cellulose nanowhiskers via the ROP catalyzed by stannous octoate; the new material has an improved Young’s modulus up to 2.70 GPa and thermal degradation property with a higher temperature of the maximum weight loss rate (355 °C).

In addition to modifying the cellulose’s surface with PLA, several studies also grafted PCL onto the cellulose chain to achieve improved mechanical properties. Composites containing

microfibrillated cellulose (MFC) films grafted with PCL have showed an enhanced ductility and improved adhesion at the interface.^{123, 124} Composites incorporating 8 wt% PCL-grafted cellulose nanowhiskers (CNW) into a polylactide (PLA) matrix improved the strength and elongation of PLA materials by roughly 1.9- and 10.7-fold respectively;¹¹⁸ PCL composites containing PCL-grafted cellulose nanocrystals showed a significant improvement in terms of Young's modulus and storage modulus;¹⁰⁵ PLA composites loaded with PLA grafted-CNW could increase the stiffness of the material above T_g , however, the reinforcing effect is at its minimum below T_g due to the plasticizing effect of the grafted PLA chains on the polymer matrix.¹¹⁹ Nordgren et al.¹²⁵ studied the PCL grafted cellulose spheres (~10 μm in diameter) via the atomic force microscopy in a colloidal probe configuration and observed an enhanced adhesion at the polymer-polymer interface with an increase of the temperature to 60 °C (close to T_m for the PCL graft) indicating the significance of entanglements in the annealing of composite materials.

However, these grafting studies were mostly accomplished by the chemical methods, which have similar disadvantages as the chemical polymerization of PLAs as discussed earlier. The use of enzymes to catalyze such ROP grafting is very limited. The Wang group¹²⁶ performed the ROP reaction of PCL onto hydroxyethylcellulose films catalyzed by porcine pancreatic lipase (PPL) or a thermophilic CLONEZYME ESL-001 lipase library, achieving the degrees of substitution of 0.10–0.32 per anhydroglucose unit. Martinelle and co-workers¹²⁷ bound the fusion protein, cellulose-binding module (CBM) of CALB, to the filter papers followed by the ROP of ϵ -caprolactone in close vicinity to cellulose fiber surfaces, and obtained PCL with molecular weight (M_w) up to 41,000 (polydispersity index = 3.1) at 60 °C under the thermodynamic water activity (a_w) of 0.11. However, they found that PCL was coated on the cellulose surface rather than covalently attached to it.

SUMMARY

This review evaluates a comprehensive list of solvents (such as solvent-free or in bulk, organic solvents, supercritical fluids, ionic liquids, and aqueous biphasic systems) on how they influence the molecular weight and polydispersity of the enzymatic ROP of lactides and lactones. Various solvent conditions have exhibited different levels of advantages and disadvantages, and it is still challenging to develop and optimize new solvents for relatively high-temperature enzymatic applications. In addition, the lipase specificity and thermal stability towards different monomers could be further genetically optimized. The enzymatic ROP synthesis of polyester-derived materials has a great potential to produce truly biodegradable polymers with enhanced mechanical properties.

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Scheme 1.
Structures of lactides.

Scheme 2.

Enzymatic ROP synthesis of PLA and poly(lactide-co-glycolide).

Scheme 3.

Enzymatic ROP of unsubstituted lactones (e.g. $m = 2$, β -propiolactone; $m = 3$, γ -butyrolactone; $m = 4$, δ -valerolactone; $m = 5$, ϵ -caprolactone).

Scheme 4.

Cellulose nanowhiskers grafted with PLA via enzymatic ROP reaction.

Table 1

Comparison of ROP of lactides under different reaction conditions

#	Lactide	Lipase ^a	Solvent ^b	Water (%)	T (°C)	t/days	Conversion (%)	Yield (%)	M _w	PDI	Ref.
1	DL	N435, 3 wt%	—	unknown	80	7	0	0	—	—	29
2	L	N435, 6 wt%	—	unknown	100	10	91	—	2,440	2.6	33
3	L	Free CALB	—	unknown	130	1	—	54.1	45,200	1.13	34
4	L	Free CALB	toluene (1/1, w/w)	unknown	120	1	100	17.3	49,800	1.17	34
5	L	Free CALB	[BMIM][BF ₄] (1/1, w/w)	unknown	110	1	96.2	24.3	68,300	1.25	34
6	L	N435, 10 wt%	[BMIM][PF ₆] (7/10, w/w)	unknown	65	11	—	29.5	700	1.2	76
7	L	N435, 10 wt%	[BMIM][PF ₆] (7/10, w/w)	unknown	90	5	—	—	23,500	1.2	77
8	L	N435, 10 wt%	[HMIM][PF ₆] (7/10, w/w)	unknown	90	7	—	63.2	49,100	1.3	78
9	L	N435, 10 wt%	[HMIM][PF ₆] (7/10, w/w)	unknown	65	9	—	51.1	1,800	1.2	78
10	L	N435, 15 wt%	scCO ₂	<i>a_w</i> < 0.16	65	3	35.2	5.16	11,900	1.25	75
11	L	N435, 12.5 wt%	toluene (1/2, g/mL)	unknown	70	3	0	0	—	—	49
12	D	N435, 12.5 wt%	toluene (1/2, g/mL)	unknown	70	3	33	25	4,000	1.2	49
13	L	N435, 10 wt%	toluene	unknown	70	2	23	23	—	—	51
14	DL	N435, 10 wt%	toluene	unknown	70	2	5	—	—	—	51
15	D	N435, 10 wt%	toluene	unknown	70	2	98	90	4,600	1.3	51
16	D	PS, 3 wt%	—	unknown	100	7	96	5	59,000	1.2	29
17	DL	PS, 3 wt%	—	unknown	100	7	82	8	69,000	1.2	29
18	L	PS, 3 wt%	—	unknown	100	7	82	8	48,000	1.2	29
19	D	PS, 5 wt%	toluene	unknown	90	2	14	5	—	—	51
20	DL	PS, 5 wt%	toluene	unknown	90	2	20	10	550	1.1	51
21	L	PS, 5 wt%	toluene	unknown	90	2	80	65	770	1.1	51
22	L	PPL, 1wt%	—	unknown	100	7	—	—	17,600	1.9	31
23	D	PPL, 1wt%	—	unknown	100	7	—	—	27,000	1.4	31
24	DL	PPL, 1wt%	—	unknown	100	7	—	—	26,600	2.1	31

Note:

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^bN435 = Novozym 435; PS = lipase PS from *Burkholderia cepacia*; lipase concentration (wt%) based on monomer;

^bthe number in parenthesis indicates the substrate/solvent ratio.