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## ARTICLE

# $\gamma$ -Thiobutyrolactone - Ethylene Carbonate Decarboxylative Copolymerization, an Original Pathway to Prepare Aliphatic Oxidizable Poly( $\gamma$ -thioether ester)

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For the first time, the ring-opening copolymerization of  $\gamma$ -thiobutyrolactone and ethylene carbonate was investigated using benzyl alcohol–phosphazene bases as initiating systems. Full conversions of both monomers were obtained when the polymerization was carried out in the bulk at 90°C. The structural analysis of the products was conducted by <sup>1</sup>H, <sup>13</sup>C, 2D NMR, FT-IR and MALDI–TOF mass spectrometry. The main propagation mechanism has been determined and alternatively involves the nucleophilic ring-opening of the thiolactone by alcoholate propagating centers and the decarboxylative S-alkylation of the thiolate propagating centers. Poly(thioether-*alt*-ester) with a low percentage of carbonate unit and controlled number-average molar masses were obtained. In a second step, the thioether embedded in the copolymer main chain were oxidized in THF. Sulfoxide functional groups were quantitatively and selectively obtained in the presence of an excess of hydrogen peroxide, without noticing any trace of overoxidation to sulfone. Finally, the solubility and thermal properties of the copolymers were investigated.

## Introduction

The lactone ring-opening polymerization (ROP) has been intensively investigated, allowing the synthesis of well-defined biocompatible aliphatic polyester with good mechanical properties. In addition, the main-chain ester groups can be hydrolyzed enabling their (bio)degradation.<sup>1–3</sup> This interest is illustrated by the large number of review papers devoted either to specific lactone families, such as macrolactones<sup>4</sup> or  $\gamma$ -butyrolactones,<sup>5, 6</sup> or to synthesis methods, such as metallo-<sup>7</sup> or organo-catalysis,<sup>8</sup> enzymatic polymerization,<sup>3</sup> rare-earth metal complexes as catalysts<sup>9</sup> or stereo-selective polymerization.<sup>10</sup> However, the preparation of functional aliphatic polyester remains a challenge. Therefore, in addition to the ROP of lactones, various polymerization routes such as ROP of O-carboxyanhydrides, radical ROP of cyclic ketene acetals, and alternating copolymerization of epoxide/anhydride or epoxide/carbon monoxide have been developed to design functional aliphatic polyesters.<sup>11</sup>

Sulfide/thioether-containing polymers are currently intensively studied because of their excellent properties.<sup>12</sup> Polythioethers are industrially used as adhesives, sealants (THIOKOL® from Toray),<sup>13</sup> and coatings<sup>14</sup> (e.g. Thioplast® M from Nouryon). Polythioethers are also promising materials for solid polymer electrolytes.<sup>15, 16</sup> In addition, the hydrophobic thioether functions are prone to oxidize into hydrophilic sulfoxide or sulfone functions. This sensitivity to oxidation can be exploited in particular in the biomedical field because of the high concentration levels of reactive oxygen species (ROS) observed in some pathological cells.<sup>17, 18</sup> For example, Hubbell and coworkers have encapsulated hydrophobic drugs in poly(ethylene oxide)-poly(propylene sulfide) micelles. Then, in an oxidizing environment, the micelle destabilization and the concomitant drug release were observed.<sup>19, 20</sup> The oxidation of thioether functions embedded in polymer main chain is also a way to prepare new materials having significantly different properties from those of the starting polymer. For example, Goethals et al. have shown that the oxidation of poly(amide-*alt*-thioether)s leads to the modification of the mechanical properties with a strong increase of the Young's modulus and a strong decrease of the elongation at break.<sup>21</sup> Poly(propylene sulfoxide) is both stealth and ROS-responsive with anti-inflammatory property.<sup>22</sup> Moreover, sulfoxides and sulfones are highly polar groups, which make them interesting to increase the solubility of lithium ions in solid electrolytes.<sup>15</sup>

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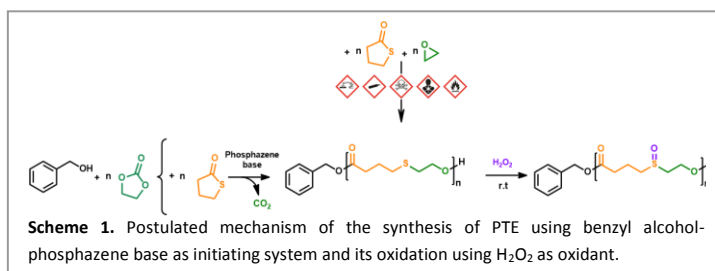
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

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Poly(thioether ester)s (PTE) are very promising (bio)materials combining the advantages of the previous polymer families with the presence in each repeating units of both (bio)degradable ester groups and oxidizable thioether groups.<sup>26</sup> Among them, poly( $\beta$ -thioether ester)s have been investigated as potential drug delivery vehicles because of the unique acid-degradable properties of the thiopropionate groups and the oxidation responsiveness of the thioether groups.<sup>23-27</sup> These poly( $\beta$ -thioether ester) polymers have been mostly synthesized by thiol-Michael addition or enzyme-catalyzed polymerization.<sup>23, 24, 28, 29</sup> Interestingly, Li *et al.* synthesized a poly( $\epsilon$ -caprolactone) analogue containing thioether groups in the main chain by living ROP of 1,4-oxathiepan-7-one.<sup>30</sup> Apart from poly( $\beta$ -thioether ester)s, there are relatively few examples in the literature of PTE having a different number of carbon atoms between the ester and thioether groups. Sato *et al.* described L-malic acid-based PTE with pendent hydroxy group to have apparent biodegradability in activated sludge.<sup>31</sup> PTE nanoparticles have been prepared by thiol-ene mini-emulsion polymerization,<sup>32, 33</sup> and have various properties, such as in vitro bio-compatibility, degradability by enzymes<sup>34</sup> or anti-oxidant activity.<sup>35</sup> Some examples of bio-based PTE have also been described using lignin-derived phenolic compounds,<sup>36</sup> furfural-derived compound,<sup>37</sup> or 10-undecenoic acid / isosorbide / butanedithiol.<sup>38</sup> Our group is interested in the use of thiolactones for macromolecular engineering<sup>39, 43</sup> and developed an easy-to-implement synthetic routes for the preparation of well-defined functional PTE by alternating ring-opening polymerization of thiolactone and epoxide monomers.<sup>41</sup> This alternating anionic ring-opening polymerization (AROP) can be applied to a large range of functional epoxides<sup>42</sup> and functional  $\gamma$ -thiolactones<sup>43</sup> opening the way to multiple promising combinations. The PTE synthesized by the alternating copolymerization of ethylene oxide and  $\gamma$ -thiobutyrolactone would be of particular interest owing to its structural simplicity, a very flexible backbone without any substituent and a very low glass transition temperature. However, ethylene oxide is a highly toxic gas, lethal by inhalation and whose handling in the laboratory is therefore specifically dangerous.<sup>44</sup> An alternative synthesis pathway is therefore highly desirable. Recently, the group of Detrembleur used the decarboxylative S-alkylation of thiol with cyclocarbonate for the design of self-blowing non-isocyanate polyurethane foams.<sup>45, 46</sup> The decarboxylation of ethylene carbonate in the presence of a soft nucleophilic thiol leading to the generation of an hydroxy group appeared to be the

ideal reactivity for an original alternating ring-opening copolymerization strategy.

In this paper, the alternating AROP of ethylene carbonate (EC) and  $\gamma$ -thiobutyrolactone (TBL) has been investigated for the first time. The resulting polymers have been thoroughly characterized and their structure fully elucidated by <sup>1</sup>H, <sup>13</sup>C, 2D-NMR, FT-IR, SEC and MALDI ToF spectrometry. Particular attention is given to the influence of the reaction conditions (solvent, temperature, strength of the base) on the control of molar mass, dispersity and the nature of the chain ends. In a second stage, the thioether groups embedded in the copolymer backbone have been oxidized by hydrogen peroxide leading to an original sulfoxide-rich copolymer structure having significantly different properties from its initial counterparts.



## Results and discussion

### PTE synthesis by AROP of $\gamma$ -thiobutyrolactone and ethylene carbonate

The aim of this study is to evaluate the feasibility of AROP of TBL and EC in order to obtain PTE alternating copolymer by using low chemical risk reactants (Scheme 1). The targeted degrees of polymerization were deliberately set at moderate values ( $X_n = 25$  and 50) so that chain ends could be easily evidenced by NMR spectroscopy.

The copolymerization of TBL and EC (Table 1, run 1) was first attempted in toluene at 25°C using benzyl alcohol and EtP<sub>2</sub> phosphazene base ( $pK_a^{MeCN} = 32.9$ )<sup>47</sup> as initiating system according to the conditions established by Puchelle *et al.* for the alternating AROP of TBL and tert-butyl glycidyl ether (tBuGE).<sup>41</sup> After 50h of reaction, no monomer conversion was noticed by <sup>1</sup>H NMR spectroscopy.

**Table 1.** Experimental conditions and molecular characteristics of PTE synthesized using benzyl alcohol and a phosphazene base as initiating system.

Run	ROH:Base:TBL:EC	Base	[M] (mol/kg)	Solvent	T° (°C)	Time (h)	Cv <sup>b</sup> (%)	Cv <sup>c</sup> (%)	M <sub>n,theo</sub> (g.mol <sup>-1</sup> ) <sup>d</sup>	X <sub>n,TBL</sub> / X <sub>n,EO</sub> / X <sub>n,EC</sub>	M <sub>n</sub> NMR (g.mol <sup>-1</sup> )	M <sub>n</sub> SEC <sup>e</sup> (g.mol <sup>-1</sup> )	Đ (SEC)
1	1:1:25:25	EtP <sub>2</sub>	2.0	Toluene	25	50	0	0	-	-	-	-	-
2	1:1:25:0	tBuP <sub>4</sub>	2.0	THF	50	48	0	0	-	-	-	-	-
3	1:1:0:25	tBuP <sub>4</sub>	2.0	THF	50	9 days	0	0	-	-	-	-	-
4	1:2:25:25	tBuP <sub>4</sub>	2.0	THF	50	46	85	86	3200	22/22/0.47	3350	2300	1.56
5	1:2:25:25	tBuP <sub>4</sub>	2.0	THF	50	46	90	95	3300	24/24/0.25	3600	2200	1.85
6	1:0.8:25:25	tBuP <sub>4</sub>	2.0	THF	50	48	49	45	1800	10/10/0.12	1600	1300	1.62
7	1:0.8:25:25	tBuP <sub>4</sub>	4.5	-	100	4.5	100	100	3750	22/22/1.37	3400	3600	2.27
8	1:0.8:25:25 <sup>a</sup>	tBuP <sub>4</sub>	4.5	-	100	3.5	92	97	3450	27/27/0.53	4000	4000	2.32
9	1:1:25:25 <sup>a</sup>	BEMP	4.5	-	100	4.5	100	100	3750	24/24/1.37	3700	3400	2.39
10	1:1:23:25	DMAP	4.5	-	100	4.5	86	96	3200	26/26/0.84	4000	3700	2.07
11	1:1:25:25	DBU	4.5	-	100	4.5	95	100	3600	27/27/0.81	4100	3800	2.05
12	1:0.8:30:25	tBuP <sub>4</sub>	4.2 / 5.0 <sup>f</sup>	-	100	4.5	80	95	3600	22/22/1.78	3500	3350	1.90
13	1:0.8:25:30	tBuP <sub>4</sub>	5.0 / 4.2 <sup>f</sup>	-	100	4.5	93	87	3300	22/22/1.60	3500	3400	2.05
14	1:0.8:50:50 <sup>a</sup>	tBuP <sub>4</sub>	4.9	-	100	8	91	99	6750	50/50/2.25	7600	7700	2.60
15	1:0.8:50:50	tBuP <sub>4</sub>	4.9	-	100	8	79	99	5500	50/50/4.17	7800	4900	2.38

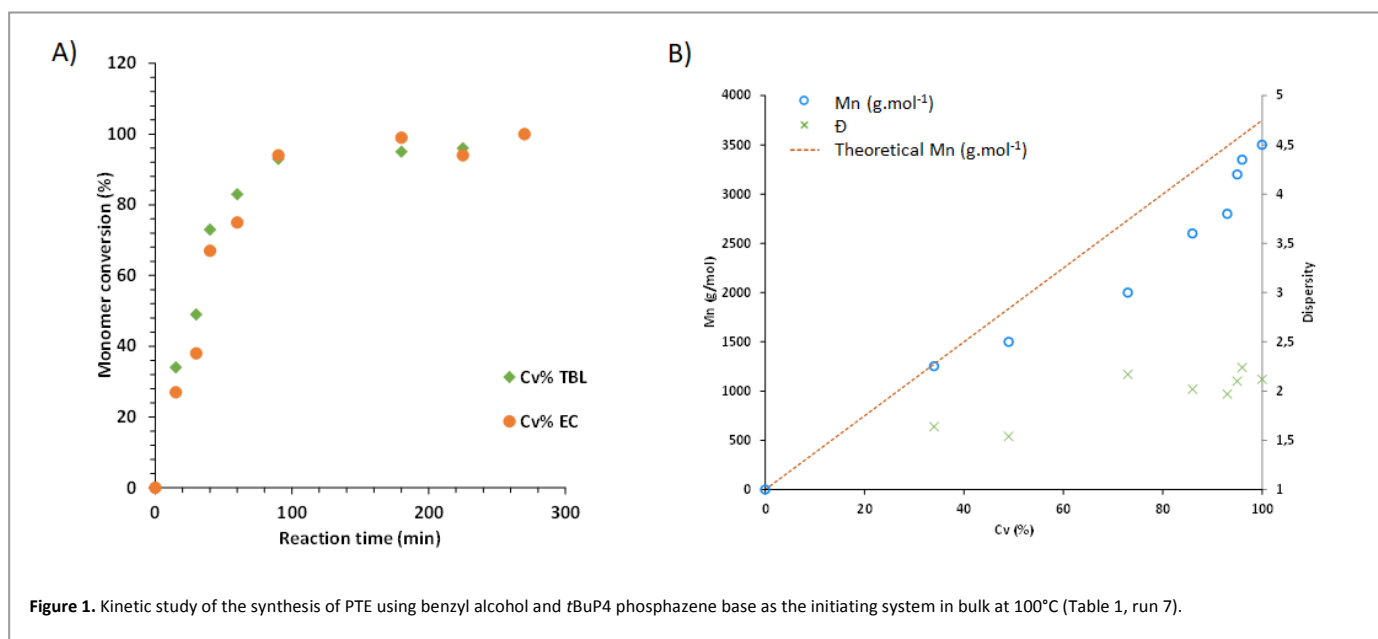
<sup>a</sup> EC dried by sublimation<sup>b</sup> γ-thiobutylolactone conversion was determined by <sup>1</sup>H NMR in DMSO-d<sub>6</sub> of the reaction media by comparing the signals corresponding to the CH<sub>2</sub> in β position of the repeating unit ester group to the corresponding CH<sub>2</sub> of the monomer.<sup>c</sup> Ethylene carbonate conversion was determined by <sup>1</sup>H NMR in DMSO-d<sub>6</sub> of the reaction media by comparing the signals corresponding to the CH<sub>2</sub> in α position of the repeating unit thioether to the corresponding CH<sub>2</sub> of ethylene carbonate.<sup>d</sup> M<sub>n,theo</sub> is calculated considering a perfectly alternating structure initiated by benzyl alcohol according to the following equation:

$$M_{n,theo} = M_{benzyl\ alcohol} + (M_{TBL} + M_{EO}) \times X_{n,limiting\ monomer}^0 \times p_{TBL}$$

<sup>e</sup> Determined by SEC (THF, 40°C, poly(methacrylate) standards).<sup>f</sup> [ethylene carbonate] / [TBL]

The use of a more polar solvent combined with a higher pKa phosphazene base improved the reactivity of the system (Table 1, run 4-6). Thus, TBL and EC were successfully copolymerized in THF at 50°C using benzyl alcohol and tBuP<sub>4</sub> (pK<sub>a</sub><sup>MeCN</sup> = 42.7)<sup>47</sup> as initiating system. Gas bubbling was observed throughout the reaction, which is consistent with the postulated polymerization mechanism and a decarboxylative S-alkylation (Scheme 1). EC conversion was determined by <sup>1</sup>H NMR of the reaction medium in DMSO-d<sub>6</sub> by comparing the signals corresponding to the -CH<sub>2</sub>- of the ethylene oxide monomer unit ester located at 2.72 ppm to the -CH<sub>2</sub>- of ethylene carbonate located at 4.48 ppm (Figure S7). TBL conversion was determined by comparing the signals corresponding to the -CH<sub>2</sub>- of the TBL monomer unit at 1.78 ppm to the -CH<sub>2</sub>- of

TBL located at 2.18 ppm (Figure S7). The final monomer conversions of both monomers are equal. In addition, under similar conditions, no homopolymerization of TBL or EC occurred (Table 1, runs 2 and 3) suggesting an alternating mechanism. The polymerization was carried out using either 1:2 or 1:0.8 benzyl alcohol/tBuP<sub>4</sub> ratios (Table 1, runs 4-5 and 6, respectively). Run 4 and 5 were performed under identical conditions in order to confirm the reproducibility. In all cases, the experimental number-average molar masses M<sub>n</sub> determined by SEC are lower than the theoretical ones. Such a difference in the molar masses as well as a broad dispersity can reflect the occurrence of side reactions such as intramolecular transesterifications resulting in the generation of alternating macrocycles as reported by Puchelle *et al.* for the alternating



**Figure 1.** Kinetic study of the synthesis of PTE using benzyl alcohol and *t*BuP<sub>4</sub> phosphazene base as the initiating system in bulk at 100°C (Table 1, run 7).

copolymerization of oxiranes and  $\gamma$ -thiobutyrolactones catalyzed by a phosphazene base.<sup>41</sup> We assume that the low-molar-masses multiple peaks, which are visible on the SEC traces, correspond to these macrocycles (Figure 2). In addition, the reaction kinetics are rather slow, thus limiting the achievable  $M_n$ .

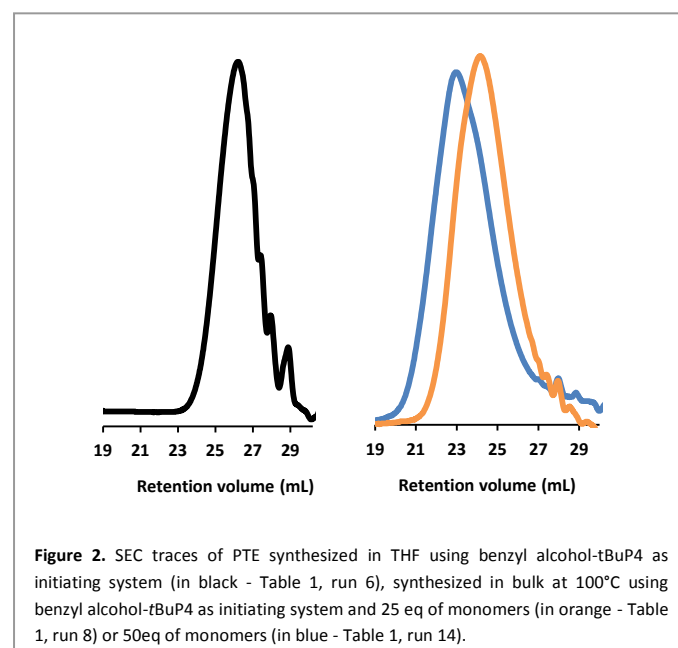
In order to increase the propagation rate, the following reactions were performed in bulk at 100°C (Table 1, runs 7-14). Under these conditions, TBL and EC are both liquid and fully miscible. A detailed kinetics experiment was carried out using *t*BuP<sub>4</sub> as base (Table 1, run 7). As shown on Figure 1.A, conversions of both monomers TBL and ethylene carbonate increased equally with time as expected for an alternating copolymerization. Full monomer conversions were achieved after only 3 h. The reaction was first order with respect to the monomer over the entire conversion range which shows the absence of termination reactions (Figure S6). Higher  $M_n$  were obtained compared to the reactions performed in THF. As shown on Figure 1.B,  $M_n$  increased linearly with the monomer conversion and a good agreement with the theoretical molar masses is observed for all the monomer conversions. However, a progressive broadening of the dispersity is observed, which suggest the occurrence of intermolecular transesterification reactions. After purification by dialysis, experimental molar masses determined by <sup>1</sup>H NMR and SEC are in good agreement with the theoretical one. Run 8 was carried out under the same conditions but using EC monomer purified by sublimation. Similar results were obtained in term of  $M_n$  and  $\bar{D}$  with or without sublimation, the use of such a time-consuming purification process has been discarded.

In Table 1, runs 9-11, the use of BEMP phosphazene base ( $pK_{a_{MeCN}} = 27.6$ ), DMAP ( $pK_{a_{MeCN}} = 17.9$ ) or DBU ( $pK_{a_{MeCN}} = 12.8$ ) instead of *t*BuP<sub>4</sub> did not have a significant impact on the results: very high monomer conversions after 4.5 h, broad  $\bar{D}$  and good agreement between  $M_{n,theo}$ ,  $M_{n,NMR}$  and  $M_{n,SEC}$ . When the copolymerization of TBL and EC were performed under different feed ratios (Table 1, runs 12 and 13), the conversion of the excess reactant is strictly lower than the one of the limiting reactant. In

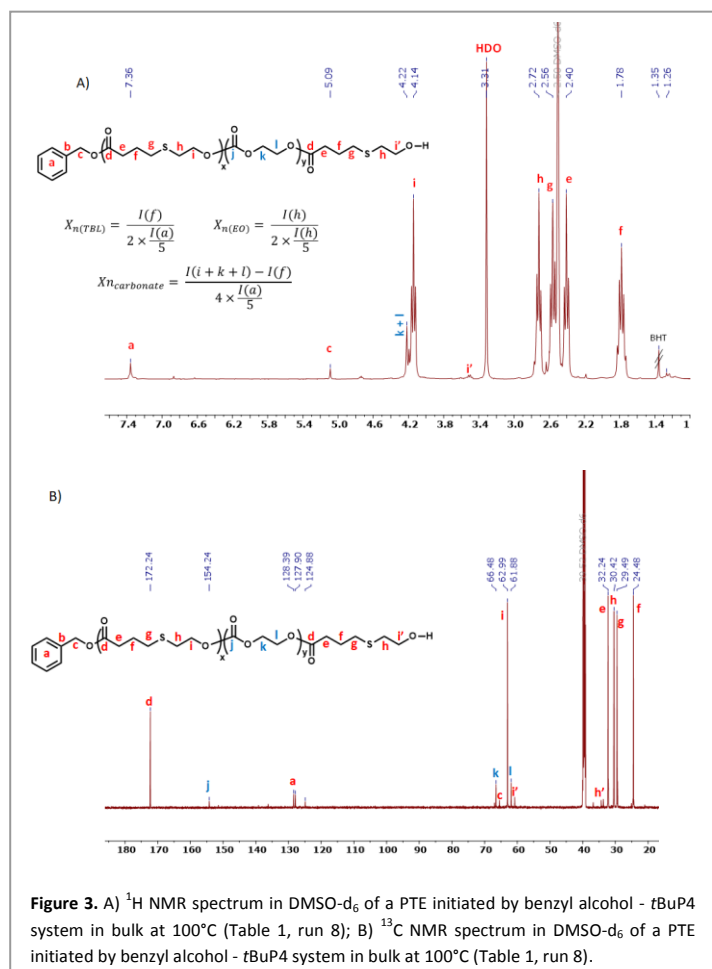
addition, as expected for strictly alternating copolymerization,  $X_{n,TBL}$  is equal to  $X_{n,EO}$ . Finally, run 14 (Table 1) was carried out using a ratio  $[OH]_0/[tBuP_4]_0/[EC]_0/[TBL]_0 = 1/0.8/50/50$ , aiming higher degrees of polymerization. Full monomer conversions were achieved within 8 h and the resulting copolymer was characterized by SEC (Figure 2).  $M_{n,SEC}$  is in very good agreement with  $M_{n,theo}$  and  $M_{n,NMR}$ .

All the copolymers were purified by dialysis in a regenerated cellulose membrane of 1 kDa molecular cut-off against THF and then carefully characterized by <sup>1</sup>H, <sup>13</sup>C NMR, <sup>1</sup>H-<sup>1</sup>H COSY and <sup>1</sup>H-<sup>13</sup>C HSQC. All copolymers display very similar spectroscopic data.

The majority of the NMR signals are consistent with the postulated alternating structure initiated by a benzyloxy group (Figures 3, S8 and S9). In particular, the <sup>1</sup>H NMR triplet at 4.14 ppm can be attributed to a -CH<sub>2</sub>- of an ethylene oxide-like unit involved in an ester link, which strongly supports an alternating mechanism.



**Figure 2.** SEC traces of PTE synthesized in THF using benzyl alcohol-*t*BuP<sub>4</sub> as initiating system (in black - Table 1, run 6), synthesized in bulk at 100°C using benzyl alcohol-*t*BuP<sub>4</sub> as initiating system and 25 eq of monomers (in orange - Table 1, run 8) or 50eq of monomers (in blue - Table 1, run 14).



In addition, the integration ratio of the signals corresponding to the  $-\text{CH}_2-$  protons of the ethylene oxide unit at 2.72 and 4.14 ppm (i and h, on Figure 3.A) and to the  $-\text{CH}_2-$  of the TBL unit at 1.78, 2.40 and 2.56 ppm (f, e and g, on Figure 3.A) are once again in favor of an alternating structure of the chains.

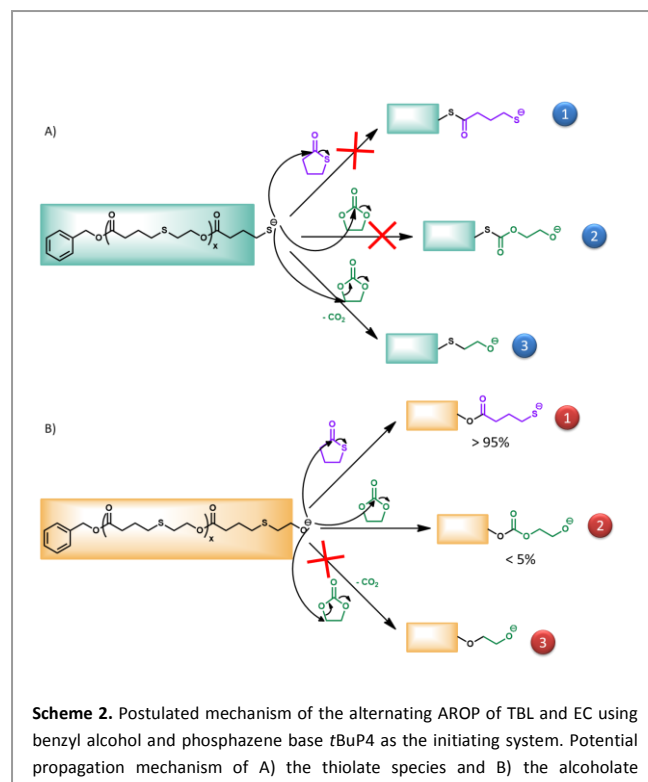
Signals corresponding to a  $-\text{CH}_2-$  next to the sulfur atom of a thiocarbonate group are not visible between 2.8 and 3.5 ppm on the  $^1\text{H}$  NMR spectrum (Figure 3.A). On the contrary, the two emerging triplets at 2.56 and 2.72 ppm are assignable to methylene groups in  $\alpha$  position of a thioether group. This demonstrates that during the propagation the thiolate anions did not undergo an ethylene oxide carbonyl attack and exclusively reacted through a decarboxylative S-alkylation mechanism (Scheme 2.A). This result is in agreement with the Pearson's hard-soft acid-base theory and the result previously reported by the group of Detrembleur for the synthesis of self-blowing polyurethane foams.<sup>45</sup>

The absence of signals corresponding to polyether blocks between 3.6 and 3.8 ppm proves that during the propagation, alcoholates did not attack the nucleophilic methylene of ethylene carbonate (Scheme 2.B, reaction 3). The alcoholates anions can therefore only undergo the nucleophilic attack of the carbonyl group of the TBL or of the EC (Scheme 2.B, reactions 1 and 2). The

signals at 4.14 and 2.40 ppm corresponding to  $-\text{CH}_2-$  next to an ester group demonstrate that the nucleophilic attack of the thiolactone is the main reaction. However, a smaller peak at 4.22 ppm can be attributed to methylene protons adjacent to a carbonate moiety corresponding to the attack and ring-opening of the EC.<sup>48</sup> The degrees of polymerization of the 3 monomer units (TBL, ethylene oxide and ethyl carbonate) were calculated using the  $^1\text{H}$  NMR spectra according to the formula in Figure S7 and are reported in Table 1. For all the synthesized copolymers, the carbonate units are a very small minority (less than 2.5 % of the total degree of polymerization). This result is supported by the  $^{13}\text{C}$  NMR spectrum in which the peak of the ester carbonyl group at 172.2 ppm is much larger than the one of the carbonate carbonyl group at 154.2 ppm (Figure 3.B).<sup>48</sup> Moreover, a single carbonyl absorption band belonging to an ester is observed at  $1726\text{ cm}^{-1}$  on the FTIR spectrum of the copolymer (Figure S10). No characteristic carbonyl band of a carbonate could be found in the spectrum. In particular, no band corresponding to a carbonate carbonyl group could be detected.

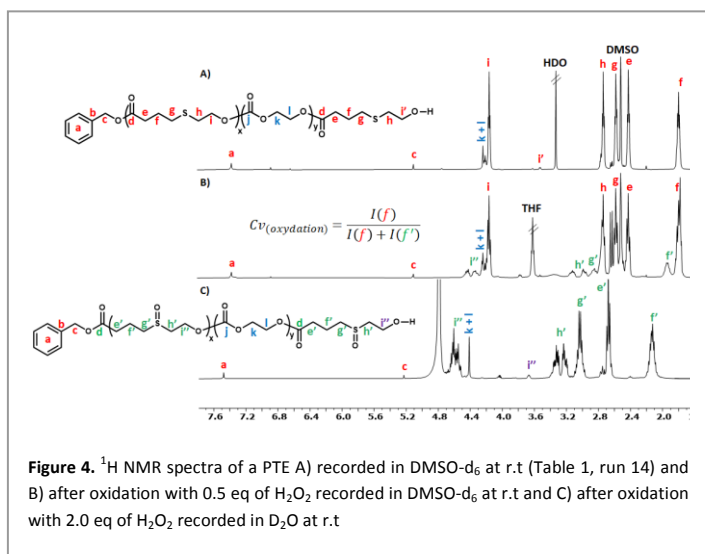
The MALDI-ToF spectrum of the copolymer synthesized in run 8 (Table 1) is shown on Figure S11. The desorption of the polymer is very challenging and it was only possible to record a spectrum in linear mode, in which several distributions are visible. It is worth noting that the molar mass difference between two consecutive peaks of a same population is always equal to the exact molar mass of the TBL/EO repeating unit of a perfectly alternating structure ( $146\text{ g}\cdot\text{mol}^{-1}$ ). The complete attribution of the different populations was not possible. However, 3 populations are attributed to macrocycles generated by backbiting reactions (Figure S12) as already observed by Puchelle *et al.*<sup>41</sup>

### PTE oxidation

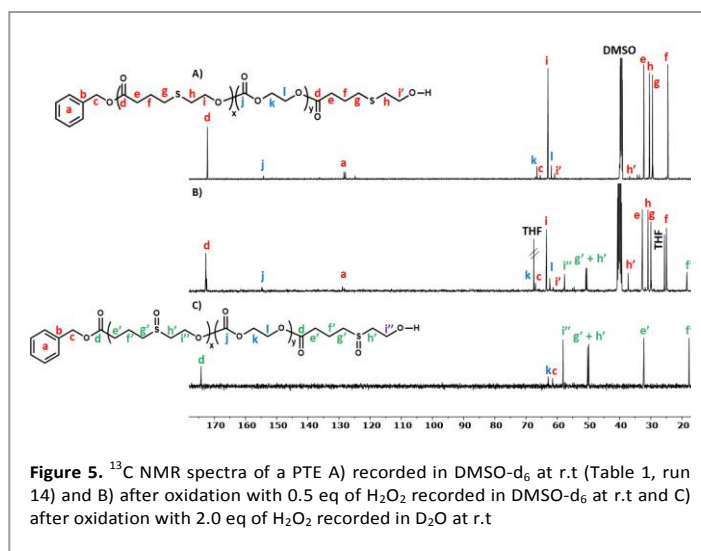


In a second time, the oxidation of the thioether groups of the copolymer main repeating unit was investigated. The PTE obtained in Table 1, run 14 was dissolved in THF and stirred overnight at room temperature in the presence of 0.5 or 2.0 eq. of  $\text{H}_2\text{O}_2$  per thioether group. After purification by dialysis, the oxidation was assessed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR, and FTIR. The  $^1\text{H}$  NMR spectra demonstrates the partial oxidation (25%, determined according to the equation on Figure 4.B) of the thioether in sulfoxide groups when 0.5 eq.  $\text{H}_2\text{O}_2$  have been used and the quantitative oxidation for 2 eq. of  $\text{H}_2\text{O}_2$  (Figure 4.C). During the oxidation, the signals of the  $-\text{CH}_2-$  in  $\alpha$  position of the thioether at 2.56 and 2.72 ppm disappear and are replaced by two multiple peaks between 2.79 - 2.87 and 2.90 - 3.15 ppm in  $\text{DMSO}-d_6$  (2.98-3.15 and 3.20-3.45 ppm in  $\text{D}_2\text{O}$ ), presumably ascribed to methylene groups in  $\alpha$  position of sulfoxides (h and g, Figure 4.B). These attributions are supported by the  $^1\text{H}-^1\text{H}$  COSY and  $^1\text{H}-^{13}\text{C}$  HSQC 2D NMR spectra (Figures 6) and are consistent with those found in the literature for polysulfoxides with a close structure.<sup>15, 24, 27</sup> It is worth noting that the singlet attributed to the carbonate unit remains visible at 4.41 ppm. The successful oxidation of the thioether in sulfoxide groups is confirmed by  $^{13}\text{C}$  NMR spectra in  $\text{D}_2\text{O}$  (Figure 5) with the disappearance of the thioether signals at 29.49 and 30.42 ppm and the appearance of the methylene in  $\alpha$  position of sulfoxide groups at 50.03 and 50.31 ppm in  $\text{DMSO}-d_6$  (49.93 and 50.21 ppm in  $\text{D}_2\text{O}$ ). Moreover, we notice that no peaks could be attributed to sulfones even in the presence of an excess of  $\text{H}_2\text{O}_2$ . This selective oxidation is in agreement with the results obtained by the group of Tew for the oxidation of poly(ether thioether)s using 10 eq. of  $\text{H}_2\text{O}_2$  per thioether group.<sup>15</sup> The selective oxidation of thioether groups was further confirmed by FT-IR analyses. After stirring overnight in an aqueous  $\text{H}_2\text{O}_2$  solution, new stretching vibration signals appeared at 1007 et 1038  $\text{cm}^{-1}$ , corresponding to the sulfoxide stretching frequency (Figure S13). These values are in agreement with those reported in the literature for polysulfoxides with comparable structures.<sup>24, 27</sup>

The oxidation reaction transformed hydrophobic thioethers into hydrophilic sulfoxides. This change led to a drastic modification



**Figure 4.**  $^1\text{H}$  NMR spectra of a PTE A recorded in  $\text{DMSO}-d_6$  at r.t (Table 1, run 14) and B) after oxidation with 0.5 eq of  $\text{H}_2\text{O}_2$  recorded in  $\text{DMSO}-d_6$  at r.t and C) after oxidation with 2.0 eq of  $\text{H}_2\text{O}_2$  recorded in  $\text{D}_2\text{O}$  at r.t



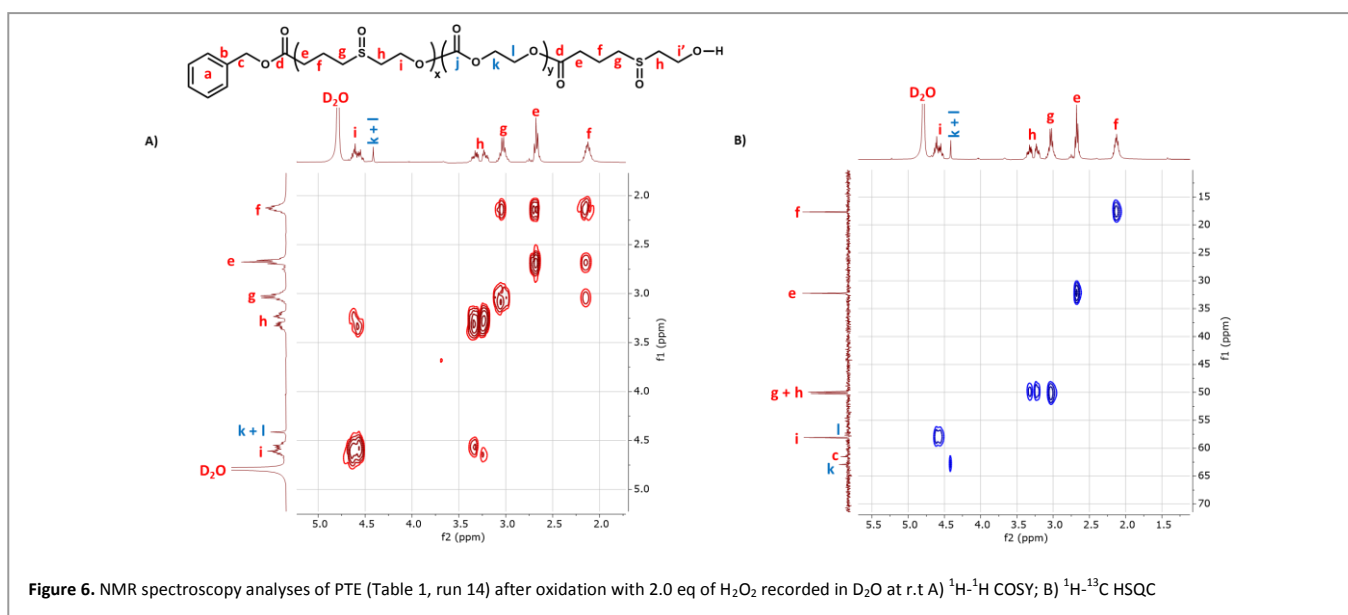
**Figure 5.**  $^{13}\text{C}$  NMR spectra of a PTE A recorded in  $\text{DMSO}-d_6$  at r.t (Table 1, run 14) and B) after oxidation with 0.5 eq of  $\text{H}_2\text{O}_2$  recorded in  $\text{DMSO}-d_6$  at r.t and C) after oxidation with 2.0 eq of  $\text{H}_2\text{O}_2$  recorded in  $\text{D}_2\text{O}$  at r.t

of the solubility properties of the copolymers after oxidation (Table 2). Interestingly, the fully oxidized copolymer is water-soluble at room temperature, whereas PTE is not soluble. In order to assess the stability of the main chain during oxidation, a PTE with a  $M_n$  of  $4900 \text{ g}\cdot\text{mol}^{-1}$  (Table 1, run 15) was oxidized and analyzed in aqueous SEC. The oxidized polymer has a molar mass of  $2600 \text{ g}\cdot\text{mol}^{-1}$  showing a partial degradation of the backbone. This degradation is nevertheless limited (approximately one cut per initial macromolecules). In addition, no ester bond scission could be detected based on the comparison of integrals of methylene i versus methylene f in  $^1\text{H}$  NMR spectrum (Figure 4).

The thermal behaviors of PTE before and after oxidation ( $\text{PTE}_{\text{ox}}$ ) were determined using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Their thermal stabilities and characteristics are summarized in Table 2.

A one-step degradation profile was observed for poly(TBL-*alt*-EO) as shown on Figure S14. The decomposition after 5% weight loss occurred at  $276^\circ\text{C}$  and is followed by a rapid weight loss with a maximum degradation rate located at  $354^\circ\text{C}$ . This degradation temperatures are similar to those of poly(TBL-*alt*-BO) and are due to the carbon-sulfur bond, which is the weakest linkage in the copolymer structure. After oxidation, the decomposition after 5% weight loss occurred at  $217^\circ\text{C}$  with a maximum degradation rate around  $243^\circ\text{C}$ . Thus, sulfoxide-containing copolymer seems significantly less thermally stable than its precursor thioether-containing polymer, which is in agreement with previously reported results.<sup>15</sup>

Poly(TBL-*alt*-EO) exhibits a  $T_g$  value equal to  $-63^\circ\text{C}$  witnessing the flexible nature of thioether bonds (Figure S15). The polymer showed no tendency to crystallize and no melting temperature was detected at any heating rate (2 or  $10^\circ\text{C}/\text{min}$ ). Thus, the polymer is amorphous contrary to what was expected for such a simple structure and to what has been observed in the literature for the semi-crystalline poly(7-heptalactone), the analogue polyester without thioether. It is possible that crystallization is prevented by carbonate unit defects. However, similar observations have previously been done for polycaprolactone and its sulfur-containing



analogue PTE. These results have been attributed to the bulkiness of the sulfur atom hindering the crystallization.<sup>23</sup>

Oxidized poly(TBL-*alt*-EO) was analyzed by DSC. The first cycle was performed at a heating/cooling rate of 10°C/min. During the first heating, a T<sub>g</sub> and a T<sub>m</sub> are visible with a latent heat of melting equal to 36 J/g. It is noteworthy that during the first cooling at 10°C/min the latent heat of crystallization is only 21 J/g, suggesting a slow and incomplete crystallization. The polymer sample was subsequently analyzed at a 2°C/min heating/cooling rate (Figure S17). During the first heating at 2°C/min, the DSC analysis shows a semi-crystalline profile with a T<sub>g</sub> value of -1°C, a cold crystallization temperature (T<sub>c</sub> = 30.5°C, 21 J/g) and a melting temperature equal to 133°C (44 J/g). The T<sub>g</sub> of oxidized poly(TBL-*alt*-EO) is +62 °C higher than the one of poly(TBL-*alt*-EO). This result is expected as the increase in polarity allows for stronger dipole-dipole interactions, which would in turn increase the T<sub>g</sub>.<sup>15</sup> A crystallization temperature (T<sub>c</sub>) equal to 89°C (45 J/g) was measured during the cooling at 2 °C/min. An additional scan was carried out at 2°C/min showing similar T<sub>g</sub>, T<sub>f</sub> and T<sub>c</sub> but without cold crystallization exotherm. It seems that a cooling rate of 10°C/min is too fast to enable an efficient crystallization process. On the contrary, at 2°C/min, the heating rate is slow enough to enable the crystallization. These results show the great impact of thioether oxidation transforming the amorphous copolymer into a slow-to-crystallize polymer with improved thermal properties and water solubility.

## Experimental part

### Materials

Ethylene carbonate (98%, Aldrich), phosphazene base 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) solution (1.0 mol.L<sup>-1</sup> in hexane, Sigma-Aldrich), phosphazene base *t*BuP<sub>4</sub> solution (0.8 mol.L<sup>-1</sup> in hexane, Sigma-Aldrich), phosphazene base P<sub>2</sub>-Et (Sigma-Aldrich), 4-(Dimethylamino)pyridine (Sigma-Aldrich), 1,8-

Diazabicyclo[5.4.0]undec-7-ene solution (Sigma-Aldrich), benzyl alcohol (99.8% anhydrous, Sigma-Aldrich), CaH<sub>2</sub> (93%, 0-2mm grain size, Sigma-Aldrich) and hydrogen peroxide H<sub>2</sub>O<sub>2</sub> (30% in water, Sigma-Aldrich) were used as received. γ-thiobutyrolactone (TBL) (98%, Sigma-Aldrich) was distilled over CaH<sub>2</sub> twice prior use. THF and toluene were dried with an MBRAUN MB SPS-800 solvent purification system under nitrogen.

### Instruments

<sup>1</sup>H, <sup>13</sup>C NMR, <sup>1</sup>H-<sup>1</sup>H COSY and <sup>1</sup>H-<sup>13</sup>C HSQC spectra were recorded in DMSO-*d*<sub>6</sub> or D<sub>2</sub>O using a Bruker 300 MHz, 400 MHz or 600 MHz spectrometer.

Dialysis membranes are Spectra/Por® Dialysis Membrane with 1 kDa cut-off size.

FT-IR spectra were collected using a Thermo-Fisher Nicolet iS5 spectrometer with an iD5 Attenuated Total Reflectance (ATR) accessory and equipped with a diamond crystal.

Size Exclusion Chromatography analyses (SEC) PTE were carried out on three PL gelMixed-C 5μm columns (7.5 × 300 mm; separation limits: 0.2 - 2000 kg.mol<sup>-1</sup>) maintained at 40°C and equipped with a Viscotek GPCmax delivery module and two modular detectors: a Viscotek 3580 differential refractive index (RI) detector and a Shimadzu SPD20-AV diode array UV detector. THF was used as the mobile phase at a flow rate of 1 mL.min<sup>-1</sup>, toluene was used as a flowrate marker. All polymers were injected (100 μL) at a concentration of 5 mg.mL<sup>-1</sup> after filtration through a 0.45 μm pore-size PTFE membrane. The OmniSEC 4.6.2 software was used for data acquisition and analysis. Number-average molar masses (M<sub>n</sub>), weight-average molar masses (M<sub>w</sub>) and dispersities Đ were calculated from poly(methyl methacrylate) standards.

The thermal decomposition of polymers was evaluated by thermogravimetric analysis (TGA) using a TA G50 apparatus. The experiments were performed under a stream of nitrogen using a 10°C/min ramp from room temperature to 600°C. Analyses by differential scanning calorimetry (DSC) were carried out using a TA



**Table 2.** Thermal properties of functional polyesters

Entry	Chemical nature	T <sub>g</sub> [°C]	T <sub>m</sub> [°C]	T <sub>d,5%</sub> [°C] <sup>a</sup>	T <sub>deg,max</sub> [°C] <sup>b</sup>	Ref
1	Poly(caprolactone) = PCL	-60	65	nd	nd	49
2	Poly(1,4-oxathiepan-7-one) = S-PCL <sup>c</sup>	-49 <sup>f</sup>	22 (2 J/g)	274	301	23, 30
3	Poly(7-heptalactone) = PolyHL <sup>d</sup>	-45 <sup>g</sup>	65 (88.7 J/g)	nd	nd	50, 51, 52
4	PTE	-63	-	276	354	This work
5	PTE <sub>ox, 0.5 eq</sub> <sup>e</sup>	-50	74 (2.5 J/g)	215	320	This work
6	PTE <sub>ox, 2 eq</sub> <sup>e</sup>	-1	133 (46.6 J/g)	217	243	This work
7	Poly(TBL- <i>alt</i> -BO)	-57 <sup>f</sup>	-	296 <sup>h</sup>	318	41

<sup>a</sup> Decomposition temperature after 5% weight loss.<sup>b</sup> Decomposition temperature at maximum degradation rate (derivative thermogravimetry).<sup>c</sup> Synthesized by ROP of non-commercially available 1,4-oxathiepan-7-one or by lipase-catalyzed polycondensation of methyl 3-((2-hydroxyethyl)thio)propanoate (MHETP).<sup>d</sup> Synthesized by ROP of 7-heptalactone.<sup>e</sup> After oxydation in THF with 0.5 or 2.0 eq of H<sub>2</sub>O<sub>2</sub> per repeating unit at room temperature and dialysis in 1 kDa membrane in water.<sup>f</sup> Determined by DSC at 10 °C/min ; <sup>g</sup> Determined by DSC at 20 °C/min<sup>h</sup> Degradation temperature after 10 % weight loss.

DSC Q2000 instrument calibrated with indium standards. The sample (10-15 mg) was placed in an aluminum cell and initially cooled at -85°C. At least two heating (10°C.min<sup>-1</sup> or 2°C.min<sup>-1</sup>) – cooling (10°C.min<sup>-1</sup> or 2°C.min<sup>-1</sup>) cycles were then applied in the -85 - 200°C range.

Mass spectra were recorded by matrix-assisted desorption and ionization time-of-flight (MALDI-ToF) mass spectrometry (MS) using a Bruker autoflex Speed mass spectrometer, equipped with a 1 kHz laser that produces pulses at 355 nm using trans-2-[3-(4-tert-Butylphenyl)-2-methyl-2-propenylidene] malononitrile (DCTB) as a matrix and NaI as cationizing agent. Spectra were recorded in linear mode at an accelerating potential of 19.5 kV. Samples were prepared by dissolving the polymer in THF at a concentration of 5 mg.mL<sup>-1</sup>. 10 µL of polymer solution was mixed to 20 µL of matrix solution and 20 µL of NaI solution (both at a concentration of 20mg.mL<sup>-1</sup>). Polyethylene glycol - diOH of known structure, M<sub>n</sub> = 1500 g.mol<sup>-1</sup> was used to calibrate the mass scale.

#### General copolymerization procedure

The copolymerization was carried out according to the following typical procedure. In a glove-box, 1.0 mL of THF, 13 µL of benzyl alcohol (1 eq, 0.1256 mmol), 277 mg of ethylene carbonate (25 eq, 3.1406 mmol) and 272 µL of γ-thiobutyrolactone (25 eq, 3.1406 mmol) were introduced under nitrogen into a polymerization tube. Then, 125µL of phosphazene base tBuP<sub>4</sub> solution (0.8 eq, 0.1 mmol) were added using a microsyringe. After closure of the flask, the reaction mixture was stirred at 50°C and left to react for the required period of time. After the reaction, the PTE was dissolved in THF and dialyzed in regenerated cellulose membrane (Spectra/Por® Dialysis Membrane with 1 kDa cut-off size) against THF for 24h in order to remove residual monomers and most of the base. After removing the dialysis solvent under vacuum at 60°C, the brown viscous product was obtained. The copolymer

was subsequently dissolved in CH<sub>2</sub>Cl<sub>2</sub>, stirred for 30 min in the presence of neutralized aluminum oxide, and purified by passing through neutralized aluminum oxide in order to fully remove the residual base. Deviations from this general procedure are summarized in Table 1. For the kinetic study (Figures 1 and S6), eight reactions were performed simultaneously under the same conditions and quenched at different times. The final reaction mixtures were then analyzed by <sup>1</sup>H NMR and SEC in THF. The monomer conversions were determined by <sup>1</sup>H NMR according to the equations shown in Figure S7. M<sub>n</sub> and Đ were determined by SEC. Table 1, run 7 corresponds to the last point of the kinetic study.

#### Polymer oxidation

In a vial, 200 mg of polymer was dissolved in 2 mL of THF. Then, 0.21 mL of H<sub>2</sub>O<sub>2</sub> at 30% in water (2 eq per repeating unit) were added to the media and left overnight under stirring at room temperature. Then, the product was dialyzed in cellulose membrane (Spectra/Por® Dialysis Membrane with 1 kDa cut-off size) against THF for 24h. After removing the dialysis solvent under vacuum at 60°C, a light brown brittle product was obtained.

#### Conclusion

We report for the first time the alternating ring-opening copolymerization of γ-thiobutyrolactone with ethylene carbonate. The prepared copolymers have been fully characterized and are mainly constituted of repeating units resulting from the ring-opening of the thiolactone followed by a decarboxylative S-alkylation of the generated thiol by ethylene carbonate. The presence of carbonate defects in the main chain results from the nucleophilic attack of the carbonyl of the cyclocarbonate but

remains limited (between 0.5 and 3 % of all the monomer units depending of the reaction conditions). This new synthesis pathway is a promising alternative to conventional thiol-ene polyaddition in order to prepare PTE with a cleavable ester group and a ROS-sensitive group in each repeating unit. The scope can potentially be extended to numerous thiolactone and cyclocarbonate monomers. In a second step, the thioether groups have been selectively and quantitatively oxidized by H<sub>2</sub>O<sub>2</sub> in order to generate water-soluble sulfoxide-containing copolymers. The properties of this new non-ionic polar polymers are currently under investigation with potential applications in nanotechnology and in various biomedical applications due to the high polarity, the high dielectric constant and oxydo-reduction properties of the sulfoxide groups.

## Supporting Information

<sup>1</sup>H, <sup>13</sup>C and COSY NMR spectra of TBL in DMSO-*d*<sub>6</sub>; <sup>1</sup>H and <sup>13</sup>C NMR spectra of EC in DMSO-*d*<sub>6</sub>; kinetic study of PTE synthesis in bulk (Table 1, run 8); <sup>1</sup>H NMR spectra of the reaction mixture of PTE in DMSO-*d*<sub>6</sub> (Table 1, run 8) and determination of monomers conversions; <sup>1</sup>H-<sup>13</sup>C and <sup>1</sup>H-<sup>15</sup>N HSQC NMR spectra of PTE in DMSO-*d*<sub>6</sub> (Table 1, run 8); ATR FT-IR of PTE before and after its oxidation (Table 1, run 14); MALDI-ToF spectra of PTE (Table 1, run 8); TGA and DSC curves of PTE (Table 1, run 8) and of PTE<sub>ox</sub> (Table 1, run 14); postulated mechanism of the transesterification reaction and the solubility of PTE and PTE<sub>ox</sub>.

## Author Contributions

Emma Mongkhoun – Investigation and writing - original draft; Philippe Guégan – Resources, supervision, review and editing; Nicolas Illy – Conceptualization, supervision, review and editing.

## Conflicts of interest

There is no conflict to declare.

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