A simple and general approach for the synthesis of biodegradable triblock copolymers by organocatalytic ROP from poly(lactide) macroinitiators

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Abstract

To overcome the present limitations in the synthesis of biodegradable triblock copolymers with PLA as central building block, three different reactional mechanisms (coordination-insertion, anionic and cationic) have been involved, while employing the transition from organometallic to organic catalysis. Even though activated chain-end mechanism with stannous octanoate is well known for the successful ROP catalytic reactivity, the synthesis of PLA based triblock copolymers according to this route revealed not negligible transesterification reactions. In the same way, the activated chain-end mechanism through nucleophilic activation (TBD) presented either no reactivity or weak control over the anionic polymerization process. Herein, we therefore propose an activated monomer mechanism as general and simple route for obtaining controlled PTMC-b-PDLLA-b-PTMC and PCL-b-PDLLA-b-PCL triblock copolymers by using cationic organocatalysis (MSA). 1H, 13C-NMR and DOSY-NMR spectra confirmed the well-controlled polymer architecture of the B-A-B triblock copolymer.

Keywords	Biodegradable block copolymers; organocatalysis; poly(caprolactone); poly(lactide); poly(trimethylene carbonate); block PLA first route.
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To the Editors-in-Chief
Of *European Polymer Journal*.

December 19th, 2019

Manuscript submission

Dear Prof. R. Hoogenboom,

We have the pleasure to submit our manuscript entitled:

"A simple and general approach for the synthesis of biodegradable triblock copolymers by organocatalytic ROP from poly(lactide) macroinitiators" by Nikola Toshikj, Jean-Jacques Robin and Sebastien Blanquer.

Biodegradable polyesters and polycarbonates are the most renowned biodegradable polymer and are synthesized by ring opening polymerization. However, reproducible and efficient catalytic approaches to synthesize biodegradable triblock copolymers with PLA first route is considering as a high challenge. To date, no study succeeded to synthesize biodegradable triblock copolymers with PLA macroinitiators using an organocatalytic pathway.

In this study we describe different catalytic approaches to achieve the most appropriate mechanism for yielding well-defined biodegradable triblock copolymers starting from PDLLA macroinitiator: PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL. Complete monomer conversion has been reached for both investigated triblock structures without observing transesterification.

We explain that an activated monomer mechanism using cationic activation was the most effective approach for leading to a controlled block copolymerization using PDLLA blocks as macroinitiators. The block copolymerization by cationic ring opening polymerization has been demonstrated *via* step and sequential copolymerizations.

We believe this work is an important contribution to the field of biodegradable polymer synthesis and will be of great interest to the readers of your journal: *European Polymer Journal*.

All authors have been listed on the manuscript and have agreed to the content of the paper.

Sincerely,

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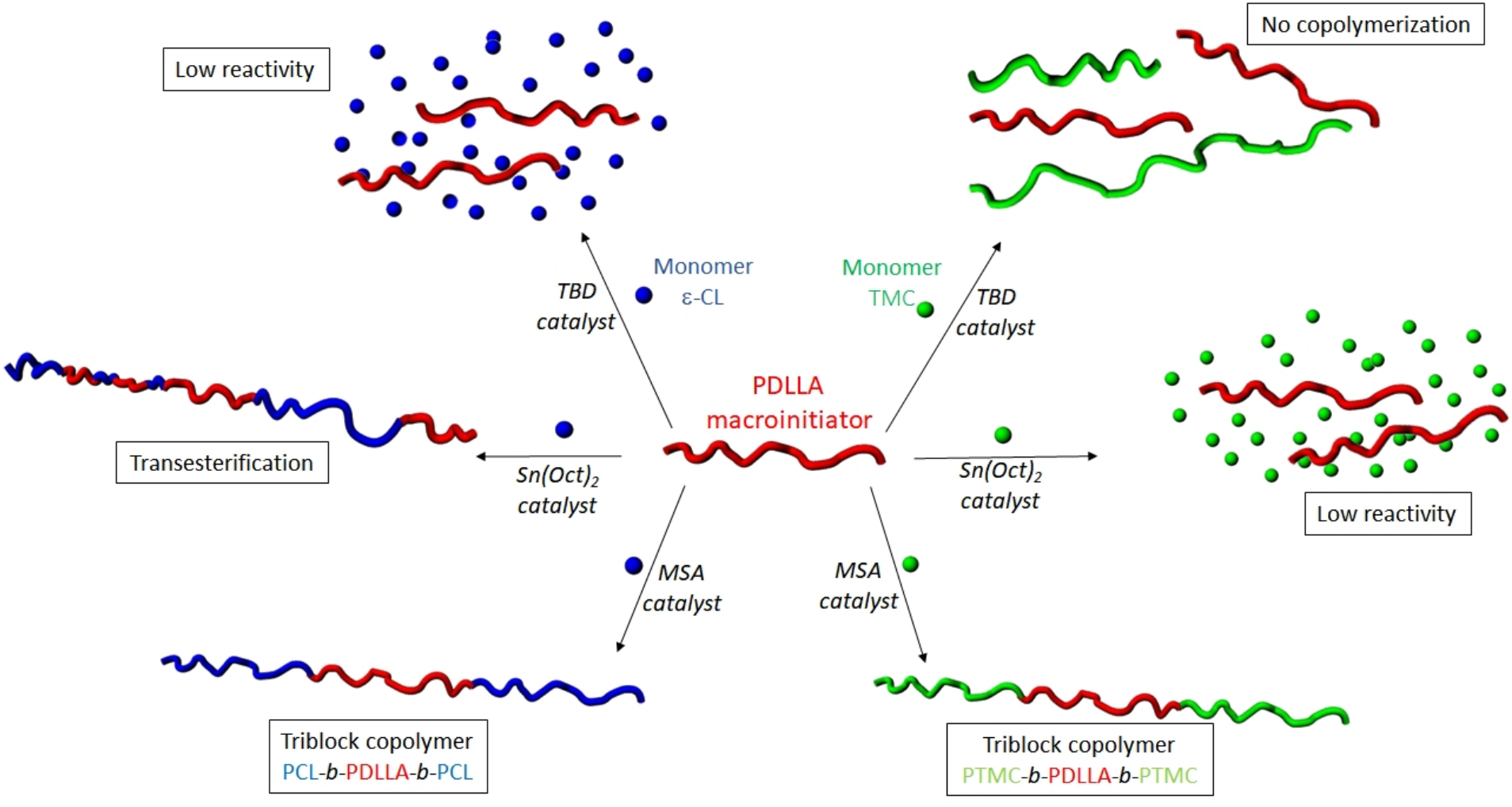
Highlights

- Synthesis of biodegradable PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL triblock copolymers by ring opening polymerization.
- General approach for biodegradable triblock copolymer synthesis with PDLLA first route with no side reactions.
- Study of the catalytic influence on the block copolymerization when PDLLA is employed as macroinitiator.
- Effective triblock copolymerization is obtained using cationic activated monomer mechanism.
- One pot sequential copolymerization is achieved *via* traceless switch organocatalysis approach.


Low reactivity
No copolymerization
Monomer
ε-CL
Monomer
TMC
TBD
catalyst
TBD
catalyst
PDLLA
macroinitiator
Transesterification
Sn(Oct)2
catalyst
Sn(Oct)2
catalyst
Low reactivity
MSA
catalyst
MSA
catalyst
Triblock copolymer
PCL-b-PDLLA-b-PCL
Triblock copolymer
PTMC-b-PDLLA-b-PTMC

A simple and general approach for the synthesis of biodegradable triblock copolymers by organocatalytic ROP from poly(lactide) macroinitiators

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Keywords

Biodegradable block copolymers; organocatalysis; poly(caprolactone); poly(lactide); poly(trimethylene carbonate); block PLA first route.

Abstract

To overcome the present limitations in the synthesis of biodegradable triblock copolymers with PLA as central building block, three different reactional mechanisms (coordination-insertion, anionic and cationic) have been involved, while employing the transition from organometallic to organic catalysis. Even though activated chain-end mechanism with stannous octanoate is well known for the successful ROP catalytic reactivity, the synthesis of PLA based triblock copolymers according to this route revealed not negligible transesterification reactions. In the same way, the activated chain-end mechanism through nucleophilic activation (TBD) presented either no reactivity or weak control over the anionic polymerization process. Herein, we therefore propose an activated monomer mechanism as general and simple route for obtaining controlled PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL triblock copolymers by using cationic organocatalysis (MSA). ^{1}H, ^{13}C-NMR and DOSY-NMR spectra confirmed the well-controlled polymer architecture of the B-A-B triblock copolymer.

1.Introduction

Biodegradable polymers are knowing growing interest, especially due to the eco-friendly concerns but also for the huge potential in biomedical applications. Consequently, in the past couple of years, degradable aliphatic polyesters and polycarbonates have gained noticeable attention and are becoming the gold standard of biodegradable synthetic materials. More particularly, poly(lactide)s (PLA) have received the highest interest due to their tuneable degradability, high mechanical strength and rigidity. Poly(caprolactone)s (PCL) polyesters have also been used for their elastic properties and likewise show remarkable drug permeability. Finally, amorphous poly(trimethylene carbonate) (PTMC) presents high flexibility and controlled bioresorption through surface erosion and is largely used for biomedical applications such as soft tissue engineering. All these polymers can be synthesized by ring opening polymerization of the corresponding cyclic monomers: lactide (LA), epsilon-caprolactone (ε-CL) and trimethylene carbonate (TMC) respectively. Block copolymerizations of their respective monomers have also been widely investigated in the goal to easily adjust the properties of the resulting copolymers. Those can generate microphase separation, essentially by controlling the composition and microstructure of the copolymers. In that context, copolymers based on PLA (with different D and L-lactide enantiomers rates), PCL and PTMC generating A-B diblocks and A-B-A triblocks are the most current block copolymers encountered in the literature [1-3]. The development of such block copolymers has resulted in new biomaterials with combination of soft and hard blocks and has therefore significantly influenced their degradability kinetics, the elasticity and the physico-chemical behaviour. The most current polymerization routes in ROP are cationic, anionic and coordination-insertion where the control of the molecular weight and dispersity greatly depends on the monomer/catalyst couple. However, it has to be noticed that the reactivity of the various monomers over specific catalytic systems are generally different making sometimes difficult to synthesize the copolymers in one pot. The choice of the catalyst, the type of macroinitiator depending on the first synthesized block and the feeding order of monomers for sequential block copolymerization are crucial parameters to claim for a controlled and effective copolymerization.

A wide variety of organometallic catalysts have been used for the synthesis of biodegradable copolymers [4-6]. However, elevated temperature is usually necessary for the polymerization, which considerably

increases the risk of transesterification [7]. Furthermore, the presence of metal in the final polymer is nowadays more and more banned, principally for environmental and biomedical applications. Hence, organocatalysis gained a growing interest in ring opening copolymerization. Curiously, the synthesis of biodegradable block copolymer while using an organocatalyst is poorly reported [8, 9]. One of the reasons of this lack can be explained by the divergent reactivity of monomers according to the catalytic mechanism employed, notably in the case of electrophilic or nucleophilic activations [10, 11]. To overcome this orthogonal activation, Wang *et al.* have recently developed the "traceless switching organocatalysis" [10], which was the first efficient approach to generate biodegradable multiblock copolymers with organocatalysis. The principle is based on the use of two orthogonal catalytic systems by switching the initial electrophilic activation of the first block synthesis by using nucleophilic catalyst to initiate the second one.

Table 1. List of the reported attempts to synthesize block copolymer with PLA macroinitiator.

Block copolymer type	**Activation process**	**Active reagents (catalyst or initiator)**	**Effect on block copolymerization**	**References**
PLLA-PDTC	Initiation	$Al(O\text{-}sec\text{-}Bu)_3$ $Zn(Et)_2$ $Bu_2Sn(OMe)_2$	Presence of transesterification	[12]
PDLLA/PCL	Initiation	Potassium poly(ethylene glycol)ate macroinitiator	No reaction	[13]
PLLA/PCL PDLLA/PCL	Catalysis	$Al(OiPr)_3$	Presence of transesterification	[14]
PLLA/PCL	Catalysis	$Al(OiPr)_3$	Presence of transesterification	[15]
PLLA/PCL	Catalysis	$K[(N(SiMe)_3]_3$	No reaction	[16]
PLLA/PCL	Catalysis	$SnOct_2$	Presence of transesterification	[17]
PDLA/PTMC PLLA/PTMC	Initiation	$Al(OiPr)_3$ + Schiff base ligand	Block copolymerization without transesterification	[18]
PLLA/PCL	Initiation	$Al(OiPr)_3$ + Schiff base ligand	Block copolymerization without transesterification	[19]
PLLA/PTMC PLLA/PCL	Catalysis + protective additive	SnOct2 + α-Methyl styrene	Block copolymerization without transesterification	[20]

PLLA/PCL	Initiation	Dimethyl(salicylaldiminato) aluminum	Block copolymerization without transesterification	[21]
PLLA/PCL PDLLA/PCL	Initiation	$Ti(OiPr)_2$ supported by aminodiol ligand	Block copolymerization without transesterification	[22]

Biodegradable block copolymerization through PLA macroinitiator faces serious limitations that have often been highlighted in the literature. Indeed, biodegradable copolymers with PLA first route are barely reported in opposition to PLA last route [13, 14]. Table 1 reports various attempts of block copolymerization using PLA first route and subsequently used as macroinitiator for copolymerization of the second monomer. From the Table 1, it is apparent that most of the attempts using traditional organometallic catalyst routes showed remarkably low reactivity or else generated significant transesterification. Till now, the only successful way of copolymerizing with PLA macroinitiator has been achieved by either using specific additives or modifying the metal complex by bulky ligands, which then act as initiator and therefore present a serious limitation for the generation of triblock copolymers [23]. Therefore, universal and controlled catalytic route to synthesize biodegradable block copolymer B-A-B from PLA macroinitiator as central block remains a considerable challenge, especially by using an organocatalytic strategy. Although, block copolymerization with PLA macroinitiator would allow to generate new type of biodegradable multiblocks that might be interesting to create new materials with rigid blocks surrounded by soft blocks which would display specific phase separation behaviour and interesting properties.

Consequently, in this article, we propose to investigate different catalytic systems from coordination-insertion, anionic and cationic mechanisms to synthesize biodegradable block copolymer B-A-B from PDLLA macroinitiator. Hence, bishydroxy terminated PDLLA are first prepared and then used as macroinitiator for the copolymerization of PCL and PTMC *via* step and sequential copolymerization to lead to PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL copolymers (Figure 1). The three classical mechanisms of ring opening polymerization have been investigated to generate these block copolymers: i/ coordination insertion has been tested using stannous octanoate, ii/ nucleophilic

activation with guanidine molecules such as TBD, iii/ electrophilic activation with methyl sulfonic acid catalyst.

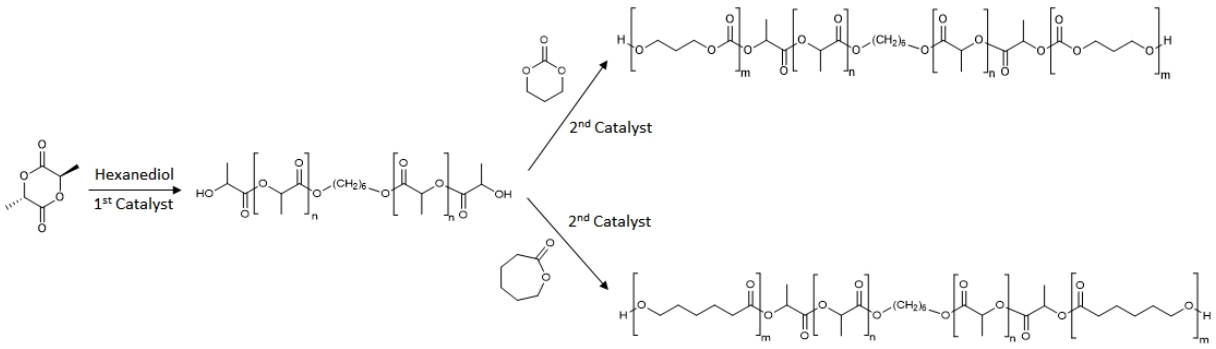

Figure 1. Synthesis of triblock PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL *via* PDLLA first route.

2.Materials and Methods

2.1 Materials

The monomers, DL-LA was purchased from Corbion (The Netherlands), ε-CL (99 %) was obtained from Santa Cruz Biotechnologies (Germany), while TMC was obtained from Foryou Medical (China). The initiator (1,6 hexane diol, 99 %) and the catalysts (MSA, TBD, $Sn(Oct)_2$) were purchased from Sigma-Aldrich (France) and used as received. Anhydrous dichloromethane was retrieved from solvent purificator Inert PureSolv™ (USA) and anhydrous toluene (99.8 %) was purchased from Sigma Aldrich (France) were used as polymerization solvents.

2.2 Synthetic procedures

All the syntheses were performed in two-necked round bottom flasks (100 ml), previously dried in an oven at 130°C, and equipped with a magnetic stirrer and a thermometer.

2.2.1 General procedure of homopolymerization of DL-LA.

DL-lactide (DL-LA) (1,05 g, 14,5 mmol, 100 eq) was solubilized in dichloromethane (DCM) (10,5 ml, $[DL\text{-}LA]_0$ = 0.7 mol/L). The initiator 1,6 hexane-diol (8,61 mg, 0,073 mmol, 1 eq) and the catalyst, 1,5,7-triazabicyclo [4.4.0] dec-5-ene (TBD) (1,42 mg, 0,051 mmol, 1.4 eq) were then added into the solution. The reaction mixture was stirred for 2 minutes at room temperature until the complete conversion of DL-LA, determined by ^{1}H-NMR. Afterwards the catalyst was neutralized by an excess of acetic acid and the reaction mixture was concentrated under vacuum. The polymer was then precipitated in cold methanol and dried in vacuum oven for 24 hours. Conversion rate was >98 % and yield reaction around 95 %.

2.2.2 General procedure for PTMC-b-PDLLA-b-PTMC and PCL-b-PDLLA-b-PCL triblock copolymers syntheses by step copolymerization using PDLLA macroinitiator.

Previously synthesized PDLLA macroinitiator (1,05 g, 0,138 mmol, 1 eq) was introduced in a flask; with TMC monomer (1,43 g, 13,8 mmol, 100 eq) or ε-CL (1,57 g, 13,8 mmol, 100 eq). The quantity of monomer and macroinitiator used were based on the desired proportions between the blocks and was fixed for this study at 50-100-50. Some cycles of vacuum and dry argon were performed before injecting the anhydrous solvent ($[TMC/\varepsilon\text{-}CL]_0$=1 mol/L). The reactions with MSA (0,026 g, 0,276 mmol, 2 eq) or TBD (0,0162 g, 0,1932 mmol, 1,4 eq) as catalyst were performed in anhydrous dichloromethane at room temperature while for stannous octoate ($Sn(Oct)_2$) (0,1 wt. % to initiator) as catalyst the used solvent was anhydrous toluene with reaction temperature of 100°C. After full reaction, an excess amount of triethylamine (3 eq in respect to catalyst) was added when using MSA, in order to neutralize this one. Likewise, when using TBD as catalyst, an excess amount of acetic acid (3 eq to TBD) was used in order to neutralize it. Finally, the polymers were slowly poured in cold methanol, the precipitated polymers were filtered and washed several times in the same solvent and dried in vacuum oven for 24 hours.

2.2.3 General procedure of sequential one-pot synthesis of PTMC-b-PDLLA-b-PTMC and PCL-b-PDLLA-b-PCL triblock copolymers.

Following the procedure for the synthesis of PDLLA homopolymer reported above, once the conversion of the previous reaches >99 % after 2 min of reaction, MSA (2.5 eq to TBD) was firstly added in the

reaction mixture in order to quench the TBD catalyst and then TMC or ε-CL monomer was added to carry on the second polymerization step. The reactions were performed at room temperature for 17 h for the synthesis of PTMC-*b*-PDLLA-*b*-PTMC triblock copolymer and 6h for the synthesis of PCL-*b*-PDLLA-*b*-PCL triblock copolymer. After complete conversion of the monomers, the MSA was quenched with an excess of trimethylamine (3 eq to MSA). Finally, the polymers were slowly poured in cold methanol, filtered and then washed several times in the same solvent and at last, dried in an oven in vacuum for 24 hours.

2.3 Instruments

Size exclusion chromatograms were recorded using a triple detection (GPC Varian 390-LC viscometer detector, Varian 390-LC refractive index detector and UV detector (at 254 nm)) from Agilent Technologies. The analyses were performed in tetrahydrofuran (THF) at a flow rate of 1.0 mL/min at 30 °C. An Agilent PLgel 5 µm guard column and two columns 5 µm PLgel Mixed D were used. Data acquisition and calculations were performed using Cirrus Multi GPC/SEC software. Universal calibration was performed with PS standards from Agilent Technologies (EasiVial) using the intrinsic viscosities given by the supplier.

Nuclear Magnetic Resonance Spectrometry - ^{1}H and ^{13}C NMR spectra were recorded on a 400MHz Bruker Aspect Spectrometer while DOSY spectra were recorded on a 600MHz Bruker Aspect Spectrometer. $CDCl_3$ was used as deuterated solvent. Chemical shifts were given in parts per million (ppm): for ^{1}H and DOSY NMR the reference peak was residual $CDCl_3$ at 7.26 ppm and for ^{13}C NMR at 77 ppm.

3. Results and Discussion

Synthesis of triblock copolymers with PLA as a central block remains as a challenge due to the absence of simple and universal catalytic approach for their preparation (Table 1). In addition, despite the

significant rising of studies devoted to ring opening polymerization by organocatalysis, block copolymerization has been very poorly studied with this type of catalysts. Therefore, we investigated the synthesis of biodegradable triblock copolymer B-A-B *via* PDLLA first route using coordination-insertion mechanisms with an organometallic catalyst, cationic and anionic mechanism with an organocatalyst.

To start, DL-LA, ε-CL and TMC have been firstly homopolymerized in order to control the reactivity of each monomer using the selected catalysts. Theoretical degree of polymerization was initially fixed to 100 for all the homopolymers synthesized using hexanediol as a bifunctional initiator. Monomer conversion and degree of polymerization were determined by ^{1}H-NMR (details in SI).

Table 2. Comparison of the conversion rate for the homopolymerization of the studied monomers using 1,6 hexanediol as initiator.

Catalysts	**Mechanism**	**T (°C)**	**Conversion of TMC**	**Conversion of DL-LA**	**Conversion of ε-CL**
MSA	Cationic	30 °C	100 % after 17 h	10 % after 17 h	100 % after 6 h
TBD	Anionic	25 °C	100 % after 1 h	100 % after 2 min	17 % after 24 h
$Sn(Oct)_2$	Coordination-insertion	100 °C	100 % after 24 h	100 % after 24h	100 % after 24 h

Table 2 shows the conversion rate of each monomer as a function of the polymerization mechanism. Monomer conversion has been determined by ^{1}H-NMR spectra by comparing the integrated areas of characteristic peaks of the monomers with those of protons from the growing polymer chains. Degree of polymerization was determined from the ratio of the peak integrals of the characteristics protons from the polymer chain with the peak integrals of the characteristic protons from the last unit of the polymer chain or with the characteristic integral peak from the hexanediol initiator. Homopolymerization of each monomer resulted in bishydroxy-terminated homopolymers but the reactivity was not identical since total conversion were note reached in similar times. Indeed, the polymerization of PDLLA *via* cationic mechanism using MSA catalyst was relatively low with 10 % of conversion after 17 h (Figure S1).

Nucleophilic activation with TBD at room temperature was faster for homopolymerization of DL-LA than for TMC (Figure S2). In the case of ε-CL, homopolymerization reached a plateau at 17 % of conversion after 6 h of reaction (Figure S3). In contrast, $Sn(Oct)_2$ successfully resulted in bishydroxy-terminated homopolymer, with a conversion rate similar for all the monomers. It has to be noted that according our experimental conditions, no transesterification has been detected for all the studied catalysts.

In order to explore the possibility to generate block copolymers with various activation mechanisms, step copolymerization was performed. This approach consisted in polymerization and purification of the first block by precipitation and elimination of residual reactive species such as initial catalyst. As previously presented, nucleophilic activation was the most efficient way to homopolymerize DL-LA and was consequently used to synthesize the first PDLLA block with terminal OH groups. This initial bis-hydroxyl PDLLA block was used to start the copolymerization of the second blocks. The synthesis of triblock PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL copolymers was therefore obtained in solution by using the three studied catalysts. Conversion rate of the second blocks was measured by ^{1}H-NMR (Figure 2A). In addition, molar fraction of each block was evaluated by ^{1}H-NMR from the ratio of characteristic proton peak integrals for each polymer chain (Figure S4). For all the copolymers PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL, the targeted ratio was fixed at 50-100-50.

$Sn(Oct)_2$ catalyst has been already investigated for diblock copolymer PLLA-*b*-PCL with PLLA first route and lead to transesterification (Table 1). Bero and Kaspercky demonstrated the strong analytical potential of ^{13}C-NMR spectroscopy to determine chain microstructure irregularities that can be due to random transesterification on the same diblock copolymer [24, 25]. Later, this study has been widely used as reference to demonstrate the presence of transesterification for any type of block copolymers based on poly(lactide) [19, 20, 22]. In full awareness of such risk, we investigated the coordination/insertion approach to synthesize the triblock copolymers with PDLLA first route. A full conversion after 24 h have been found for the triblock PCL-*b*-PDLLA-*b*-PCL and monomer sequencing in the triblock was characterized by ^{13}C-NMR. Figure 2C shows the carbon spectra of the triblock, and the expanded carbonyl carbon region from 169-174 ppm. Carbonyl peaks from PDLLA is characterized

by a sharp multiplet at 169.5 ppm due to the stereochemistry from the sequential units of L and D lactide. However, the presence of various peaks in between the carbonyl peaks of PDLLA block at 169.5 ppm and the carbonyl peaks of PCL block at 173.5 ppm are also clearly visible and confirm the random monomer sequencing (triads assigned in figure 2C), and therefore demonstrate the presence of significant transesterification.

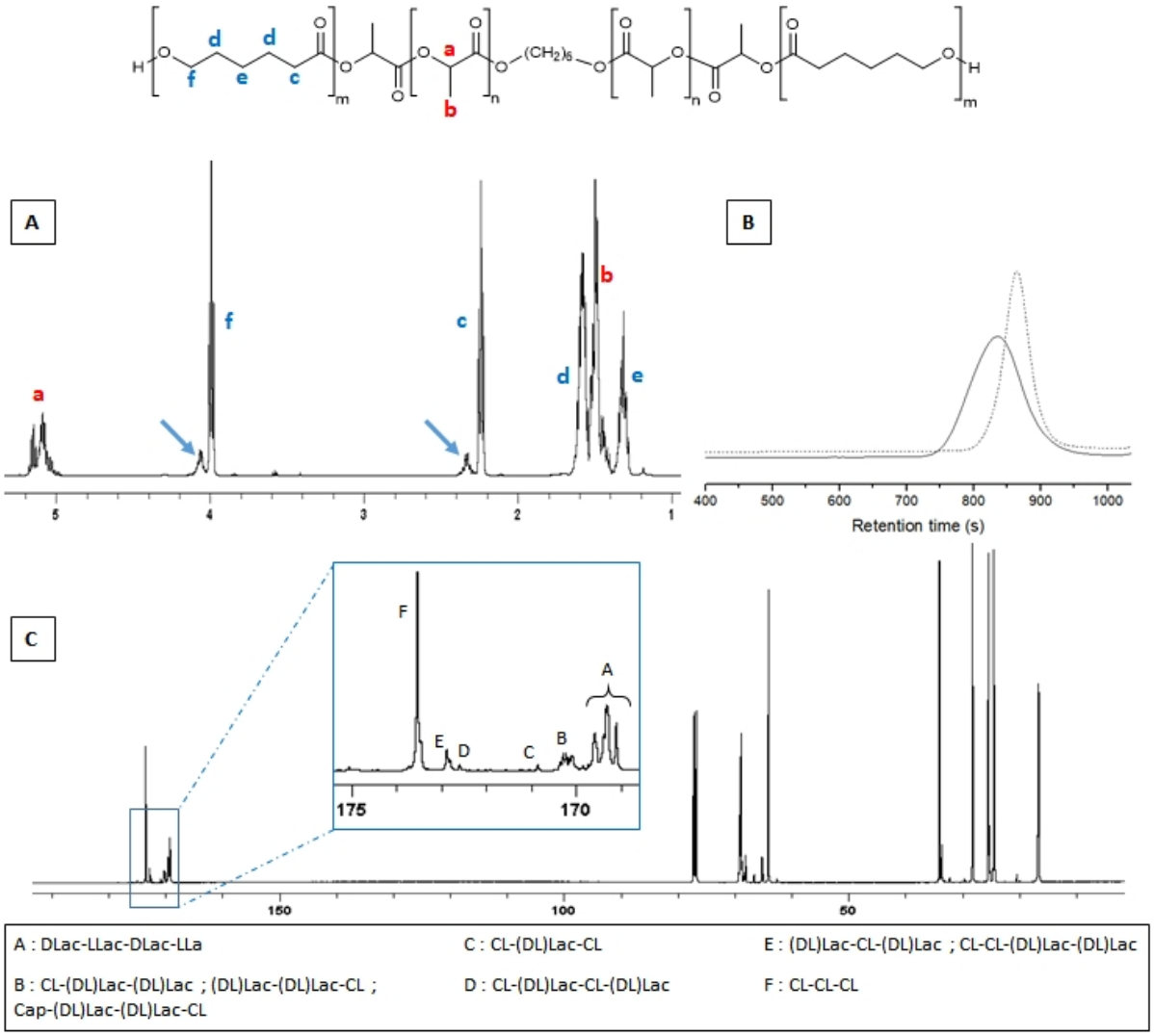

Figure 2. NMR analyses of the copolymer PCL-PDLLA-PCL formed upon $Sn(Oct)_2$ catalysis. A/ ^1H-NMR spectrum in $CDCl_3$ of the copolymer with the assigned signals. The arrows represent the characteristic peaks of random sequence of copolymer coming from the transesterification, B/ SEC chromatograms of the initial homopolymer PDLLA (dots) and the PCL-PDLLA-PCL copolymer (solid

line), C/ ^{13}C-NMR spectrum in $CDCl_3$ of the copolymer with expanded carbonyl region. Peak assignments are listed below the graph.

In addition, ^{1}H NMR spectrum also allows to determine the presence of transesterification by the apparition of characteristic peaks at 2.4 ppm and 4.15 ppm (represented by the blue arrows in the Figure 2A). Consequently, ε-CL monomers was incorporated within the PDLLA chain by transesterification during the reaction of copolymerization. Such transesterification influenced also the chromatogram where the detected copolymer showed a wide signal with dispersity of 2.3 (Figure 2B). In parallel, synthesis of triblock PTMC-*b*-PDLLA-*b*-PTMC by $Sn(Oct)_2$ showed extremely low reactivity compared to the homopolymerization of TMC, with conversion rate that reached only 33 % after 72 h of reaction (Figure 3A). By contrast, TMC was nicely homopolymerized by anionic mechanism with TBD and the attempt to synthesize PTMC-*b*-PDLLA-*b*-PTMC showed also the same reactivity with a total conversion after 1 h of reaction. However, DOSY NMR analyses showed different diffusion coefficients between the PTMC homopolymer and the synthesized copolymer which thus means a mixture of PDLLA and PTMC homopolymers (Figure 3B). Furthermore, diffusion coefficient of the initial PDLLA was exactly similar to that of PDLLA block after copolymerization which therefore confirms that PDLLA did not act as initiator. To corroborate this result, SEC analysis of the synthesized block copolymer PTMC-*b*-PDLLA-*b*-PTMC was performed (Figure 3C and Table 3). From the SEC, it was expected to detect chain extension approximately double that of initial PDLLA block size. However, the chromatogram from the copolymer shows a wide Gaussian curve leading to huge dispersity calculated around 11.9 while the initial PDLLA was around 1.24 (Table 3). In addition, calculated Mp was around 44000 g.mol^{-1} instead of 17400 g.mol^{-1} for the expected copolymer which probably means homopolymerization of PTMC. In summary, it was not possible to synthesize PTMC-*b*-PDLLA-*b*-PTMC triblock copolymer *via* anionic mechanism.

As previously mentioned for the homopolymerization of ε-CL with anionic organocatalysis using TBD, the copolymerization of ε-CL using PDLLA macroinitiator shows a total absence of reaction after 72 h where the monomer ε-CL is still present as observed by ^{1}H-NMR where no characteristic peaks from

PCL appeared. As a result, no PCL-*b*-PDLLA-*b*-PCL triblock could be obtained from anionic catalysis (Figure S5).

Finally, step copolymerization was also studied using cationic catalysis with MSA. For both synthesized PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL triblocks, complete conversion was reached after 17 h and 6 h, respectively. ^{13}C-NMR spectroscopy was used to determine the sequential distribution of copolymers. Surprisingly, carbon spectrum of PCL-*b*-PDLLA-*b*-PCL in the carbonyl region did not show the presence of triad peaks that would have come from the transesterification (Figure 4).

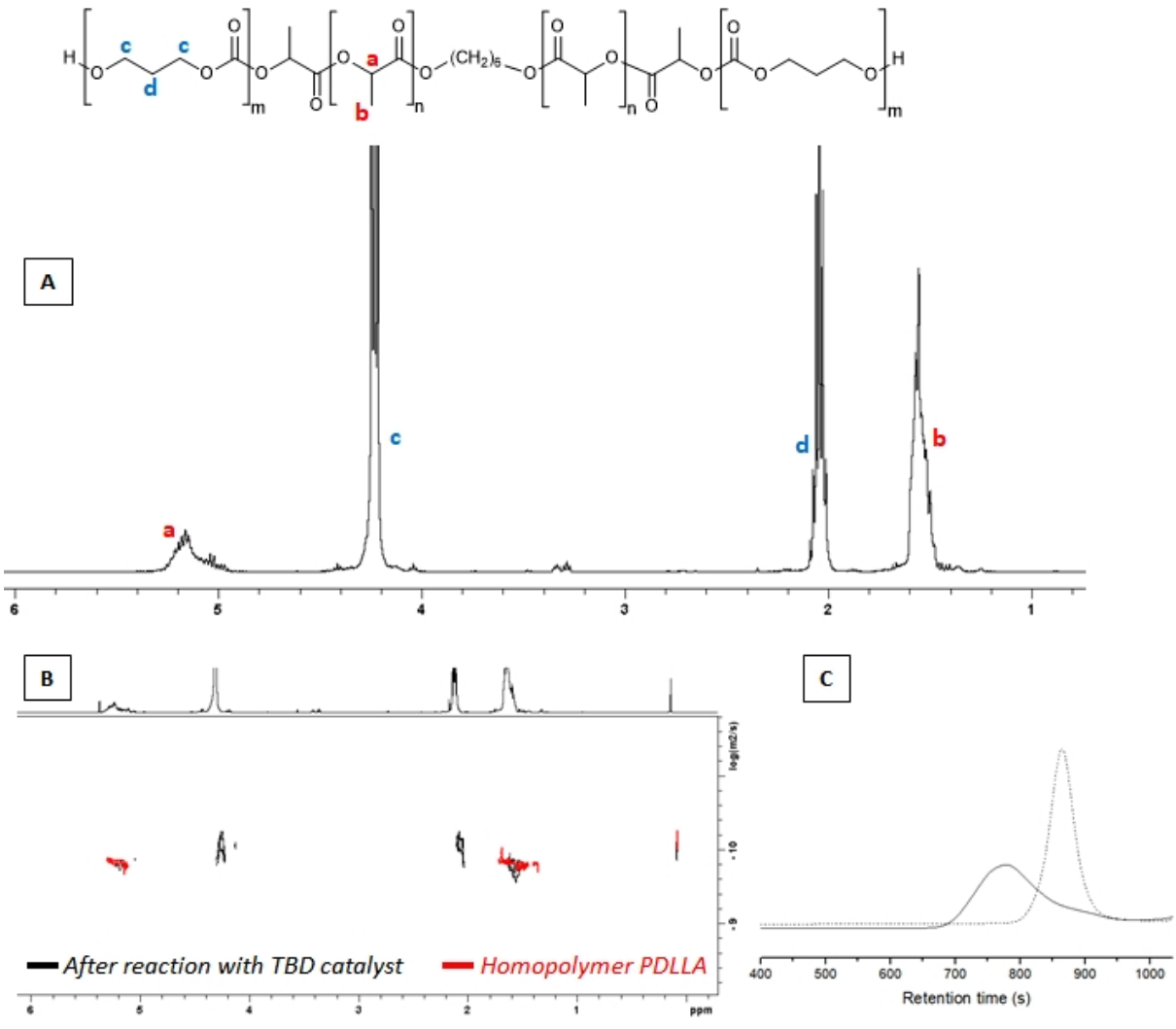

Figure 3. Spectroscopy analyses after copolymerization of TMC using PDLLA macroinitiator through anionic activation with TBD. A/ ^{1}H NMR spectrum in $CDCl_3$ of the copolymer with the assigned signals, B/ 2D DOSY ^{1}H-NMR spectrum shows the different diffusion coefficient after reaction, the peaks of

PDLLA and PTMC blocks in black, and the peak of the initial homopolymer PDLLA in red, C/ SEC chromatograms of initial homopolymer PDLLA (dots) and after copolymerization (solid line).

Table 3. Molecular weights and dispersities of the synthesized copolymers measured by SEC.

Catalysis approach	**Block copolymer ***	**Mn th ($g.mol^{-1}$)**	**Mn SEC ($g.mol^{-1}$)**	**Mp SEC ($g.mol^{-1}$)**	***Đ***
TBD step copolymerization	PTMC-*b*-PDLLA-*b*-PTMC	17400	3900	43900	11,9
MSA step copolymerization	PTMC-*b*-PDLLA-*b*-PTMC	17400	17200	27000	1,34
MSA step copolymerization	PCL-*b*-PDLLA-*b*-PCL	17400	14822	17000	1,31
MSA sequential copolymerization	PTMC-*b*-PDLLA-*b*-PTMC	17400	12191	16036	1,23
MSA sequential copolymerization	PCL-*b*-PDLLA-*b*-PCL	17400	13300	14858	1,37

* Initial PDLLA block was synthesized by TBD activation and led to M nth = 7200 $g.mol^{-1}$; Mn SEC = 9881 $g.mol^{-1}$; Mp SEC = 11370 $g.mol^{-1}$.

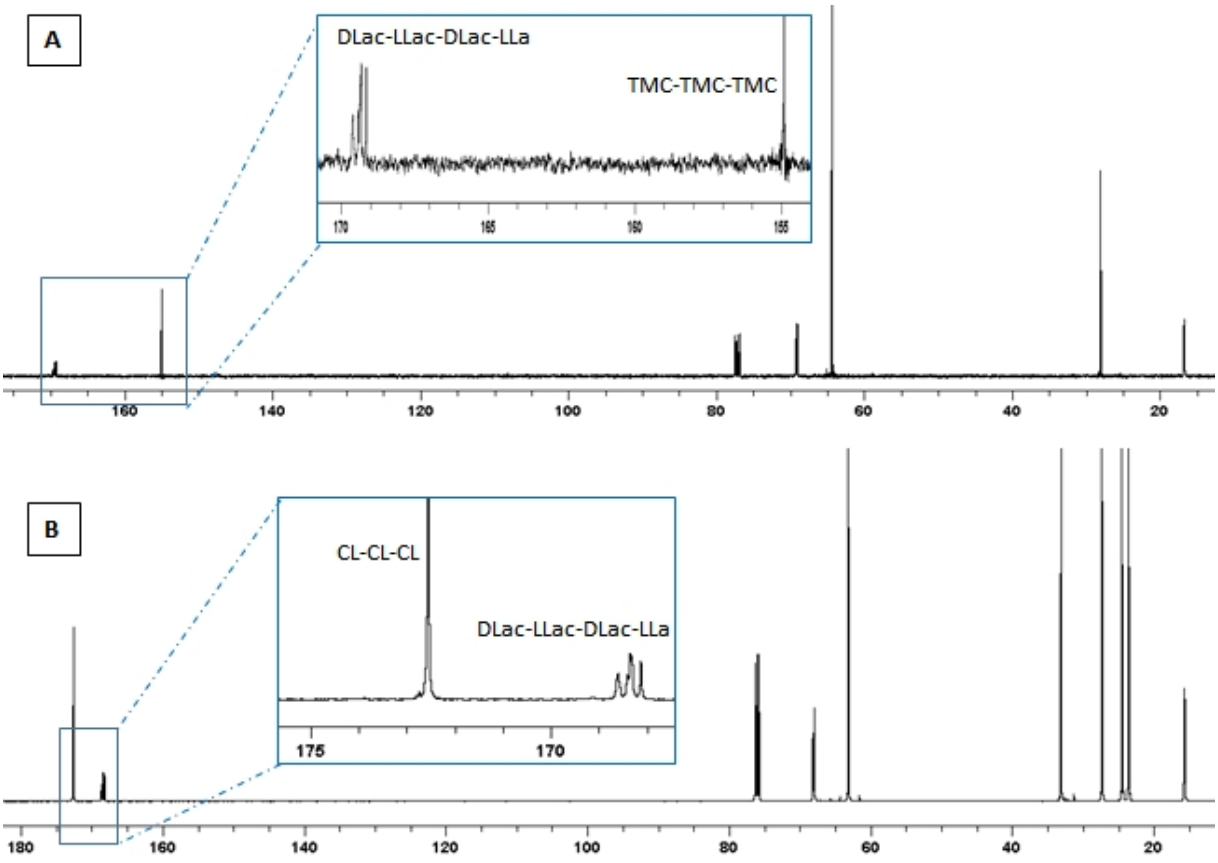

Figure 4. ^{13}C-NMR spectra in $CDCl_3$ for each triblock PTMC-*b*-PDLLA-*b*-PTMC (A) and PCL-*b*-PDLLA-*b*-PCL (B) obtained by cationic activation using MSA catalyst, with expanded carbonyl region. Specific assignment signals are specified.

Same result was observed for the PTMC-*b*-PDLLA-*b*-PTMC triblock copolymer in the carbonyl carbon region from 153-170 ppm, which includes the carbonyl region of PDLLA block and PTMC block at 154 ppm (Figure 4). Carbon NMR indicated that the transesterification processes did not occur when MSA was used as catalyst. DOSY-NMR spectra for both copolymers (Figure 5A and 5C) clearly identifies an uniform diffusion coefficient which confirms the formation of block copolymerization for both investigated copolymers. For SEC chromatograms for both triblock copolymer, the curves noticeably shifted toward lower retention times compared to those of corresponding PDLLA macroinitiators (Figure 5B and 5D et Table 3).

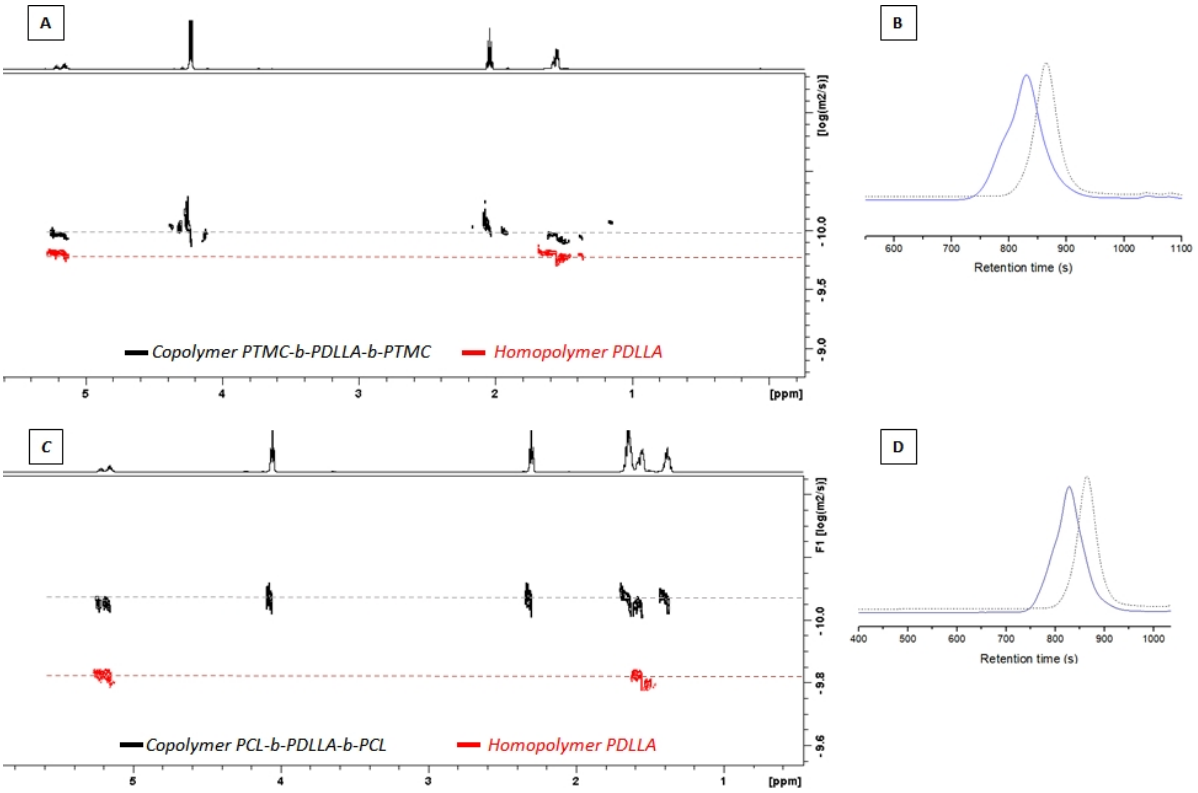

Figure 5. A/ 2D DOSY ^{1}H-NMR spectrum of PTMC-*b*-PDLLA-*b*-PTMC, diffusion coefficients (black for block copolymer and red for the initial PDLLA homopolymer, B/ SEC chromatograms of initial homopolymer PDLLA (dots) and PTMC-*b*-PDLLA-*b*-PTMC (solid line), C/ 2D DOSY ^{1}H-NMR spectrum of PCL-*b*-PDLLA-*b*-PCL, diffusion coefficients (black for block copolymer and red for initial PDLLA homopolymer), D/ SEC chromatograms of initial homopolymer PDLLA (dots) and of PCL-*b*-PDLLA-*b*-PCL (solid line).

Clearly, the reactivity of secondary alcohols is known to be lower compared to that of primary alcohols. Such reactivity issue for different protic compounds has also been found for the initiation of ring opening polymerization [26, 27]. Consequently, the presence of bis-hydroxy terminal groups on PDLLA influences the reactivity of the block copolymerization. Steric hindrance from methyl group of lactic acid unit might significantly impair the ring opening polymerization. In addition, it has been suggested from the literature that the activation of the hydroxyl end groups of poly(lactide) is lowered by the well-dispersing negative charges which reduces the nucleophilicity of the protic group and consequently weaken the ROP initiation from that site [13, 17]. In this study, we demonstrated that B-A-B block

copolymers with PDLLA central block can only be efficiently activated without any transesterification via an activated monomer mechanism (AMM) (Figure 6).

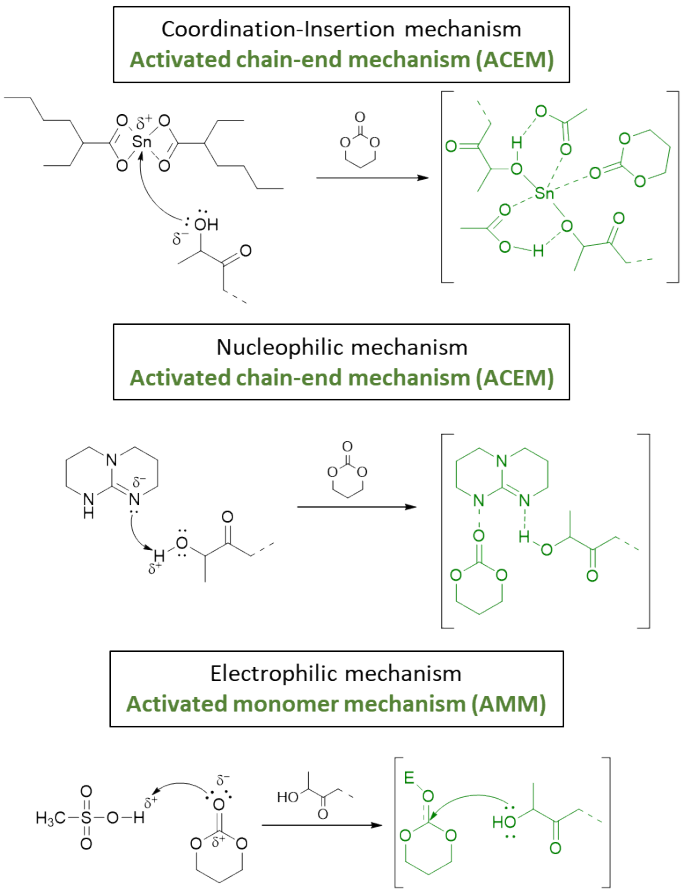

Figure 6. Activation mechanisms of the different employed catalysts through ACEM or AMM approaches.

Hence, electrophilic activation with MSA catalyst generated proper B-A-B triblock without transesterification while activated chain-end mechanism (ACEM) caused by $Sn(Oct)_2$ and nucleophilic TBD (Figure 6) lead to transesterification or no copolymerization and is therefore not appropriate for copolymerization with PLA first route.

Lastly, the study on step copolymerization allowed to determine that MSA activation was the only solution to generate block copolymers based on PLA macroinitiator. This catalytic approach would take a remarkable advantage if sequential one-pot copolymerization could also lead to controlled block

copolymer with PDLLA first route and without transesterification. Traditionally, sequential copolymerization is the classic approach for obtaining highly defined and well-controlled block copolymerization with low molecular weight dispersity. Typically, sequential copolymerization consists on feeding the reaction by addition of a second monomer once the initial block polymer has been achieved. Hence, we tried to generate triblock copolymers PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL in one pot by sequential copolymerization, with a particular interest in the conversion rate and absence of transesterification (Figure S6, S7). As we mentioned in the introduction, block copolymerization by sequential polymerization using organocatalysis is not frequent in the literature especially due to the divergent reactivity between the monomers/catalysts couples [10]. In the traceless switching approach from Wang *et al.*, sequential one pot block copolymerization has been obtained by switching the catalysis from a Bronsted cationic acid to a nucleophilic base one. A similar approach was thus used in our block copolymerization, where the first PDLLA block was synthesized by nucleophilic activation and then switched to an electrophilic one for the synthesis of the second block. Hence, a traceless switch organocatalysis strategy from Bronsted guanidine base to cationic sulfonic acid was employed for one pot PDLLA first-route block copolymerization. The conversion of the second block was similar to those obtained by step copolymerization, and no trace of transesterification was detected by NMR and SEC.

4. Conclusions

Owing to the deep investigation of the different ring opening polymerization mechanisms, we succeeded in the determination of the most appropriate catalytic pathway for the preparation of well-defined triblock copolymers starting from PDDLA as macroinitiator. In particular, cationic catalysis using electrophilic MSA was the single approach to synthesize PTMC-*b*-PDLLA-*b*-PTMC and PCL-*b*-PDLLA-*b*-PCL triblock copolymers without any secondary reactions such transesterification. Activated monomer mechanism was the most convenient approach leading to a controlled block copolymerization. In such a way, sequential copolymerization was achieved via traceless switching organocatalysis using

sequentially TBD and MSA catalysts to successfully generate triblock copolymer according to the PDLLA first route.

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Declaration of interests

 The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Supplementary Information

A simple and general approach for the synthesis of biodegradable triblock copolymers by organocatalytic ROP from poly(lactide) macroinitiators

Monomer conversion is followed by the disappearance of the characteristic monomer peaks and by appearance of new, shifted ones, polymer peaks. The monomer conversion is calculated by the following formula:

$$\% \text{ monomer conversion} = \frac{peak\ area\ of\ polymer}{peak\ area\ monomer\ +\ peal\ area\ polymer} \text{ x } 100$$

Homopolymerization of DL-LA.

In the case of DL-LA homopolymerization, the polymer peak area at 5.17 ppm and the monomer peak area at 5.02 ppm are taken into consideration for the calculation of monomer conversion percentage. In Figure S1A, we observe no presence of any monomer peaks after 2 minutes of reaction (catalyzed by TBD) and therefore we conclude that the reaction is complete (> 97 % conversion). TBD catalyst residues are present between 3.2 and 3.3 ppm, observable in the reaction mixture and later eliminated through precipitation. On the opposite, on the spectra in Figure S1B, we note weak DL-LA conversion of around 10 % after 17 hours of reaction (catalyzed by MSA). Figure S1C represents PDLLA homopolymer after precipitation in methanol. ^{1}H-NMR spectrum of PDLLA homopolymer obtained by stannous octanoate catalysis is similar to the spectra of Figure S1C and is therefore not represented. The degree of polymerization equals to the initially desired 100 units is calculated by comparing the ratio of the peak area at 4.14 ppm (belonging to 4 equivalent H of the hexane diol initiator) with the peak area at 5.17 ppm (belonging to the -CH- in the PDLLA repeating unit).

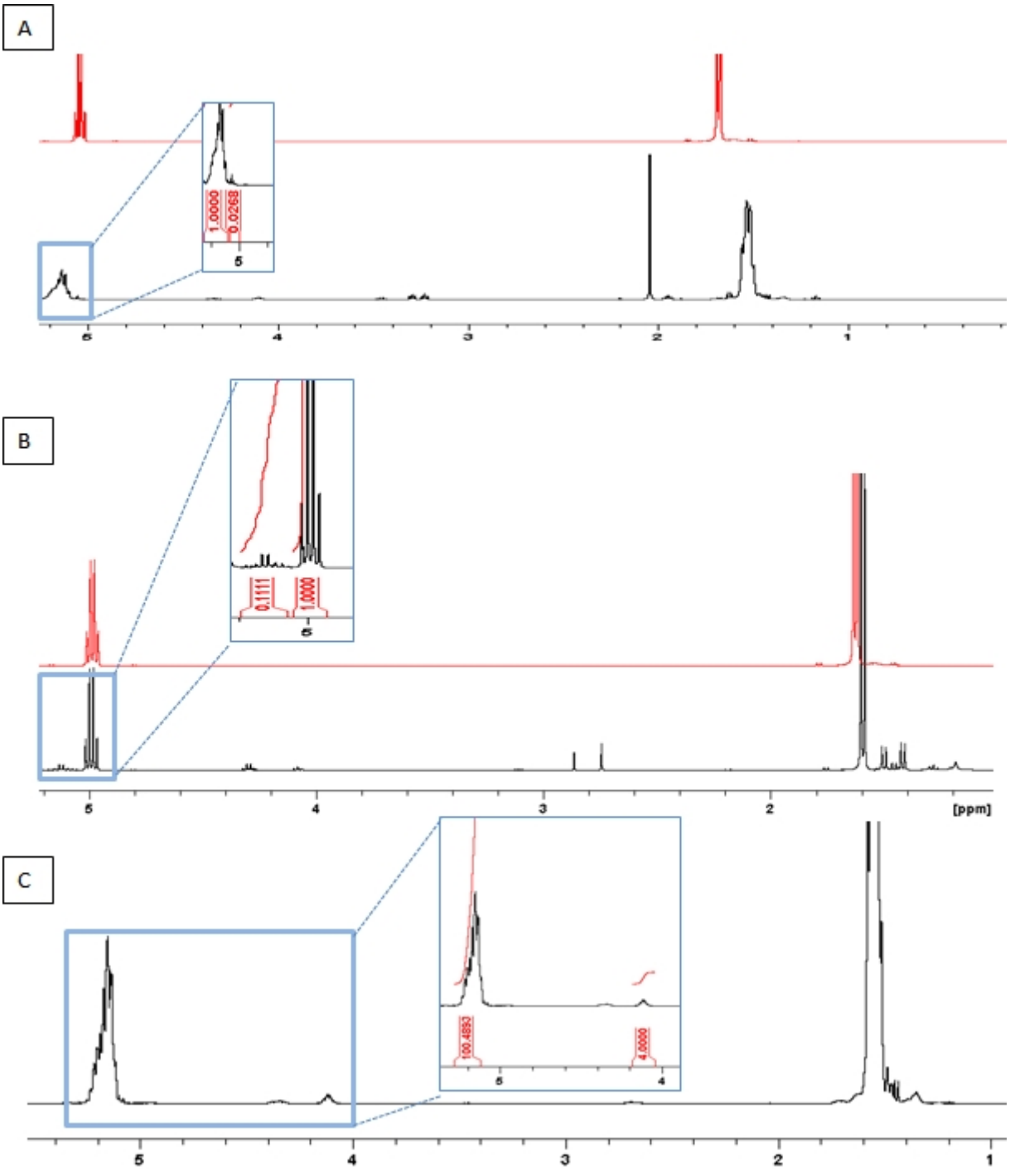

Figure S1. ^{1}H-NMR spectra of DL-LA homopolymerization. A/ Full conversion of DL-LA after 2 minutes of reaction, catalyzed by TBD (in red - DL-LA monomer, in black - PDLLA after full conversion, before precipitation: absence of all monomer peaks); B/ 10% of DL-LA conversion after 17 hours of reaction, catalyzed by MSA (in red - DL-LA monomer, in black -

the reaction mixture); C/ Final spectrum of PDLLA homopolymer after precipitation with end-chain functionalities present at 4.2 ppm.

Homopolymerization of TMC.

In the case of TMC homopolymerization, the polymer peak area at 4.18 ppm and the monomer peak area at 4.35 ppm are taken into consideration for the calculation of monomer conversion percentage. On the spectrum represented in Figure S2A we note a conversion of 99% (by MSA catalysis) and therefore absence of all monomer peaks. The ^{1}H-NMR spectra of TMC homopolymer obtained by stannous octanoate and TBD catalysis are similar to Figure S2B and is not represented. The degree of polymerization equals to the initially desired 100 units is calculated by comparing the ratio of the peak area at 3.67 ppm (belonging to 4 equivalent H of the hexane diol initiator) with the peak area at 4.18 ppm (belonging to the 2-CH_2- in the PTMC repeating unit).

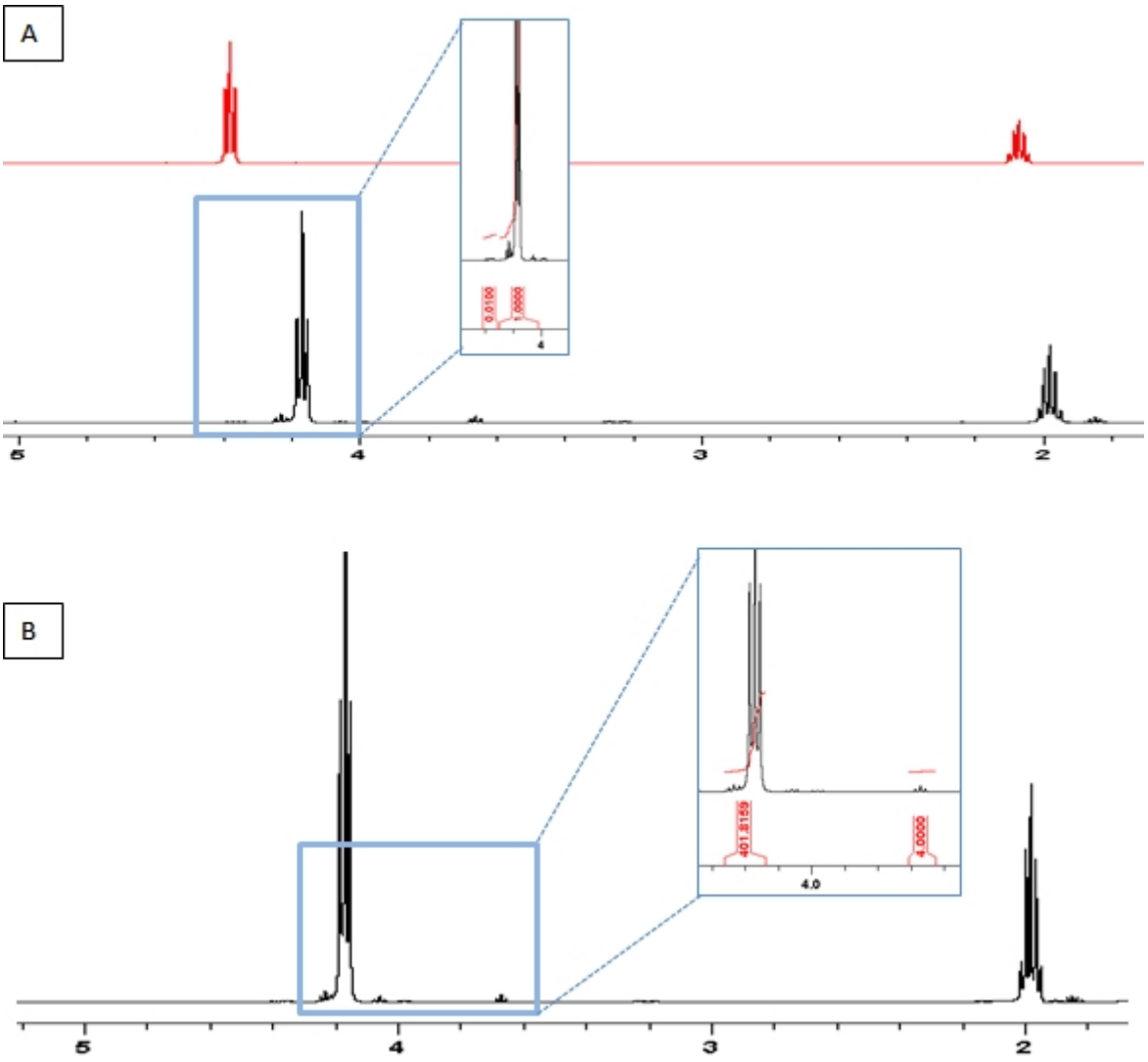

Figure S2. ^{1}H-NMR spectra of TMC homopolymerization. A/ Full conversion of TMC after 17h of reaction, catalyzed by MSA (in red - TMC monomer, in black - PTMC after full conversion, before precipitation: absence of all monomer peaks) B/ Final spectrum of PTMC homopolymer after precipitation with end-chain functionalities present at 3.67 ppm.

Homopolymerization of ε-CL.

In the case of ε-CL homopolymerization, the polymer peak area at 4.06 ppm and the monomer peak area at 4.15 ppm are taken into consideration for the calculation of monomer conversion percentage. On the spectra represented in Figure S3A, we observe no presence of

any monomer peaks after 24 hours of reaction (catalyzed by stannous octanoate) and therefore we conclude that the reaction is complete (> 99 % conversion). On the opposite, on the spectra in Figure S3B, we note weak DL-LA conversion of around 17 % after 24 hours of reaction, catalyzed by TBD, with catalyst residues present between 3.2 and 3.3 ppm. The ^{1}H-NMR spectrum of DL-LA homopolymer obtained by MSA catalysis is not represented because it is similar to the spectrum of Figure S3C. The degree of polymerization equals to the initially desired 100 units and is calculated by comparing the ratio of the peak area at 3.67 ppm (belonging to 4 equivalent H of the hexane diol initiator) with the peak area at 4.06 ppm (belonging to the $–CH_2$- in the PCL repeating unit).

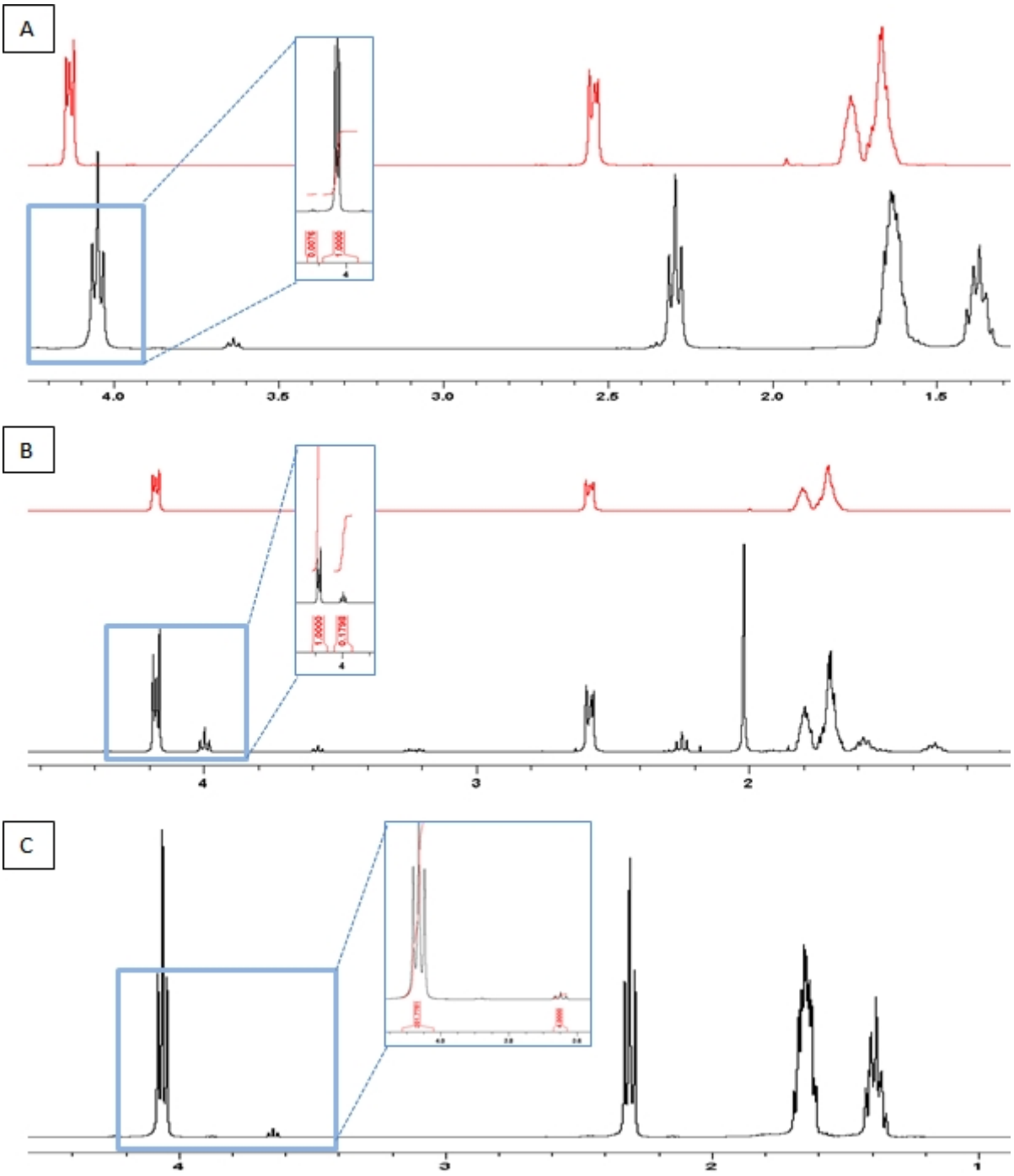

Figure S3. ^{1}H-NMR spectra of ε-CL homopolymerization. A/ Full conversion of ε-CL after 24 hours of reaction, catalyzed by stannous octanoate (in red - ε-CL monomer, in black - PCL homopolymer after full conversion, before precipitation); B/ 17% of ε-CL conversion after 24 hours of reaction, catalyzed by TBD (in red - ε-CL monomer, in black - the reaction mixture); C/ Final spectrum of PCL homopolymer after precipitation with end-chain functionalities present at 3.67 ppm.

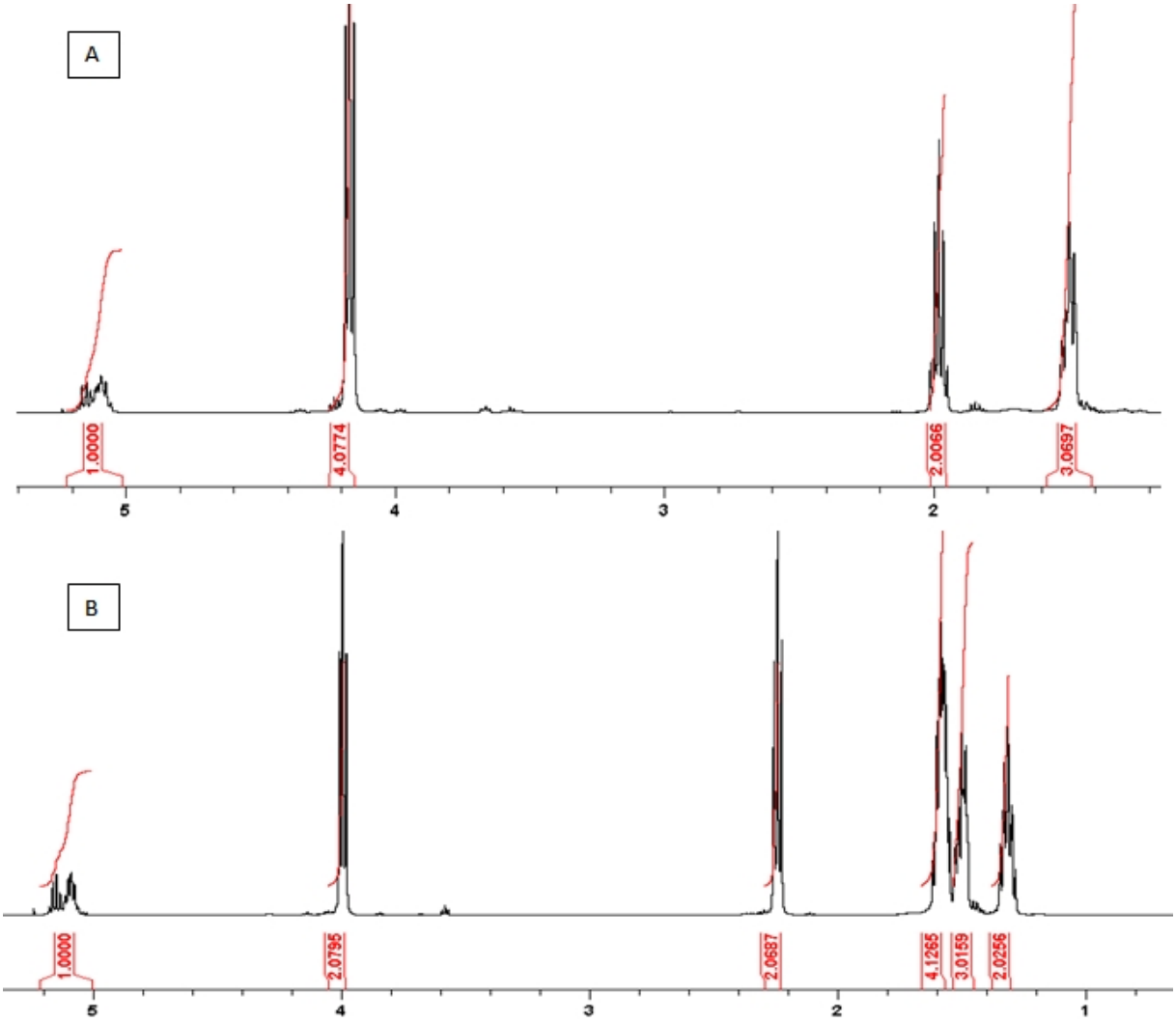

Figure S4. ^{1}H-NMR spectra of block copolymers with PDLLA first route. A/ ^{1}H-NMR spectra of $PTMC_{50}$-$PDLLA_{100}$-$PTMC_{50}$ triblock copolymer; B/ ^{1}H-NMR spectra of PCL_{50}-$PDLLA_{100}$-PCL_{50} triblock copolymer.

The molar ratios of (50/50) were determined by comparing the characteristic peak areas of the –CH- repeating unit of PDLLA situated at 5.17 ppm with the peak area of the 2-CH_2- repeating units of PTMC at 4.18 ppm for the $PTMC_{50}$-$PDLLA_{100}$-$PTMC_{50}$ triblock copolymer represented in Figure S4A.

For the PCL_{50}-$PDLLA_{100}$-PCL_{50} triblock copolymer represented in Figure S4B the molar ratios of 50/50 were determined by comparing the characteristic peak areas of the –CH- repeating unit of PDLLA situated at 5.17 ppm with the peak area of the $–CH_2$- repeating unit of PCL at 4.06 ppm.

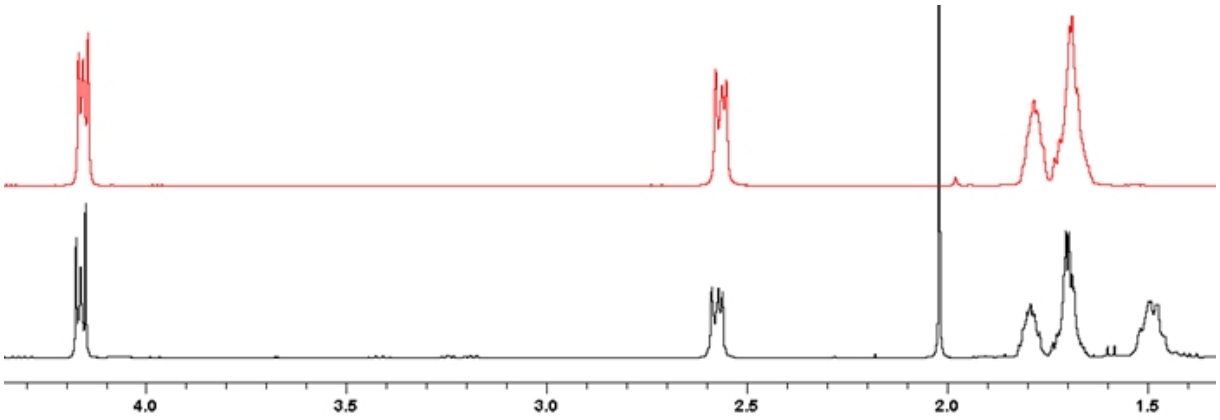

Figure S5. ^{1}H-NMR spectra of PCL-*b*-PDLLA-*b*-PCL triblock copolymer formation catalyzed by TBD after 72 hours of reaction (in black - the reaction medium; in red - ε-CL monomer).

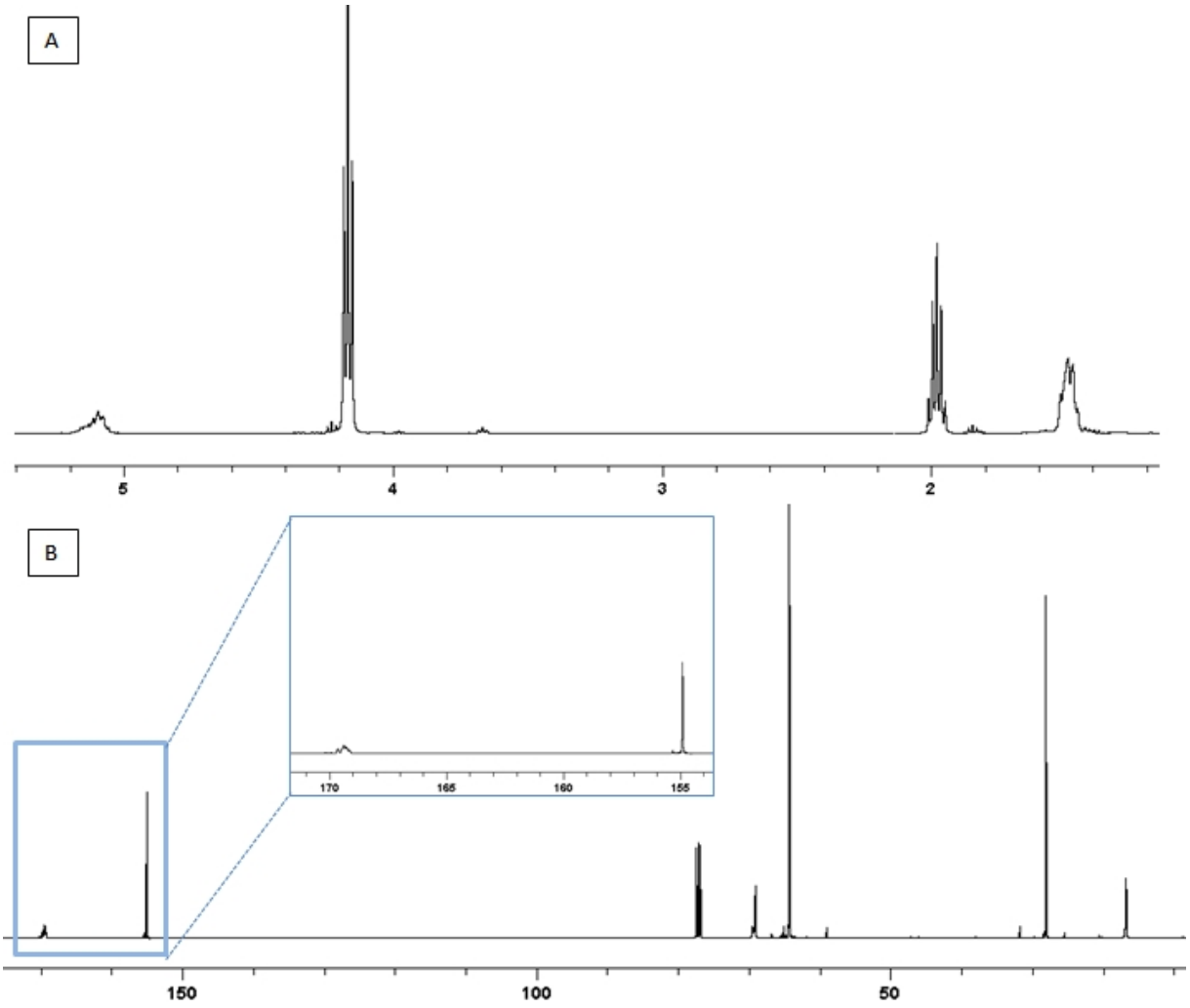

Figure S6. Characterization of PTMC-*b*-PDLLA-*b*-PTMC by sequential one-pot copolymerization A/ ^{1}H-NMR; B/ ^{13}C-NMR spectra; C/ SEC chromatogram.

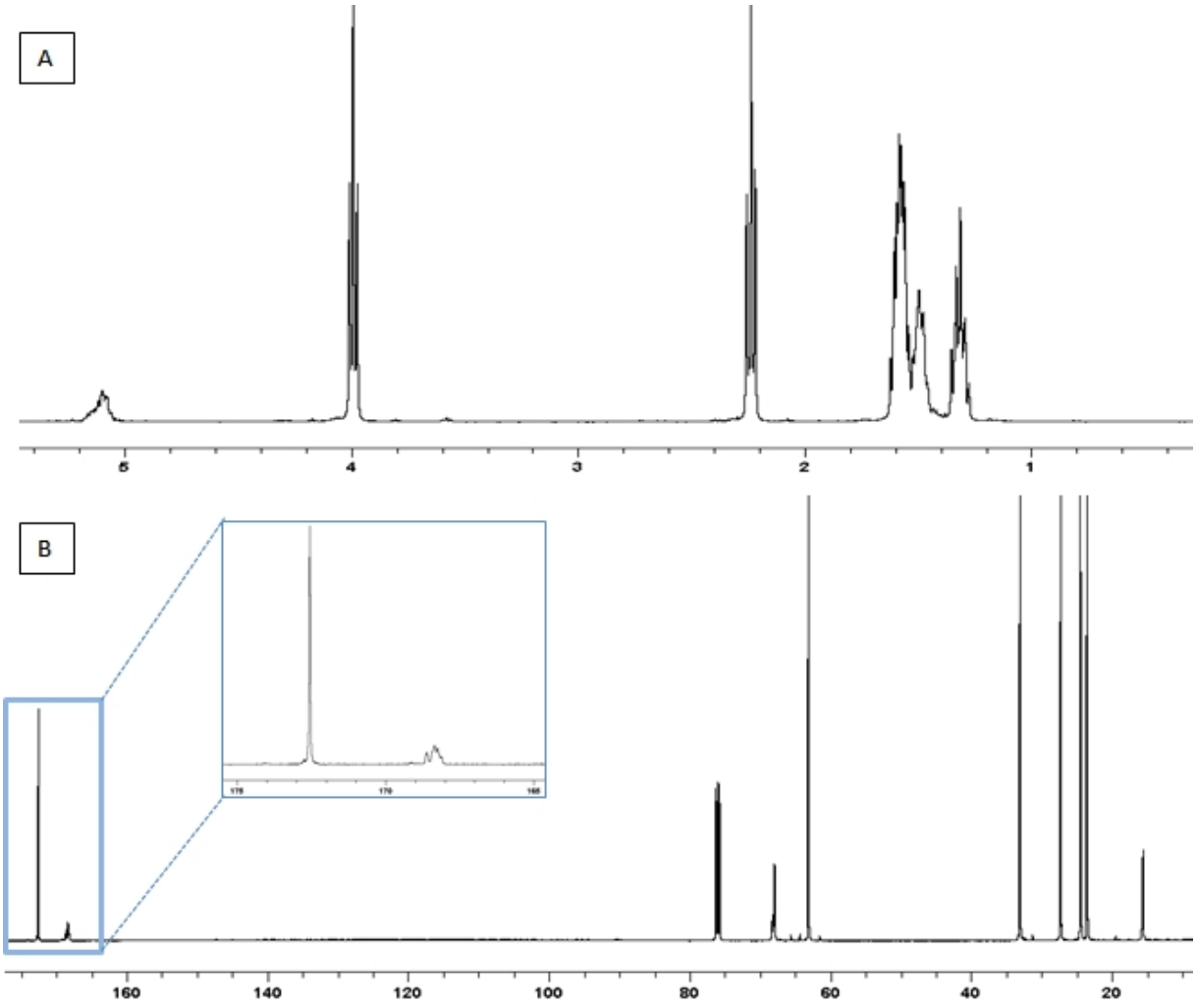

Figure S7. Characterization of PTMC-*b*-PDLLA-*b*-PTMC by sequential one-pot copolymerization A/ ^{1}H-NMR; B/ ^{13}C-NMR spectra; C/ SEC chromatogram.