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# On-demand degradation of thioester/thioketal functions in vinyl pivalate-derived copolymers with thionolactones

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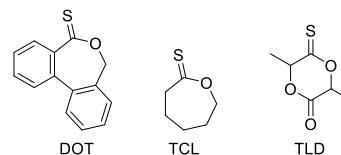
**ABSTRACT:** Copolymers containing thioester and thioketal groups were obtained by copolymerization of 5- to 7-membered ring thionolactones (TL) with vinyl pivalate (VP). With the help of a degradation study on thioester and thioketal model compounds, we report orthogonal reactivity of such incorporated links with thioesters being selectively cleaved by aminolysis and thioketals by peroxides. Orthogonal stepwise degradation of poly(TL-co-VP) copolymers was achieved using isopropylamine and benzoyl peroxide as shown by SEC. Bleach was identified as a universal agent for accelerated degradation. A good correlation between oligomer length after degradation and estimated polymer mass loss is also reported.

## INTRODUCTION

Polymer-based stimuli responsive materials form a rapidly growing section of polymer science. They find applications in many domains including drug delivery vehicles<sup>1,2</sup> and biosensors<sup>3,4</sup> to name a few.<sup>5</sup> The design of such materials depends on the trigger which will elicit changes in the material properties (the response). The triggers typically promote a change in polymer solubility or conformation at the molecular level, and can be amplified to result in a change in nanoscale structure and/or material properties.<sup>6</sup> Most polymer-based stimuli responsive materials are designed to respond to changes in pH, solvent polarity, temperature or UV-*vis* irradiation without disrupting the integrity of the component macromolecules.<sup>7</sup> Other materials can be designed to change the chemical structure of the polymer and thus its properties via chemical reactions. Moreover, the development of truly “smart” functional materials requires multi-responsiveness in a single system in order to control the performance of functional polymer. Such multi-responsive systems are being developed for applications as gene delivery vectors<sup>8</sup> and as drug carriers in targeted cancer treatment.<sup>9,10</sup> Notably, it has been shown that stepwise degradation of dual pH- and redox-responsive cross-linked polypeptides based on poly(L-lysine-co-N,N-bis(acryloyl)cystamine-co- $\gamma$ -glutamic acid) nanoparticles enhanced cellular uptake and led to more effective cancer therapy.<sup>11</sup>

Recently, thionolactone dibenzo[*c,e*]-oxepane-5-thione (DOT, Scheme 1) was reported to undergo a radical ring-opening copolymerisation (rROCoP) with common vinylic monomers according to a radical addition-ring opening (TARO) mechanism, resulting in the incorporation of thioester links in the copolymer backbone.<sup>12,13</sup> TARO polymerization of DOT proved to be an effective tool to prepare copolymers with acrylates,<sup>12,13</sup> acrylamides,<sup>12,14</sup> styrene,<sup>15,16</sup> acrylonitrile<sup>12</sup>, maleimides.<sup>17</sup> The thioester containing copolymers prepared from DOT are degradable by basic hydrolysis, aminolysis, thiolysis, and oxone-induced oxidative cleavage.<sup>13,14</sup> Moreover, DOT-containing polyacrylate covalent networks were degraded by cysteine and glutathione, mimicking intracellular conditions and their degradation products were found to be non-cytotoxic,

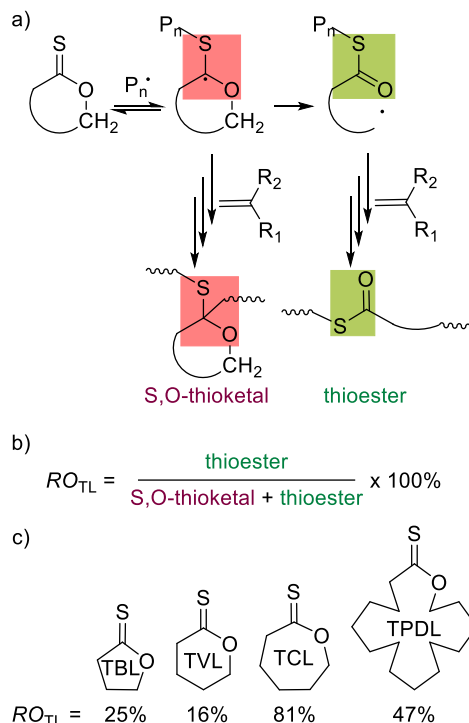
making thioester backbone-functional polymers promising for drug delivery applications.<sup>18</sup> Later, our group<sup>19</sup> and independently Plummer et al.<sup>20</sup> discovered that  $\epsilon$ -thionocaprolactone (TCL, Scheme 1) is able to undergo rROCoP via TARO mechanism with vinyl esters. Moreover, we revealed that the bulk copolymerization of TCL with vinyl esters yielded copolymers with a significant fraction of thionolactone incorporated in a ring-closed form.<sup>19</sup> Later, we showed that for unsubstituted thionolactones (TLs) of different ring size, copolymerization proceeds in both ring-opened (thioester) and ring-closed (S,O-thioketal) form with vinyl pivalate (Scheme 2a).<sup>21</sup> The fraction of ring-opened units (Scheme 2b) was calculated for several TLs and varies from 16 to 81% (Scheme 2c). Additionally, 3,6-dimethyl-5-thioxo-1,4-dioxan-2-one (TLD, Scheme 1) has been reported to undergo rROCoP with acrylates,<sup>22,23</sup> styrene,<sup>22,23</sup> and methyl methacrylate.<sup>22</sup> Contrary to DOT, TLD incorporated in the copolymers in both thioester and thioketal forms. Bleach<sup>22</sup> and silver salts<sup>23</sup> were found to be the most efficient degrading agents for copolymers of TLD with acrylates and styrene, cleaving both types of links.



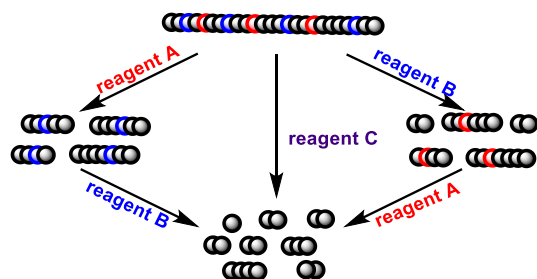
**Scheme 1. Thionolactones reported in rROCoP**

Based on this knowledge, it should be possible to identify selective degrading agents for thioester and thioketal links within the copolymer backbone to offer different stimuli responsive behavior (Scheme 3). Thioesters are reactive compounds that can be degraded using several approaches. They predominantly undergo acid-mediated hydrolysis at low pH and base-mediated hydrolysis at high pH. Additionally, they can react with nucleophiles such as amines<sup>24</sup> or with thiols through exchange reactions.<sup>25</sup> Under oxidative conditions (e.g. treatment with oxone), the thioester is oxidized to an acyl sulfoxide, followed by rearrangement and then hydrolysis.<sup>26</sup> The reactivity of S,O-thioacetals and S,O-thioketals is located between those of O,O-acetals

(ketals) and *S,S*-dithioacetals (dithioketals).<sup>27</sup> The hydrolysis of *S,O*-thioacetals is rather slow under acid catalysis,<sup>27,28</sup> but is greatly accelerated in the presence of soft metallic ions ( $\text{Ag}^+$ ,  $\text{Hg}^{2+}$ ,  $\text{Ti}^{3+}$  etc.).<sup>27</sup> Also, thioacetals used as protective groups are reductively cleaved by  $\text{H}_2$  /Raney nickel reagent in slightly basic conditions.<sup>29</sup> However, *S,O*-thioacetals appear to be stable to practically all alkaline or neutral reaction conditions, including dioxolanes, nucleophilic reagents (e.g.,  $\text{RLi}$ ,  $\text{AlH}_4^-$ ,  $\text{OH}^-$ ) and mildly acidic conditions such as *p*-toluenesulfonic acid.<sup>29</sup>



**Scheme 2.** Two main propagation mechanisms during the rROCoP of thionolactones (a), equation for calculation of  $RO_{\text{TL}}$  units for more details see Fig. S5 (b) and thionolactones selected for investigation in radical copolymerization with VP (c).



**Scheme 3.** Two-step orthogonal degradation of copolymer containing two types of degradable links (reagent A selective towards red links and reagent B selective towards blue links), and complete degradation of both types of links with universal reagent C. In the case of rROCoP of TL with vinyl pivalate, blue links are thioesters and red ones are thioketals.

Degradation of (di)thioacetal-containing polymers has been systematically investigated in several studies. Successful polymer degradation via acidolysis<sup>30</sup> and oxidative hydrolysis<sup>31</sup> were reported. Moreover, thioacetals were reported to be responsive to reactive oxygen species (ROS) such as  $\text{OCl}^-$  and  $\text{H}_2\text{O}_2$ .<sup>31</sup>

In organisms ROS are formed as byproducts of the normal oxygen metabolism with important roles in cell signaling and homeostasis.<sup>32</sup> Their overexpression can be harmful to the cells, with implications in pathological disorders such as cancer, inflammatory reactions and others.<sup>33–36</sup> Therefore, the balance between the biological processes and the cause (or marker) of pathogenic conditions has made these species a target of investigation. Strategies to sensitively detect ROS in biological media have been developed.<sup>37</sup> Additionally, oxidation responsive polymer assemblies that could release drug molecules in response to elevated concentrations of ROS are also of great interest.<sup>38,39</sup>

The sensitivity of thioketals and thioesters to degradation agents available in the intracellular environment makes them promising for biomedical applications. To our knowledge, the selective degradability of copolymers containing both thioester and *S,O*-thioketal links has not been comprehensively investigated. In the following paper, with the help of model compounds mimicking thioester and thioketal links in the copolymer backbone, we have identified degrading agents offering orthogonal reactivity for thioesters/thioketals as well as a non-selective degradation method leading to complete conversion of all degradable links (Scheme 3). The model copolymers containing thioester and thioketal links were then tested in the chosen degradation conditions and the resulting oligomers were characterized after degradation. Finally, the stepwise degradation of the copolymers is presented.

## EXPERIMENTAL SECTION

**Materials and methods** 2-mercaptopropionic acid methyl ester *O*-ethyl dithiocarbonate (XA),<sup>40</sup>  $\gamma$ -thionobutyrolactone (TBL),<sup>41</sup>  $\delta$ -thionovalerolactone (TVL)<sup>41</sup> and  $\epsilon$ -thionocaprolactone (TCL)<sup>42</sup> were synthesized according to literature procedures. TBL, TVL and TCL were redistilled prior to use.

The following chemicals were used as received: acetyl chloride (99%, Sigma-Aldrich), benzoyl peroxide (BPO), 75% in water, Luperox® A75, Sigma-Aldrich), bleach ( $\text{NaOCl}$ , 11–15% aqueous solution, Alfa Aesar), butanone (99%, Sigma-Aldrich),  $\gamma$ -butyrolactone (99%, Sigma-Aldrich),  $\epsilon$ -caprolactone (97%, Sigma-Aldrich), hexamethyldisiloxane ( $\geq 98\%$ , Sigma-Aldrich), hydrogen peroxide ( $\text{H}_2\text{O}_2$ , 30% aqueous solution, Sigma-Aldrich), isopropylamine (99%, Sigma-Aldrich), octanethiol (98%, Sigma-Aldrich), phosphorus pentasulfide (97% grade, Acros Organics), triethylamine (99%, Sigma-Aldrich), *p*-toluenesulfonic acid (99%, Sigma-Aldrich),  $\delta$ -valerolactone (98%, Alfa Aesar), 1,1'-azobis(cyanocyclohexane) (VAZO-88, 98%, Sigma-Aldrich) and 2-mercaptoethanol (99%, Sigma-Aldrich). The following chemicals were purified before use: 2,2'-azobis(2-methylpropanitrile) (AIBN, 98%, Sigma-Aldrich), was recrystallized from methanol and dried under vacuum, and vinyl pivalate (VP,  $>99\%$ , Sigma-Aldrich) was purified by passing through neutral  $\text{Al}_2\text{O}_3$ .

The following solvents were used as received: dichloromethane (Sigma-Aldrich, HPLC grade), diethyl ether (VWR, HPLC grade), cyclohexane (Sigma-Aldrich, HPLC grade) and ethyl acetate (EtOAc, Sigma-Aldrich, HPLC grade). Acetonitrile (Acros, HPLC grade), tetrahydrofuran (Sigma-Aldrich, HPLC grade) and toluene (Sigma-Aldrich, HPLC grade) were further dried using a solvent purifier (MBRAUN SP5).

Copolymers of VP with TCL, TVL and TBL were prepared as reported in a previous article.<sup>21</sup>

Monomer conversions as well as the copolymer microstructure were determined by  $^1\text{H}$  NMR following methods reported in our previous work.<sup>19</sup> For detailed information on the microstructure analysis, see Fig. S5-S7; for an example of calculation of  $N_{\text{av}}(\text{VP})$  and %  $RO_{\text{TL}}$  units, see Fig. S8. In order to show monomer composition, individual copolymers are described as poly( $\text{TL}_x\text{-co-VP}_y$ ), where  $x = F_{\text{TL}}$  and  $y = 1 - F_{\text{TL}}$ .

Nuclear magnetic resonance (NMR) spectra ( $^1\text{H}$ ,  $^{13}\text{C}$ ) were recorded at 25 °C on a Bruker Avance 300 MHz instrument.  $^1\text{H}$  NMR spectra were recorded at 300.13 MHz. The resonance multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet).  $^{13}\text{C}$  NMR spectra were recorded at 75.47 MHz. Chemical shifts  $\delta$  are reported in parts per million (ppm) and are referenced to the residual solvent peak ( $\text{CDCl}_3$ : H = 7.26 ppm and C = 77.16 ppm).

Size-exclusion chromatography (SEC) analyses in THF were performed on a system composed of an Agilent Technologies guard column (PLGel20  $\mu\text{m}$ , 50  $\times$  7.5 mm) and a set of three Shodex columns (KF-805 + KF-804 + KF-802.5). Detections were conducted using a Wyatt Optilab® rEX refractive index detector and a Varian ProStar 325 UV detector (dual wavelength analysis). Analyses were performed at 35°C and a flow rate of 1.0 mL  $\text{min}^{-1}$ . Poly(methyl methacrylate) (PMMA) standards ( $960 - 2.37 \times 10^5$  g  $\text{mol}^{-1}$ ) were used for calibration.

Gas Chromatography–Mass Spectrometry with Electrospray Ionization (GC-MS-EI) was performed using GC column Agilent J&W - VF1ms - 60m - 0.32mm internal diameter - film thickness 1.00 $\mu\text{m}$ ; He feed 1ml/min; injection temperature 250°C; injected volume 1 $\mu\text{l}$ . Oven program: 70°C for 5 min ; heat to 250°C at +10°/min ; 250°C for 40 min ; heat to 300°C at +2°/min ; 300°C for 32min (overall duration : 120 min). MS detector GCT-premier Waters in electrospray ionization in positive mode (source temp 180 °C, electron energy 70.0 eV). Samples were diluted 10 times in DCM before injection.

**Synthesis of 1-(octylsulfanyl)ethan-1-one TE.** Octane-1-thiol (1g, 6.8mmol) and acetyl chloride (0.53 g, 6.8 mmol) were dissolved in dry THF, and then triethylamine (0.7 g, 6.8 mmol) was added dropwise and stirred overnight. After reaction, the solvent was evaporated and the crude product was dissolved in ethyl acetate and filtrated to remove triethylammonium salt. The filtrate was concentrated and transferred on column (eluent 5% DCM / Petroleum ether 95% => 30% DCM / Petroleum ether 70%). Fractions containing product were combined and the eluent was removed under vacuum. Pure product (0.9g) was collected as a colorless oil, yield 70%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 2.9 (m, 2H), 2.35 (s, 3H), 1.75-1.25 (m, 12H), 0.89 (m, 3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 196, 31.9, 30.7, 27.6, 22.7, 12. ESI-MS: 188.1243 g/mol (calculated 188.1235 g  $\text{mol}^{-1}$ )

**Synthesis of 2-ethyl-2-methyl-1,3-oxathiolane TK.** 2-Mercaptoethanol (1g, 13mmol), p-toluenesulfonic acid (22mg, 0.13 mmol) and an excess of butanone (5 ml) were dissolved in 100 ml of dry toluene and refluxed for 24 h. After the reaction, the crude mixture was washed twice with 10%  $\text{NaHCO}_3$  and twice with brine. The crude product after extraction was gently concentrated. The product was separated by column chromatography eluent 2.5% DCM/ 2.5%  $\text{Et}_2\text{O}$ / 95% petroleum ether. The fractions containing product **TK** were combined and the eluent removed under vacuum. Pure product (0.94g) was collected as a colorless oil, yield 54%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 4.18 (m, 2H), 3.08 (m, 2H), 1.88 (m, 2H), 1.60 (s, 3H), 1.03 (m,

3H).  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 94; 71; 35; 33; 28; 5.8. ESI-MS: 132.0600 g/mol (calculated 132.0609 g  $\text{mol}^{-1}$ )

**General procedure for preparation of poly(TL-co-VP).** Based on previous procedures,<sup>21</sup> TL and VP were mixed together with 0.5 mol% VAZO-88 relative to comonomers. The solution was transferred into a Carius tube which was sealed under vacuum after degassing by three freeze-pump-thaw cycles. Then the tube was put in an oil bath at 100°C for a predetermined time. The polymerization was stopped by rapid cooling. After opening the tube, part of the solution was immediately transferred to an NMR tube for conversion analysis. The polymer for SEC analysis was used after evaporation of residual monomer. For detailed information about preparation of copolymers see Table S2. For more information on  $^1\text{H}$  NMR characterization of selected purified polymer samples, see Fig. S5-S7.

1) poly( $\text{TBL}_{0.09}\text{-co-VP}_{0.91}$ )  $M_w = 8.3$  kg  $\text{mol}^{-1}$   $\bar{D} = 1.8$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.3-5.8 (m,  $\text{CH}_2\text{-C}(\text{Piv})\text{H-S}$ ) 5.3-4.5 (m,  $\text{CH}_2\text{-C}(\text{Piv})\text{H-CH}_2$ ), 4.1 – 3.6 (m,  $\text{CH}_2\text{-CH}_2\text{-O}$ ), 2.8-2.5 (m,  $\text{S-C}(\text{O})\text{-CH}_2\text{-CH}_2$ ), 2.25 – 1.2 (m,  $-\text{CH}_2\text{-} + \text{-CH}_3$ ).

2) poly( $\text{TVL}_{0.19}\text{-co-VP}_{0.81}$ ):  $M_w = 4.5$  kg  $\text{mol}^{-1}$   $\bar{D} = 1.9$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.5-5.8 (m,  $\text{CH}_2\text{-C}(\text{Piv})\text{H-S}$ ) 5.3-4.5 (m,  $\text{CH}_2\text{-C}(\text{Piv})\text{H-CH}_2$ ), 4.18 – 3.35 (m,  $\text{CH}_2\text{-CH}_2\text{-O}$ ), 2.4-2.7 (m,  $-\text{S-C}(\text{O})\text{-CH}_2\text{-CH}_2$ ), 2.25 – 1.2 (m,  $-\text{CH}_2\text{-} + \text{-CH}_3$ ).

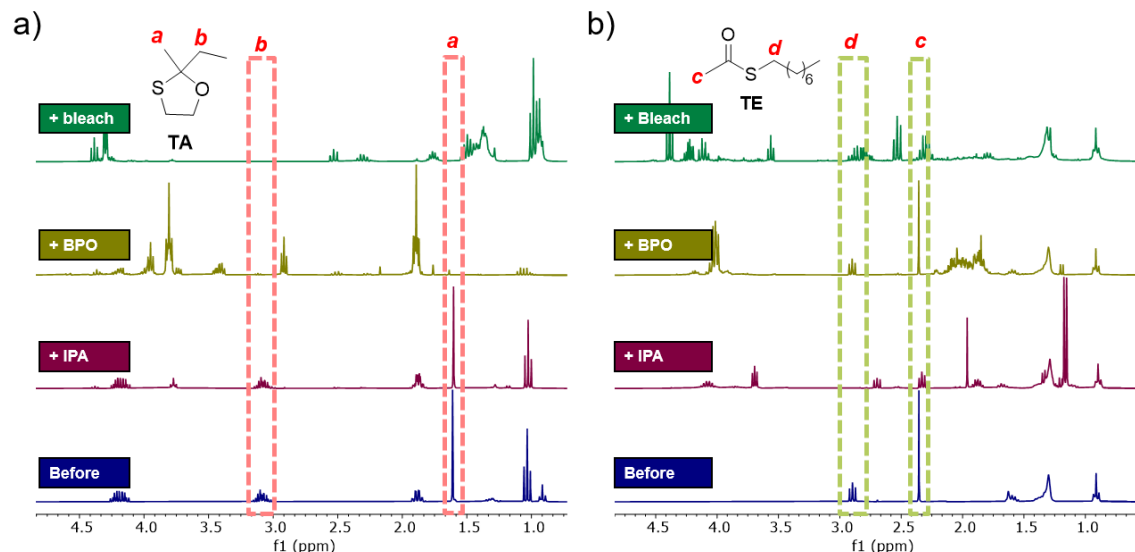
3) poly( $\text{TCL}_{0.29}\text{-co-VP}_{0.71}$ )  $M_w = 198.2$  kg  $\text{mol}^{-1}$   $\bar{D} = 7.3$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 6.6-5.8 (m,  $\text{CH}_2\text{-C}(\text{Piv})\text{H-S}$ ) 5.3-4.5 (m,  $\text{CH}_2\text{-C}(\text{Piv})\text{H-CH}_2$ ), 4.2 – 3.4 (m,  $\text{CH}_2\text{-CH}_2\text{-O}$ ), 2.87 (t,  $\text{CH}_2\text{-CH}_2\text{-S}$ ), 2.57 (m,  $\text{S-C}(\text{O})\text{-CH}_2\text{-CH}_2$ ), 2.25 – 1.2 (m,  $-\text{CH}_2\text{-} + \text{-CH}_3$ ).

**Chemical degradation in accelerated conditions.** 10 mg of copolymer or model compound was diluted in 1 mL of THF. The degradation agent (isopropyl amine (1mL) for aminolysis; bleach solution (1 mL) for bleaching; 40 mg of benzoyl peroxide in 1mL of THF for peroxidation; 1mL of 30% aqueous  $\text{H}_2\text{O}_2$  for hydroxyperoxidation) was added. The mixture was stirred in a sealed vial at room temperature for 3 days. All volatiles were evaporated under reduced pressure. For SEC analysis the residue was dissolved in 1 mL of THF and filtered through PTFE 40 $\mu\text{m}$  filter. For GC-MS-ES or NMR the residue was dissolved in DCM or in  $\text{CDCl}_3$ , respectively.

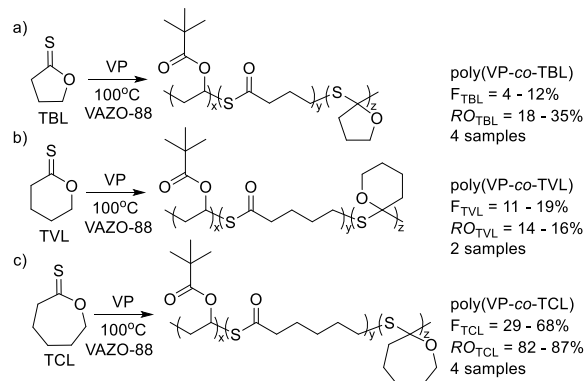
## RESULTS AND DISCUSSION

TBL, TVL and TCL, which were recently reported<sup>21</sup> for the preparation of copolymers with vinyl pivalate (VP), were used in the present study. Copolymers of TL with VP were prepared with different fractions of incorporated TL and different ratios between TL incorporated in thioester or S,O-thioetheral forms (Scheme 4). VP was chosen as comonomer due to its bulky pivalate groups which are more resistant to hydrolysis than other vinyl esters.<sup>19,21</sup>

$M_w$  values rather than  $M_n$  are used for characterization of oligomers after degradation because  $M_w$  is less sensitive to low molar mass species including by-products derived from degrading agents. Therefore,  $M_w$  is a better representation of a "typical" polymer chain, from the point of view of the mass distribution. We used a PMMA calibration curve for analysis of SEC results. Hence, the molar masses reported are relative. In general, we discuss comparative results between the various types of degradation for a given polymer, rather than comparing after degradation the experimental  $M_n$  and theoretical  $M_n$  calculated from copolymer composition.



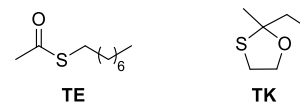
**Figure 1.** <sup>1</sup>H NMR in CDCl<sub>3</sub> before and after treatment with different degrading agents of (a) 2-ethyl-2-methyl-1,3-oxathiolane **TK** and (b) 1-(octylsulfanyl)ethan-1-one **TE**.



**Scheme 4.** Preparation of poly(TL-co-VP) copolymers (10 samples, see Table S2 for more details) of different fractions of incorporated thionolactone with corresponding fraction of ring-opened units ( $RO_{TL}$ ).

We chose degrading agents which reflect different axes of degradation: nucleophilic degradation by IPA which should be selective towards thioesters, peroxide-induced degradation (BPO or H<sub>2</sub>O<sub>2</sub>) targeting thioketals and bleaching for total degradation. Acid-catalyzed hydrolysis was discarded as a method to degrade both thioacetals and esters because degradation of thioacetals was reported to proceed rapidly only in the presence of 1M HCl and H<sub>2</sub>SO<sub>4</sub> solutions, while 0.01M HCl, 1M H<sub>3</sub>PO<sub>4</sub> or CH<sub>3</sub>COOH had hardly any effect.<sup>30</sup> Moreover, acidic hydrolysis of thioesters is slower than basic hydrolysis.<sup>25</sup> Conversely, NaOCl (bleach) combines both high pH and strong oxidative ability to afford rapid base-induced cleavage of thioesters and oxidative hydrolysis of both thioesters and thioketals.<sup>22</sup> The degradation time was selected to ensure complete degradation of the selected links in the sample. All degradation agents were tested on RAFT-derived homopolymers of PVP of similar  $M_w$  to the copolymers (Fig. S10) and no significant change before and after degradation was observed by SEC. The model compounds 1-(octylsulfanyl)ethan-1-one **TE** and 2-ethyl-2-methyl-1,3-oxathiolane **TK** (Scheme 5) were synthesized to aid in the

analysis of degradation products after cleavage of thioester and thioketal links.

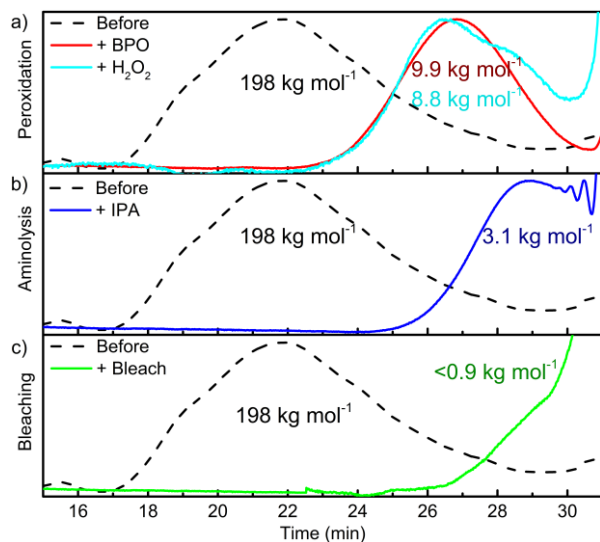


**Scheme 5.** Model compounds used to simulate the thioester (**TE**) and the S,O-thioketal (**TK**) moieties in the studied copolymers.

**Selective degradation of thioester/ thioketal-containing copolymers.** In order to validate the selectivity of degrading agents chosen for degradation of copolymers, NMR investigation of model compounds before and after degradation was conducted (Fig. 1). The chosen degradation conditions showed that thioester **TE** is resistant to BPO and cleaved by aminolysis (Fig. 1b), while thioketal **TK** is fully consumed by BPO and unaffected by the treatment with IPA (Fig. 1a). The treatment of both model compounds by bleach leads to a complete degradation of both **TE** and **TK**.

Poly(TCL<sub>0.29</sub>-co-VP<sub>0.71</sub>) was chosen for investigation as it contains a high fraction of incorporated TCL and a high thioester content  $RO_{TCL} = 81\%$ . Firstly, the peroxidation with BPO and H<sub>2</sub>O<sub>2</sub> was investigated (Fig. 2a). Monomodal SEC chromatograms before and after degradation with 96% decrease in  $M_w$  indicate a random distribution of degraded links among polymer chains. As the SEC chromatograms of oligomers after degradation (Fig. 2a) were quite similar regardless of the peroxide used, BPO was used as a model for ROS in subsequent peroxidation studies because it is easier to handle and less dangerous than H<sub>2</sub>O<sub>2</sub>. Nucleophilic degradation (aminolysis) yielded oligomers with  $M_w = 3.1 \text{ kg mol}^{-1}$  after degradation (98% decrease in  $M_w$ , Fig. 2b). The larger size of chain fragments after treatment with BPO ( $M_w = 9.9 \text{ kg mol}^{-1}$ ) relative to those obtained after aminolysis agrees with the larger fraction of thioester over thioketal linkages in the copolymer. It indicates cleavage of different links in the copolymer depending on the use of BPO or IPA. Finally, bleaching of poly(TCL<sub>0.29</sub>-co-VP<sub>0.71</sub>) allowed complete degradation of the sample (more than 99% decrease in  $M_w$ , see Fig. 2c) with generation of oligomers with  $M_w < 0.9$

kg mol<sup>-1</sup>. Significantly lower  $M_w$  values than from treatment with IPA or peroxides suggest complete cleavage of both thioester and thioketal links in the copolymer.



**Figure 2.** Degradation of poly(TCL<sub>0.29</sub>-co-VP<sub>0.71</sub>) with  $RO_{TCL}=82\%$  via three different treatments: (a) peroxidation, (b) nucleophilic substitution (via aminolysis) and (c) bleaching.  $M_w$  values corresponding to the peaks are shown underneath in the same color. For details see Table S3 entry 9-12.

**Oligomer chain end investigation.** In order to characterize the oligomer chain ends after degradation, we used Gas Chromatography–Mass Spectrometry with Electrospray Ionization (GC-MS-ESI) to analyze the mixture of oligomers obtained after degradation by aminolysis, peroxidation and bleaching. Unfortunately, GC-MS-ESI of poly(TCL<sub>0.29</sub>-co-VP<sub>0.71</sub>) after degradation did not yield any reliable data, as most of the peaks from GC appeared in the superposition for different products, making it impossible to identify the obtained oligomers with an acceptable degree of certainty. Conversely, the reaction mixtures of model compounds **TE** or **TK** after treatment with IPA, BPO and bleach have been successfully characterized by GC-MS-ESI.

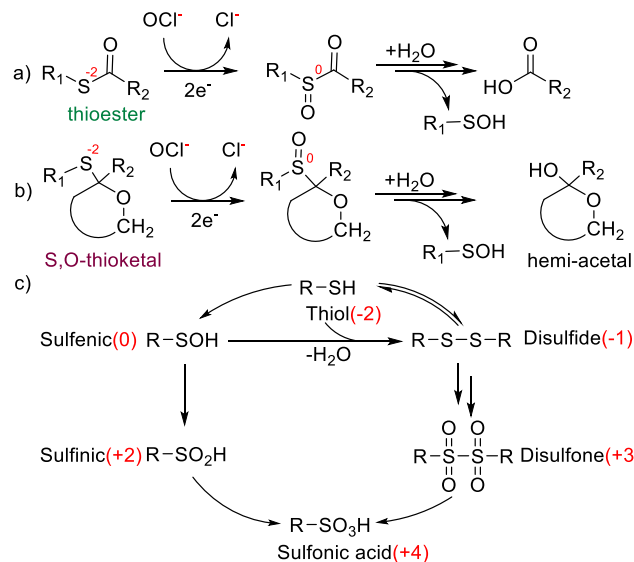
The major degradation products detected are organized in Table 1. Aminolysis of **TE** yielded typical degradation products for nucleophilic substitution reaction of thioesters such as thiol **D2** and N-isopropylamide **D1**. The peroxidation of **TK** with BPO yielded fragments including characteristic hemi-acetal **D6** and disulfide **D4**. **D6** can be only obtained by the oxidation of S<sup>-2</sup> to S<sup>0</sup> of **TK**, followed by rearrangement of sulfine to sulfenic derivative and consequent hydrolytic cleavage of thioketal derivative. The hemi-acetal **D6** is then slowly converted into the corresponding alcohol (detected in the oxidized disulfide form **D4**) and ketone (not detected, removed by evaporation before injection to GS-MS-ESI).

Analysis of the reaction mixtures of **TE** or **TK** after bleaching was more complicated due to the presence of many sulfur derivatives in different oxidation states ranging from the thiol to the sulfonic acid (Scheme 6).<sup>43-45</sup> As a consequence, we were unable to identify by GC-MS-ESI any products of the bleaching reaction of **TK** with a high degree of certainty. For the bleaching of **TE** we detected (Table 1) disulfide **D3** and octyl sulfonic acid **D9** which suggests that initially-formed sulfenic acid is oxidized to sulfinic acid and eventually sulfonic acid (Scheme 6c).

Based on the detected species after peroxidation, we could assume that bleaching of **TK** leads to oxidation of the sulfur and formation of hemi-acetal **D6** (Scheme 6b). Due to the highly alkaline conditions, this is immediately hydrolyzed to the corresponding ketone and thiol. More details on the characterization of degradation products is located in the ESI under the Table S1.

**Table 1.** Some of the degradation products detected by GC-MS-ESI after treatment of model compounds **TE** with IPA or bleach and **TK** with BPO. For more details on degradation products see Table S1.

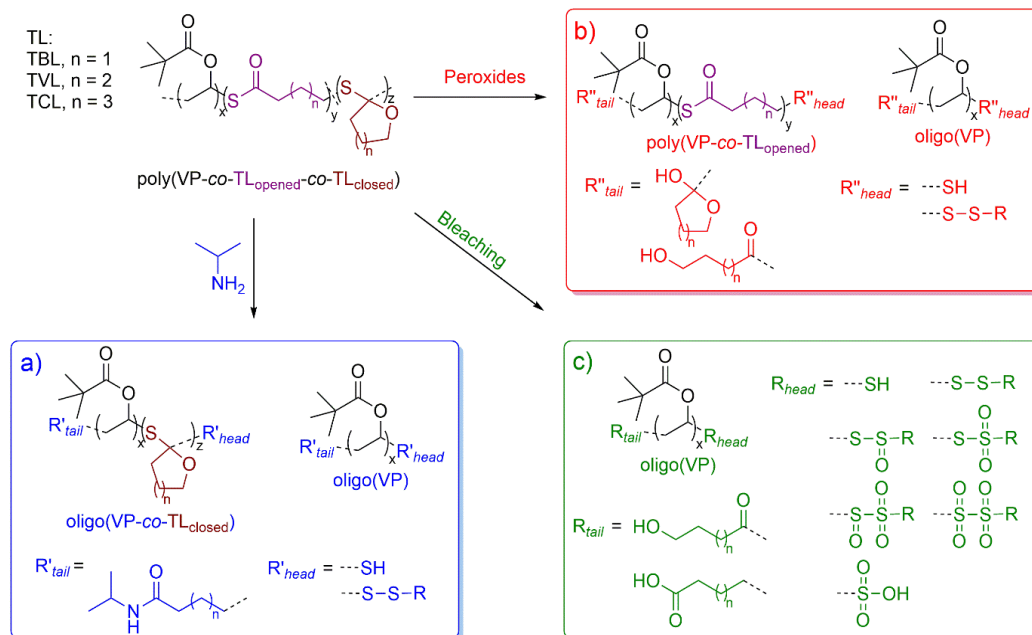
IPA	BPO	Bleach NaClO



**Scheme 6.** Proposed mechanism of reaction of NaOCl (bleaching) with thioester (a) and thioketal (b) and oxidation routes for thiol and other derivatives (c). For more detailed information see Scheme S1.

Scheme 7 shows the major products obtained after degradation of poly(VP-co-TL) by aminolysis, peroxidation or bleaching. When possible, chain ends were proposed after degradation. Chain ends produced from conventional radical polymerization (initiation, chain termination and chain transfer reactions) are not shown.  $R_{tail}$  and  $R_{head}$  groups are used to describe corresponding chain ends of the oligomers after degradation. The disulfide chain ends reported in Scheme 7 may suggest formation of oligo(VP)-S-S-oligo(VP) (similarly to **D3**, **D4** or **D6**) when in  $R_{head} = S-S-R$ , R is oligo(VP). However, the fraction of macromolecular disulfides oligo(VP)-S-S-oligo(VP) should be less pronounced in comparison to disulfides formed between low molar mass thiol and oligo(VP)-SH or oligo(VP)-SOH.



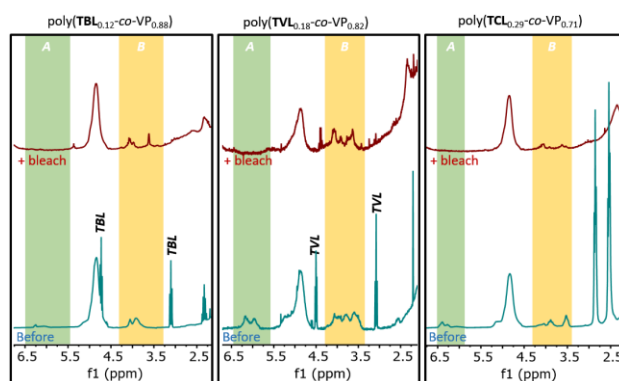


**Scheme 7.** The map of the main degradation products of poly(VP-co-TL) coming from aminolysis with IPA (a), peroxidation (b) and bleaching (c).

After treatment of the copolymer with IPA (Scheme 7a), the formed oligo(VP) or oligo(VP-co-TL<sub>closed</sub>) bears an N-isopropyl amide  $R'_{tail}$  group (similar to **D1**) and a thiol  $R'_{head}$  group (similar to **D2**, Table 1) or disulfide from aminolytic cleavage. Peroxidation (Scheme 7b) yields oligo(VP) or oligo(VP-co-TL<sub>opened</sub>) which bear a cyclic hemi-acetal  $R''_{tail}$  group (similar to **D6**) which is eventually hydrolyzed with ring-opening to the corresponding  $\omega$ -hydroxyketone derivative (Scheme S1c) on one side of the oligomer, and thiol derivatives on the other side. After bleaching, all oligomers consist only of VP units in the backbone (Scheme 7c). One chain end of oligo(VP) ( $R_{tail}$  group) is an  $\omega$ -hydroxyketone if it is derived from cleavage of a thioether, or an  $\omega$ -carboxylic acid (Scheme 6a) if it is derived from a thioester. Another chain end ( $R_{head}$  group) consists of thiol-derived species, predominantly sulfonic acid (similarly to **D9**) if the copolymer was exposed to an excess of bleach.

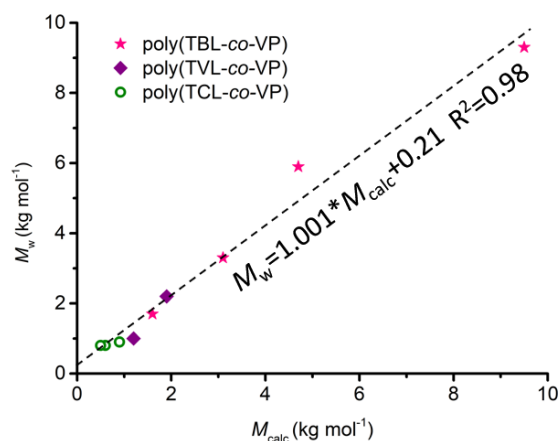
**Prediction of molar mass of degradation products.** Comparison of  $^1\text{H}$  NMR of the copolymers before and after bleaching reveals the complete disappearance of the C-H signal at 6.3 ppm from units of VP that adjoin a sulfur atom from thioester or thioketal structures (Fig. 3). Also, the signal of the methylene  $\alpha$  to the thioester carbonyl ( $-\text{S}(\text{C}=\text{O})\text{---CH}_2$ ) at 2.55 ppm disappears, and the signal of the thioketal attributed to  $\text{CH}_2\text{---O}$  at 4.1–3.2 ppm changes its shape. These changes in the NMR spectra suggest that after bleaching, the degraded oligomer fragments contain only oligo(VP) moieties. Thus, we can calculate the average sequence length of the vinyl pivalate links in between sequences of incorporated TL ( $N_{av}(\text{VP})$ ) by comparing the integrated signals from  $^1\text{H}$  NMR (Fig. S8).

We compared  $M_w$  values for oligomers obtained from SEC with the average sequence length of VP fragments after degradation calculated from NMR (Fig. 4). A set of copolymers prepared from TBL, TVL or TCL with VP containing different  $F_{TL}$  and exhibiting different  $N_{VP}$  were analysed by SEC after bleaching. A strong correlation between  $M_w$  and  $M_{calc}$  derived from  $N_{VP}$  was observed for a set of 9 different copolymers.

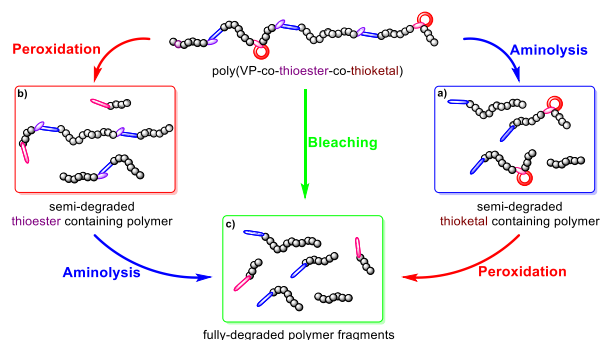


**Figure 3.**  $^1\text{H}$  NMR stack of different poly(TL-co-VP) before and after bleaching. Full disappearance of signal A corresponding to the C-H from VP connected to sulfur of thioester/thioketal groups and change in signal B corresponding to the  $\text{CH}_2$  of thioketal connected to oxygen suggesting the presence of new species. For more information see Table S3 entry 4,7,8.

**The two-step degradation.** To demonstrate the orthogonal reactivity of thioesters/thioketals in the copolymer we conducted stepwise degradation. The thioester-rich poly(TCL<sub>0.68</sub>-co-VP<sub>0.32</sub>) was treated with degrading agents in different sequences and analyzed by SEC at each step in order to determine the effect on the polymer chains (Scheme 8). Degradation of poly(TCL<sub>0.68</sub>-co-VP<sub>0.32</sub>) with BPO afforded semi-degraded polymer (70% decrease in  $M_w$ ) which was subsequently cleaved to lower molar mass oligomers via aminolysis (96% decrease in  $M_w$ , see Fig 5a). When the copolymer was first degraded by aminolysis, low molar mass semi-degraded thioketal-containing oligomers (95% decrease in  $M_w$ ) were further cleaved by BPO to achieve complete polymer degradation (96% decrease in  $M_w$ , see Fig. 5b). Additionally, SEC chromatograms after bleaching were almost identical to those from the two-step degradations (96% decrease in  $M_w$  in all cases, see Fig. 5c).



**Figure 4.** Correlation between  $M_w$  of PVP after bleaching derived from different poly(TL-co-VP) obtained from SEC chromatograms using PMMA calibration versus the calculated average sequence lengths of PVP from NMR (See Fig. S8). For more information about degradation data, see Table S3 entries 1-4, 7, 8, 13-15.

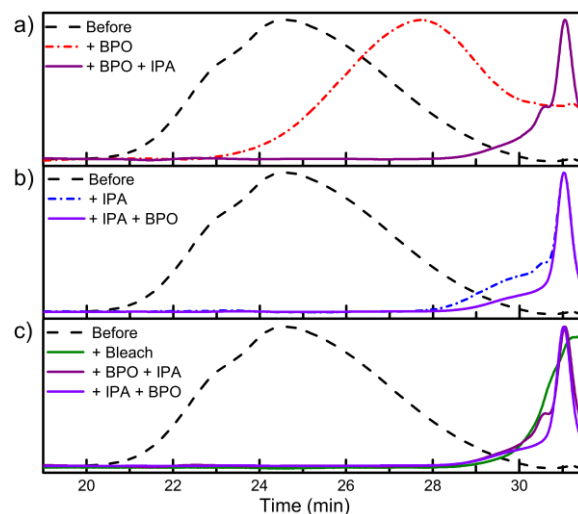


**Scheme 8.** Schematic representation of the two-step (peroxidation/aminolysis) and one-step (bleaching) degradation processes for poly(VP-co-TL)

Since semi-degraded copolymers still contain thioketal (after aminolysis) or thioester (after peroxidation) links in the backbone and different possible chain ends (Schemes 7a and 7b, respectively), they may not all match well the molar masses of PMMA standards used for SEC analysis. However, we observe a clear correlation between the predicted decrease in molar mass of semi-degraded copolymers obtained by SEC and the one estimated by NMR (Table 3; entry 2, 4). For instance, for semi-degraded poly(TCL<sub>0.68</sub>-co-VP<sub>0.32</sub>) + BPO (Table 3 entry 2) to poly(TCL<sub>0.68</sub>-co-VP<sub>0.32</sub>) + BPO + IPA (Table 3 entry 2), the calculated decrease in molar mass is estimated to be 83%, while for results obtained from SEC, the decrease in  $M_w$  is 87%. Similarly, for semi-degraded copolymer in the reverse order, that is poly(TCL<sub>0.68</sub>-co-VP<sub>0.32</sub>) + IPA (Table 3 entry 4) to poly(TCL<sub>0.68</sub>-co-VP<sub>0.32</sub>) + IPA + BPO (Table 3 entry 5), the calculated decrease is 17% while SEC gives 20%.

**Conclusions.** Radical ring-opening copolymerization of TLs with VP allows the incorporation of two different types of degradable links with orthogonal reactivity. Thioesters are reactive towards common nucleophiles and strong oxidants. On the other hand, thioketal links are resistant to hydrolysis and can be selectively cleaved by oxidation under milder conditions. Bleach was identified as a universal degrading agent for accelerated degradation which mimics physiologically-relevant ROS. These orthogonal redox-sensitive and nucleophilic degradation pathways may find applications in the biomedical field

where different responses are required depending on the environment of the polymer.



**Figure 5.** SEC chromatograms before and after degradation: poly(TCL<sub>0.68</sub>-co-VP<sub>0.32</sub>) with (a) BPO and subsequent addition of IPA; (b) IPA and subsequent addition of BPO and (c) bleaching in comparison to the two-step degradation. For more information see Table 3.

**Table 3.** SEC results before and after degradation of poly(TCL<sub>0.68</sub>-co-VP<sub>0.32</sub>) via two-step (peroxidation/aminolysis) and one-step (bleaching) degradation process.

Entry	Samples	$M_{calc}^b$ kg mol <sup>-1</sup>	$M_w$ kg mol <sup>-1</sup>	$\bar{D}$
1	poly(TCL <sub>0.68</sub> -co-VP <sub>0.32</sub> ) <sup>a</sup> $RO_{TCL} = 84\%$	-	22.4	2.7
2	poly(TCL <sub>0.68</sub> -co-VP <sub>0.32</sub> ) + BPO	2.9 <sup>c</sup>	6.8	2.7
3	poly(TCL <sub>0.68</sub> -co-VP <sub>0.32</sub> ) + BPO + IPA <sup>e</sup>	0.5	0.9	1.1
4	poly(TCL <sub>0.68</sub> -co-VP <sub>0.32</sub> ) + IPA	0.6 <sup>d</sup>	1	1.3
5	poly(TCL <sub>0.68</sub> -co-VP <sub>0.32</sub> ) + IPA + BPO <sup>e</sup>	0.5	0.8	1.2
6	poly(TCL <sub>0.68</sub> -co-VP <sub>0.32</sub> ) + Bleach	0.5	0.8	1.9

<sup>a</sup> Samples prepared following protocols as in Table S2. <sup>b</sup>  $M_{calc} = N_{av}(\text{VP}) * 128$  for degradation with bleach, IPA + BPO and BPO + IPA. <sup>c</sup>  $M_{calc} = N_{av}(\text{VP}) * 128 / (1 - 0.01 * RO_{TL})$  for peroxidation. <sup>d</sup>  $M_{calc} = N_{av}(\text{VP}) * 128 / (0.01 * RO_{TL})$  for aminolysis. <sup>e</sup> The second degrading agent was added 3 days after the first one.

## ASSOCIATED CONTENT

**Supporting Information** includes reaction conditions and polymer characterization tables, SEC results for degradation of all polymer samples, NMR spectra of model compounds and polymers, ESI-MS spectra of degradation products as well as characterization of degradation products and possible reaction mechanisms. This material is available free of charge via the Internet at <http://pubs.acs.org>.



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### Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡ These authors contributed equally. (match statement to author names with a symbol)

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### Notes

Any additional relevant notes should be placed here.

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