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Eric Beuille, Vincent Darcos, Jean Coudane, Patrick Lacroix-Desmazes, Benjamin Nottelet. Regioselective Halogenation of Poly(lactide) by Free-Radical Process. *Macromolecular Reaction Engineering*, 2014, 8 (2), pp.141-148. 10.1002/mren.201300136 . hal-00992399

**HAL Id: hal-00992399**

**<https://hal.science/hal-00992399>**

Submitted on 23 Jan 2024

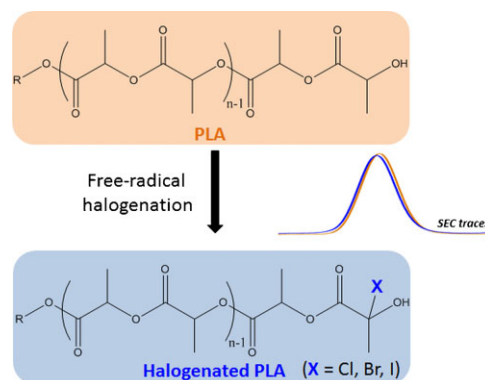
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# Regioselective Halogenation of Poly(lactide) by Free-Radical Process<sup>a</sup>

Eric Beuille, Vincent Darcos, Jean Coudane, Patrick Lacroix-Desmazes,\*  
Benjamin Nottelet\*

Modification of the biodegradable and renewable poly(lactide) (PLA) to provide functional aliphatic polyesters is highly desirable to meet application requirements. In this context, the objective of this work is to evaluate the possibility of using free-radical substitution as a simple and non-degrading method to yield the desired functional PLA. Halogenation of PLA is carried out in solution and various reaction conditions are evaluated. Halogenated PLAs are characterized by <sup>1</sup>H NMR spectroscopy and size exclusion chromatography (SEC) to evaluate the substitution ratios and to check the non-degrading character of the radical modification. Furthermore, reactions on model compounds as well as MALDI-TOF analyses are performed to elucidate the involved mechanism. The combined results prove the free-radical halogenation of PLA in solution to be regioselective with only the ω-halogenated PLA being obtained without main-chain substitution.



## 1. Introduction

Poly(lactide) (PLA) is a biodegradable polyester that can be polymerized from renewable resources. It presents properties close to the ones of polyolefins and it is believed to become an alternative to many petroleum-based diffusion

polymers. However, like other well-known aliphatic polyesters, including poly( $\epsilon$ -caprolactone) (PCL) and poly(glycolide) (PGA), its major drawback is the lack of functionality on the backbone which prevents modulation of its properties to meet specific applications.

For this reason, the preparation of functional aliphatic polyesters has attracted much attention and various strategies have been reported so far. In particular, main-chain functionalization is generally obtained via two main approaches. The first one consists of the ring-opening polymerization (ROP) of functional lactones.<sup>[1]</sup> Many lactide (LA)/glycolide derivatives have been synthesized to offer a wide range of available functional groups on the PLA backbone and, without being exhaustive, one can mention LA derivatives bearing hydroxyl groups,<sup>[2–4]</sup> carboxylic, and amine groups,<sup>[5]</sup> alkyl or alkyne groups.<sup>[6–8]</sup> However, this first strategy presents a main drawback: scale-up possibilities are limited due to the complexity of the synthetic pathways and the number of required purifications steps. Consequently, a second strategy based on the modification of preformed aliphatic polyesters can be preferred. In this

E. Beuille, Dr. V. Darcos, Prof. J. Coudane, Dr. B. Nottelet  
Faculty of Pharmacy, Institut des Biomolécules Max Mousseron –  
Département Biopolymères Artificiels (IBMM-BA), UMR5247  
CNRS-University Montpellier 1 University Montpellier 2, 15,  
Avenue Charles Flahault, BP 14491, 34093, Montpellier, France  
E-mail: benjamin.nottelet@univ-montp1.fr  
Dr. P. Lacroix-Desmazes  
Institut Charles Gerhardt, UMR5253 CNRS-UM2-ENSCM-UM1,  
Ingénierie et Architectures Macromoléculaires (IAM), Ecole  
Nationale Supérieure de Chimie de Montpellier, 8 rue de l'École  
Normale, 34296 Montpellier Cedex 5, France  
E-mail: patrick.lacroix-desmazes@enscm.fr

<sup>a</sup>Supporting Information is available online from the Wiley Online Library or from the author.

regard, our group investigated the possibility to use anionic chemical modification reactions to functionalize aliphatic polyesters in solution.<sup>[9]</sup> Using a sterically hindered strong base like lithium diisopropyl amide (LDA), proton in the  $\alpha$ -position of the ester carbonyl of preformed aliphatic polyesters can be abstracted to form macropolycarbanion intermediates to be used in “grafting from” or “grafting onto” strategies. This strategy allowed us to access to functional PCLs whose main chain is substituted by small functional groups ( $-\text{COOH}$ ,  $-\text{I}$ , etc.)<sup>[10,11]</sup> or polymer side chains (polyvinylpyridine, poly(2-(dimethylamino)ethyl methacrylate), polylysine, etc.)<sup>[12,13]</sup> Although very powerful for PCL, this approach is however of limited interest for the modification of PLA in solution due to its high sensitivity towards hydrolysis. Indeed, ester groups being susceptible to nucleophilic attack originating from the formed polyanion, the more fragile PLA is highly fragmented during the anionic modification process.<sup>[14]</sup> Only a recent adaptation of the conditions allowed us to modify PLA surfaces without degradation to provide bioactive surfaces for temporary applications.<sup>[15]</sup>

Beside anionic modification procedure, free-radical modification can also be considered. One main advantage of this approach is that radical processes are easier to scale-up because they are less sensitive to impurities than ionic processes. However, reactive extrusion is the only radical process used for PLA and is limited to batch modifications for the compatibilization of blends,<sup>[16–20]</sup> chain extension or crosslinking reactions,<sup>[21–24]</sup> whereas only very few works reported the use of reactive extrusion for the synthesis of functional PLA. To the best of our knowledge, this approach (reactive extrusion for the synthesis of functional PLA) is limited to the maleation of PLA to introduce carboxyl groups that are then exploited in coupling reactions with amines or hydroxyl-functionalized groups like citrate plasticizers or poly(ethylene glycol)s (PEG).<sup>[25–28]</sup> Even less work has been reported so far on the modification of LA or PLA main chain by solution free-radical processes. Brominated-LA was synthesized by Jing et al. in good yields but without use of this monomer to yield halogenated PLA. Instead, the functional monomer was used as an intermediate for the preparation of a tricyclic monomer leading, after ROP, to a toughened PLA.<sup>[29]</sup> More recently, Nugroho et al. reported on the radical photoactivation of PLA micro-particles by introducing on their surface benzophenone moieties, which were subsequently exploited for the polymerization of acrylic and acrylamides by a grafting-from strategy.<sup>[30]</sup> However, like in our previous work,<sup>[15]</sup> this modification was limited to the surface of PLA without bulk modification of PLA.

Our main objective in the present work was to study the possibility to use free-radical substitution as a non-destructive technique for the bulk functionalization

of the sensitive biodegradable PLA main chains. The technique should be versatile and applicable to a wide range of substituents including the herein proposed halogens while guarantying the PLA backbone integrity.

## 2. Experimental Section

### 2.1. Materials

L-Lactide (>98%) was purchased from Purac biochem (Goerinchem, The Netherlands). All other chemicals were purchased from Sigma–Aldrich (St-Quentin Fallavier, France) and were used as received unless specified. Toluene and anisole were dried over calcium hydride for 24 h at room temperature and distilled under reduced pressure. Benzoyl peroxide (BPO) was recrystallized from a 50/50 mixture of chloroform and ethanol. *N*-Bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) were recrystallized from water.

### 2.2. Methods

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker spectrometer (AMX300) operating at 300 and 75 MHz, respectively. Deuterated chloroform or deuterated dimethyl sulfoxide were used as solvents. Chemical shifts were expressed in ppm with respect to tetramethylsilane (TMS).

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using the attenuated total reflectance (ATR) method.

Mass spectrometry analyses were conducted with a Bruker Ultra-Flex MALDI-TOF mass spectrometer, equipped with a nitrogen laser (LSI, 337 nm, 10 ns pulse length) and one detector. The ions were accelerated by a potential of 25 kV and reflected with a 26.3 kV potential. Measurement was recorded in the reflection mode using *R*-cyano-4-hydroxycinamic acid (HCCA) as matrix with NaI as cationization agent.

Size exclusion chromatography analyses were performed at 25 °C on a Waters system equipped with a guard column, a 600 mm PLgel 5 mm Mixed C column (Polymer Laboratories), and a Waters 410 refractometric detector. Calibration was established with poly(styrene) standards from Polymer Laboratories. THF was used as eluent at a flow rate of 1 mL · min<sup>-1</sup>.

Micro-wave activation was performed with a TM CEM equipment (Discover model).

### 2.3. Synthetic Methodologies

#### 2.3.1. Synthesis of Poly(lactide)

Poly(lactide) was synthesized by ROP of L-lactide (LA). Polymerization was carried out in toluene using standard Schlenk technique under an inert atmosphere of argon. In a typical experiment, LA (10 g, 69.4 mmol), benzyl alcohol (360  $\mu\text{L}$ , 3.5 mmol), Sn(Oct)<sub>2</sub> (347  $\mu\text{L}$  of a 1 M stock solution in toluene, 0.35 mmol) and 15 mL of toluene were placed in an oven dried Schlenk tube. The tube was

fitted with a rubber septum. The solution was further degassed by three freeze–pump–thaw cycles. The solution was further degassed by three freeze–pump–thaw cycles. The resulting mixture was stirred at 80 °C under argon for 180 min. Polymerization was quenched at 70% conversion by addition of an excess of 1 N HCl. The reaction mixture was then poured in cold diethyl ether. The precipitated polymer was then collected by filtration and dried in vacuo to yield pure PLLA (yield 70%). The polymer was characterized by <sup>1</sup>H NMR, SEC, and MALDI-TOF analyses. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) = 1.5 (m, CH–CH<sub>3</sub>); 4.35 (q, CH<sub>3</sub>–CH–OH); 5.1 (m, CH–CH<sub>3</sub>); 7.3 (m, C<sub>6</sub>H<sub>5</sub>).  $\overline{M}_{n,SEC} = 2\,500\text{ g}\cdot\text{mol}^{-1}$ ,  $\mathcal{D} = 1.1$ ;  $\overline{M}_{n,NMR} = 2\,200\text{ g}\cdot\text{mol}^{-1}$ ;  $\overline{M}_{n,MALDI} = 2\,000\text{ g}\cdot\text{mol}^{-1}$ .

### 2.3.2. Halogenation of Poly(lactide)

The procedure was adapted from the literature.<sup>[29]</sup> In a typical experiment PLA (500 mg, 3.47 mmol of lactyl units), NBS (618 mg, 3.47 mmol), BPO (17 mg, 0.07 mmol), and 5 mL of benzene were placed in an oven dried Schlenk tube. The tube was fitted with a rubber septum. The solution was further degassed by three freeze–pump–thaw cycles. The resulting mixture was stirred at 80 °C under argon for 3 h. Halogenation under micro-wave activation was performed similarly except that it was performed in the TM CEM Discover equipment. After cooling to room temperature, the insoluble NBS was filtered. The clear reaction medium was poured into heptane. The resulting polymer was further purified by precipitation in MeOH/H<sub>2</sub>O (80/20) and stirring at 0 °C. The purified polymer was collected by filtration as a white solid and dried in vacuum at 40 °C (90% yield). The polymer was characterized by <sup>1</sup>H NMR. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) = 1.5 (m, CH–CH<sub>3</sub>); 2.45 (s, CBr–CH<sub>3</sub>); 4.35 (q, CH<sub>3</sub>–CH–OH); 5.15 (m, CH–CH<sub>3</sub>); 7.35 (m, C<sub>6</sub>H<sub>5</sub>).

### 2.3.3. Acetylation of Poly(lactide)

In a typical experiment PLA (300 mg, 0.15 mmol –CH(CH<sub>3</sub>)–OH chain end), acetic anhydride (0.142 mL, 1.5 mmol) and 4 mL of pyridine were introduced in a round-bottom flask. Reaction was let to run overnight at room temperature. The polymer was recovered by precipitation in cold methanol. The purified acetylated PLA was collected by filtration as a white solid and dried in vacuum at 40 °C (85% yield, 100% acetylation). The polymer was characterized by <sup>1</sup>H NMR. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) = 1.5 (m, CH–CH<sub>3</sub>); 2.1 (s, O–CO–CH<sub>3</sub>); 5.1 (m, CH–CH<sub>3</sub>); 7.3 (m, C<sub>6</sub>H<sub>5</sub>).

### 2.3.4. Bromination of Ethyl Lactate

In a typical experiment ethyl lactate (0.5 mL, 4.24 mmol), NBS (830 mg, 4.66 mmol), BPO (20 mg, 0.08 mmol) and 5 mL of benzene were placed in an oven dried Schlenk tube. The tube was fitted with a rubber septum. The solution was further degassed by three freeze–pump–thaw cycles. The resulting mixture was stirred at 80 °C under argon for 3 h. After cooling to room temperature, the insoluble NBS was filtered. The product was solubilized in dichloromethane (100 mL) and purified by four extractions with water (4 × 50 mL). After removal of dichloromethane under vacuum, 1-bromoethyl lactate was recovered as colorless oil. The compound was characterized by <sup>1</sup>H NMR. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) = 1.25 (m, CH<sub>3</sub>–CH<sub>2</sub>; CH<sub>3</sub>–CH–OH); 2.35 (s, CH<sub>3</sub>–CBr–OH); 4.25 (m, CH<sub>2</sub>–CH<sub>3</sub>; CH<sub>3</sub>–CH–OH).

## 3. Results and Discussion

### 3.1. Halogenation of PLA

In the present study, low molecular weight PLAs have been synthesized in order to evaluate the possibility to modify preformed PLA via a straightforward radical modification. Indeed, a targeted molecular weight of 2 000 g·mol<sup>-1</sup> was chosen to help polymer characterization. LA monomer was polymerized by ring opening polymerization process in toluene using stannous(II) 2-ethylhexanoate (Sn(Oct)<sub>2</sub>) as catalyst. Kinetic studies (Supporting Information, Figure S1) were used to stop the polymerization at 70% conversion to obtain a PLA with the expected molecular weight. <sup>1</sup>H NMR spectrum of PLA showed a signal at 4.35 ppm corresponding to the methine protons of the chain end moiety (Figure 1A), whereas the peaks at 5.14 and 1.55 ppm were associated with the polyester backbone. The peak at 7.30 ppm is related to the aromatic protons of the initiator moiety. The molecular weight ( $\overline{M}_{n,NMR}$ ) was calculated from the relative intensity of <sup>1</sup>H NMR signals of the monomeric units and the aromatic group (d protons) using Equation 1 where  $I_{b+c}$  and  $I_d$  are integrals of the peaks b + c, and d, respectively in Figure 1A.

$$\overline{M}_{n,NMR} = M(\text{initiator}) + \frac{5 \times (I_{b+c} - 2/5I_d)}{I_d} \times M(\text{lactic acid unit}) \quad (1)$$

The molecular weight was found to be  $\overline{M}_{n,NMR,NMR} = 2\,200\text{ g}\cdot\text{mol}^{-1}$ . This value was in good agreement with MALDI-TOF results: molecular weight determined by MALDI was found to be 2 000 g·mol<sup>-1</sup>. On the other hand,

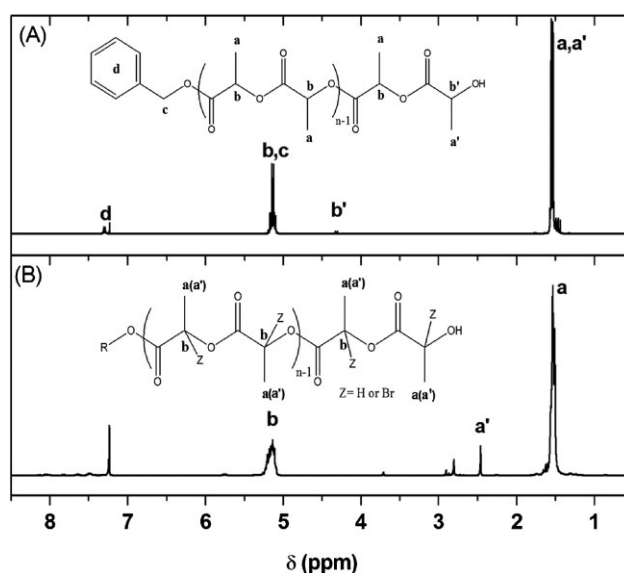
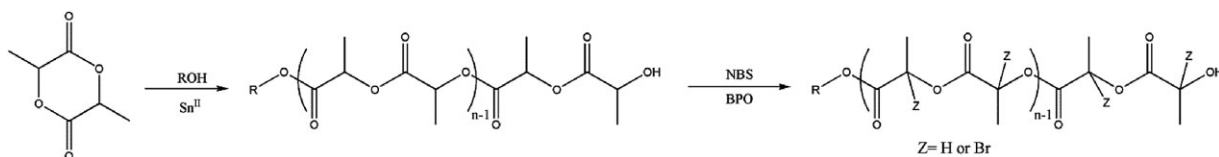


Figure 1. <sup>1</sup>H NMR of native poly(lactide) (A) and brominated poly(lactide) (B).



■ Scheme 1. Synthesis of brominated poly(lactide).

PLA molar masses determined by SEC with PS standards are slightly over-estimated ( $\overline{M}_{n,SEC} = 2\,500\text{ g}\cdot\text{mol}^{-1}$ ). Nevertheless, such PLA was obtained with a good control of molecular weight and low dispersity ( $\mathcal{D} = 1.1$ ). These data confirmed the well-controlled behavior of the polymerization process.

This well-defined PLA was further used for radical halogenation studies (Scheme 1). NBS is a widely-used brominating agent.<sup>[31]</sup> Reaction conditions were evaluated and selected conditions are summarized in Table 1. In a first attempt, conditions similar to those initially used by Scheibelhoffer and more recently by Jing et al. to yield brominated L-LA were used.<sup>[29,32]</sup> NBS was chosen as the halogenating agent, benzene as the solvent and the reaction was performed at 80 °C (Table 1, run 1). After purification, the substitution ratio ( $F_X$ ) of halogenated lactic acid monomer unit was calculated by  $^1\text{H}$  NMR using Equation 2 with the intensity  $I_{a'}$  of the signal at 2.45 ppm corresponding to the methyl protons in the vicinity of bromine and  $I_a$  the intensity of the signal at 1.5 ppm corresponding to the methyl protons of the non-substituted units (Figure 1B).

$$F_X = \frac{I_{a'}}{I_a + I_{a'}} \times 100 \quad (2)$$

The substitution ratio ( $F_{\text{Br}}$ ) under these conditions was 3.2% without any detectable degradation of the polymer chains as demonstrated by SEC ( $\overline{M}_{n,SEC} = 2\,600\text{ g}\cdot\text{mol}^{-1}$  and  $\mathcal{D} = 1.12$  for PLA-Br against  $\overline{M}_{n,SEC} = 2\,500\text{ g}\cdot\text{mol}^{-1}$  and  $\mathcal{D} = 1.10$  for neat PLA (Figure 2). Bromination was

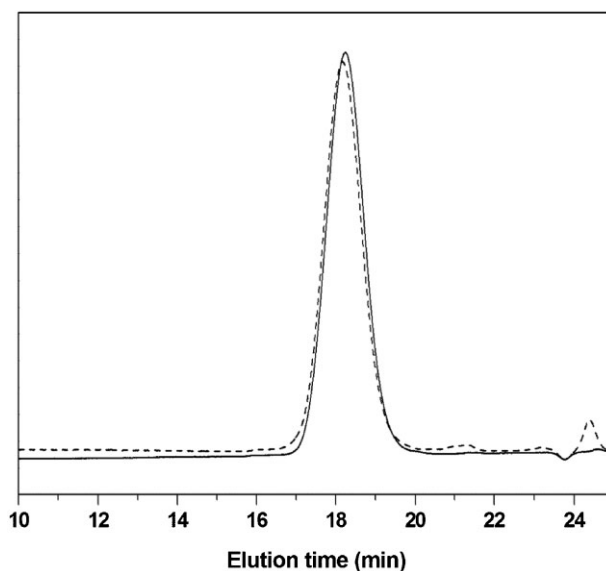
further confirmed by SEC using UV detection with an increased absorbance at  $\lambda = 245\text{ nm}$  for PLA-Br (A.U. = 0.08 [PLA] = 5 mg mL<sup>-1</sup>) compared to neat PLA (A.U. = 0.004 [PLA] = 5 mg mL<sup>-1</sup>). Following this first trial, other halogenating reagents (NCS and *N*-iodosuccinimide) have been used to yield chlorinated and iodinated PLA. As can be seen from runs 2 and 3 (Table 1), two different behaviors were found as a function of the halide used. Whereas the chlorination gave results similar to the bromination reaction with a 3.2% substitution, iodination was far less efficient with less than 0.5% of substituted lactic units. This was attributed to the relative poor stability of carbon–iodine bond, which is prone to side-reactions.

The overall substitution ratio on the polymer backbone (ca. 3%) was low compared to the one reported for the LA monomer (62%). Considering the lower solubility of PLA compared to LA in benzene, as well as the steric hindrance of the polymer chain that may hinder the radical hydrogen abstraction, reaction parameters were studied in order to increase the substitution ratio. These parameters included the nature of the solvent (trifluorotoluene (TFT) or anisole vs. benzene), the temperature value (100–110 °C vs. 80 °C),

Table 1. Halogenation of PLA using benzoyl peroxyde as radical source.

Entry	NXS <sup>a)</sup>	$F_{\text{Br}}$ <sup>b)</sup> [%]	$\overline{M}_{n,SEC}$ <sup>c)</sup> [g · mol <sup>-1</sup> ]	$\mathcal{D}$ <sup>c)</sup>
1	Br	3.2	2 600	1.12
2	Cl	3.2	2 700	1.10
3	I	<0.5	2 700	1.13

Conditions: 80 °C, benzene, 3 h (equiv. of lactyl units in the polyester)/[NXS]/[BPO]: 1/1/0.02). <sup>a)</sup>NXS: *N*-halo succinimide; <sup>b)</sup>Determined by  $^1\text{H}$  NMR (Equation 2); <sup>c)</sup>Determined by SEC (calibration with PS standards).



■ Figure 2. SEC traces of poly(lactide) (solid line) and brominated poly(lactide) (dashed line).

Table 2. Reaction parameters study for the bromination of PLA.

Entry	Solvent	T [°C]	t [h]	$\overline{M}_{n,SEC}^a$ [g · mol <sup>-1</sup> ]	$F_{Br}^b$ [%]
1	Benzene	80	3	2 500	3.2
2	Benzene	80	16	2 500	3.4
3	Benzene	80	3	6 000	1.7
4	Anisole	80	3	2 500	0.6
5	TFT	80	3	2 500	3.1
6	TFT	100	3	2 500	3.6
7	TFT	110	3	2 500	4.3

<sup>a</sup>)Determined by SEC (calibration with PS standards); <sup>b</sup>)Determined by <sup>1</sup>H NMR (Equation 2).

the reaction time (16 h vs. 3 h) and the initial PLA molecular weight (2 500 g·mol<sup>-1</sup> vs. 6 000 g·mol<sup>-1</sup>). Results are summarized in Table 2. At fixed reaction temperature, substitution was not increased by longer reaction times (Table 2, runs 1 and 2) or by the change of solvent (Table 2, runs 1 and 5) with ca. 3% in all cases. It was even decreased in the more polar anisole (Table 2, run 4). Only increasing the reaction temperature gave a trend toward higher substitution ratio (Table 2, runs 5–7) with a significant increase when substitution was carried out at 110 °C instead of 80 °C, leading to a substitution ratio of 4.3% compared to 3.1%, respectively. In this context, it is interesting to note that for radical substitution by reactive extrusion, typical substitution ratios of 0.5–4% are reported in good agreement with our values although higher temperatures in the range of 160–200 °C are used for melting purpose.<sup>[21,25–27]</sup>

Higher temperatures were not tested herein as it was not possible under the standard Schlenk conditions used. Instead, the normal thermal activation was replaced by micro-wave activation (Table 3). Under these conditions, higher temperatures could be achieved but similar results were obtained in benzene for the two activation types (Table 3, runs 1 and 2). This was not the case in TFT where micro-wave activation led to 8.0% substitution against 3.1% in Schlenk conditions. However, a degradation of the

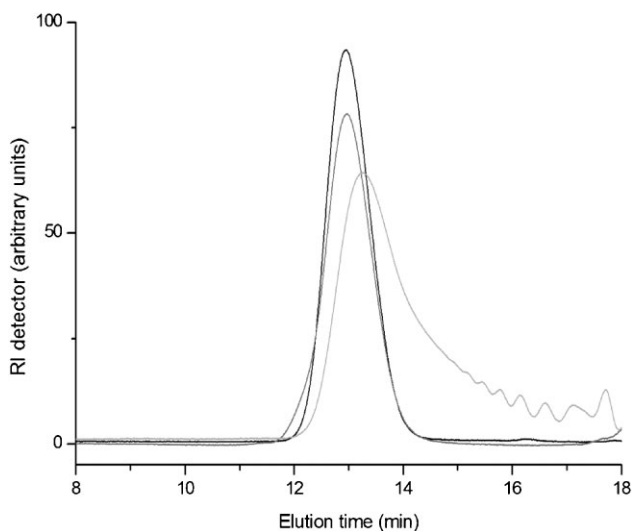
polymer chain was concomitant to this increase of substitution. Indeed, Figure 3 shows the broadening of the size exclusion chromatogram corresponding to a decrease of  $\overline{M}_{n,SEC}$  from 2 500 to 1 550 g·mol<sup>-1</sup> and an increase of dispersity from  $\mathcal{D} = 1.1$  to 2.5. Two hypotheses could explain this result: (i) higher reactivity for substitution on the polymer backbone and degradation occur concomitantly as a result of the temperature increase or (ii) the substitution increases subsequently to the degradation due to a higher reactivity of the shorter chains. This last hypothesis would lead to an inhomogeneity in terms of composition with the shorter chains being more substituted than the longer ones.

To discriminate between these possibilities, a last bromination was conducted on longer PLA chains to evaluate the influence of the molecular weight (Table 2, run 3). Approximately doubling the molecular weight from  $\overline{M}_{n,SEC} = 2 500$  g·mol<sup>-1</sup> to  $\overline{M}_{n,SEC} = 6 000$  g · mol<sup>-1</sup> induced a decrease of the substitution ratio by a factor of two. This result confirmed the strong dependence of the halogenation of PLA on the initial molecular weight. One should note that considering the degree of polymerization of these PLA, respectively being equal to 29 and 57 as determined by NMR, the 3.4% and 1.7% substitution ratios correspond to the halogenation of a single lactic unit. This led us to

Table 3. Influence of the activation process on the bromination of PLA.

Entry	Solvent	Activation	T [°C]	t [h]	$F_{Br}^a$ [%]
1	Benzene	Thermal	80	3	3.2
2	Benzene	Micro-wave	120	0.5	3.5
3	TFT	Thermal	80	3	3.1
4	TFT	Micro-wave	150	0.5	8.0

<sup>a</sup>)Determined by <sup>1</sup>H NMR (Equation 2).



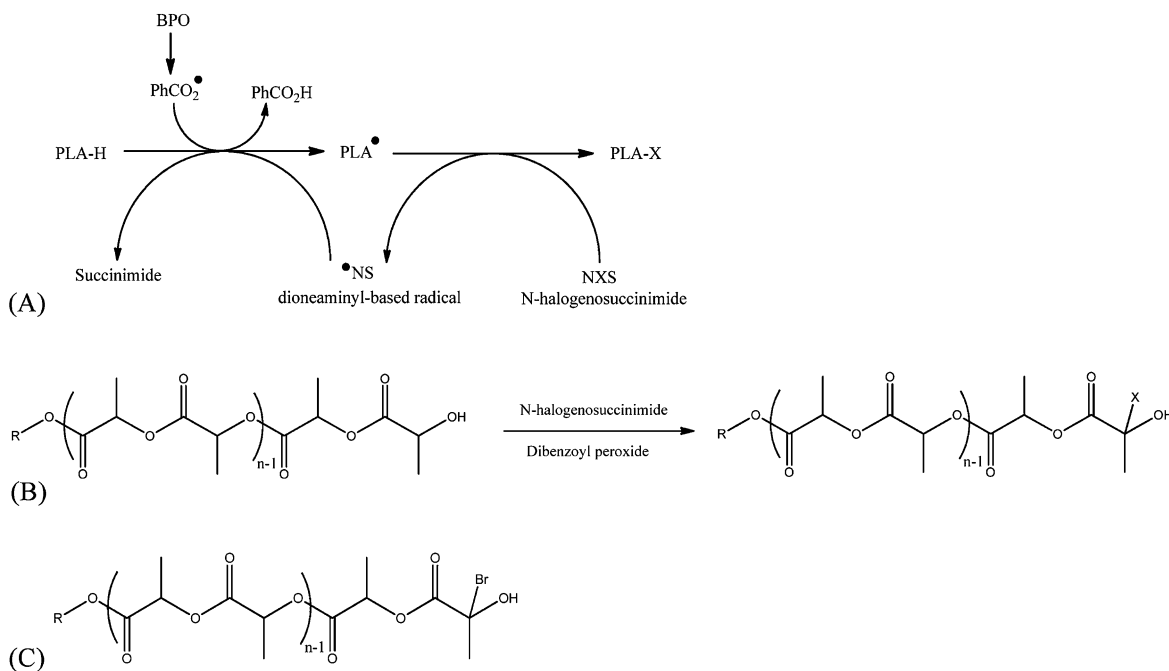
**Figure 3.** SEC traces of poly(lactide) (black line) and brominated poly(lactide) obtained by micro-wave activation in benzene (dark gray line) and TFT (light gray line).

consider as main the hypothesis the regioselective halogenation of the PLA terminal unit as shown in Scheme 2.

### 3.2. Model Compounds and Mechanism Insights

To validate this hypothesis (regioselective halogenation of PLA), halogenation was conducted on model compounds. In

a first approach, ethyl lactate was chosen to mimic the terminal lactic unit of PLA chains. Indeed, the methine proton of ethyl lactate is geminal to a hydroxyl group and presents as such a similar environment to the one of the hydroxyl chain end moiety of PLA (Supporting Information, Scheme S1). If the halogenation of PLA is regioselective and only takes place on the chain end, the halogenation of ethyl lactate is expected to be quantitative. The reaction was carried out under classical conditions, i.e., with NBS in benzene at 80 °C for 3 h. After purification, the extent of halogenation was calculated by comparison of the intensities of the signals found at 2.36 ppm corresponding to the methyl protons in the vicinity of bromine and at 1.25 ppm corresponding to the methyl protons of ethyl group (Supporting Information, Figure S2). A 75% bromination was calculated. The reaction, although not quantitative, was highly facilitated on ethyl lactate compared to PLA and even higher than the reported 62% for L-LA bromination.<sup>[29]</sup> This first result tends to support the proposed hypothesis of regioselective halogenation of PLA. To further confirm it, a second experiment was carried out on acetylated PLA. Thanks to this acetylation, the methine proton of the hydroxyl chain end moiety should now behave as the methine protons of the backbone. Thus, if occurring, the halogenation would have to take place on the lactic units of the polymer backbone too. The bromination was conducted under the same conditions as above. No substitution could be detected on the <sup>1</sup>H NMR spectrum with no detectable peak at 2.36 ppm corresponding to the



**Scheme 2.** A) Simplified mechanism of free-radical halogenation. B) Regioselective halogenation of poly(lactide) by free-radical process. C) Structure of the regioselectively brominated poly(lactide).

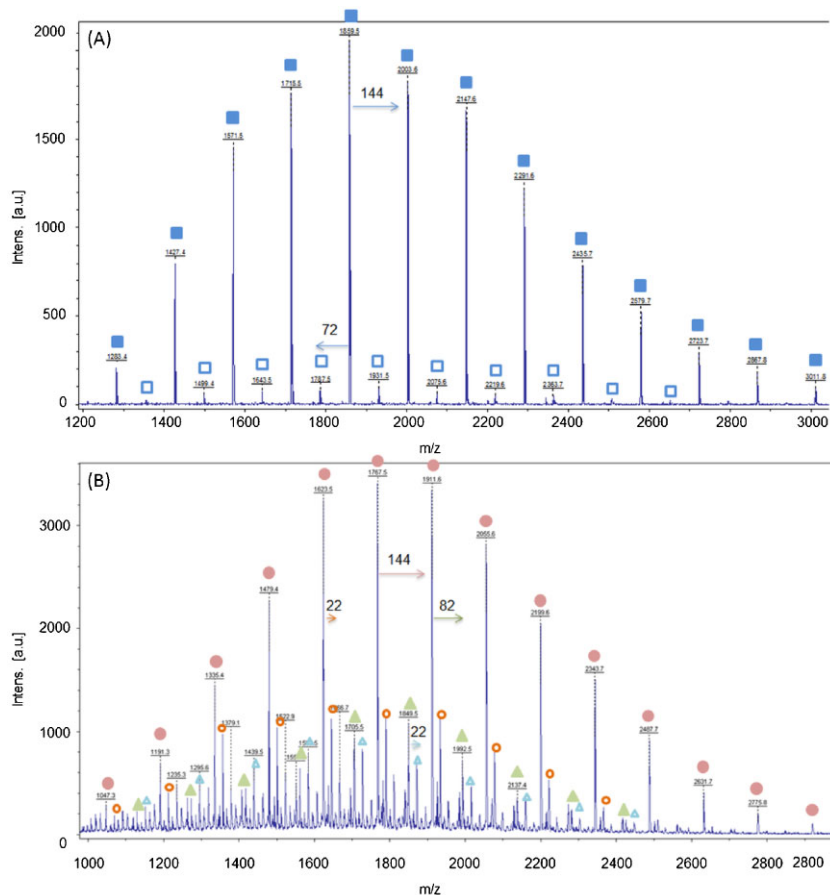


methyl protons of the bromo-substituted lactic acid moieties and only a peak at 2.10 ppm corresponding to the terminal acetyl group (Supporting Information, Scheme S2, Figure S3). This second model reaction confirmed the previous result, indicating that the halogenation of PLA is regioselective under the considered conditions and only takes place on the terminal hydroxylated moiety. This assertion was finally confirmed by MALDI-TOF analyses (Figure 4). For neat PLA analysis, the expected polymer fingerprint with ions separated by the mass of the LA dimer (144 Da) was clearly detected (Figure 4A). Indeed, the spectrum exhibited a single distribution centered at  $m/z = 1859.5$  Da, which corresponds to a sodium charged PLA chain of  $DP_{\text{lactyl unit}} = 12$  with a benzyl alcohol end-group. The minor ion distribution was assigned to the same polymer after the loss of one lactic unit by transesterification reaction ( $M_i - 72$ ). For the brominated PLA, a fingerprint with ions separated by the mass of the LA dimer (144 Da) was also obtained but more ion species were

detected compared to the neat PLA (Figure 4B). This was explained by the presence of secondary reactions occurring during the analysis of the brominated PLA. Indeed, the major ion distribution was assigned to the polymer after loss of the  $\alpha$ -terminal benzyl moiety and elimination of HBr on the  $\omega$ -terminal moiety (Supporting information, Scheme S3). The other populations found were assigned to  $\omega$ -brominated PLA ( $M_i + 82$ ) and the same polymers with  $\alpha$ -terminal sodium carboxylic acid instead of hydrogen carboxylic acid ( $M_i + 22$ ). These combined results involving  $^1\text{H NMR}$  and MALDI-TOF analyses of the PLA derivatives as well as model compounds reactions confirmed the presence of bromine on the PLA  $\omega$ -chain end. They also proved the regioselective halogenation of PLA under the considered radical process on the terminal lactic unit without substitution of the monomer units of the polymer chain (Scheme 2). Comprehensive explanation of this regioselectivity is beyond the scope of this work, but three parameters could be considered: (i) steric hindrance of the active sites on

the polymer backbone, (ii) deactivation of the reaction site on the polymer backbone, and (iii) stabilization of the radical formed at the chain end. Deactivation may occur as a result of the presence of the electro-withdrawing groups, namely the two ester groups surrounding the methine of the polymer backbone. In halogenation reaction by free-radical substitution, such electro-withdrawing groups greatly deactivate the adjacent position.<sup>[33]</sup> This is not the case for the terminal methine group which is adjacent to one ester group and geminal to a hydroxyl group which is less electro-withdrawing than ester groups and that may stabilize the formed radical by lone pair donor effect.

Beside these considerations, it is thought that the regioselectivity observed in solution reactions may also occur in reactive extrusion melt processes. First, similar substitution ratios are obtained by the two approaches. Second, it is often reported that by increasing temperature and/or the initiator concentration, an increase of substitution is obtained.<sup>[25–27]</sup> This is likely to be related to the observed slight molecular weight decrease that provides a higher concentration of chain ends available for substitution as a result of the well-described back-biting and thermohydrolysis processes. In fact, the real extent of molecular weight decrease might be



**Figure 4.** MALDI-TOF spectra of (A) PLA with ■ PLA main population; □ PLA after loss of a lactic unit by transesterification and (B) brominated-PLA with ● brominated PLA after elimination of HBr and loss of  $\alpha$ -benzyl moiety under the MALDI conditions; ▲ brominated PLA after loss of  $\alpha$ -benzyl moiety under the MALDI conditions; ○ and △ same populations as sodium adduct.



partially masked by the well-known secondary cross-linking reactions that occur in reactive extrusion process. The simultaneity of the two processes may indeed support the hypothesis of an actual higher concentration of chain ends in reactive extrusion, thus explaining the substitution behavior observed in such reactive extrusion processes.

#### 4. Conclusion

The transposition of free-radical halogenation reaction from LA to PLA has been assessed in the present work. Brominated and chlorinated PLA were successfully synthesized with a 3.5% substitution ratio (iodinated PLA was obtained with a lower substitution ratio of 0.5%, presumably because of prominent side reactions due to the fragile carbon–iodine bond). The substitution ratio was found to be independent of the studied parameters with exception to the initial molecular weight of the PLA. These results led us to hypothesize a regioselective halogenation of the methine group of the terminal lactic acid unit. This assertion was confirmed by reactions on model compounds as well as MALDI-TOF analyses. Free-radical halogenation of PLA can therefore be considered as a simple and straightforward non-degrading method for the preparation of  $\omega$ -halogenated PLA.

**Acknowledgements:** The authors thank Sylvie Hunger for NMR analyses, Aurélien Lebrun for MALDI-TOF analyses, David Rayeroux and Pascale Guiffrey for micro-wave assisted activation.

**Keywords:** biopolymers; free-radical halogenation; functionalization of polymers; poly(lactide); regioselectivity

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