Low-Temperature and Purification-free Stereocontrolled Ring-Opening Polymerisation of Lactide in Supercritical Carbon Dioxide

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Abstract

A stereoselective, solvent-free ring-opening polymerisation (ROP) of lactide (LA) in supercritical carbon dioxide (scCO$_2$) is reported for the first time. The key aim is to exploit scCO$_2$ to lower the temperature of traditional melt polymerisations, lowering the energy requirement and leading to cleaner polymeric materials. We have utilised a zirconium amine-trisphenolate initiator-stereoselective catalyst [(^{i}PrO)Zr(OPh(^{t}Bu)$_2$-CH$_2$)$_3$N] to yield highly heterotactic poly(lactide) (PLA) homopolymer (P$_r$ = 0.74 − 0.84) from *rac*-LA, demonstrating control of the PLA microstructure in scCO$_2$. In addition, high monomer conversion (86 − 93%) was achieved in short reaction time (1 h), affording poly(lactide) with a very low degree of transesterification and narrow molecular weight distribution. Most importantly, all the reactions were performed at only 80 °C, almost 100 ^{o}C lower than the conventional melt process (typically performed at 130-180 °C), representing a very significant potential energy saving.

Introduction

Biodegradable and bio-derived materials are receiving significant research interest, both as potential replacements for petrochemically-derived commodity polymers and for use in biomedical applications;[1-6] polyesters represent one such class of these materials.[7, 8] Poly(lactic acid) (PLA), a linear polyester that can be derived from sugars, has shown particular promise through its unique physical properties, biocompatibility and biodegradability.[9-12] PLA is synthesised through ring-opening polymerisation (ROP) of lactide, the cyclic dimer of lactic acid, which facilitates control of the polymer molecular weight and dispersity,[13] and end-group functionality.[14, 15] ROP of LA has been demonstrated utilising a wide variety of metal,[16-21] and organo-catalytic species,[22-27] and is employed commercially in the production of PLA.[28]

The toxicity associated with, and cost of removal of, residual organic solvents mean that PLA is produced industrially in solvent-free, melt-phase conditions at high temperature (up to 180°C). [29] Such high temperatures are required to maintain mobility of the polymer and this leads to high production costs and significant challenges in maintaining control over polymerisation.[30] For example, whilst many catalysts can control the PLA microstructure at lower temperatures,[31] examples of stereoselective ROP of lactide at 180 °C or above are very rare because transesterification reactions are significant at T ≥ 150 °C.[32] To our knowledge, Nomura *et al.* have reported the only system to date that attains useful levels of stereocontrol at 180 °C.[29] Furthermore, at these

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elevated temperatures transesterification reactions, in addition to catalyst deactivation, can often occur to produce atactic PLA. Unwanted polymer degradation pathways are also operative, which can impact molecular weight control. [33]

Supercritical carbon dioxide (scCO₂) has found utility as a "green" solvent. It is abundant, inexpensive, is easily removed at the end of the reaction, and can even be recycled. Furthermore, diffusion of scCO₂ into the free volume between polymer chains can weaken intermolecular interactions and increase chain mobility. The resulting reduction in melt and glass transition temperatures and the lowering of polymer viscosity can bring many advantages, including facilitating low-temperature processing.[34-37] The use of scCO₂ as the medium for a variety of polymerisations has been demonstrated,[38-40] including ROP of cyclic esters (including lactide) using both metal and organic catalysts.[41-49] These synthetic strategies have largely required lengthy reaction times (5 – 24 h).[50, 51] Significantly, none of these approaches have demonstrated stereocontrolled ROP.

Zirconium amine trisphenolate species [e.g. (^{i}PrO)Zr(OPh(^{t}Bu)$_2$-CH$_2$)$_3$N] (**1**)] have been reported as highly heterotactic-selective initiators for the ROP of rac-LA. Notably, they demonstrate enhanced air stability that facilitate manipulation avoiding glove-box technology.[52, 53] In this regard, Chmura et al. [53] reported the synthesis of highly controlled and heterotactic PLA. However, to make this happen required either toluene as reaction solvent or high temperatures for the melt polymerization conditions (130 °C); a series of organic solvents (*e.g.* DCM, methanol) were also required for the purification step of the final product.

In this report, we demonstrate that use of scCO₂, as an industrial scalable alternative could facilitate the stereoregular ROP of *rac*-LA under organic solvent-free conditions at significantly lower temperatures (80 °C) than those used in the conventional melt-phase polymerisation (130 – 180 °C). This not only represents a more energy-efficient greener and scalable process for the synthesis of PLA, but also affords products with controlled microstructure.
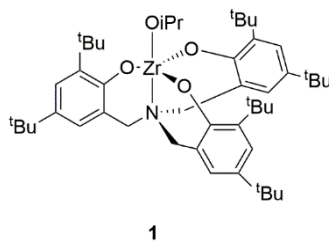

Figure 1. Zr trisphenolate initiator **1** employed in this study

Monomer and Polymer solubility in scCO₂

To investigate the reaction in detail, we observed first the solubility of *rac*-LA in scCO₂ through view cell experiments. Thus, different amounts of monomer were charged into a view cell autoclave, which was then heated and pressurised with CO_2. At 80 °C and 240 bar we found that 5 wt/v% *rac*–LA, was almost completely CO_2-soluble. Raising the pressure to *ca*. 300 bar, and hence raising the density, led to full solubility (Figure 2). At increased monomer loading (7 wt/v%), solubility was again observed at 80 °C and *ca*. 300 bar CO_2. However, saturation was quickly reached upon further increase in monomer loading (10 wt/v%) and full solubility in scCO₂ could no longer be achieved at 300 bar and 80 °C (Figure 2, right). This is consistent with the findings of Stassin and Jerome, who studied the solubility of L-LA at a range of temperatures and pressures showing that scCO₂ can lower the melt temperature of L-lactide, that it has partial solubility in scCO₂.[54, 55] In addition, the T_m of L-LA is lowered from ~100 °C to ~ 50 °C and we recently showed that similarly the T_m of *rac*-LA can be lowered from ≈ 130 °C to 95 °C in the presence of scCO₂.[56] This monomer solubility in scCO₂ can be exploited to ensure there are minimal monomer residues in the final polymeric materials. [56]

By contrast, the polymers are completely insoluble in scCO₂. But, CO_2 is soluble in the polymer and this leads to plasticisation[56, 57] and a liquefied polymer system, essentially a polymer melt. These studies and others[54] suggest that ROPs conducted at 80 °C would initially consist of a homogeneous monomer solution in scCO₂. As the polymerisation progresses, the polymer precipitates out of scCO₂, leading to a biphasic system consisting of a CO_2-rich phase and a polymer-rich phase, with lactide monomer likely in both phases. The polymeric products were found to be of moderate molecular weight (entries 2-6: 6700 – 9350 Da (triple detection), consistently slightly lower than predicted ($M_{n(theor)}$). We expect that the polymer growth may be hindered once precipitated, leading to lower than expected molecular weights and slight broadening of the molecular weight distribution (Đ = 1.05 – 1.40), relative to PLA generated in conventional solvent-free ROP.[53]

5 wt/v%
5 g in 100 mL
283 bar, 81 °C

7 wt/v%
7 g in 100 mL
294 bar, 80 °C

10 wt/v%
10 g in 100 mL
300 bar, 83 °C

Figure 2. View cell solubility tests for rac-LA in scCO₂. The first two conditions show complete solubility but there is only partial solubility at 10 wt/v% (right)

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Stereoselective *rac*-LA Polymerization in scCO$_2$

The polymerisation of *rac*-LA in scCO$_2$ over a range of temperatures (80 to 130 °C) was conducted (Table 1) utilising initiator **1**. Ring opening polymerisations conducted at 80 °C afforded PLA at good conversion after 1 h (Table 1,entry 2: 86%), similar to the room temperature solvent-mediated polymerization with the same catalyst (50% yield in 48 hr) and conventional melt polymerisation at 130 °C (78% yield in 0.1 h).[53] MALDI-TOF mass spectrometry and homonuclear decoupled NMR spectroscopy were used to investigate the degree of control of polymerisations in scCO$_2$. Significantly, the PLA from all polymerisations in scCO$_2$ was found to have high levels of heterotactic enchainment (P$_r$ = 0.73 – 0.84), representing the first demonstration of a stereocontrolled ROP of *rac*-LA in scCO$_2$. There is though a lower temperature limit, and polymerisations conducted at 60 °C did not produce any polymer in one hour (Table 1, entry 1: 0 % conversion). The poor solubility of the monomer at these conditions likely prevents the polymerisation from initiating.

Table 1. PLA synthesis in scCO$_2$*

Entry	*p* / bar	T / °C	M/I	t / h	Conv. / %[a]	P$_r$[b]	$M_{n(theor)}$[c]	$M_{n,}$[d]	Đ[d]	MALDI-TOF
1	240	60	100	1	0	-	-	-	-	
2	240	80	100	1	86	0.83	12450	9350	1.34	Figure 3
3	240	100	100	1	86	0.80	12450	6200	1.35	Figure S13
4	240	130	100	1	93	0.76	13450	6700	1.40	Figure S14
5	240	80	100	0.1	59	0.84	8550	7950	1.30	Figure S15
6	240	100	100	0.1	76	0.79	11000	8500	1.23	Figure S16
7	Melt	180	100	1	94	0.72	13600	15350	1.70	Figure 3

[a] Determined by ^{1}H NMR spectroscopy. [b] P$_r$ is the probability of heterotactic enchainment calculated through analysis of the homonuclear decoupled ^{1}H NMR spectra. [c] Theoretical M_n (Da) calculated using the formula(([*rac*-LA]$_0$/[**1**]$_0$) x M_{rac-LA} x conversion/100 + M_{OiPr}).[d] Molecular weight (Da) determined by triple detection SEC in THF.

* GPC traces (Figure S1-S12) and ^{1}H homonuclear decoupled NMRs (S18-26) for key entries in Table1 and S1 are reported in Support Information.

Polymerisations at lower temperatures exhibited a greater degree of stereocontrol (Table 1, entries 2 & 5 Figure 3 and Figure S3: 80 °C, P_r = 0.83 & 0.84, Figure S5 right) than those conducted at higher temperatures (Table 1, entries 3 & 4, Figure S1 and S2: 100 °C, P_r = 0.74; 130 °C, P_r = 0.76). By contrast, an analogous reaction ([rac-LA]:[**1**] = 100:1, 1 h) (Figure 3 - LEFT) conducted at ambient pressure and at an industrially-relevant temperature (180 °C) [29] afforded a polymer of much broader molecular weight distribution (Đ = 1.71), with a more atactic microstructure (P_r = 0.72, Figure S5 left) and displayed significant evidence of extensive transesterification; most notably in the observed MALDI-TOF which shows all the peaks separated by 72 Da (Figure 3 LEFT)

The MALDI-TOF mass spectra from $scCO_2$ are dominated by a single distribution with an average mass separation of 144 Da, corresponding to the LA repeat unit and also demonstrating minimal transesterification. The data also allow definitive identification of the end group confirming that the ^{i}PrO group from **1** is transferred to the growing polymer chain during the initiation of ROP. A low intensity second series of 72 Da mass difference (1 lactyl unit) to the main distribution was identified for some samples and points towards transesterification being just a minor side reaction (Figure 3 RIGHT). The intensity of this second series, and thus the amount of transesterification, was found to increase with reaction temperature, as observed in the spectra obtained for PLA synthesised at 100 °C (entry 3, Figure S1), and 130 °C (entry 4, Figure S2).

In order to probe the polymerisation system further, a series of reactions at different M/I ratios, pressures and monomer concentrations were performed to broaden the initial understanding of the effects of these parameters.

For Pressure: At 60 bar (Table S1 entry 8) no reaction was observed, likely due to the very low solubility of the monomer under these conditions, and also the minimal effect of plasticisation. At 120 bar a conversion of above 80% with a P_r of 0.82 was observed (Table S1 entry 9). This is close to the best yield obtained at our optimal 240 bar, but with only poor control in terms of dispersity. This likely reflects the lower level of plasticisation at the lower pressure (and hence lower density of CO_2).
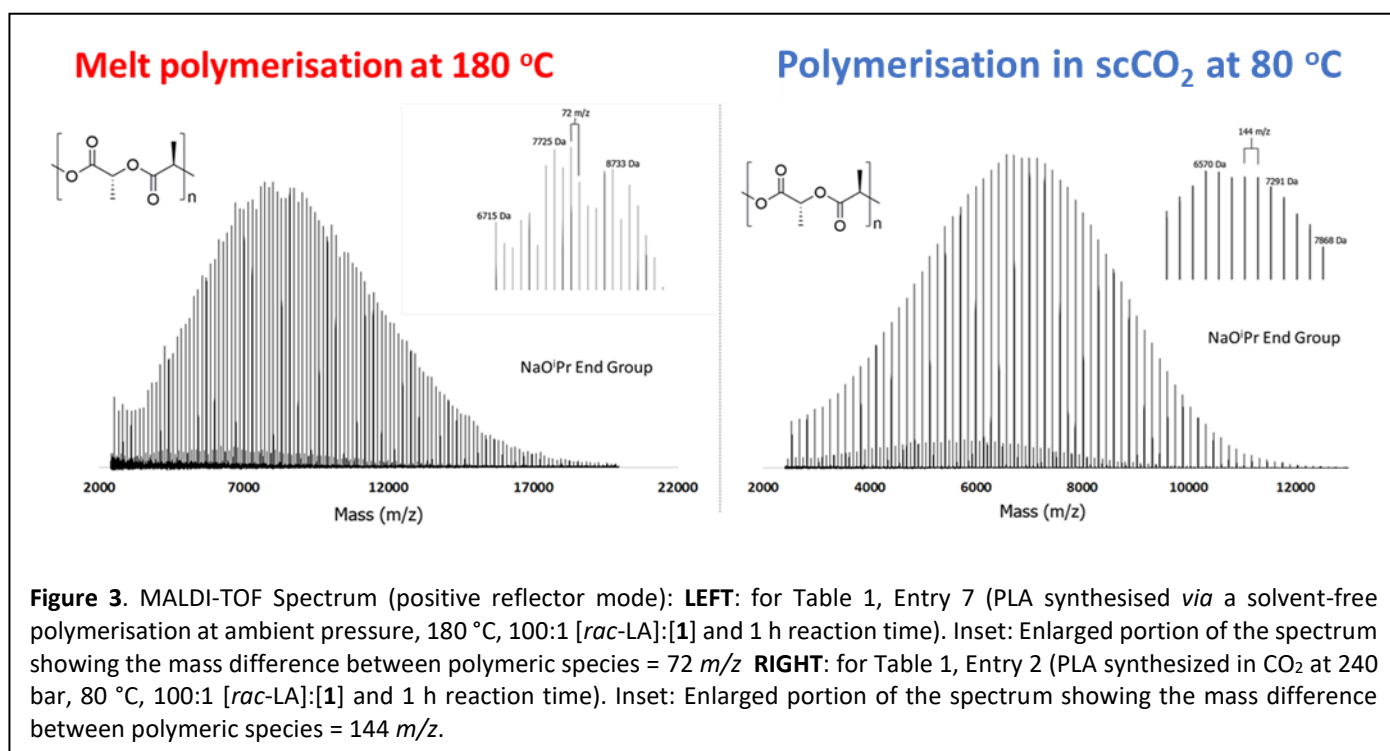
For monomer concentration: when 0.1 g (Table S1 entry 10) of monomer was loaded no reaction was observed, likely due to the high dilution of the specific condition.

For M/I Ratio: At an M/I ratio of 150:1 (at 80 °C and after 1h, Table S1 entry 11), reasonable agreement was detected between the theoretical and the measured molecular weight ($M_{n,theo}$ = 13,200 Da; M_n = 14,100 Da) with a Pr of 0.82 and a conversion of monomer into polymer of around 60%. When the M/I was raised to 300:1 (at 80 °C and after 1h, Table S1 entry 12) a drop in monomer conversion to around 45% was observed. Under these conditions, we still see good control in terms of Pr and dispersity but the resulting polymer showed a molecular weight of only 15000 Da. In an attempt to increase the monomer conversion, and the final PLA molecular weight, two further reactions were carried out for longer time periods of 16 and 24h. Despite the higher conversion (circa 85%), we still find that the molecular weights plateau between 10000 and 12000 Da and there is no significant increase. Instead, a direct consequence of the longer reaction time was the disruption of the Pr values that dropped from 0.82 after 1h (Table S1 entry 12) to 0.76-0.74 after 16 and 24 h respectively.

For M/I ratio and Temperature: Maintaining a high M/I of 300 and raising the temperature from 80 to 100 °C increased the monomer conversion from 40% to 70% after 1h of reaction (Table S1 entry 15). However, the final

molecular weight observed was still limited to around 15000 Da as with all the other attempts with the same M/I ratio of 300; different temperatures and reaction times.

The limitation of molecular weight is puzzling. It could be that residual contaminants e.g. water in the scCO$_2$ are having a deleterious effect. Or, it could be that as the polymer molecular weight increases, we reach a point where the viscosity in the melt is sufficiently high that monomer penetration to the active metal site is limited. In both cases further studies and optimisation will help us. However, this should not detract from our key message that use of scCO$_2$ effectively lowers the temperature required for ROP of lactide, suppressing transesterification reactions, with a concomitant increase in the stereo-control of the polymerisation. There is also a significant additional benefit with our novel proposed route. On the current industrial scale process, a high temperature devolatilisation step is required to remove residual lactide monomer. In fact, we have already successfully demonstrated that the monomer can be easily extracted from crude reaction mixtures by scCO$_2$-assisted extraction (exploiting the monomer solubility and the polymer insolubility in scCO$_2$).[56]

Figure 3. MALDI-TOF Spectrum (positive reflector mode): **LEFT**: for Table 1, Entry 7 (PLA synthesised *via* a solvent-free polymerisation at ambient pressure, 180 °C, 100:1 [*rac*-LA]:[**1**] and 1 h reaction time). Inset: Enlarged portion of the spectrum showing the mass difference between polymeric species = 72 *m/z* **RIGHT**: for Table 1, Entry 2 (PLA synthesized in CO$_2$ at 240 bar, 80 °C, 100:1 [*rac*-LA]:[**1**] and 1 h reaction time). Inset: Enlarged portion of the spectrum showing the mass difference between polymeric species = 144 *m/z*.

Conclusions

Routinely, conventional melt-phase polymerisations require high temperature (over 130°C). On the commercial scale temperatures are much higher and the residence time at high temperature is long and these

extreme conditions preclude the use of a wide range of stereo-selective ROP initiators/catalysts. Hence, there is loss of control of the microstructure of PLA.

For the first time, we have demonstrated that a stereocontrolled ROP of *rac*-LA can be performed in organic solvent-free conditions at only 80°C using pure scCO$_2$ as a processing aid. Heterotactic PLA with a high degree of control (P$_r$ = 0.75 – 0.86) was produced by adopting [(^{i}PrO)Zr(OPh(^{t}Bu)$_2$-CH$_2$)$_3$N], as robust air-stable stereoselective initiator-catalyst. Although this catalyst was not specifically designed for scCO$_2$ environment, it was used without any chemical or structural alteration. The promising quality of the polymers and the mild reaction temperatures open up a completely new green, scCO$_2$-based strategy that could facilitate the facile use of other newly developed stereoselective catalysts. Furthermore, the reaction time (1 h or less) is significantly shorter than for previous reports of PLA synthesis in scCO$_2$ and affords PLA with little or no detectable transesterification as well as narrower molecular weight distribution. In addition, the MALDI-TOF data allowed definitive identification of the end group confirming that the ^{i}PrO group from **1** is transferred to the growing polymer chain during the initiation step remarking the controlled nature of the reaction.

The preliminary results presented in this work suggest that the initiator/catalyst system could be used in organic-solvent-free ROP and will provide access to a range of PLA stereo-architectures at lower temperatures with only minimal transesterification observed at those temperatures. In addition, the current commercial processes require a devolatilization step to remove residual monomer which requires a very significant additional energy input. Since the monomer is soluble in scCO$_2$, we can envisage a completely new approach, lowering the number of steps by exploiting the scCO$_2$ to eliminate the separate energy intensive devolatilisation steps that are currently essential on the commercial scale.

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