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"Isotactic Degradable Polyesters derived from *O*-Carboxyanhydrides of *L*-lactic and *L*-malic acid using a Single Organocatalyst/Initiator System"

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Abstract

The preparation of stereoregular isotactic P(*L*-BnMA) and PLLA by ring-opening polymerization (ROP) of 5-(*S*)-[(benzyloxycarbonyl)methyl]-1,3-dioxolane-2,4-dione (*L*-malOCA) and (*S*)-5-methyl-1,3-dioxolane-2,4-dione (*L*-lacOCA) is reported. The polymerization process was shown to be well controlled using two easily accessible single organocatalyst/initiator systems, pyridine/*L*-benzyl(Bn)malate and pyridine/lactic acid (Py·LA) ion pair adducts respectively. The obtained biodegradable polymers displayed narrow dispersity ($Đ_M$) and excellent molar mass control. All ROP reactions were conducted at ambient temperature. The stereoregularity and thermal properties of the materials were thoroughly studied, demonstrating the retention of high levels of isotactic enrichment.

Keywords

O-carboxyanhydride, stereoregularity, isotacticity, organocatalysis, ring opening polymerization, polyesters, lactide

Introduction

Aliphatic polyesters, poly(α-hydroxyl acid)s (PAHAs), such as polylactide (PLA), polyglycolide (PGA) and poly(lactide-*co*-glycolide) (PLGA), have been extensively studied and utilized for

controlled drug delivery, gene therapy, tissue replacement, and implantation devices as a consequence of their desired degradability and biocompatibility, as well as their excellent mechanical, physical, and thermal properties.[1-4] The degradation of PAHAs generally takes place through hydrolysis in a moist environment and eventually forms monomers and oligomers that are soluble in aqueous media. PAHAs are generally considered both biodegradable and bioresorbable in a living body.[5] The most widely studies PAHAs, polyesters derived from lactide and glycolide, lack structural diversity and increasing efforts have been devoted to the introduction of pendant groups along the polymer chain in order to modify and modulate the physicochemical properties of poly(α-hydroxyacid) and to expand thereby their applications.[6-11]

Considering the structural similarity between α-hydroxy acids and amino acids and the availability of a wide range of terminal group functionalities on amino acids, much effort has been made to develop new monomers and prepare PAHAs with side-chain functionalities *via* ROP of the corresponding monomers. One such example is the readily available 1,3-dioxolane-2,4-diones, so-called *O*-carboxyanhydrides, a class of five-membered ring compounds derived from functionalized α-amino acids or α-hydroxy acids that have been proved to be promising candidates for the synthesis of functionalized PAHAs in a highly controlled manner.[10-26] OCAs are mostly polymerized using pyridine-based organocatalysts, such as 4-dimethylaminopyridine (DMAP),[13] which acts in a bifunctional nature, activating both the initiating nucleophile (alcohol) through its basic nitrogen center with H-bonding and the carbonyl oxygen of the monomer *via* its more acidic α-hydrogen.[14] Unfortunately, the α-hydrogen in the OCA monomer is quite acidic and DMAP not only polymerizes the OCA monomer but can also racemize the enantiopure stereocenter of OCAs with activating side chain groups during the course of the reaction, leading to a loss of enantiopurity that results in materials with poor mechanical and thermal properties.[15, 20] While other catalytic systems such as a Zn-based organometallic catalyst have been studied in this process,[27] or lipase-catalyzed ROP has been studied,[17] Buchard *et al.* showed that the use of acid/base ion pairs (crystalline adducts of mandelic acid and pyridine) as organocatalysts for the ROP of

enantiopure OCAs derived from mandelic acid suppressed the racemization of the monomers to minimum and thereby, produced highly stereoregular isotactic polymers which displayed excellent thermal properties.[20] From a mechanistic point of view, this is achieved as the pyridine activates the hydroxyl group of the initiator through hydrogen bonding. Subsequently, this activated moiety, attacks the carbonyl of the OCA at the 5-position of the ring, causing the ring-opening and the release of a CO_2 molecule in a stepwise manner through tetrahedral intermediates mediated by pyridine.

As we have previously demonstrated, malic acid presents an excellent, renewable resource for constructing functional polyester materials on account of its readily functionalisable β-ester.[15, 28] Previous detailed work from our group[15] has shown that by employing DMAP as well as a range of other substituted pyridines as organocatalysts for the ROP of *L*-malOCA, well-defined polyesters of high molar mass have been realized, but with a significant number of side reactions occurring as a result of the complexity of the mechanistic pathways involved as well as their dependence on the reactions' conditions. Even though these byproducts could easily be removed by column chromatography, the high basicity of DMAP accounts for a significant racemization of the OCA monomer, which leads to the formation of atactic polymeric structures as evidenced by ^{13}C NMR spectroscopy.

The ROP of the corresponding OCAs to produce highly stereoregular PAHAs is of high importance due to the wide array of applications of these materials.[9] For instance, stereocomplexation of the pure *L*-PAHA and D-PAHA can be investigated. Stereocomplex-blends of poly(*L*-lactide) and poly(*D*-lactide) were first reported by Ikada *et al.* in 1987 and resulted in the formation of a PLA stereocomplex with a new crystalline structure quite different from that of each homopolymer.[29] [30] Despite our previous efforts, attempts to directly access stereocomplexing poly(malic acid) derivatives was thwarted by low levels of racemization in the polymerization process and was only able to be demonstrated by the increase in stability of micellar constructs composed of both poly(*L*-malic acid) and poly(*D*-malic acid) derivatives. Herein, we demonstrate that acid/base ion pair organocatalysts are able to mediate the highly

controlled ring-opening polymerization of functional OCAs derived from lactic and malic acids lead to high levels of retention of stereochemistry.

Experimental

Materials

All chemicals and solvents, unless otherwise stated, were ordered from Sigma-Aldrich or Fisher Scientific and used without further purification. $CDCl_3$ (99.8%; Apollo Scientific), was dried over CaH_2, distilled, and stored over activated 3 Å molecular sieves under an inert atmosphere in a glovebox. Acidic Amberlyst® ion exchange resin (A15) was washed repeatedly with methanol and air-dried prior to use. Dry solvents were obtained by purification over an Innovative Technology SPS alumina solvent column. Solvents used for polymerizations were also degassed with three consecutive freeze-pump-thaw cycles prior to use. Benzyl bromide (98%, Sigma Aldrich) and acetone (for HPLC; ≥99.9%) were dried and stored over 3 Å molecular sieves before use. Lithium *L*-lactate (97%; Alfa Aesar) and *L*-lactic acid (anhydrous; 98%; Alfa Aesar) were dried over P_2O_5 in a desiccator for 5 days in *vacuo* and then stored in a nitrogen atmosphere glovebox prior to use. (*S*)-5-methyl-1,3-dioxolane-2,4-dione (*L*-lacOCA),[13] *L*-β-benzyl malate and 5-(S)-[(benzyloxycarbonyl)methyl]-1,3-dioxolane-2,4-dione, (*L*-malOCA)[15] were synthesized as reported previously.

General considerations

All polymerizations were carried out in oven pre-dried glassware, within an MBRAUN stainless steel glove box equipped with a gas purification system, in a dry, inert nitrogen atmosphere. The moisture and oxygen contents of the glove box were monitored by an MB-MO-SE 1 and MB-OX-SE 1 detectors respectively. All monomers and initiators/catalysts were stored at -35 °C inside the glove box. All ^{1}H NMR, ^{13}C NMR and DOSY NMR spectra were recorded on Bruker DPX-400 and DRX-500 spectrometers at 298 K. Chemical shifts are reported as δ in parts per million (ppm) and referenced to residual solvent signals ($CDCl_3$: ^{1}H, (singlet) δ = 7.26 ppm; ^{13}C, (triplet) δ = 77.16 ppm). Size Exclusion Chromatography (SEC) was used to determine the

number average molar mass (M_n) and dispersities ($Đ_M$) of the polymers. SEC analysis in tetrahydrofuran (THF) was conducted on a system composed of a Varian 390-LC-Multi detector suite fitted with differential refractive index, light scattering, and viscometer detectors equipped with a guard column (Varian Polymer Laboratories PLGel 5 µM, 50 × 7.5 mm) and two mixed D columns (Varian Polymer Laboratories PLGel 5 µM, 300 × 7.5 mm). The mobile phase was THF containing 2% TEA + 0.01% BHT (topanol) at a steady flow rate of 1.0 mL min^{-1}. MALDI-ToF (matrix-assisted laser desorption ionization time of flight) mass spectra of low molar mass samples were recorded using a Bruker Daltonics Ultraflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with a positive ion ToF detection and performed using an accelerating voltage of 25 kV. Samples were spotted onto a Bruker ground steel MALDI-ToF analytical plate through application of 1 µL of a solution containing trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propylidene] malonitrile (DCTB) as a matrix (20 µL of a 40 $mg.mL^{-1}$ solution in THF), sodium trifluoroacetate as a cationization agent (20 µL of a 2 $mg.mL^{-1}$ solution in THF), and analyte (20 µL of a 1.0 $mg.mL^{-1}$ solution in THF) followed by solvent evaporation. The samples were measured in reflectron ion mode and calibrated by comparison to PEG-2k/5k standards. Typical spectra were accumulated using 20,000 laser shots added to a sum buffer. MALDI-ToF mass spectra of higher molar mass samples were recorded using a Waters QToF Premier mass spectrometer equipped with a Nd:YAG (third harmonic) operating at 355 nm with a maximum output of 65 µJ delivered to the sample in 2.2 ns pulses at 50 Hz repeating rate. Time-of-flight mass analyses were performed in the reflectron mode at a resolution of about 10,000. All the samples were analyzed using trans-2-[3-(4-tert-butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB) as matrix. That matrix was prepared as 40 $mg.mL^{-1}$ solution in $CHCl_3$. The matrix solution (1 µL) was applied to a stainless-steel target and air-dried. Polymer samples were dissolved in THF to obtain 1 $mg.mL^{-1}$ solutions and 50 µL of 2 $mg.mL^{-1}$ NaI solution in acetonitrile has been added to the polymer solution. Therefore, 1 µL of this solution was applied onto the target area already bearing the matrix crystals, and air-dried. For the recording of the single-stage MS spectra, the quadrupole (rf-only mode) was set to pass all the ions of the distribution, and they were transmitted into

the pusher region of the time-of-flight analyzer where they were mass analyzed with 1s integration time. Differential scanning calorimetry (DSC) analysis was performed using a Mettler Toledo DSC1 star system. DSC heating and cooling curves were run in triplicate in series under a nitrogen atmosphere at a heating rate of ±10 °C min^{-1} in a 40 µL aluminum crucible. Thermogravimetric analyses (TGA) were performed on a TGA/DSC-STAR from Mettler Toledo in an aluminum pan, under a flow of nitrogen using a heating rate of 5 °C/min.

Synthesis

Pyridine and *L*-lactic acid adduct. To a solution of *L*-lactic acid (2.0 g, 22.0 mmol) in dry diethyl ether (10 mL), anhydrous pyridine (1.8 mL, 22.0 mmol) was added drop-wise at 0 °C and the resulting mixture was stirred for 3 hours. The solution was left in the freezer overnight. The solvent was removed under high vacuum and the resulting residue was triturated with dry pentane, and dried *in vacuo*. A colorless oil was retrieved (3.55 g, 21.0 mmol, 95%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 8.75 (d, *J* = 4.7 Hz, 1H, -C$H_{ortho\ aromatic}$), 8.27 (s, 1H, O*H*-N), 8.03 (dd, *J* = 10.8, 4.6 Hz, 1H, -C$H_{para\ aromatic}$), 7.61 (dd, *J* = 7.6, 6.1 Hz, 1H, -C$H_{meta\ aromatic}$), 4.34 (d, *J* = 7.0 Hz, 1H, -CH_3C*H*-), 1.46 (d, *J* = 7.0 Hz, 3H, -CH_3CH). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ = 179.61 (*C*OOH), 145.63 (-$C_{para\ aromatic}$), 140.49 (-$C_{ortho\ aromatic}$), 125.37 (-$C_{meta\ aromatic}$), 66.74 (-*C*HOH), 20.24 (-*C*H_3OH).

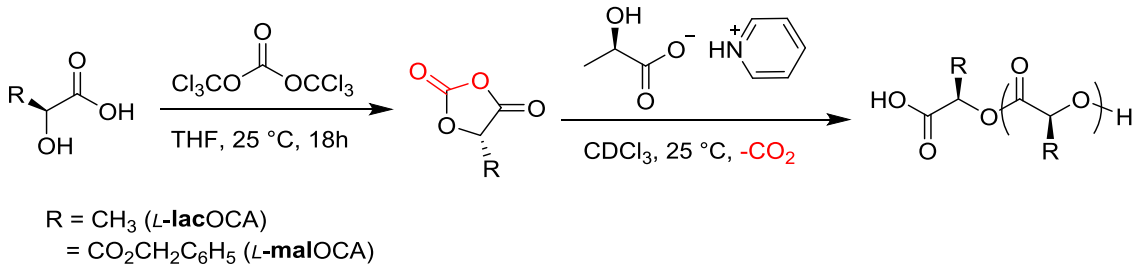
Pyridine and *L*-β-benzyl malate adduct. To a solution of *L*-β-benzyl malate (1.39 g, 6.2 mmol) in dry diethyl ether (10 mL), anhydrous pyridine (0.5 mL, 6.2 mmol) was added drop-wise at 0 °C and the resulting mixture was stirred for 3 h. The solution was left in the freezer overnight. The solvent was removed under high vacuum and the resulting residue was triturated with dry pentane, and dried *in vacuo*. A colorless oil was retrieved (1.71 g, 5.64 mmol, 91%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 7.42-7.33 (5H, m, -C$H_{aromatic}$); 5.14 (2H, s, - CH_2Ar); 5.09 (1H, dd, $^2J_{HH}$ = 5.57 Hz, $^3J_{HH}$ = 4.11 Hz, -C*H*CH_2COOCH_2Ar); 3.13 (2H, dd, $^2J_{H\text{-}H}$ = 5.57 Hz, $^3J_{H\text{-}H}$ = 4.11 Hz, -CH_2COOCH_2Ar). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ = 167.8 (-CH_2*C*OOCH_2Ar); 166.7 (-OCOO*C*OCH-); 145.4 (-O*C*OOCOCH-); 134.4 (-$C_{ipso\ aromatic}$); 128.9 (-$C_{meta\ aromatic}$); 128.8 (-$C_{para\ aromatic}$); 128.7 (-$C_{ortho\ aromatic}$); 75.0 (-OCOOCO*C*H-); 68.2 (-*C*H_2Ar); 34.4 (-CH*C*H_2COOCH_2Ar).

4-Methoxypyridine and *L*-lactic acid adduct. To a solution of *L*-lactic acid (2.0 g, 22.0 mmol) in dry diethyl ether (10.0 mL), *p*-methoxypyridine (2.23 mL, 22.0 mmol) was added drop-wise at 0 °C and the resulting mixture was stirred for 3 h. The solution was left in the freezer overnight. The solvent was removed under high vacuum and the resulting residue was triturated with dry pentane, and dried *in vacuo*. A colorless oil was retrieved (4.10 g, 20.5 mmol, 93%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 9.96 – 9.67 (s, 2H), 8.71 – 8.46 (m, 1H), 7.14 – 6.95 (m, 1H), 4.35 – 4.13 (q, J = 6.9 Hz, 1H), 4.01 – 3.86 (s, 1H), 1.51 – 1.29 (d, J = 6.9 Hz, 2H). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ = 179.49 (*C*OOH), 168.81 (-$C_{\text{ipso aromatic}}$), 146.35 (-$C_{\text{ortho aromatic}}$), 111.15 (-$C_{\text{meta aromatic}}$), 67.05 (-*C*HOH), 56.21 (-O*C*H$_3$), 20.61 (-*C*H$_3$OH).

General procedure for the ring-opening polymerization of *L*-malOCA ([M]/[I] = 250, [*L*-malOCA]$_0$ = 2.0 M). *L*-malOCA (250 mg, 0.001 mol) was dissolved in 490 µL $CDCl_3$. *L*-lactic acid/pyridine adduct (67.0 mg, 0.4 mmol) was dissolved in 1 mL of $CDCl_3$ in order to prepare a stock solution, from which 10 µL were transferred to the vial containing the *L*-malOCA whereby the reaction was initiated. The solution was then transferred into a Young's tapped NMR tube and was sealed and taken out of the glovebox. ^{1}H NMR spectroscopy was used to determine the conversion. After the allotted polymerization time, the reaction was quenched by adding acidic Amberlyst® A15 into the polymerization solution. The polymer was then precipitated from ice-cold hexanes, centrifuged, and dried under high vacuum. ^{1}H NMR spectroscopy and SEC analysis were performed to determine the final characteristics of the polymer. (Yield: 72%). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 7.45 – 7.06 (m, 5H, Ar-*H*), 5.52 (dd, 1H, -C*H*COO-), 5.14 (d, 1H, C*H*$_2$-Ar), 4.54 (s, 1H, -C*H*COO$_{\text{chain end}}$-), 2.91 (ddd, 1H, -C*H*$_2$COO-), 1.46 (s, 1H, C*H*$_3$COO$_{\text{end group}}$). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ = 168.21 (-*C*OCHCO-), 166.94 (-*C*OCH$_2$CH-), 135.32 (-*C*H$_2$COO-), 128.58-128.42 ($C_{\text{aromatics}}$), 68.98 (*C*H$_2$-Ar), 67.09 (-*C*HCH$_2$COO), 35.65 (*C*H3COOH). **SEC (THF + 2% NEt_3 + 0.01% BHT):** M_n = 10800 Da, M_w = 12900 Da, $Đ_M$ = 1.19.

Results and Discussion

Monomer and catalyst synthesis. The OCAs were prepared by ring-closing of the relevant α-hydroxy acids (Scheme 1a).[13, 15] The OCAs were purified and dried by repeated recrystallizations from dry Et_2O/pentane in the glovebox before use (Fig. S1-S2). The pyridine and 4-methoxypyridine salts of *L*-lactic acid and β-benzyl α-(*L*)-malate (Fig. S3-S5) were prepared in anhydrous conditions by simple addition of the dry base in the suspension of acid into dry Et_2O followed by a single washing with dry Et_2O or dry pentane.



R = CH_3 (*L*-**lac**OCA)
= $CO_2CH_2C_6H_5$ (*L*-**mal**OCA)

Scheme 1. Synthesis of *O*-carboxyanhydride (OCA) and subsequent polymerization.

Ring-opening polymerization studies. Initial studies focused on the application of the pyridine salts of *L*-lactic acid and β-benzyl α-(*L*)-malate for the ROP of *L*-lacOCA (Scheme 1). Monomer conversion was monitored by ^{1}H NMR spectroscopy by the observation of the reduction of the methyl group doublet resonance of the monomer at δ = 1.69 – 1.67 ppm and the appearance of the corresponding polymer methyl group doublet at δ = 1.56 – 1.53 ppm. Upon completion of the allotted time, polymerizations were quenched with the addition of acidic Amberlyst ® (A15) ion exchange resin to remove the pyridine, before being precipitated into ice cold *n*-hexane in order to obtain pure poly(*L*-lacOCA)s, PLLAs (Figure 1).

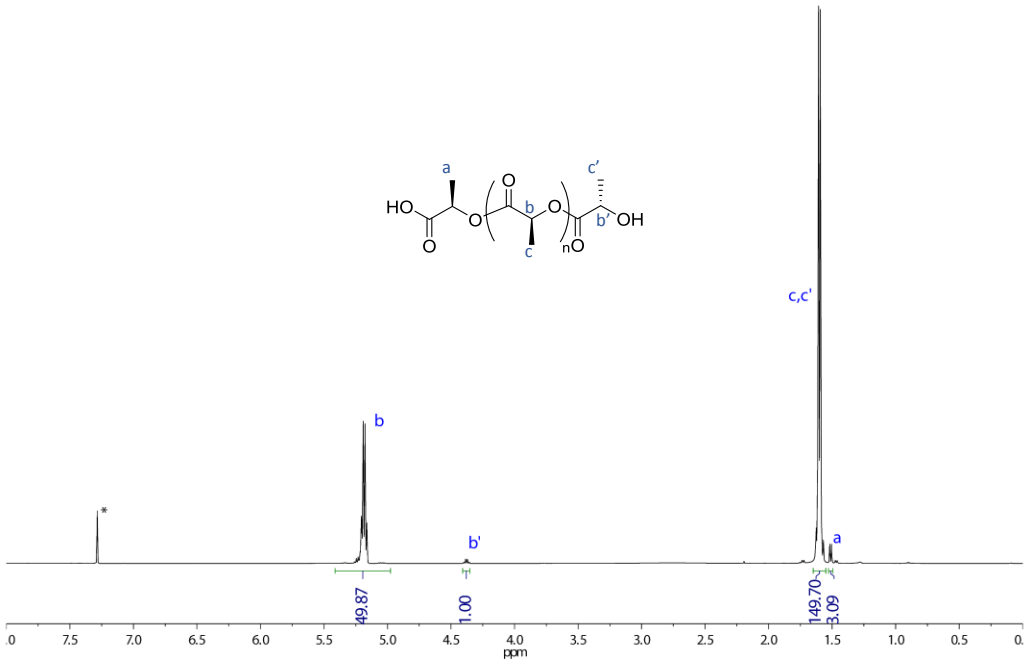


Figure 1. ^{1}H NMR spectrum of a $PLLA_{50}$ initiated by pyridine/*L*-lactic acid ($CDCl_3$; 400 MHz), (*$CHCl_3$).

Table 1. Polymerisation of *L*-lacOCA using ion pairs.

Entry	$[M]_0/[I]_0$	Conv. (%)[a]	time (h)	DP[a]	M_n^{theor} (Da)[b]	M_n (Da)[c]	M_n (Da)[e]	$Đ_M$[c]
1	10	99	3	10	810	1180	685	1.12
2	20	99	6	20	1530	2030	1180	1.10
3	50	95	18	47	3500	6460	3745	1.12
4	100	99	36	100	7290	11770	6830	1.07
5	250	94	120	235	17000	28640	16610	1.11
6	250[d]	96	336	240	17500	45450	26360	1.10

[a] Determined by ^{1}H NMR spectroscopy by integration of the end group and main chain signals; [b] ($FW_{rep.\ unit} \times [M]_o/[I]_o \times$ % conversion) + $FW_{initiator}$ [c] Determined by SEC analysis in THF, calibrated against polystyrene standards; [d] Initiated by pyridine/β-benzyl α-(L)-malate adduct; [e] Using a correction factor 0.58 for M_n^{SEC}; Conditions: $[M]_0$ = 2.0 M, 25 °C, $CDCl_3$.

In order to study the polymerization control of *L*-lacOCA across a range of molar masses, PLLAs targeting different target DPs were synthesized (Table 1). SEC analysis for all polymers targeted showed narrow dispersities ($Đ_M \leq 1.12$); however, bimodality in the chromatogram was observed for the higher molar mass polymers (DP > 100) (Fig. S6). The number average molar

mass (M_n) calculated by ^{1}H NMR spectroscopy was significantly lower than the one obtained from SEC. It is postulated that this is the result of a difference in hydrodynamic volume between SEC polystyrene standards and PLLA polymers. However, applying a correction factor of 0.58 to the obtained M_n values by SEC returned values which are better correlated with the theoretical ones.[31-33] Despite this, a linear correlation between number-average molar mass (M_n) and $[M]_0/[I]_0$ (Figure 2A) indicates that the polymerization is well-controlled. Furthermore, based on the linearity of the semi-logarithmic plot of monomer consumption over time (Figure 2B), it is proposed that *L*-lacOCA ROP followed first order kinetics in relation to the monomer, which is indicative of a high number of active chains throughout the reaction.

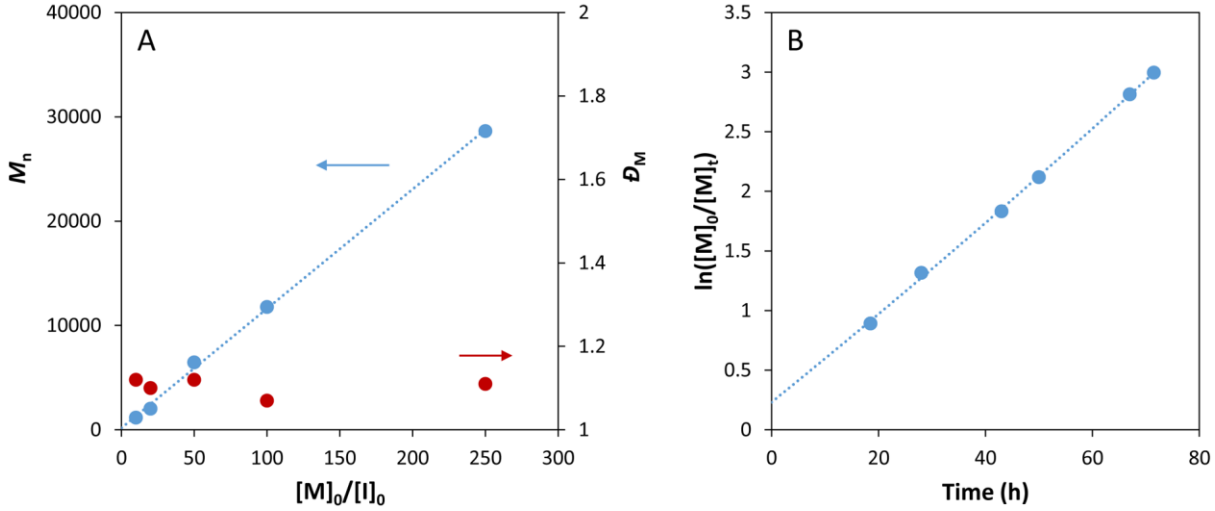
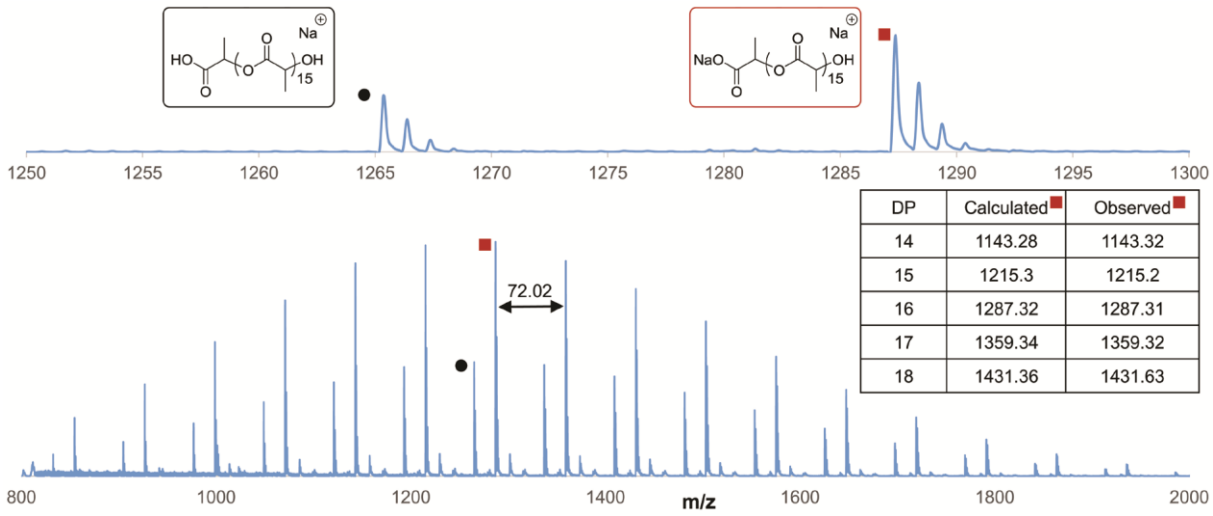


Figure 2. (A) Number-average molar mass (M_n) and dispersity ($Đ_M = M_w/M_n$) against monomer-to-initiator concentration ratio ($[M]_0/[I]_0$) for the ROP of *L*-lacOCA; (B) Semi-logarithmic plot of monomer consumption for the ROP of *L*-lacOCA, $[M]_0/[I]_0 = 100$.

Analysis of a $[M]_0/[I]_0 = 20$ PLLA initiated by pyridine/*L*-lactic acid by MALDI-ToF MS revealed two major distributions, each displaying regular spacings equal to the molar mass of the monomeric repeat unit ($\Delta m/z$ 72.02) (Figure 3). The mass spectrum is mainly composed of two distributions separated of 22 Th. The less intense population corresponds to the sodium cationized oligomers with the expected structure (PLLA.Na^+) while the main distribution, higher

in mass of 22 Th, corresponds to the same polymer where a H^+ is exchanged with a Na^+ ([PLLA-H^++Na^+].Na^+). The observation of this second distribution is usually considered as the "finger print" of the presence of the carboxylic acid end-group.[34, 35]



DP	Calculated	Observed
14	1143.28	1143.32
15	1215.3	1215.2
16	1287.32	1287.31
17	1359.34	1359.32
18	1431.36	1431.63

Figure 3. MALDI-ToF MS spectrum of $PLLA_{16}$ initiated by pyridine/*L*-lactic acid (reflectron mode).

The success of this approach led us to extend it to the study of the ROP of *L*-malOCA. In a similar fashion, the polymerization progress for *L*-malOCA was monitored by ^{1}H NMR spectroscopy by the observation of the reduction of the methylene resonance of the monomer at δ = 3.21 ppm and the appearance of the corresponding broadened multiplets at δ = 3.02 – 2.85 ppm in poly(*L*-malOCA), P(*L*-malOCA) (Fig. S7). Upon completion of the allotted time, polymerizations were quenched with the addition of acidic Amberlyst® (A15) ion exchange resin to remove the pyridine, before precipitation of the polymers into ice cold *n*-hexane in order to obtain pure P(*L*-BMAs) (Figure 4, S8, S9). To study the control of the polymerization of *L*-malOCA over a range of molar masses under these conditions, P(*L*-malOCA) of different targeted DPs were synthesized (Table 2). Notably, while the molar mass distributions of the resultant obtained polymers were quite narrow, their molar masses and corresponding degrees of polymerization were markedly lower than those predicted by the monomer: initiator ratio. Comparable to the previous report

of the ROP of this monomer,[15] this is most likely a result of inefficient initiation and is attributed to the ratio of pyridine to initiator in this single initiator/catalyst system which is 1:1. In turn this causes undesirable side reactions which consume monomer without yielding the desirable polymer products.[15] SEC analysis of the P(*L*-malOCA)s produced (Figure S10), revealed a significant high molar mass shoulder for all polymers with DP ≥ 100. This was independent of the catalyst/initiator used during the ROP and provides further evidence for the presence of side reactions that cause termination of the polymerization returning polymers with diminished molar masses.

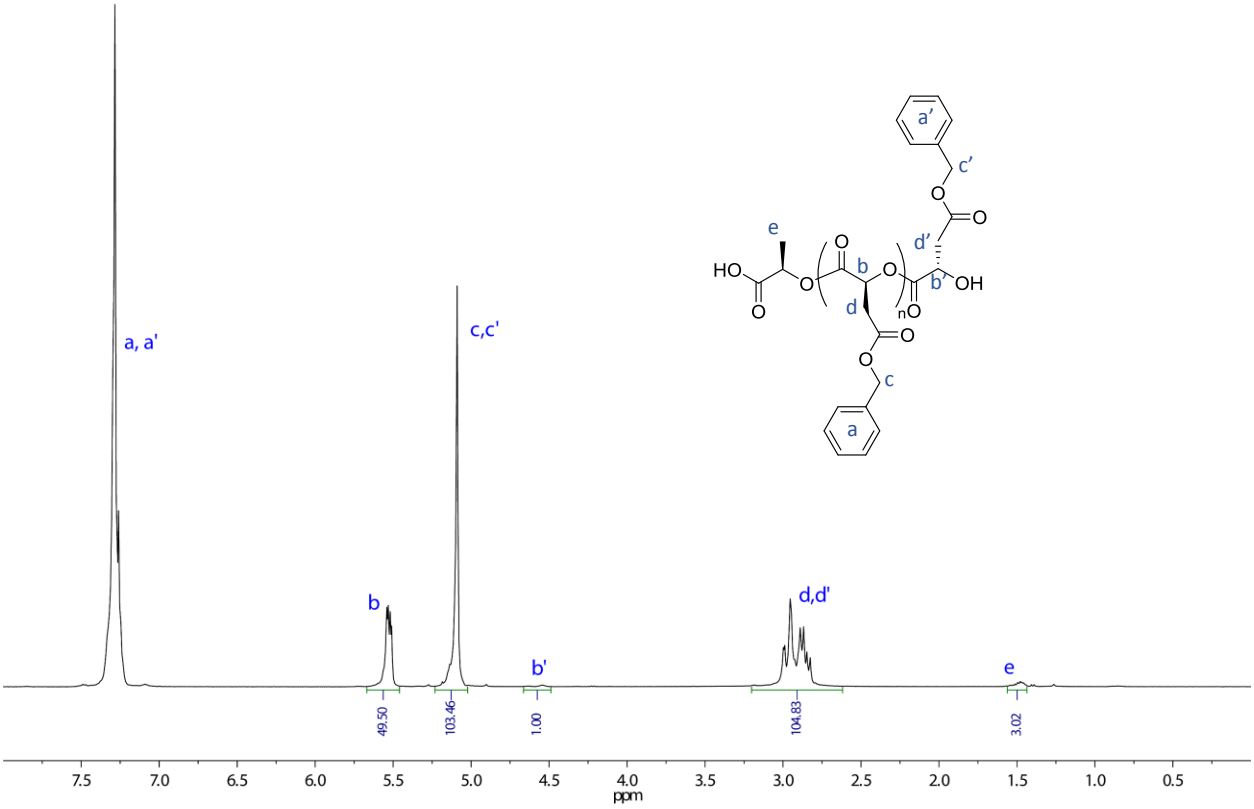


Figure 4. ^{1}H NMR spectrum of P(*L*-malOCA)$_{50}$ initiated by pyridine/*L*-lactic acid adduct ($CDCl_3$; 400 MHz); (*$CHCl_3$).

Table 2. Polymerization of *L*-malOCA using ion pairs.

Entry	$[M]_0/[I]_0$	Conv. (%)[a]	time (h)	DP[a]	M_n^{theor} (Da)[b]	M_n (Da)[c]	$Đ_M$[c]

1	10	99	5	10	2150	2500	1.12
2	20	92	6	18	3800	3530	1.09
3	50	95	24	47	9800	5030	1.11
4	100	99	48	100	20600	7350	1.15
5	250	94	63	235	48500	16910	1.23
6	100[d]	94	127	94	19600	10000	1.21

[a] Determined by ^{1}H NMR spectroscopy by integration of the end group and main chain signals; [b] ($FW_{rep.\ unit} \times [M]_o/[I]_o \times$ % conversion) + $FW_{initiator}$ [c] Determined by SEC analysis in THF, calibrated against polystyrene standards; [d] Initiated by pyridine/β-benzyl α-(*L*)-malate adduct; Conditions: $[M]_0$ = 2.0 M, 25 °C, $CDCl_3$.

Further analysis of the polymerization demonstrated that the semi-logarithmic plot of monomer consumption against time indicated first order kinetics (Figure S11) in relation to the monomer and a linear correlation between M_n and initial monomer to initiator ratio as well as monomer conversion (Figure 5) was observed, in keeping with the controlled nature of the polymerization. A $Đ_M$ lower than 1.2 was observed in all polymerizations. To demonstrate the living nature of the chain end, a second-feed experiment in which the chain extension of a P(*L*-malOCA)$_{20}$ macroinitiator (M_n = 3770 Da; $Đ_M$ = 1.06) with 20 equiv. *L*-malOCA resulted in the isolation of a P(*L*-malOCA)$_{40}$ that exhibited an increase in molar mass (M_n = 7280 Da), while maintaining a low dispersity of 1.10. Furthermore, leaving the resultant P(*L*-malOCA)$_{40}$ for 6 h (twice the time than required to reach > 90% monomer conversion) in the presence of the catalyst resulted in negligible changes in both the molar mass (M_n = 7290 Da) and molar mass distribution ($Đ_M$ = 1.12) which indicates that transesterification side reactions were minimal after full monomer consumption.

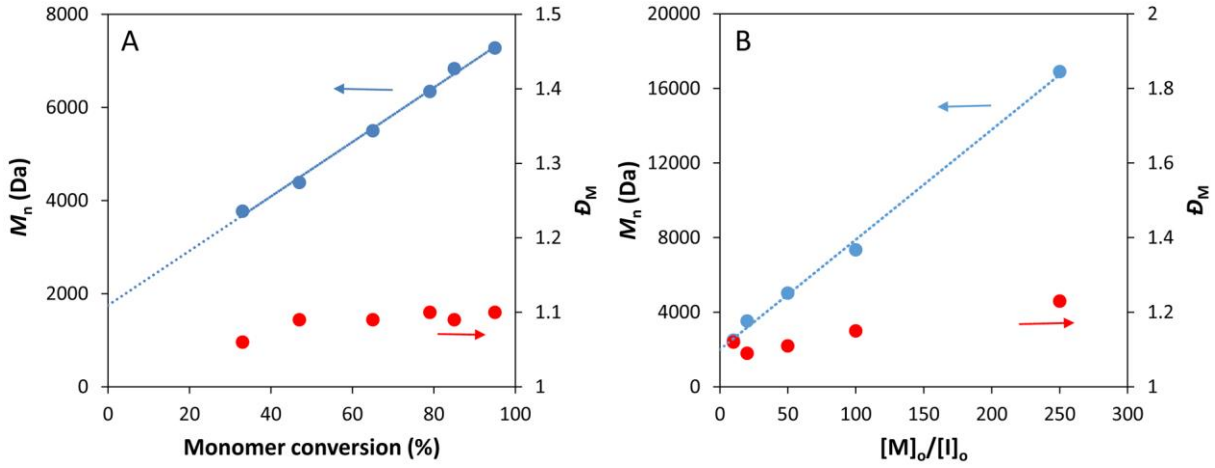


Figure 5. Number-average molar mass (M_n by SEC) and dispersity against (A) monomer conversion and (B) $[M]_0/[I]_0$ for the ROP of *L*-malOCA, $[M]_0/[I]_0 = 50$.

Further analysis of the polymers by MALDI-ToF MS enabled the identification of the side reactions that take place in this polymerization. While analysis of a low molar mass sample (Figure S12) demonstrated primary distributions that were consistent with the sodium charged polymer and the sodium carboxylate terminated analogue, analysis of a higher molar mass sample ($[M]_0/[I]_0 = 250$) initiated by pyridine/*L*-lactic acid was revealed multiple polymeric distributions (Figure 6 and S13). Each distribution displayed regular spacings equal to the molar mass of the β-benzyl α-(*L*)-malate repeat unit ($\Delta m/z$ = 206.06). The two most intense distributions were observed that correspond to simulations of a sodium-charged polymer with an acid end group (green simulations, Figure 6) and lactic acid end group (black simulations, Figure 6) which are most likely generated by initiation with water and the desired lactic acid salt respectively. For each of these distributions a minor distribution in which the carboxylic acid proton has been substituted by to a sodium carboxylate chain end can also be observed. Contrary to the observations by SEC, other distributions are assigned to be the result of transesterification side reactions during the polymerization. Firstly, the distribution highlighted at *m/z* 16680 (brown simulations, Figure 6) corresponds to a sodium charged chain with a lactic acid end group and an additional lactate within the repeat unit; a sodium carboxylated terminated distribution is also observed. We postulate that this species originates from intermolecular transesterification of one chain adding to another and eliminating water. In turn

this may explain the higher molar mass distribution. Finally, two distributions (red simulations, Figure 6) originating from lactic acid and water initiation are present in which the simulation correlates to the absence of a single benzyl group. These chains correspond to either single ester hydrolysis in the polymer or by a branching event at the side chain ester. The increased presence of these distributions in the main lower molar mass area indicate that hydrolysis is the most likely explanation. It is postulated that all these side reactions act antagonistically to each other and are the reason of the bimodality which is observed by SEC for both the P(*L*-lacOCA) and P(*L*-malOCA) higher molar mass polymers. This is more stressed for the polymerizations initiated by pyridine/β-benzyl α-(*L*)-malate adduct, where prolonged reaction times compared to the polymerizations initiated by pyridine/*L*-lactic acid adduct for the same $[M]_0$:$[I]_0$ indicate further loss of molar mass control which lead to polymers with higher M_n than targeted.

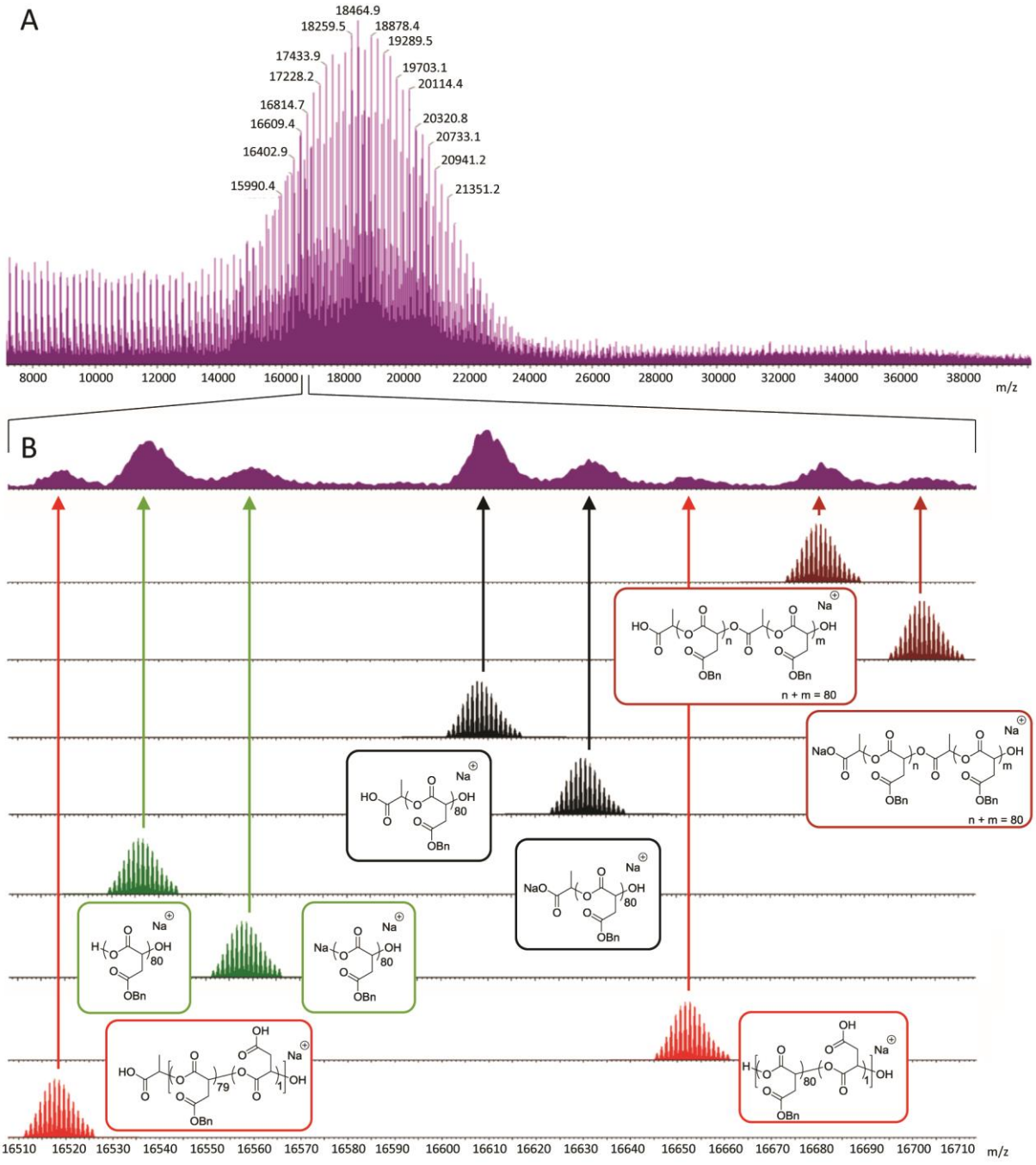


Figure 6. (A) MALDI-ToF MS spectrum of a P(L-BMA)$_{80}$ initiated by pyridine/*L*-lactic acid; (B) Expansion of region from *m/z* 16510 to 16710 (purple) and simulated mass distributions (brown, black, green and red).

In order to accelerate the polymerizations, the adduct of *L*-lactic acid and 4-methoxypyridine, a stronger Brønsted–Lowry base than pyridine was prepared and was screened as an organocatalyst for the ROP of *L*-malOCA. A polymerization with target $[M]_0/[I]_0$ = 100 was attempted with an initial $[L\text{-malOCA}]_0$ = 1.0 M. As anticipated, the polymerization was much more rapid significantly in comparison to the pyridine adducts such that after 3.5 h, monomer conversion was 90%. After precipitation and isolation of the polymer, ^{1}H NMR spectroscopy showed an experimental DP of 55 and M_n = 11.6 kDa which was lower than expected based on the $[M]_0$:$[I]_0$ ratio. SEC in THF displayed a distribution with $Đ_M$ = 1.17 however, a small shoulder at the high molar mass region could still be observed. The experimental M_n was found 9000 Da, which while it was in agreement with the obtained NMR spectroscopy value, was again lower than the targeted molar mass based on monomer conversion. Therefore, it was determined that the issue of side reactions was still present even with the use of a different, more basic pyridine.

Stereoregularity of P(*L*-malOCA) and PLLA polymers. The isotacticity of the P(*L*-malOCA) and PLLA polymers in this study is of great importance as it directly translates to the thermal performance of these materials. Therefore, ^{1}H (homo-decoupled) (Figure S14) and quantitative ^{13}C NMR spectroscopy[36] (Figure 7 & S15, Table S1) were used to verify and quantify any racemization of the stereogenic carbon of the monomers during the ROP process.

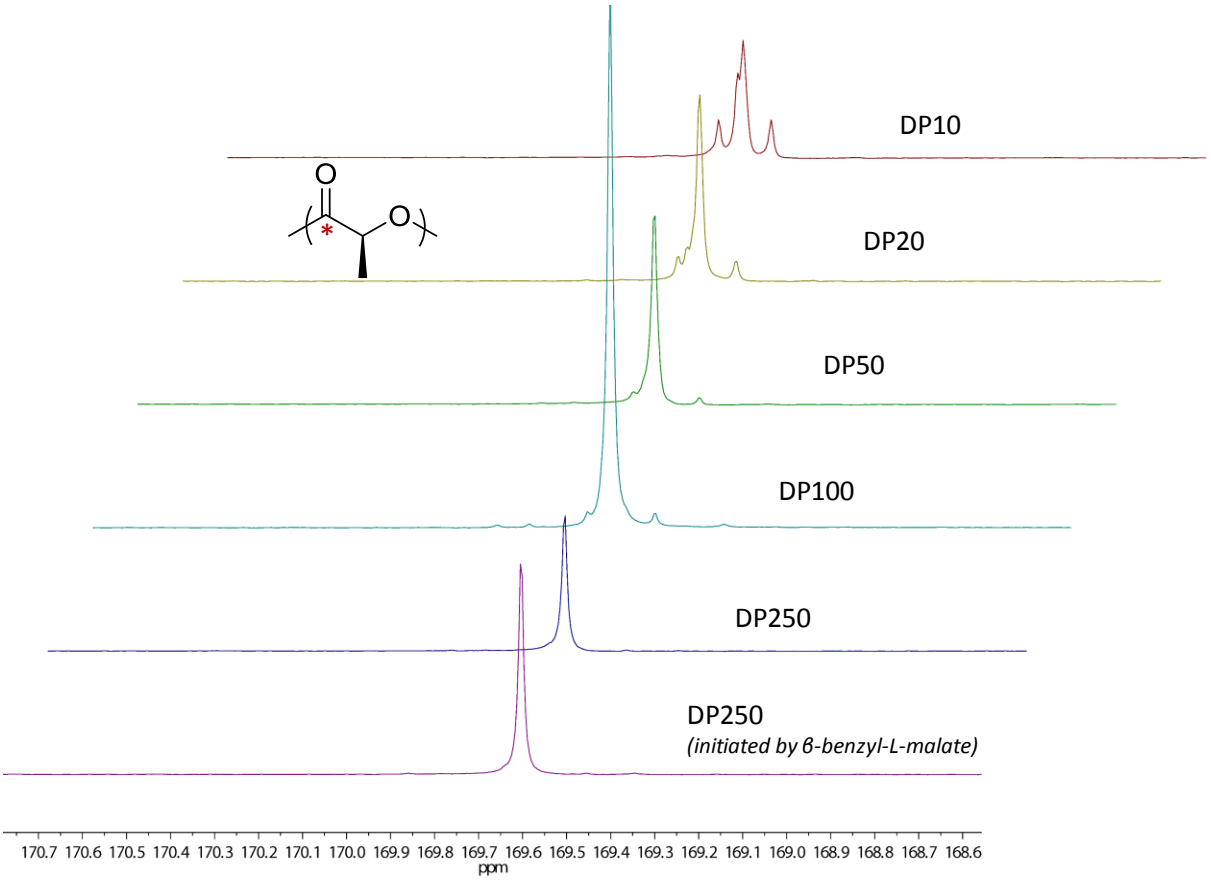


Figure 7. Quantitative ^{13}C NMR spectra of PLLA, expansion of carbonyl region (100MHz, $CDCl_3$).

For ^{13}C NMR spectroscopy, this was determined by relative integration of the resonance of the carbonyl carbon of the polymer backbone in relation to any neighboring signals indicative of racemization or other polymer impurities, whereas for the homo-decoupled ^{1}H NMR spectra of PLLA polymers, the decoupling of the methine resonance to a singlet gives a strong indication of the isotactic enrichment of the polymeric structure. These analyses reveal that at low $[M]_0$:$[I]_0$ ratios, polymers tend to lose their isotactic enrichment, especially P(*L*-malOCA) polymers, while at higher $[M]_0$:$[I]_0$ ratios, PLLA and P(*L*-malOCA) polymers (initiated by both adducts) exhibit a highly isotactic stereoregular structure. The reasons behind these are still unclear however, a closer inspection of the carbonyl region of a ^{13}C NMR spectrum of a P(*L*-BMA) polymer reveals the signal of the carbonyl carbons of the enantiopure polymer at δ = 182.2 ppm, while all the

stereo-errors can be found downfield at δ = 182.3-182.6 ppm. For low DP polymers, the chain end signals which are significantly enhanced compared to their higher DP analogues, can be identified as intense peaks at the same region, which could interfere with the absolute determination of the enantiomeric purity of the polymers. This can also be clearly seen for PLLA polymers, where the isotactic carbonyl carbons' resonance is at δ = 169.61 ppm and the two carboxylic acid chain ends' resonances can be observed at δ = 169.55 and 169.66 ppm respectively. Alternatively, in accordance with what previously reported,[20] it is possible that for short polymeric chains, the higher catalyst (pyridine) loading creates harsher polymerization conditions and could possibly lead to racemization during the ROP process. Nevertheless, this is an improvement compared to what has been previously reported for the DMAP-catalyzed ROP of *L*-malOCA, where significant racemization of the stereogenic carbon of the monomer was evident by ^{13}C NMR spectroscopy of the pure polymers.[15]

Thermal analysis of P(*L*-malOCA) and PLLA polymers by TGA and DSC. It is well known that the thermal degradation of polymers may involve thermohydrolysis, zipper-like depolymerization reactions, thermo-oxidative degradation, or transesterification reactions[37] and hence in order to understand the thermal properties of the resultant polymers, analysis of their behavior using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) was undertaken. High molar mass P(*L*-malOCA) and PLLA polymers were extensively dried and annealed in a vacuum oven at 80 °C for 48 h before testing their thermal degradation and resistance. Highly isotactic PLLAs are expected to be semi-crystalline materials with their glass transition temperature (T_g) and melting temperature (T_m) to be highly dependent on their tacticity.[38] P(*L*-malOCA)$_{100}$ polymers were found to begin their degradation profile at 280 °C, while PLLA$_{100}$ polymers displayed no degradation until 300 °C (Figure S16 & 17). DSC analysis of the same polymers displayed a binary nature of PLLA polymers (both amorphous and crystalline) depending on their annealing process. Non-annealed PLLA displayed amorphous behavior with a T_g = 47.7 °C (a T_m = 168 °C appeared only during the first heating scan), while annealed PLLA displayed a repeated melting peak at 165 °C, thus proving the highly isotactic nature of the polymer (Figure S18-S20). P(*L*-malOCA)$_{100}$ polymers were subjected to the same thermal routine

and surprisingly, even after extensive annealing, they did not display any crystalline behavior. T_gs were reproducible (with every thermal scan) within a range of >2 °C and in three separate samples were measured in the range of 19.9 – 21.0 °C, however, no crystallization or melting peaks were observed. This is an increase of approximately 10 °C to what has been previously reported using DMAP as the ROP catalyst of *L*-malOCA, potentially a consequence of the higher isotacticity. The absence of crystallinity could be ascribed to the pendant benzyl ester group in the polymer chain which could interfere with the crystal packing and formation of the structure.

Conclusions

In summary, we have reported the organocatalyzed synthesis of P(*L*-malOCA) and PLLA polymers derived from activated monomers (OCAs) of *L*-lactic and *L*-malic acid. Ion pairs of pyridine and 4-methoxypyridine with *L*-lactic acid and β-benzyl α-(*L*)-malate were prepared and were employed as single initiator/catalyst systems for the ROP process. The reactions were consistent with those expected in a well-controlled polymerization as evidenced by ^{1}H NMR spectroscopy, size exclusion chromatography as well as chain extension experiments. Analysis of the polymers *via* MALDI-ToF mass spectrometry provided an insight into the different side-reactions which occurred during the ROP, especially for the higher molar mass polyesters. The stereoregularity of these polymers was investigated *via* ^{1}H homo-decoupled and ^{13}C NMR spectroscopy techniques. Polymers of higher molar mass were found to be almost 100% isotactic, whereas lower molar mass polymers displayed an atactic nature. The thermal analysis of these polymers revealed the highly crystalline and thermal resisting nature of PLLA with high melting temperatures, while P(*L*-malOCA) polymers remained in amorphous state as a consequence of their microstructure.

Acknowledgements

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