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Ring-opening polymerization of L-lactide in the presence of α -hydroxy- γ -butyrolactone

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Abstract

Among the polymer families, aliphatic polyesters stand out from this category thanks to their degradable and biocompatible properties. In particular, the γ -lactones differ from other lactones by yielding polyesters that can be depolymerized back to the monomer and offer the advantage of counting various biobased monomers. As an example, α -hydroxy- γ -butyrolactone (HBL) is a hydroxy-functionalized monomer that can be obtained by a biological synthetic route from glucose. In this article, the ring-opening copolymerization (ROCP) of HBL and L-lactide (LLA) using *t*-BuP₄ as catalyst is investigated. The copolymerizations were conducted within a temperature range of 5–100°C, affording monomer conversions exceeding 80%. The characterization of the copolyesters revealed a branched structure consisting of different HBL patterns, including cyclic, linear, and branched motives. Performing a kinetic study of the copolymerization at room temperature provided a deeper understanding of the mechanism. By modulating the reaction parameters, copolymers of low molar masses with an HBL content of up to 33% were synthesized. High molar mass LLA/HBL-based copolyesters, with \overline{M}_w up to 290,000 g/mol, were synthesized by a straightforward chain coupling reaction with a diisocyanate.

KEYWORDS

functional polyesters, L-lactide, organocatalytic ring-opening copolymerization, sustainable polymers, α -hydroxy- γ -butyrolactone

1 | INTRODUCTION

For decades, the scientific community has faced the challenge of developing more sustainable and degradable polymers. To address this purpose, aliphatic polyesters such as polyhydroxyalkanoates, poly(ϵ -caprolactone) or poly(lactide) have shown special interest in this regard due to their biocompatibility and degradability.^{1–3} The synthesis of aliphatic polyesters by ring-opening (co)polymerization (ROP and ROCP) of cyclic esters has promoted the development of diverse catalysts and reaction conditions for fine-tuning the architecture of

such polymers.^{4–7} The broad variety of these materials allows their use in a multitude of applications, including biomedical areas, 3D printing or packaging.^{8–13} By introducing diverse side chains along the polymer backbone, specific applications can be targeted through post-modification reactions.^{14–16} Indeed, the use of functionalized monomers is a key factor in the design of polymers with tailored properties.

Achieving closed-loop recycling of a polymer enables the reformation of the monomer for subsequent repolymerization.¹⁷ In this category, poly(γ -butyrolactone) (PyBL) is a highly attractive polymer thanks to its ability to depolymerize, allowing a complete recovery of the monomer. The polymerization of γ -lactones has remained a challenge over the years due to the unfavorable thermodynamic

Dedicated to Professor Stanislaw Penczek on the occasion of his 90th birthday.

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constraints.^{18–22} Because of the low strain energy of these monomers, the ROP of γ -lactones results in a positive free energy of polymerization (ΔG_p) at ambient temperature and pressure. Hong and Chen²³ demonstrated in 2016 that the use of efficient catalyst and specific reaction conditions, including monomer concentration and working below the ceiling temperature, enabled the synthesis of P γ BL. In addition to their degradable properties, various γ -lactones can be derived from natural resources.^{24–26} As an example, α -hydroxy- γ -butyrolactone (HBL) is a α -hydroxy functionalized γ -lactone that can be obtained from glucose using a biological synthetic route.^{27–29}

Among the biobased polymer family,^{30–33} poly(lactide) (PLA) is a widely marketed polymer derived from renewable resources such as corn starch and potato.^{34,35} Despite its numerous advantages, the degradation of PLA in the environment remains a challenge due to its resistance to microorganisms attack.³⁶ Thermal properties of PLA can easily be modulated depending on the chain length and the stereoregularity of the polymer. As an example, atactic PLA is an amorphous polymer, whereas poly(L-lactide) (PLLA) is a semi-crystalline polymer with a melting temperature of approximately 170°C.^{37,38} Performing random copolymerization with a comonomer allows modulation of the copolymer crystallinity and its associated thermal and degradable properties.³⁹ The random introduction of a degradable unit is a way of enhancing the degradability of the final material. The degradability of a material can also potentially be improved by incorporating a hydrophilic function, such as the hydroxyl group carried by HBL. In addition to its impact on the degradability, the main advantage offered by this function is the ability to perform post-polymerization reactions.

Over the past few decades, a panel of catalysts and reaction conditions have been developed to achieve and improve the (co)polymerization of lactones, with a special focus on γ -lactones.^{40–43} Phosphazene bases were widely used for the RO(C)P of γ -lactones, but also for the ROP of LLA^{44–46} and ROCP of LLA with γ -butyrolactone.⁴⁷ ROP of HBL has also been the subject of research projects.^{48–52} According to a previous study, the *t*-BuP₄ catalyst showed efficiency in the synthesis of HBL/ ϵ -caprolactone copolyesters, affording copolymers with high molar masses (up to 15,000 g/mol) and monomer conversions ($\approx 90\%$) in short reaction times (5 min).⁵²

In this article, the organocatalytic ROCP of LLA and HBL monomers using *t*-BuP₄ as the catalyst is investigated. Kinetic studies and precise characterization of the functional polyesters allowed to elucidate the reaction mechanism. The influence of various reaction parameters (temperature, monomer concentration, monomer feed, and M/C/I ratios) on the synthesis and thermal properties of the so-formed copolyesters were also studied. Finally, a straightforward chain coupling reaction was performed to demonstrate the possibility of synthesizing LLA/HBL-based copolyesters with high molar masses.

2 | EXPERIMENTAL SECTION

2.1 | Materials

L-Lactide (LLA) was purchased from TCI and recrystallized three times in toluene. Then, LLA was dried by azeotropic distillation with dry

toluene (four times), kept under dynamic vacuum until the compound was dry and stored in an argon-filled glovebox. ADISSEO provided the monomer α -hydroxy- γ -butyrolactone (HBL). For the purification step, HBL was put overnight under dynamic vacuum at 40°C and cryo-distilled. Only the second fraction was kept for the experiments. 1-*tert*-Butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylideneamino]-2 λ 5,4 λ 5-catenadi(phosphazene) (*tert*-BuP₄, ~ 0.8 M in hexane) was purchased from Sigma-Aldrich, stored in a glovebox and used without purification. The solvent was evaporated prior to use. Tetrahydrofuran (THF) was dried on alumina column and cryo-distilled over Na/benzophenone. The toluene used for the azeotropic distillation was dried on an alumina column.

2.2 | General polymerization method(s)

Polymerization example with the following parameters: M/C ratio = 200/1; [M] = 1.5 M; THF. First, two flame-dried Schlenk tubes were introduced into an argon-filled glovebox. One was loaded with the catalyst (1 equivalent; 0.021 mmol; 26 μ L of a 0.8 M solution in hexane) and closed with a rotaflow stopcock. The second Schlenk tube was charged with the LLA monomer (152 equivalents; 3.195 mmol; 0.46 g) and closed with a rotaflow stopcock. Once taken out of the glovebox, the Schlenk tubes were linked to a dual-manifold Schlenk line to perform the following steps under argon atmosphere. HBL (46 equivalents; 0.9575 mmol; 75 μ L) and part of the solvent (2.2 mL) were added to the reactor containing LLA and stirred until complete solubilization of the compounds. The other part of the solvent (0.1 mL) was added to the reactor containing the catalyst and stirred 10 min. Then, the catalyst and the solvent were added to the Schlenk tube containing the solubilized monomers. The reactor was closed and placed in a preheated oil bath, which marked the start of the polymerization. Finally, 1 mL of a 0.1 mol/L solution of acetic acid in chloroform was added to stop the polymerization. The reaction medium was analyzed by ¹H NMR and SEC. The polymer was precipitated in an ethanol/cyclohexane mixture (75/25) and dried under dynamic vacuum overnight.

2.3 | Polymerization kinetic study at 1.5 M

As before, two flame-dried Schlenk tubes were placed in an argon-filled glove box, one was loaded with the catalyst and the other with LLA. Once taken out of the glovebox, the Schlenk tubes were linked to a dual-manifold Schlenk line to perform the following steps under argon atmosphere. HBL and part of the solvent were added to the reactor containing LLA and stirred until complete solubilization of the compounds. The other part of the solvent was added to the reactor containing the catalyst and stirred 10 min. The catalyst and solvent were then added to the Schlenk tube containing the solubilized monomers. The mixture was then separated into several Schlenk tubes, closed and placed in a preheated oil bath. A solution of acetic acid in chloroform was added to stop the polymerization and the reaction medium was analyzed by ¹H NMR and SEC.

2.4 | Polymerization kinetic study at 6 M

For the kinetic at high concentration, several flame-dried Schlenk tubes were introduced into an argon-filled glove box. One Schlenk tube was loaded with the catalyst and all the others with LLA. The reactors were taken out of the glovebox and linked to a dual-manifold Schlenk line to perform the following steps under argon atmosphere. Part of the solvent was added to the reactor containing the catalyst, and stirred 10 min. Then, HBL and the other part of the solvent were added to all the other reactors containing LLA. These reactors were placed in a preheated oil bath at 80°C and stirred until complete solubilization of the compounds. Finally, the catalyst and solvent were rapidly added to all the Schlenk tubes containing the solubilized monomers. A solution of acetic acid in chloroform was added to stop the polymerization and the reaction medium was analyzed by ¹H NMR and SEC.

2.5 | Chain coupling reaction

The mole number of hydroxy functions n_{OH} was calculated for each copolymer sample, considering the number of HBL units, since each unit will produce an OH-terminated chain end or a pendant OH group along the backbone.

All reactions were performed in flame-dried Schlenk tubes and under an argon atmosphere using a dual-manifold Schlenk line. Here is a chain coupling example for the copolymer Table 1, run 1. For the reaction, the copolymer (200 mg, $n_{\text{OH}} \approx 0.407$ mmol) was first put under dynamic vacuum overnight. The copolymer was then solubilized in 1 mL of dry THF. Hexamethylene diisocyanate (16 μL , $n_{\text{NCO}} \approx 0.204$ mmol) was added to the mixture along with dibutyltin dilaurate (three droplets, $n \approx 0.0367$ mmol). The reaction medium was heated at 50°C and changes in viscosity were visually monitored to stop the reaction prior to crosslinking. When the medium increased in viscosity, the mixture was diluted in an excess of THF and then quenched with water.

For the FTIR and SEC measurements, aliquots from the medium were taken after the addition of the diisocyanate (copolymer at the beginning of the chain coupling t_{0+}) and after dilution of the medium with THF (copolymer after chain coupling t_f).

2.6 | Characterization of the polymers

For the determination of the monomer conversions, HBL type units, copolymer compositions and degrees of branching (DB), samples were analyzed by liquid-state ¹H NMR at 298 K on a Bruker Avance 400 spectrometer operating at 400 MHz in THF-d₈ and CDCl₃. The structure elucidation was carried out at 298 K on a Bruker Prodigy spectrometer operating at 400 MHz in THF-d₈ and CDCl₃, performing liquid-state ¹H NMR, ¹H-¹³C HSQC NMR, and ¹H-¹H COSY NMR.

The number average molar masses (\overline{M}_n) and dispersities ($\overline{D} = \overline{M}_w/\overline{M}_n$) of the polymers were determined by size exclusion chromatography (SEC) using THF as the eluent. An Ultimate 3000 system from ThermoScientific with diode array detector DAD was used for the measurements. A differential refractive index detector dRI and a multi-angle light scattering detector (MALS) from Wyatt technology are also part of the system. Separation of the polymers was performed at a flowrate of 1 mL/min using three G2000, G3000, and G4000 TOSOH HXL gel columns (exclusion limits from 1000 to 400,000 Da) (300 \times 7.8 mm) with a temperature of 40°C. Data were determined using polystyrene as the standard.

The thermal properties of the copolyesters were determined by differential scanning calorimetry (DSC). A DSC Q100 RCS apparatus from TA Instruments was used for the measurements. Copolyester samples (≈ 2 mg) were first heated from -80 to 200°C (10°C/min), cooled to -80 °C (5°C/min) and finally reheated to 200°C (10°C/min). The first cycle was used for the thermograms.

Fourier transform infrared (FTIR) spectra were recorded at room temperature on a Bruker VERTEX 70 instrument (4 cm⁻¹ resolution, 32 scans, DLATGS MIR) equipped with a Pike GladiATR plate (diamond crystal) for attenuated total reflectance (ATR).

3 | RESULTS AND DISCUSSION

Ring-opening copolymerization (ROCP) of HBL and LLA monomers with *t*-BuP₄ as a catalyst was first conducted at 25°C. As already reported,⁵² there is no need to add an initiator for HBL/ ϵ -caprolactone copolymerization in the presence of *t*-BuP₄ as it was shown that HBL could act as an initiator. Therefore, in this study, HBL was used as an inimer (initiator-monomer) for its copolymerization with LLA.

TABLE 1 LLA/HBL ROCP with *t*-BuP₄ as catalyst at various temperatures (LLA/HBL/C = 154/46/1; [LLA + HBL] = 1.5 M; THF; $t = 7$ h).

Run	Temperature (°C)	Conversion ^a		HBL incorporation (mol%) ^a	$\overline{M}_{n\text{SEC}}$ (g/mol) ^b	\overline{D}^b
		LLA (mol%)	HBL (mol%)			
1	5	99	81	20	1400	3.1
2	25	98	82	20	1200	3.3
3	50	98	82	20	950	2.6
4	80	95	74	19	750	2.1
5	100	95	81	20	730	2.2

^aCalculated from ¹H NMR of the crude product.

^bObtained from SEC analysis in THF with polystyrene standards.

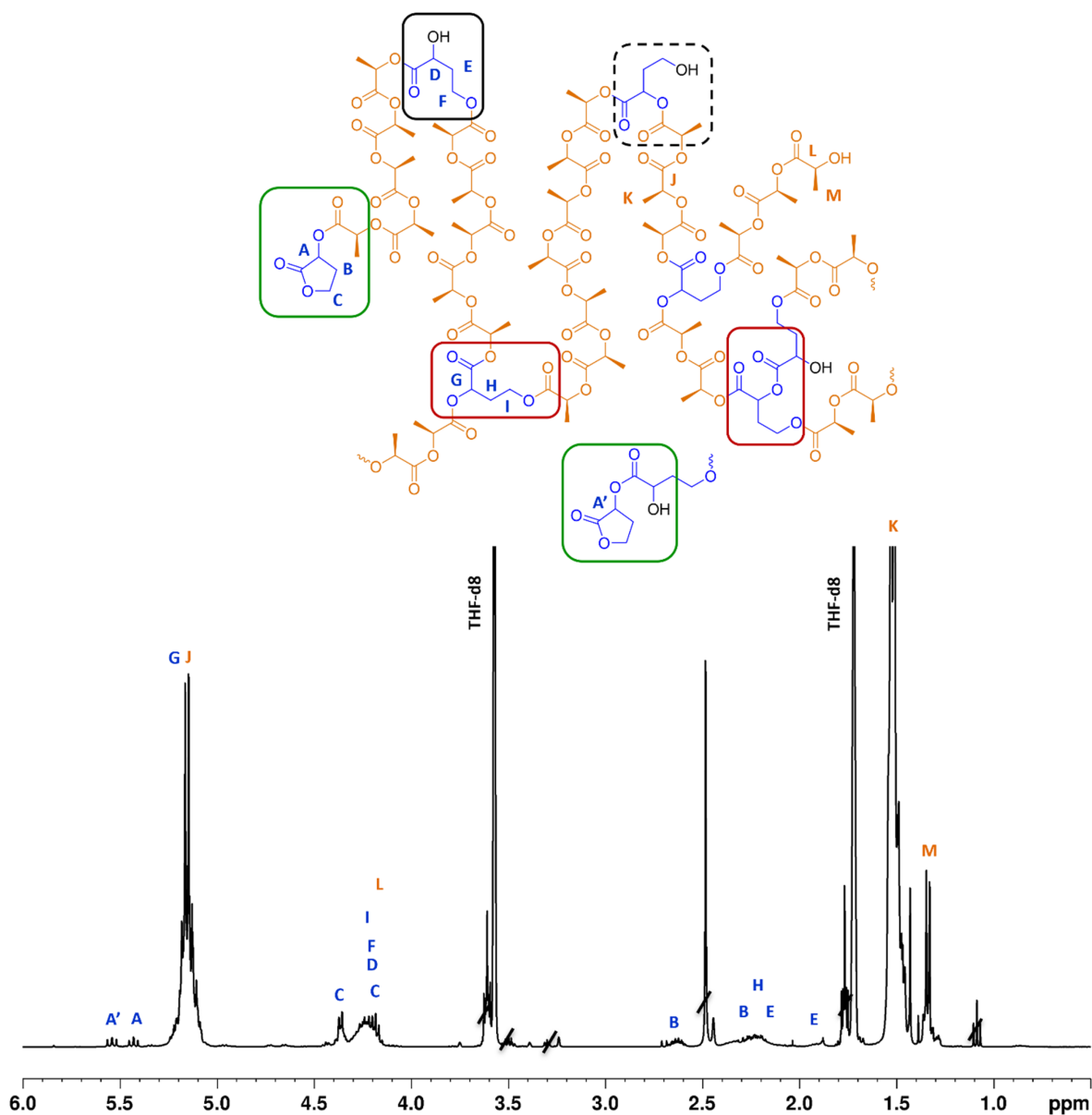


FIGURE 1 ^1H NMR spectrum of the LLA/HBL-based copolyesters in THF- d_8 (Table 1, run 2).

SEC measurements showed the formation of a mixture of oligomeric and polymeric chains with average molar masses $\overline{M}_n = 1200$ g/mol and a dispersity of $D = 3.3$. The precise structural characterization of the so-formed copolymer was investigated by NMR (Figure 1 and Figures S1–S6). Both LLA and HBL repeating units were identified in the copolymer. LLA units are represented in orange and the HBL units in blue. High monomer conversions were achieved, 98% for LLA and 82% for HBL. In comparison to a previous study,⁵² a similar structure with various HBL patterns was identified through NMR analysis: cyclic (green rectangle), linear (black rectangle), and branched (red rectangle). Thus, a comparable polymerization mechanism is supposed to occur in the ROCP of HBL and LLA (Scheme S1).

In addition, two distinct peaks associated with the cyclic HBL at the chain end were identified at 5.55 (proton A') and 5.45 (proton A)

ppm. As depicted in Figure S6, both peaks exhibit comparable intensities when the reaction is performed using an LLA/HBL monomer feed ratio of 77/23. Decreasing the LLA/HBL ratio to 50/50 resulted in an increase in proton A' intensity as compared to the proton A. It is assumed that the self-initiation of HBL and the initiation of LLA by HBL can be attributed to proton A' and to proton A, respectively.

The reactivity of the monomers was then evaluated as a function of temperature. Copolymerization reactions were conducted over a wide temperature range, ranging from 5 to 100°C, while keeping other parameters constant (Table 1).

Similar monomer conversions were achieved for both LLA ($\geq 95\%$) and HBL ($\approx 80\%$) at all tested temperatures. The HBL incorporation remains constant as well around 20%. However, a decrease in the molar masses from 1400 to 730 g/mol and a decrease in the

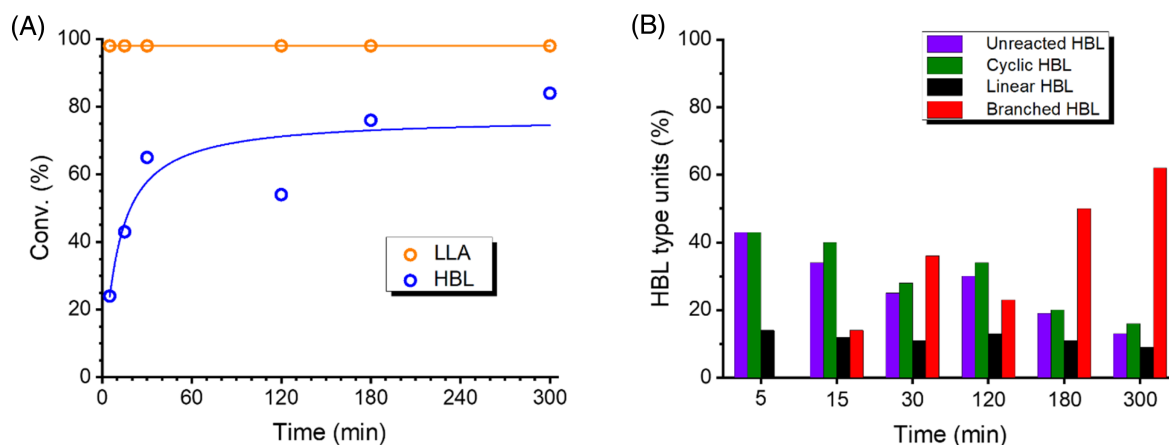


FIGURE 2 Kinetic study of the LLA/HBL ROCP at 25°C. (A) Monomer conversions over time. (B) HBL type units over time. LLA/HBL/C = 154/46/1; [LLA + HBL] = 1.5 M; THF; $T = 25^{\circ}\text{C}$.

dispersities from 3.1 to 2.2 are observed with increasing temperature. To explain this feature, the ratio of the different HBL patterns was evaluated as a function of the temperature (Figure S7). As the temperature increases, a decrease in branched HBL units from $\approx 62\%$ to $\approx 52\%$ and an increase in cyclic ones from $\approx 17\%$ to $\approx 27\%$ are observed, thus explaining the decrease in molar masses. HBL depolymerization cannot be excluded as it was observed in a previous study.⁵²

For a deeper understanding of the copolymerization mechanism, the monomers conversion and HBL structural patterns were monitored over time using the following experimental parameters: $T = 25^{\circ}\text{C}$; 1.5 M; LLA/HBL/C = 154/46/1; THF; $t = 5\text{ h}$ (Figure 2). After 5 min of reaction, LLA is almost completely converted (98%) and stays at this constant conversion rate over time (Figure 2A). Meanwhile, the HBL conversion shows a slower rate, increasing from 24% at 5 min to 84% after 5 h of reaction. The molar masses and dispersities remain constant over time, with $\overline{M}_n \approx 1100\text{ g/mol}$ and $\mathcal{D} \approx 2.6$ (Figure S8 and Table S1). These results indicate that the majority of the HBL incorporation is achieved through transesterification reactions (Scheme 1A).

The evolution of the different HBL structural patterns was also studied over time (Figure 2B). During short reaction times (5 and 15 min), HBL mainly acted as an initiator, yielding high amount of cyclic HBL units ($\approx 42\%$). After 30 min of reaction, branched and linear units became predominant representing 36% and 11%, respectively. These results indicate that after the initiation step, HBL is converted and incorporated into the copolymer. Furthermore, a decrease of the cyclic HBL units from 43% to 16% and a corresponding increase of the branched HBL units from 14% to 62% were observed over time. With longer polymerization times, the HBL cycles at the chain end underwent ring-opening, leading to the formation of branching points (Scheme 1B).

MALDI-TOF mass spectrometry analysis of a copolymer sample revealed that HBL initiated three distinct populations (Figure S9). The first population was attributed to a PLLA chain, while the second

population consisted of PLLA with half units of LLA and one unit of HBL. The third population was identified as a PLLA containing half units of LLA and two units of HBL. The presence of half units of LLA evidenced by the MALDI-TOF analysis confirms the occurrence of transesterification reactions. These results also testify the good incorporation of HBL into the copolymer.

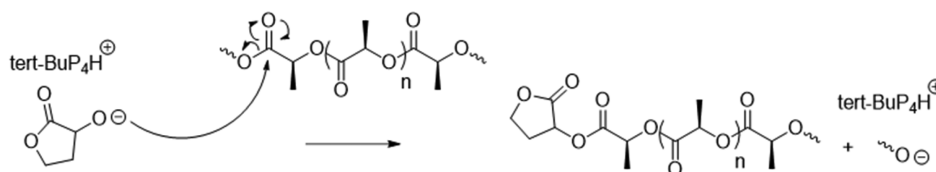
In a second step, a kinetic study was conducted with a higher monomer concentration of 6 M while keeping other parameters constant (Table S2 and Figure S10). To solubilize the monomers, the temperature was elevated to 80°C . Under these reaction conditions, LLA and HBL were both almost completely converted with 95% and 89%, respectively, within 5 min of reaction. The conversions, as well as the molar masses and the different structural patterns of HBL, remained constant for 7 h.

Furthermore, the influence of monomer feed and M/C ratios on the copolymer synthesis was also investigated at a high monomer concentration (6 M) and elevated temperature (80°C) (Table S3). Performing the polymerization from a 50/50 monomer feed ratio led to a decrease in HBL conversion to 47% and an increase in HBL cyclic patterns to 42% (Table S3, run 2). This suggests that a higher amount of HBL in the monomer feed leads to more chains initiation, resulting in decreased molar masses from 1100 to 700 g/mol. A decrease in the degree of branching from 0.24 to 0.16 is also observed due to the decrease in branched HBL units from 76% to 30%. However, the incorporation of HBL into the copolymer increased to 33%.

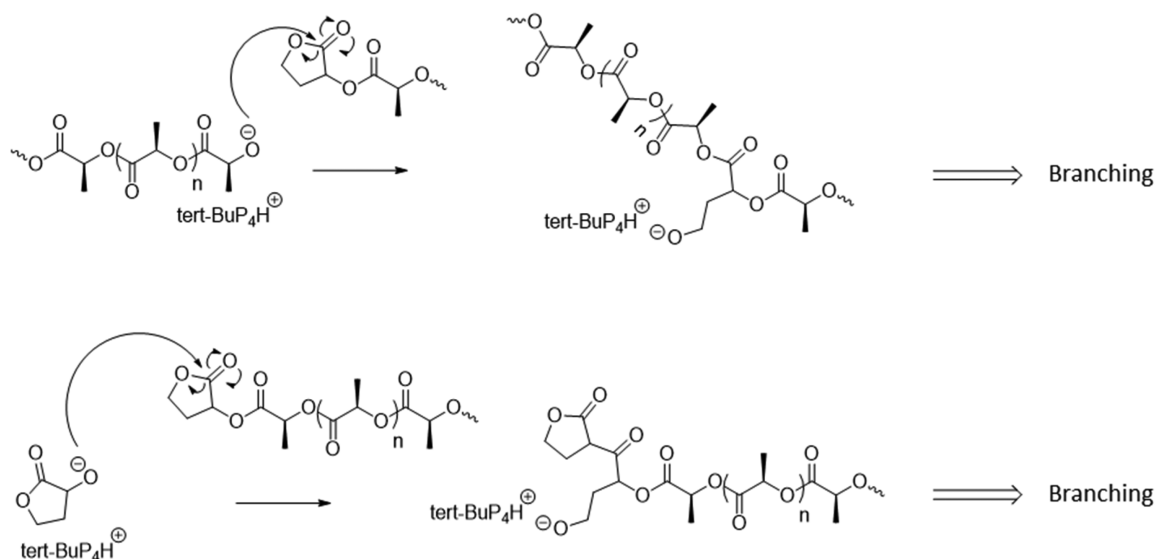
As low molar masses were obtained in all copolymerizations, a higher M/C ratio of 400/1 was employed for the reaction (Table S3, run 3). Like the previous reaction, a decrease in HBL conversion (36%) and molar masses ($\overline{M}_n = 980\text{ g/mol}$) was observed. Due to the high concentration of HBL in the medium, the monomer primarily acts as an initiator with 76% of cyclic HBL units, thereby preventing an increase in molar masses.

The thermal properties of the copolyesters were investigated using differential scanning calorimetry (DSC) analysis on two copolymer samples containing 20% and 33% of HBL units (Figure S11).

(A) Transesterification



(B) Reaction of the chain ends



SCHEME 1 Possible reactions for the LLA/HBL ROCP. (A) Transesterification reaction. (B) Reaction of the chain ends.

Increasing the HBL content in the copolymer resulted in a decrease of the glass transition temperatures from 33 to -19°C . Additionally, the literature reports the ability of PLLA to crystallize even at low molar masses, as evidenced by the presence of an endothermic melting peak observed for $\overline{M}_n = 1100\text{ g/mol}$, $\mathcal{D} = 1.08$.⁵³ Both copolymer samples exhibited a significant decrease or complete disappearance of PLLA crystallinity. The loss of crystallinity due to LLA sequences in the copolymers testifies the random structure of the so-formed copolyesters.

Despite testing various reaction conditions for the copolymerization, only copolymers with low molar masses $\overline{M}_n \approx 1000\text{ g/mol}$ were obtained. A chain-extension reaction was finally performed between the copolyesters and hexamethylene diisocyanate (HDI) to achieve high molar mass LLA/HBL-based copolymers. SEC measurements were performed on copolymer samples (Figures S12 and S13) before and after chain coupling. The chromatograms reveal a significant increase in molar masses, which raise from $\overline{M}_w = 2700\text{ g/mol}$ to $\overline{M}_w = 12,500\text{ g/mol}$ for the first sample (Figure S12). The molar masses could be increased to higher values with the second sample (Figure S13, $\overline{M}_w = 5000\text{ g/mol}$), reaching $\overline{M}_w = 290,000\text{ g/mol}$ after chain coupling but a very large dispersity was observed (Figure S13). To have a better understanding on the chain extension FTIR

monitoring was performed (Figure S14). The chain extension reaction was followed through the peak corresponding to the N–H bending and C–N stretching of the urethane group observed at 1530 cm^{-1} .⁵⁴ The urethane formation was further evidenced by the reaction of the alcohol function, leading to a decrease in O–H stretching vibrations at around 3500 cm^{-1} and an increase in N–H stretching vibrations of the urethane group at around 3390 cm^{-1} . Moreover, the complete consumption of the diisocyanate was confirmed by the disappearance of the peak 2270 cm^{-1} attributed to the $-\text{NCO}$ group. The successful coupling reaction between OH-functionalized copolyesters and isocyanates suggests that the average functionality of the copolyesters is at least equal to 2. It provides opportunities for the development of polyurethane thermosets.

4 | CONCLUSION

LLA/HBL-based copolyesters of low molar masses were successfully synthesized by ROCP using $t\text{-BuP}_4$ as the catalyst. The copolymers exhibit a branched structure with various HBL units, including cyclic, linear, and branched motives. High monomer conversions for copolymerization carried out between 5 and 100°C range ($\geq 95\%$ for LLA and

>80% for HBL) and random copolymers with molar masses around 1000 g/mol were achieved. A kinetic study demonstrated that LLA was almost completely converted at the beginning of the reaction, whereas HBL conversion showed a gradual increase over time, indicating the incorporation of most HBL into the copolymer through transesterification reactions. Analysis of the HBL patterns confirmed that, initially, most of the HBL acts as an initiator and subsequently as a monomer, leading to the formation of branched units. Using a higher monomer concentration of 6 M and a lower LLA/HBL ratio (50/50) enabled the synthesis of copolyesters with high monomer conversions (>85%) or with an HBL content of up to 33% in a short reaction time (5 min). A straightforward chain coupling between hydroxy-terminated copolyesters with a diisocyanate derivative allowed to get copolymers with much higher molar masses. Finally, the synthesis of LLA/HBL-based copolyesters with pendant hydroxyl groups paves the way for post-modification reactions or for tuning the hydrophilicity/degradability of PLLA-based materials.

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CONFLICT OF INTEREST STATEMENT

There are 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.

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