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Microwave-assisted poly(D,L-lactide) synthesis in toluene and tetrahydrofuran

Nicolas A. Patience[1] | **Halie Mei Jensen**[2] | **Xavier Banquy**[3] | **Daria C. Boffito**[1]

[1]Department of Chemical Engineering, Polytechnique Montreal, Montreal, Canada

[2]Department of Electrical, Computer, and Biomedical Engineering, Toronto Metropolitan University, Toronto, Canada

[3]Department of Pharmacy, University of Montreal, Montreal, Canada

Correspondence
Daria C. Boffito, Department of Chemical Engineering, Polytechnique Montreal, Montreal, Canada.
Email: daria-camilla.boffito@polymtl.ca

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Abstract

Poly(D,L-lactide) is a biocompatible and biodegradable polymer with applications in the biomedical field (drug delivery, implants) and packaging. Conventional synthesis with stannous octoate is slow (>4 h) and can climb to over 30 h. In order to reduce reaction times, we developed a microwave reactor process to ring-open polymerize D,L-lactide to form poly(D,L-lactide) in the presence of stannous octoate and an initiator, benzyl alcohol. We evaluated the suitability of toluene and tetrahydrofuran as solvents at 130, 150, and 170°C for the polymerization. Their respective dielectric loss (ε'') values are 0.1 and 0.35. Compounds with larger dielectric loss values are better at converting microwave energy to heat. The microwave's power input peaked at 420 W to reach 170°C with toluene, whereas with tetrahydrofuran the peak was 330 W; afterwards, the power input to maintain that temperature was 10 W for both solvents. A reaction in toluene at 170°C after 1 h produced poly(D,L-lactide) with a molecular weight of 31 kDa and a dispersity index of 1.5. In tetrahydrofuran, at the same temperature, the molecular weight peaked at 11 kDa after 4 h with a dispersity index of 1.2. Moreover, in the absence of microwaves the polymerization does not occur. Tetrahydrofuran is hygroscopic and water cleaves poly(D,L-lactide) chains resulting in a lower molecular weight despite the longer reaction time and larger dielectric loss compared to toluene, a water immiscible solvent.

1 | INTRODUCTION

Polylactic acid (PLA) is an aliphatic polyester derived from α-hydroxy acids. It is a biocompatible and biodegradable polymer that degrades by hydrolysis of its ester bonds.[1] In addition, it is produced from lactic acid, which in turn is sourced from renewable feedstock (e.g., corn, sugarcane). These properties have cemented PLA as one of the most promising replacements for petroleum-based plastics, with uses in food packaging, medical device manufacture, and drug delivery purposes.[2–5] PLA's monomer, lactic acid (LA), is an ingredient in the food industry and functions as an acidic flavoring buffer and a bacterial inhibitor in processed foods. Bacterial fermentation with lactic acid bacteria (LAB) accounts for 90% of all lactic acid production. This process consumes little energy, operates at low temperatures, selectively produces D-lactic acid or L-lactic acid, and consumes renewable carbohydrate biomass.[1]

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Polymerization of D- and L-lactic acid yields poly-D-lactic acid (PDLA) and poly-L-lactic acid (PLLA). The former is amorphous while the latter is semi-crystalline.[6] The conventional method for synthesizing PLA requires heating lactic acid or lactide above 100°C for 4 h or more,[7] and with no dedicated initiator this climbs to over 30 h.[8] On the other hand, NatureWorks LLC patented a continuous ring-opening polymerization process of lactide with a tin-based catalyst at 160°C for 8 h.[9] ROP of lactide to form PLA follows a coordination-insertion mechanism.[10]

Microwave irradiation is a non-conventional way to provide energy to chemical processes and belongs to the pool of process intensification technologies[11] and provides volumetric and uniform heating.[12] It has proved to increase reaction rates for polymerizations (step-growth, ring opening) compared to conduction heating.[13] Some advantages include faster heat transfer, which leads to shorter reaction times as well as inner heating of the reactor contents and reduced heat loss.[14] The two mechanisms of microwave heating are dipolar polarization and ionic conduction.[15,16] In the former, molecules with dipoles rotate as a result of the electromagnetic field and in turn generate heat via molecular friction and collisions.[17,18] In the latter, the microwave makes charged particles oscillate to generate heat through collisions.[17,19] The three parameters that determine a material's ability to interact with microwaves are the loss tangent ($\tan\delta$, Equation 1), the dielectric constant (ε), and the dielectric loss (ε'').[20]

$$\tan\delta = \varepsilon''/\varepsilon, \tag{1}$$

ε represents the ease with which a material becomes polarized in the presence of an electric field, ε'' is the conductance of a material, and $\tan\delta$ is a parameter that indicates a material's efficiency in converting microwave energy into thermal energy.[21] Microwave heating accelerates the ROP of lactide compared to conduction heating—24 h to produce PLA with a weighted-average molecular weight (MW) of 18 kDa at 140°C compared to 6 h for 20 kDa at 160°C.[22,23] Ultimately, all microwave reactors operate at a frequency of 2.45 GHz[24] to avoid interfering with other microwave frequencies, for example, FM radio plus TV broadcasts (0.08–0.8 GHz), mobile phones (0.045–1.98 GHz), radar (0.03–300 GHz).[25]

There are many viable catalysts for the ROP of lactide—so far, in microwave reactors, researchers have tested tin-based catalysts, titanium-based catalysts,[26,27] zinc-based catalysts,[28] and solid super-acids.[29] The most common catalyst for ROP is tin(II) octoate ($Sn(Oct)_2$)—stannous octoate. It is soluble in lactones, can produce low and high molecular weight PLA (from thousands to millions of Dalton), and is FDA-approved.[1,30] However, the two octoate groups must be substituted by two alkoxide groups to form tin(II) alkoxide, the true initiator of the polymerization. OH groups derived from alcohols typically enable this substitution. $Sn(Oct)_2$ also reacts with water, hydroxy acids, and other OH-bearing impurities in the reaction mixture.[31] This increases the dispersity ($Đ$) of the resulting PLA because more chains of likely unequal length are initiated. Kinetically, ROP of lactide is first order.[32] The polymerization rate reaches a maximum when the ratio of $Sn(Oct)_2$ and the alcohol is 0.5.[31,32] In addition, the polymerization involves reversible deactivation and intermolecular, and intramolecular (back-biting) transesterification reactions, which decrease the final molecular weight of PLA.[10,33] We denote an umbrella term—MW reduction events—for the processes (depolymerization and transesterification) that reduce the final MW of PLA. These processes are also catalyzed by $Sn(Oct)_2$, and other metals (e.g., Zn, Al, and Fe)[34] and are exacerbated by long reaction times (>2 h) and high temperatures (>180°C). Depolymerization involves chain scission of the polymer due to oxidative cleavage[35] while transesterifications (mainly between polymer chains) modify the polymer end-groups and consequently the MW and dispersity.[10]

L-lactide polymerized in a domestic microwave oven in the presence of $Sn(Oct)_2$ at 180 W, 360 W and between 5 and 30 min at monomer-to-initiator (M:I) ratios of 1040/1, 2534/1, 5069/1. As the monomer-to-initiator ratio increased, so did the MW of the PLA. Fewer initiator molecules formed fewer but longer chains. An M:I ratio of 2534:1 for 20 min at 180 W produced the highest MW (77 kDa) with a $Đ$ of 2.[36] Similarly, another ROP of L-lactide in a microwave at 180°C, 180 W, a M:I ratio of 5069:1 with $Sn(Oct)_2$ and no initiator produced PLA with a MW of 11 kDa—further microwave irradiation degraded the PLA.[37] In addition,[38] compared a second catalyst, dibutyltin dimethoxide (DBTM), to $Sn(Oct)_2$ at 150°C with ratios of 1040:1, 2534:1, 5069:1, 10 069:1. DBTM outperformed $Sn(Oct)_2$ producing a MW a 30 kDa with a $Đ$ of 1.66 versus a MW of 22 kDa and a $Đ$ of 2 after 20 min. A microwave reactor under vacuum with N_2 sparging assisted the ROP of D-lactide in the presence of $Sn(Oct)_2$, BnOH, and toluenesulfonic acid (TSA). $Sn(Oct)_2$ paired with BnOH at an unspecified ratio was added at 0.03% by weight of lactide and TSA at 0.4% by weight of lactide. The highest MW was 20 kDa after 25 min at 280 W and 215°C.[39] In another instance, L-lactide polymerized and grafted onto polyhedral oligomeric silsesquioxanes (POSS) in the presence of $Sn(Oct)_2$ and in the absence of solvent. At 45 W, 120°C, and 45 min, a catalyst concentration of 1.5 wt% with respect to lactide and a molar ratio of L-lactide:POSS-$(OH)_{32}$ of 600 synthesized PLA tails with a molecular number of 50 kDa.[40] Alternatively, castor oil

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and $Sn(Oct)_2$ initiated the polymerization of L-lactide in a microwave reactor at 150 W and lactide:castor oil ratios ranging from 113 to 533 The optimal conditions were a ratio of 533:1 for 50 min which produced a MW of 25 kDa and a *Đ* of 1.18.[41]

Thauvin et al. compared the effectiveness of $Sn(Oct)_2$ to 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) for the synthesis of PEG-PLA diblock copolymers; the monomers were mPEG2000 and D,L-lactide.[42] Conversion with DBU in chloroform after 5 min was 100%, 94%, and 40% at 100, 170, and 60°C, respectively. $Sn(Oct)_2$ was active at 170°C and converted 95% of the lactide but was inactive below 100°C. Polyhydroxyalkanoates (PHAs)—thermoplastic polyesters produced from bacterial microorganisms under stress (reduced access to nutrients)—can also initiate the ROP of lactide. Microwave irradiated a mixture of D,L-lactide, PHA, toluene and $Sn(Oct)_2$ at 115°C for 5 min. A lactide:PHA ratio of 250:1 produced a MW of 81 kDa with a *Đ* of 1.8 and a conversion of 85%.[43] ROP of lactide is quicker and achieves higher MWs in a microwave reactor compared to a vacuum-sealed vessel with conventional heating or a pressurized reactor. Conventional heating in a vacuum sealed vessel led to PLA with a MW of 250 kDa and a *Đ* of 3 after 150 h at 150°C. The pressurized reactor produced PLA with a MW of 190 kDa and a *Đ* of 2.4 after 6 h at 120°C and 140 kPa. In contrast, microwave irradiation led to PLA with a MW of 300 kDa and a *Đ* of 1.7 at 100°C for 30 min.[44] All monomer:initiator (M:I) ratios were 5000:1. A microwave-assisted ROP method synthesized PLA–PEG copolymers in 5 min in chloroform at 125°C; the catalysts were $Sn(Oct)_2$ and DBU. The initiators were D,L-lactic acid and mPEG2000. A M:I ratio of 278:1 resulted in PLA–PEG polymers with a MW of 40 kDa and conversions of up to 35% or 83% with $Sn(Oct)_2$ or DBU, respectively.[45] Overall, despite plentiful literature (Table 1) on microwaves and the polymerization of lactide, none mention the dielectric properties of the reagents. The property of interest is the dielectric loss as it represents the amount of microwave energy released as heat. Compounds with larger dielectric loss values will attain desired temperatures with less power input (Figure 1).

The literature lacks data on the dielectric properties of D,L-lactide as well as solvent selection for ring-opening polymerizations in microwave reactors. We thus evaluated the suitability of six different solvents (toluene, THF, acetone, acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) with dielectric loss values of 0.096, 0.348, 1.12, 2.33, 6.1, and 37.1, respectively) in the synthesis of PLA in a lab-scale Monowave 400 microwave reactor from Anton Parr. In addition, for the first time, we measure the dielectric properties of D,L-lactide at 2.45 GHz, the frequency at which the microwave reactor adopted in this study operates. Moreover, the high operational capacities of the latter (300°C, 3000 kPa) permitted the polymerization of D,L-lactide high temperatures (130, 150, 170°C) in THF. In other batch systems and modified domestic microwaves, the pressure generated from boiling THF at these temperatures would be dangerous. Furthermore, we developed a statistical model to predict MW and applied it to other microwave polymerization data in the literature.

TABLE 1 Literature summary.

Reference	Catalyst	Solvent	M:I ratio	°C/W	Min	MW (kDa)	*Đ*
26	Titanium-based	None	1000:1	130/200	80	27	1.2
27	Titanium-based	None	500:1	180/400	45	43	2.4
28	Zinc-based	Toluene	–	130/–	180	1.3	1.8
29	Solid-Super Acids	None	–	260/–	50	22	–
36	$Sn(Oct)_2$	None	2534:1	–/180	20	77	2
37	$Sn(Oct)_2$	None	5069:1	180/180	20	11	–
38	$Sn(Oct)_2$	None	5069:1	150/–	20	102	1.6
38	DBTM	None	2534:1	150/–	10	40	1.7
39	$Sn(Oct)_2$	None	–	215/280	25	20	3.5
40	$Sn(Oct)_2$	None	600:1	120/45	45	50	–
41	$Sn(Oct)_2$	None	533:1	–/150	50	25	1.2
43	$Sn(Oct)_2$	Toluene	250:1	115/–	5	81	1.8
44	$Sn(Oct)_2$	None	5000:1	100/–	30	300	1.7
45	$Sn(Oct)_2$	Chloroform	278:1	125/–	5	40	–
This work	$Sn(Oct)_2$	Toluene	380:1	170/–	60	31	1.5
This work	$Sn(Oct)_2$	THF	380:1	170/–	240	11	1.2

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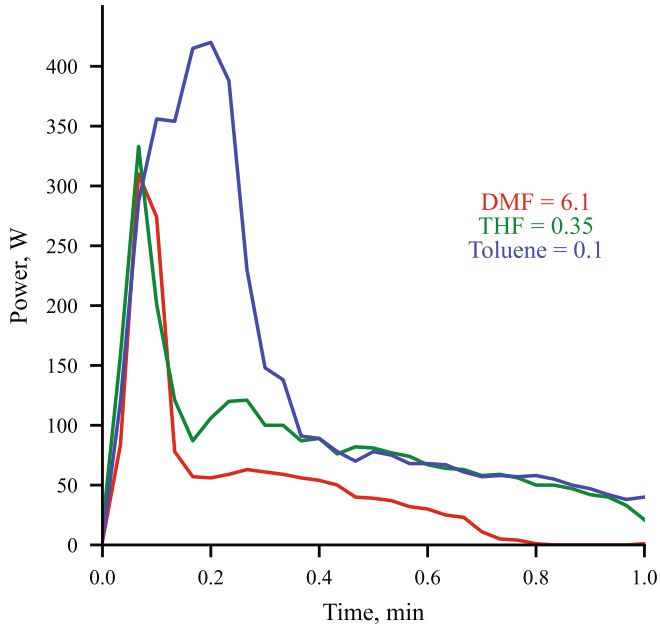

FIGURE 1 Power required to heat 4 mL of solvent to 170°C. The values associated to each solvent are the dielectric loss value.

2 | EXPERIMENTAL

2.1 | Materials

We purchased D,L-lactide, $Sn(Oct)_2$, anhydrous toluene, and benzyl alcohol (BnOH) from Sigma-Aldrich. We purchased THF with butylated hydroxytoluene (BHT) as a stabilizer, DMF, methanol, ethanol, and acetone from Fisher Scientific. All reagents, aside from D,L-lactide, were used without further treatment or purification. D,L-lactide was first recrystallized in ethanol and then in toluene and left to dry overnight in an oven under vacuum at 50°C. It was then stored in the fridge at 4°C under a nitrogen atmosphere. We did all the experiments with the same batch of purified lactide and within a 2-week timeframe to minimize variation in water content or other impurities. According to a Karl-Fischer analysis the water content of THF and BnOH was 250 and 300 ppm, respectively. The anhydrous toluene had less than <0.001% water. $Sn(Oct)_2$ cannot undergo Karl-Fischer titration because it reacts with the titrant (Composite 5 from Honeywell). In addition, we did not distill it to remove impurities such as 2-ethylhexanoic acid because it reappears shortly after distillation.[46] Thus, its water content is unknown.

2.1.1 | Solvent list

The CEM Corporation has a list of common solvents and their dielectric loss values on their website (Table 2).

TABLE 2 Solvents and their dielectric loss values.

Solvent	Dielectric loss (ε'')
Ethylene glycol	50
Formic acid	42
DMSO	37
Ethanol	23
Methanol	21
Nitrobenzene	21
1-Propanol	15
2-Propanol	15
Water	9.9
1-Butanol	9.7
NMP	8.9
Isobutanol	8.2
2-Butanol	7.1
2-Methoxyethanol	6.9
DMF	6.1
o-Dichlorobenzene	2.8
Acetonitrile	2.3
Nitromethane	2.3
MEK	1.5
1,2-Dichloroethane	1.3
Acetone	1.1
Acetic acid	1.1
Chloroform	0.45
Dichloromethane	0.38
Ethyl acetate	0.35
THF	0.35
Chlorobenzene	0.26
Toluene	0.1
o-Xylene	0.05
Hexane	0.04

We eliminated all solvents that bear any OH groups. An excess of hydroxyl moieties hinders polymerization by deactivating the catalyst, inducing chain scission, hydrolyzing PLA's ester linkages, and increasing chain transfer reactions.[31,35,47] All these processes result in a PLA with a lower MW and higher dispersity. Furthermore, we excluded nitrobenzene as it is highly toxic and nitromethane for the risk of explosion at our reaction conditions. We then evaluated the suitability of toluene, THF, acetone, acetonitrile, DMF, and DMSO with dielectric loss values of 0.096, 0.348, 1.12, 2.33, 6.1, and 37.1, respectively (Table 2). Chlorobenzene, chloroform, and o-xylene are also suitable candidates but toluene is more common and was selected as the low dielectric loss

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solvent. Dichloromethane and hexane could function as low-dielectric-constant solvents but their boiling points are lower than toluene (40 and 69 vs. 110°C) and the pressure in the system at 170°C with THF (boiling point = 66°C) already reaches 800 kPa. Our vial caps for the reactor cannot withstand pressures above this for reaction times over 4 h, at which point they are already too deformed to be used again. Thus, we retained toluene and THF for the polymerization experiments.

2.2 | Microwave synthesis

The MWs of synthesized PLAs at identical reaction conditions differed across batches of re-crystallized D,L-lactide as well as different bottles of $Sn(Oct)_2$. For example, different fresh bottles of $Sn(Oct)_2$ produced lower MW PLAs compared to a one-year old bottle. Thus, to ensure reproducibility, all experiments were done with the same batch of re-crystallized D,L-lactide and $Sn(Oct)_2$ within the span of 2 weeks. An oven at 105°C dried all glassware prior to the reactions to eliminate any traces of water. The reactor vials (made of quartz) were loaded with THF or toluene, $Sn(Oct)_2$, BnOH as the initiaitor, D,L-lactide and then filled with N_2. The amount of solvent and D,L-lactide was constant at 4 mL and 2 g, respectively. The molar ratios for D,L-lactide:$Sn(Oct)_2$ and $Sn(Oct)_2$:BnOH were fixed at 1550 and 0.25. On average, the monomer:initiator (D,L-lactide:BnOH) molar ratio was 380. The polymerization did not occur at D,L-lactide: $Sn(Oct)_2$ molar ratio of 3000. At 100, it is difficult to eliminate the catalyst from the synthesized PLA. The rest of the ratios are dependent on and derived from the D,L-lactide:$Sn(Oct)_2$ ratio. The reaction lengths and temperatures ranged from 0.25 to 6 h and 130–170°C. We precipitated the resulting PLA in a cooled methanol:water (3:1 volume ratio) bath twice and then evaporated any residual solvent in a furnace operating at 100°C for 6 h and then 60°C for 18 h to remove toluene first and then water. In cases where THF was the solvent, the furnace operated at 60°C for 24 h. The samples were stored in vials in N_2 and placed in fridge at 4°C. Theoretical values for number-average molecular weights of PLA can be predicted from the monomer-to-initiator ratio and the actual conversion of lactide to PLA.[31,48–51] We assume 100% conversion to calculate the maximum number-average molecular weight possible for our PLA. We then divide this value with our experimental data to yield our actual conversion. In our case, we were required to purify the polymers after the reactions and store them for several days before NMR analysis. As little to no free monomer remains after purification, calculating conversion (%) from NMR was not feasible. The MW values shown in the text refer to the weighted-average molecular weight unless otherwise specified. The number-average molecular weight served only to calculate the conversion. All experiments were conducted in an Anton Paar Monowave 400 microwave reactor. Temperature, pressure, and power input were recorded for the duration of the reactions. Its operational capacities are 300°C and 3000 kPa and a max power input of 850 W.

2.3 | Characterization

2.3.1 | Proton nuclear magnetic resonance

A Bruker AV-III 400 MHz spectrometer confirmed the structure of the PLA; samples were dissolved in $CDCl_3$. We analyzed the data with the help of the NMRium software. GPC was the method of choice to determine the molecular weight (number-average and weighted-average) as proton nuclear magnetic resonance (H NMR)'s resolution begins to suffer and sensitivity decreases at higher molecular weights; purity also becomes an issue.[52]

2.3.2 | Gel permeation chromatography

A Thermo Scientific UltiMate 3000 HPLC with a gel permeation chromatography (GPC) module and columns (PL1110-6504, PL1510-1520, the latter being a guard column) from Agilent determined the MW of the PLA samples. THF eluted the samples at a flow rate of 1 mL min^{-1} at room temperature. We dissolved PLA samples of 0.1 g in 2 mL of THF and then filtered them with PTFE syringes (13 mL diameter, 0.2 μm pore size). A conventional calibration was done with polystyrene standards (from 0.3 to 100 kDa) and a refractive index detector. However, this is a relative technique. The Mark-Houwink-Sakurada (MHS) equation enables the conversion of the MW values from relative ones to absolute ones. It relates the intrinsic viscosity of polymers to empirical constants (k, α) that depend on the analysis conditions (polymer, solvent, and temperature).[53] It is ever-present in the MW analysis of polymers (e.g., chitosan,[54] acrylamides,[55] cellulose[56]) and dates as far back as the 1980s for atatic polystyrene.[57] To correct the values of our PLA, we adopted a modified version of the MHS equation[10,53] (Equation 2). The constants for k and α were taken from the literature; for polystyrene[57] and PLA[58] in THF the values are 0.014, 0.70, 0.014, and 0.75, respectively. However, we analyzed the uncorrected MW data for direct comparison with the microwave-synthesized PLA literature, much of which does not report any MHS corrections.

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$$\log M_X = \left(\frac{\alpha_{std}+1}{\alpha_X+1}\right)\log M_{std} + \left(\frac{1}{\alpha_X+1}\right)\log\frac{k_{std}}{k_X}. \quad (2)$$

2.3.3 | Differential scanning calorimetry

A Q2000 DSC (TA Instruments) ramped the temperature from 40 to 150°C at 10°C/min in N_2 and stabilized at this upper temperature for 10 min before returning to 40°C for a 2nd cycle. A hermetic aluminum pan held the samples.

2.3.4 | Thermal gravimetric analysis

A thermal gravimetric analyzer Q50 (TA Instruments) operated with N_2, a mass flow of 40 mL min^{-1} and a ramp of 10°C min^{-1} up to 400°C and maintained for 20 min.

2.3.5 | Dielectric property measurement of D,L-lactide

We measured the dielectric properties of our D,L-lactide with the HP 85070 dielectric probe kit at 2.45 GHz. The probe was calibrated in air and water at room temperature. The loss tangent, dielectric loss, and dielectric constant for lactide at room temperature were 0.017, 0.04, and 2.33. Thus, it requires more power to heat lactide alone compared to it being coupled with a solvent bearing a higher dielectric loss value.

3 | RESULTS AND DISCUSSION

3.1 | Solvent selection

Two solvents were appropriate for the experiments, toluene and THF. $Sn(Oct)_2$ and BnOH, the catalyst and initiator, respectively, were not soluble in acetone, acetonitrile, and DMSO—they formed cloudy mixtures. DMF is also unsuitable as it reacts violently with tin-based compounds (i.e., $Sn(Oct)_2$). After less than an hour at 170°C the solution degraded and blackened.

3.2 | Evolution of the experimental design

The initial iteration of the experimental design was a partial factorial that considered temperature and time as the two primary variables at three levels (2, 4, 6 h and 130, 150, and 170°C) and solvent at two levels (THF: $\varepsilon'' = 0.348$, toluene: $\varepsilon'' = 0.096$). It comprises the first 13 experiments of Table 3. In these experiments with toluene, the variation of the $Đ$ and MW across the times and temperatures were minimal—all the reactions produced MWs between 23 and 27 kDa (Figure 2). Thus, we assumed that the levels for time were insufficient to identify the growth of the chains and as a result added three experiments. One at 1 h, the other at 0.5 h, and the last at 0.25 h. The MWs at 1, 0.5, and 0.25 h were 31, 17, and 8 kDa, respectively, indicating that chain growth outpaces MW reduction events (ester bond breakage, intramolecular transesterification caused by tin(II) alkoxide, intermolecular transesterifications with OH groups). At the 2 h mark, the overall MW begins to reduce as tin(II) alkoxide, $Sn(Oct)_2$'s initiating form, also catalyzes the above events that reduce MW.[59]

3.3 | Results of the polymerizations in toluene and THF

3.3.1 | Dependency of MW and conversion on reaction conditions

The solvent explained 80% of the variance in the MW, $Đ$, and conversion data. Reactions with toluene produced PLA with MWs from 8 to 31 kDa (Figure 2), whereas with THF the range was 1.5–11 kDa (Table 3).

Toluene is immiscible with water. On the other hand, THF is hygroscopic so the water molecules within it hydrolytically cleave the PLA chains,[60] which explains the different MW between solvents. THF's hygroscopic nature overshadowed any positive microwave coupling effect that would result from its larger dielectric loss value. In other words, water-miscbile solvents that absorb moisture from the air lead to lower MW PLAs. He et al. also reported higher MWs in their conduction-heated reactions with toluene compared to THF despite their THF being anhydrous (22 kDa vs. 7.3 kDa).[61] This also occurred in ethylene polymerizations with a terphenyl derivative complex (2-Py) catalyst precursor—38 kDa in toluene versus 12 kDa in dried THF.[62] Thus, the water content in our THF is not the only driving factor for the difference in MWs. Further research into how the properties of solvents affect polymerizations is warranted. The reaction in toluene peaks at 1 h after which the risk of MW reduction events increases causing chains to break[48] and lowering the MW. This also accounts for the large standard deviation in the data past 1 h (Figure 2) as these events, like transesterifications, occur randomly.[63] Thus, we demonstrate the effect of long reaction times on the polymerization—the variation in the data is as high as 50% after 2 h as depolymerization

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TABLE 3 Design of experiments. The solvent column lists the dielectric loss values (0.096 = toluene, 0.348 = THF). The experiment number refers to the order in which the experiments were completed. The MHS-Mn column lists the corrected values for the number-average molecular weight.

t (h)	*T* (°C)	Solvent	MW (kDa)	Mn (kDa)	MHS-Mn (kDa)	Conv. (%)	*Đ*	Exp.
0.25	170	0.096	8	4.2	3.3	7	1.9	17
0.5	150	0.096	18	12	9.2	25	1.5	16
0.5	150	0.348	4.4	4.1	2.9	7	1.1	18
0.5	170	0.096	17	11	8.2	20	1.6	15
1	170	0.096	31	21	16	34	1.5	14
2	130	0.096	23	18	13	35	1.3	2
2	130	0.348	1.5	1.4	1.1	3	1.1	13
2	150	0.348	4.5	4.1	3.2	7	1.1	8
2	170	0.096	27	18	14	32	1.5	1
2	170	0.348	5.2	4.7	3.7	9	1.1	4
4	130	0.348	4	3.6	2.9	7	1.1	10
4	150	0.096	26	17	13	33	1.5	11
4	170	0.348	11	9.2	7.1	17	1.2	5
6	130	0.096	27	18	14	35	1.5	9
6	130	0.348	4.2	3.8	3.0	7	1.1	12
6	150	0.348	6.7	6.1	4.8	11	1.1	3
6	170	0.096	26	16	12	33	1.6	7
6	170	0.348	3.4	3.1	2.5	6	1.1	6

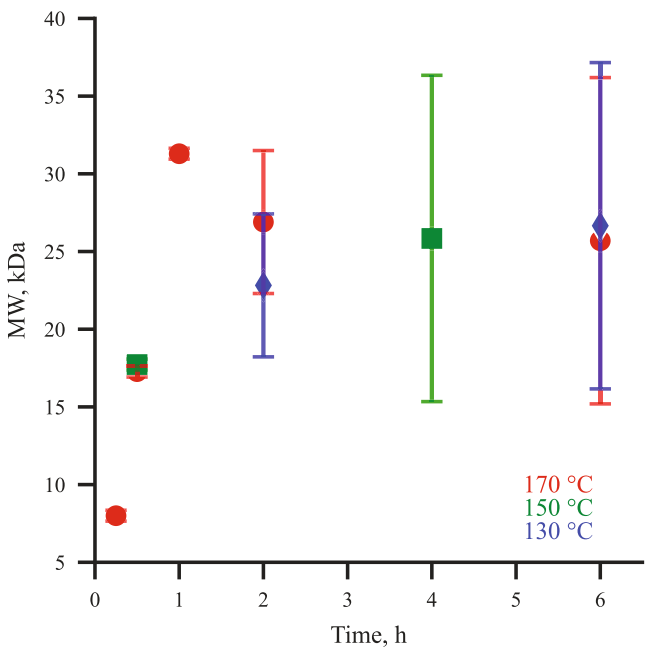

FIGURE 2 Molecular weight (MW) as a function of time and temperatures in toluene. Error bars represent the standard deviation. For the data between 0 and 1 h the standard deviation is 15% and increases past 1 h due to the stochastic nature of the MW reduction events and their prevalence. Please refer to the main text for a more detailed explanation.

and transesterification begin to dominate. This variation is not a result of impurities in the reagents, as all the experiments were carried out with the same batch of reagents, but rather the random nature of MW reduction events that dominate after 2 h. Three repeat experiments at 6 h, 170°C in toluene produced MWs of 12, 27, and 38 kDa. However, the trend is one of decreasing MW. The variation in molecular weight for experiments at 1 h and less is 15%. Other articles that synthesize PLA with microwaves maintain reaction times between 5 and 50 min[7,36,37,41,43,44] because longer reaction times do not necessarily lead to higher molecular weights but rather larger variations and thus the reproducibility begins to suffer. Higher temperatures and toluene (Figure 4) as a solvent instead of THF (Figure 5) produced higher MW PLA. Polymerization rate increases with increasing temperature.[48,64] The highest MW achieved was 31 kDa with a *Đ* of 1.5 in toluene, at 170°C, for 1 h with a conversion of 34%. Conversions in the literature range from 2%[36] to 95%.[42,45] Impurities (OH-bearing species predominantly from water) are the cause of this large variance—the more there are, the lower the conversion, and hence lower MW. OH groups induce chain scission and can also prematurely terminate growing chains by acting as an initiator and forming OH-terminated chains.

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Water can also hydrolyze the lactide monomers to lactic acid and reduce the pool of available lactide—an increase in lactic acid and consequently OH groups also increases the likelihood of chain scission.[35] Itzinger et al. ring-open polymerized lactide and purposefully doped the reaction medium with increasing amounts of ethanol as an impurity (0.1% by weight, 1% by weight, 1.5% by weight). The MW decreased from 30 kDa at an impurity level of 0.1% by weight to 10 kDa at 1.5% by weight[65] representing a 50% drop in conversion. Our experimental procedure was unable to completely eliminate the sources of impurities which is reflected in the conversion. THF innately carries more impurities (water) than toluene, which partly explains the approximate threefold decrease in conversion between the two solvents. For these reasons, $Sn(Oct)_2$ catalyzed the polymerization as opposed to DBU despite the latter's improved performance (higher conversion rates, yields, and is active at lower temperatures). For example, Thauvin et al. studied the performance of DBU versus $Sn(Oct)_2$ and found that there was 100% D,L-lactide conversion in DBU at 100°C while $Sn(Oct)_2$ was inactive at this temperature; at 170°C the conversion was still lower (95%).[42] In another ROP of D,L-lactide, at 125°C, DBU and $Sn(Oct)_2$ had similar conversions (>90%) but yields with DBU were higher (60% to 83% vs. 23% to 35%).[45] However, DBU is more susceptible to impurities compared to $Sn(Oct)_2$; acidic protons deactivate DBU and induce a cascade effect until there is none left to continue the polymerization.[66] However, the MW can still be increased/decreased despite the limited conversion by modifying the M:I ratio. For example, the reaction in THF at 2 h, 170°C and a M:I of 380 produced PLA with a MW of 5.2 kDa and a $Đ$ of 1.1 for a total conversion of 9%. At an M:I of 1000, the MW would be 13 kDa assuming the same conversion. However, this does not continue indefinitely—in one instance, there was no significant difference in MW between M:I ratios of 1041, 2534, and 10 069 and the conversion dropped from 9% at 1041 to 2% at 10069.[38] Overall, we are able to control the MW of our synthesized PLA between 1 and 31 kDa. This range can be modified by changing the M:I ratio.

3.3.2 | Dispersity

Dubois et al. found that dispersity ($Đ$) increased with increasing temperature as a result of intermolecular transesterifications with $Al(O\text{-}i\text{-}Pr)_3$ as the catalyst. The $Đ$ went from 1.25 to 1.4 as the temperature increased from 75 to 85°C with conduction heating.[48] $Đ$ was independent of temperature in our system. For example, experiments 3, 6, 12 at 6 h and 130, 150, and 170°C, respectively, in THF all resulted in a $Đ$ of 1.1 (Table 3). In addition, $Sn(Oct)_2$ is more active between 125 and 180°C than $Al(O\text{-}i\text{-}Pr)_3$, with which it can take days to achieve MWs of 104–105 Da.[50] Toluene produced higher $Đ$ (an average of 1.5) compared to THF (an average of 1.1). A lower $Đ$ indicates more uniformity among the lengths of the polymer chains. As the polymer chains lengthen and less monomer remains for the reaction, the polymerization slows while the risk of intermolecular transesterification increases.[10,67] This leads to increased $Đ$. Nonetheless, these are both lower than most of the other reported $Đ$'s for microwave-synthesized PLA (Table 1).

3.4 | Microwaves versus conduction heating

In an effort to compare a conduction-heated reaction to the microwave reactions, we replaced the usual quartz vessels with a silicon carbide vessel. Silicon carbide will absorb all the microwaves and thus heat the reaction medium via conduction.[68] At 170°C for 4 h in THF with silicon carbide, the D,L-lactide did not polymerize at all. On the other hand, when the reaction medium is heated via microwaves, the resulting PLA had a MW of 11 kDa and a $Đ$ of 1.2. In addition, the same reaction without a dedicated initiator still produced PLA with a MW of 10 kDa and a $Đ$ of 1.2, whereas with conduction heating it could take more than 30 h.[8] Despite the shortcomings of the experimental setup at removing impurities, it still outperforms the traditional synthesis and functions as an example of process intensification.

3.5 | Predictor screening of toluene and THF

The solvent dominated the predictor screening for the entire dataset. As a result, we redid a screening for THF and toluene, separately. For THF, temperature explained 61% of the variance for the MW, while time accounted for 39%. In contrast, for toluene, time accounted for 93% of the variance in MW. Temperature's influence is more pronounced in the THF data. THF's boiling point is 66°C—at 130, 150, 170°C the corresponding pressures in the reactor were 250, 500, and 800 kPa. The reactions with toluene were all at atmospheric pressure. Higher pressures favor polymerization ([69,70]), which explains temperature accounting for 61% of the variance in MW for THF while with toluene it is only 7%.

3.6 | Proton nuclear magnetic resonance

Signals at $\delta_H = 5.10$ and $\delta_H = 1.50$ belong to methine (a) and methyl (b) groups while the signal at $\delta_H = 4.30$

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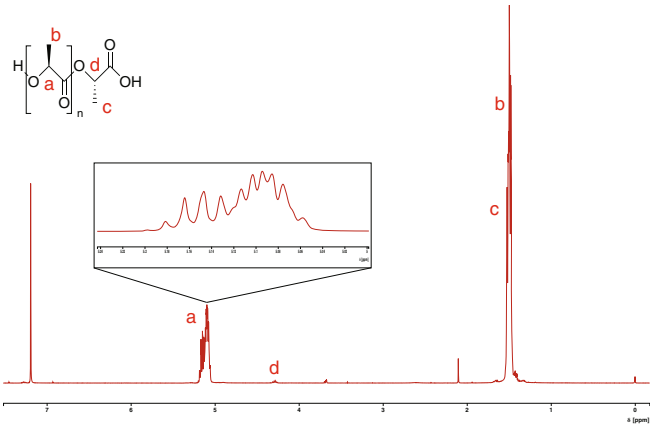

FIGURE 3 Proton nuclear magnetic resonance (H NMR) spectra of poly(D,L-lactide).

represents the methine end-group.[71] The presence of many tetrads in the range of the $\delta_H = 5.04$ to $\delta_H = 5.20$ indicates no stereocontrol in our PLA[71,72] (Figure 3).

3.7 | Differential scanning calorimetry

The PLA samples had an average melting temperature of 150°C and a glass transition temperature of 55°C, the latter being similar to other reported values while the former is 10–20°C lower.[73,74]

3.8 | Thermal gravimetric analysis

Three samples of PLA with MWs of 10, 23, and 31 kDa underwent a TGA analysis. The 10 kDa PLA sample lost 10% of its mass at 259°C and 99% of its mass at 311°C. The 23 kDa sample lost 10% of its mass at 255°C and 99% of its mass at 305°C. The 31 kDa sample lost 10% of its mass by 269°C (including the residual toluene that begins to evaporate at 105°C) and 99% of its mass at 318°C. There is a minor dependence on degradation temperature and MW. The degradation temperature of our PLA is consistent with some of the literature[61,74] and a little lower than others (269 vs. 290°C).[75]

3.9 | Statistical model

We fit the data from our experimental design to a non-linear model that describes the growth and decay phases of the polymerization. The model contains three fitted parameters with two independent variables, reaction time (from 0.25 to 6 h) and temperature (from 130 to 170°C) (Equation 3). The latter corresponds to an

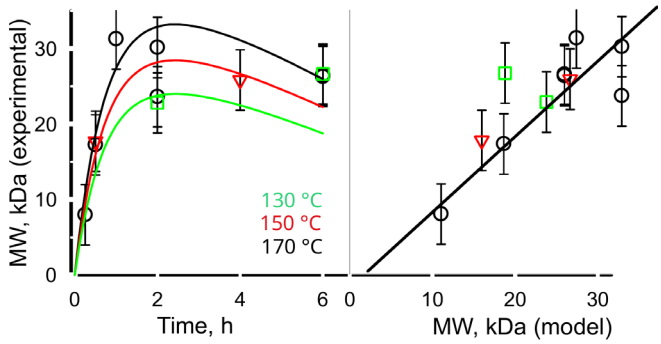

FIGURE 4 Polylactic acid (PLA) molecular weight (MW) as a function of time in toluene (left) and a standard parity plot (right). The lines represent the non-linear regression model (Equation 3) and the symbols the experimental data. $R^2 = 0.91$.

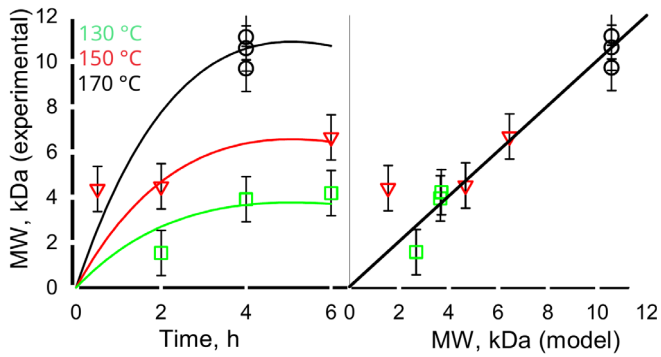

FIGURE 5 Polylactic acid (PLA) molecular weight (MW) as a function of time in THF (left) and a standard parity plot (right). The lines represent the non-linear regression model (Equation 3) and the symbols the experimental data. $R^2 = 0.94$.

exponential Arrhenius expression. The model's (eq3) R^2 for toluene and THF are 91% (Figure 4) and 94% (Figure 5), respectively.

$$\mathrm{MW} = \beta_0 \times \left[-e^{-\beta_1 t} + e^{-\beta_2 t^2}\right] \times e^{\frac{-Ea}{R}\left[\frac{1}{T+273} - \frac{1}{T_{\mathrm{ref}}+273}\right]}. \quad (3)$$

T_{ref} is the average temperature (150°C), R is the universal gas constant in J mol^{-1} K^{-1}, and t is in hour. The pseudo activation energies for toluene and THF are 12 and 39 kJ.

The predicted MW begins to decrease as t approaches 4 h for toluene and as t approaches 6 h for THF as a result of depolymerization and transesterification reactions (represented by β_2), which are exacerbated at longer reaction times (Figure 4, Figure 5). The onset of MW reduction events is quicker in toluene ($\beta_2 = 0.009$) compared to THF ($\beta_2 = 0.007$) because it peaks sooner (31 kDa at 1 h versus 11 kDa at 4 h). Prior to this, the chains are growing

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exponentially, which is represented by β_1 term (1.45 for toluene, 0.34 for THF). The β_0 often represents the maximum achievable MW for a given system. The standard deviation between the experimental data and model predictions is 4 kDa in toluene (Figure 4). At longer reaction times (>2 h) the MW reduction events become more prominent thereby decreasing the MW of the polymer chains. This process, however, is random[63] and thus so is the degree to which the molecular weight decreases. As a result, the MW at longer reaction times varies more than those at shorter times. The data point at 6 h and 130°C (Figure 4) is an example of this as it is 30% above the predicted MW. On the other hand, the standard deviation of 3 repeats for the experiments in THF was 7% (0.7 kDa). The deviation between the model and experimental data was 1.1 kDa, which is reasonable considering the reproducibility was 0.7 kDa (Figure 5). The model explains 94% of the variance in the experimental data for THF and captures the increasing MW with time as well as the plateau. However, during the initial reaction period, the PLA MW of one experimental test (0.5 h, 150°C), increased much faster than expected.

3.9.1 | Model applied to literature data

We evaluated the efficacy of our statistical model by fitting it to three other datasets, at similar reaction conditions (microwave reactor, $Sn(Oct)_2$ as the catalyst), in the literature. The experiments from the first dataset were at a constant temperature (150°C) but varying M:I ratios (1041, 2534); their MWs ranged from 15 to 46 kDa.[38] Thus, the pseudo Arrhenius term equals 1, which leaves the power aspect of the model. For the data at an M:I of 1041, the model explained 71% of the variance, with a β_0 of 24 500, a β_1 of 14, and a β_2 of 0.35. However, the R^2 drops to 0.4 for the data at an M:I of 2534 with a β_0, β_1, and β_2 of 46 000, 7.4, and 3.6, respectively. Moreover, by combing both datasets into one and incorporating a new term (β_3) to the model (eq4) to account for the change in M:I, the R^2, β_0, β_1, β_2, β_3 become 0.59, 59 000, 14, 1, and − 0.12, respectively. This low β_3 indicates that M:I had little effect on the final MW in their data.[38]

$$\mathrm{MW} = \beta_0 \times \left[-e^{-\beta_1 t} + e^{-\beta_2 t^2}\right] \times \mathrm{MI}^{\beta_3}. \tag{4}$$

The second dataset had a constant temperature of 180°C.[36] We focused on the data at a constant M:I (1041) and power (360 W) with reaction times from 5 to 20 min. The final data point (at 20 min) had no MW value as it significantly degraded. To increase the total number of data points, we assigned a MW to the 30 min sample equal to 10% of the max MW in the dataset. The MWs ranged from 7 to 10 kDa. The resulting R^2, β_0, β_1, and β_2 were 0.64, 9500, 29, and 8.8, respectively. The R^2 only varies between 0.68 and 0.61 if the assumption for the MW of the degraded sample is 20% or 2% of the max MW from the dataset.

The final dataset had a constant temperature of 100°C. However, there were only 3 data points, and the model has 3 parameters so the resulting R^2 is 0.99, with a β_1 of 0.1. The latter is of interest as it represents the chain growth aspect of the polymerization, a lower value represents higher growth. At 10, 18, and 30 min the respective MWs were 80, 176, and 300 kDa[44]—the model predicts that the chains are growing linearly and not exponentially as evidenced by the low β_1. The M:I ratio is not specified in the article so the theoretical max is unknown.

4 | CONCLUSION

We polymerized D,L-lactide in a microwave reactor in the presence of $Sn(Oct)_2$, BnOH and toluene or THF. The solvent had the greatest influence on the final molecular weight of PLA: the molecular weights in toluene were 2-3x higher compared to THF. The presence of water in THF overshadowed any positive microwave-coupling effects of its higher dielectric loss; eliminating traces of water in all of the reagents would lead to larger molecular weights. After 1 h at 170°C in toluene, the MW was 31 kDa. In THF, after 4 h at 170°C, the molecular weight only reached 11 kDa. In addition, we were able to eliminate numerous solvents as unfit for the ROP of D,L-lactide. Some, such as THF, are hygroscopic and will hinder the polymerization, while others are unsafe at our reaction temperatures (130–170°C). We also developed a statistical model that predicts the molecular weight as a function of temperature, time, and the estimated max achievable molecular weight for a given system. Future work should involve a continuous experimental setup coupled with microwaves for the synthesis of PLA on a larger scale—strategies for scale-up are already present in the literature[76] and are present in the agri-food industry, cosmetics, and vulcanization of rubber.[77] However, due to D,L-lactide's low dielectric loss (0.04) we recommend the addition of polar species to improve energy transfer.

AUTHOR CONTRIBUTIONS

Nicolas A. Patience: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; software; formal analysis; project administration; data curation; supervision; resources. **Halie Mei Jensen:** Investigation; data curation; methodology. **Xavier Banquy:** Conceptualization;

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investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; supervision; resources. **Daria C. Boffito:** Conceptualization; investigation; funding acquisition; writing – original draft; writing – review and editing; visualization; methodology; project administration; resources; supervision; validation; formal analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Daria C. Boffito https://orcid.org/0000-0002-5252-5752

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