Chemistry Publications

Chemistry Department

Fall 12-14-2016

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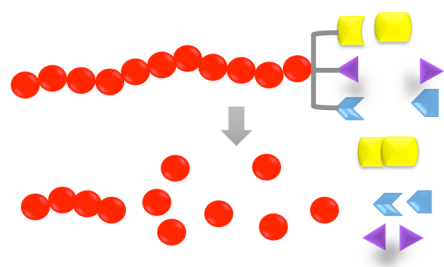
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End-capping strategies for triggering end-to-end depolymerization of polyglyoxylates

Bo Fan, John F. Trant, and Elizabeth R. Gillies*

Abstract

Polymers that undergo end-to-end depolymerization in response to the cleavage of a stimuli-responsive end-cap are promising for diverse applications from drug delivery to responsive coatings and plastics. It is critical that the end-cap is designed to respond to an appropriate stimulus for the application. In the current work, end-caps for triggering the depolymerization of poly(ethyl glyoxylate) (PEtG) were explored. First a phenylboronate, a disulfide, and an azobenzene were utilized to impart redox-responsive properties to PEtG. Then, methoxy-substituted trityl groups were used to provide sensitivity to mild acid. A multi-responsive platform was also introduced, allowing PEtG to respond to multiple stimuli, either simultaneously or independently. Incorporation of a cross-linkable trialkene end-cap enabled the preparation of networks that could subsequently be depolymerized. Finally, high molar mass PEtG could be depolymerized by mechanical stimulation independent of the end-cap. It is anticipated that the versatility in end-capping strategies and potential depolymerization stimuli will not only expand PEtG's utility for different applications, but will also be useful for other classes of end-to-end depolymerizable polymers.

Introduction

Degradable polymers are of significant interest, both as environmentally-friendly replacements for traditional non-degradable polymers and for wide range of biomedical applications from tissue engineering to drug delivery.[1-3] Biodegradable polyesters such as poly(lactic acid),

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poly(glycolic acid), polycaprolactone, and polyhydroxybutyrate have been extensively

investigated and show promise in many applications.[4,5] However, their tendency to undergo slow

degradation in a variety of environments is a potential limitation as they may decompose

prematurely while still in use or may decompose more slowly than desired in other cases.[6,7]

While their degradation rates can be tuned to some extent based on their chemical structure,

molar mass and through formulation adjustments,[8,9] the ability to "turn on" their degradation at

the desired time and place is still quite limited.

Over the past decade, a new class of degradable polymers that depolymerize end-to-end upon

the cleavage of a stimuli-responsive end-cap from the polymer terminus was introduced.[10-12]

These have often been referred to as "self-immolative" polymers as they were initially inspired

by the analogous dendritic structures composed of "self-immolative spacers" that were developed

for pro-drug chemistry.[13] Following cleavage of the stabilizing end-cap, the mechanism of

depolymerization can involve sequential elimination or cyclization reactions that result in

conversion of the polymer to small molecules that differ from the monomers from which they

were prepared. Alternatively, it can involve sequential loss of monomer units from the polymer

terminus due to the low ceiling temperature of the polymer. Thus far, a number of

depolymerizable backbones have been introduced including polycarbamates,[14-17]

polycarbonates,[18] polythiocarbamates,[19] polythiocarbonates,[18] poly(benzyl ether)s[20] and

polyacetals.[21-27]

For end-to-end depolymerizable polymers, a single end-cap cleavage reaction is theoretically

sufficient to trigger degradation of the entire polymer backbone. This potentially provides higher

sensitivity to stimuli than traditional stimuli-responsive polymers that require many stimuli-mediated events to degrade the backbone. This has made these polymers attractive for a variety of applications, and proof-of-concept studies have been performed to demonstrate their potential utility as drug delivery systems,[16,28-30] molecular sensors,[14,16,31,32] micropumps,[33] responsive films or plastics,[21,34,35] stimuli-responsive microcapsules,[36,37] and for simple polymer reprogramming or recycling.[27,35,38] A key aspect determining the potential of the polymer for a given application is the ability to match the polymer end-cap with suitable triggering conditions that are relevant to that application. For example, end-caps responsive to light,[28,30,39] enzymes[29] and reducing conditions[19,30] have been used to trigger release from proof of concept drug delivery systems. End-caps sensitive to fluoride ions have been used in responsive adhesives,[34] plastics,[21,40] and microcapsules.[37] Furthermore, end-caps responsive to H_2O_2 have been used in sensors.[31,32]

Polyglyoxylates were recently reported by our group as a class of end-to-end depolymerizable polymers with attractive features such as ease of synthesis from readily available monomers, degradation to non-toxic products,[41] and the ability to undergo depolymerization in the solid state to volatile products (Figure 1).[35] In comparison with earlier polyglyoxylates that were not responsive to stimuli,[42,43] the development of stimuli-responsive polyglyoxylates was made possible through end-capping with chloroformates. This chemistry was feasible because of the high reactivity of chloroformates, which allows the reaction to be performed at low temperature (- 20 °C), below the ceiling temperature of the polyglyoxylate in solution. However, thus far only UV light-responsive polyglyoxylates were reported.[24] In the current study, using poly(ethyl glyoxylate) (PEtG) it is demonstrated that this end-capping

strategy can be extended to other end-caps responsive to oxidizing and reducing conditions. In addition, the development of new end-caps responsive to mildly acidic conditions is described. It is further shown that an end-cap responsive to multiple stimuli as well as one that enables subsequent cross-linking of the polyglyoxylate to afford a depolymerizable gel can be designed. It is also demonstrated that mechanical force can be used to selectively depolymerize high molar mass PEtG.
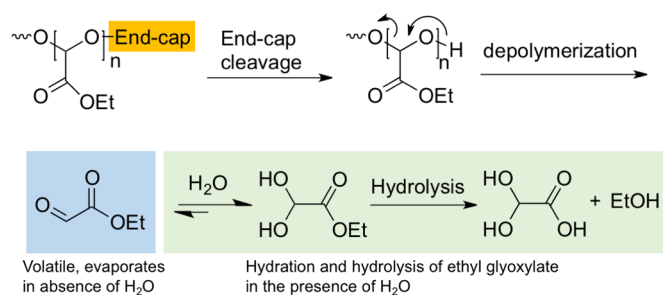

Figure 1. Schematic illustrating the end-cap cleavage and depolymerization process for PEtG.

Experimental section

General procedures and materials. Compounds 2^{44}, 3^{45}, 9^{46}, 12^{47}, 13^{48} and **PEtG-control**[35] were prepared as previously reported. Additional experimental procedures are included in the supporting information. NEt$_3$, pyridine, and CH$_2$Cl$_2$ were distilled from calcium hydride before use. Anhydrous tetrahydrofuran (THF) was obtained from a solvent purification system using aluminum oxide columns from Innovative Technology (Newburyport, MA). All the other chemicals were purchased from chemical suppliers and used without further purification. NMR spectra were obtained on 400 MHz or 600 MHz Varian Inova spectrometers (Agilent Tech., Santa Clara, CA). NMR chemical shifts (δ) are reported in ppm and are calibrated against the residual

solvent signals of CDCl$_3$ (δ 7.27; 77.4), CD$_3$CN (δ 1.94; 116.4), d_6-DMSO (δ 2.50; 40.8) or D$_2$O (δ 4.75). Fourier transform infrared (FT-IR) spectra were obtained using a Bruker Tensor 27 instrument (Billerica, MA) using thin films of the molecules drop cast from CH$_2$Cl$_2$ on KBr plates. High-resolution mass spectrometry (HRMS) was performed using a Finnigan MAT 8400 electron impact (EI) mass spectrometer or Bruker microOTOF 11 electrospray mass spectrometer (ESI). Size exclusion chromatography (SEC) was performed using a Viscotek GPC Max VE2001 solvent module (Agilent Tech.), a Viscotek VE3580 RI detector operating at 30 °C, two Agilent Polypore (300 x 7.5mm) columns connected and a Polypore guard column (50 x 7.5mm). THF (glass distilled grade) was used as the eluent. A calibration curve was obtained from poly(methyl methacrylate) (PMMA) standards with molar masses from 1540 – 1126000 g/mol. Differential scanning calorimetry (DSC) was performed using a Q2000 from TA Instruments (New Castle, DE) and thermogravimetric analysis (TGA) was performed on Q50 from TA Instruments. For TGA the heating rate was 10 ºC/min between 35 - 500 ºC under nitrogen. For DSC, the heating/cooling rate was 10 ºC/min from -75 to +120 ºC. Glass transition temperatures (T$_g$) were obtained from the second heating cycle.

Synthesis of chloroformate 5 (representative procedure for chloroformate synthesis).

Compound **2**[44] (500 mg, 2.7 mmol, 1.0 equiv.) was dissolved in THF (10 mL). The resulting solution was then added dropwise into a phosgene solution (15 wt% in toluene, 5.8 mL, 8.1 mmol, 3.0 equiv.) under an argon atmosphere at room temperature and the resulting solution was stirred for 24 h. The residual phosgene and solvent were then removed by distillation *in vacuo* to yield chloroformate **5** (750 mg, 98%) as a pale brown solid. Phosgene collected in the liquid

nitrogen-cooled trap was then quenched with methanol (20 mL) and saturated sodium hydroxide

solution (20 mL) (**Caution! phosgene is toxic**). ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.76-8.84 (m,

1H), 8.20-8.30 (m, 1H), 8.17 (d, J = 8.2 Hz, 1H) 7.65-7.73 (m, 1H), 4.61 (t, J = 5.9 Hz, 2H), 3.34

(t, J = 5.9 Hz, 2H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 156.9, 150.5, 145.2, 142.9, 125.0, 123.9, 68.8,

37.8. HRMS (EI) calc'd. for [M]$^+$ C$_8$H$_8$ClNO$_2$S$_2$: 248.9685; found: 248.9689.

Synthesis of PEtG-boronate (representative procedure for the synthesis of end-capped PEtG).

Ethyl glyoxylate in toluene (20 mL) was distilled under vacuum (55 ºC, 125 mbar) over P$_2$O$_5$ to

remove toluene and trace water in the first, discarded fraction. The residue was then distilled twice

successively over P$_2$O$_5$ at atmospheric pressure under argon at 130 ºC to obtain the highly pure

monomer. Purified ethyl glyoxylate (5.0 mL, 50 mmol, 1.0 equiv.) was dissolved in CH$_2$Cl$_2$ (5.0

mL), cooled to -20 °C, and Et$_3$N (3.5 μL, 25 μmol, 0.0005 equiv.) was added. The solution was

stirred for 1 h at -20 °C. Chloroformate **4** (0.22 g, 730 μmol, 0.014 equiv.) and Et$_3$N (100 μL, 730

μmol, 0.014 equiv.) were added. The solution was allowed to slowly warm to room temperature

over a few hours, and then stirred overnight. The resulting polymer was purified by precipitation

into methanol. After decanting the excess methanol, the residue was dried *in vacuo* to provide 3.3

g of a white, sticky polymer in 63% yield. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.80 (d, J = 8.6 Hz, 2H),

7.53 (d, J = 8.6 Hz, 2H), 5.46-5.78 (m, 675H), 4.10-4.33 (m, 1367H), 1.34 (s, 12H), 1.21-1.44 (m,

2000H). IR (KBr, thin film): 2986, 2943, 2908, 1759, 1469, 1446, 1377, 1302, 858, 735, 702 cm^{-1}.

SEC: M$_n$ = 131 kg/mol, M$_w$ = 304 kg/mol, Đ = 2.3. T$_g$ = -1 °C.

Procedure for the study of PEtG-boronate depolymerization by ^{1}H NMR spectroscopy

(representative depolymerization procedure). PEtG-boronate (15 mg) was dissolved in a 9:1

CD$_3$CN:D$_2$O (1.2 mL). The solution was then divided between two NMR tubes and 4 μL of H$_2$O$_2$ (50 wt% in water solution) was added to one tube to provide an H$_2$O$_2$ concentration of ~100 mM. The tubes were sealed, maintained at ambient temperature (20 °C), and ^{1}H NMR spectra were obtained at time points over 48 h for both the triggered polymer and the control. At the same time, a non-stimuli-responsive **PEtG-control** with a benzyl carbonate end-cap was also exposed to the same concentration of H$_2$O$_2$ following the same procedure as above and its depolymerization was also monitored by ^{1}H NMR spectroscopy. The extent of depolymerization was calculated as: % depolymerization = 100 – x, where x is the integration of the peak at 5.5 ppm, when the integration of the peak at 4.2 ppm was set to 200 (which remained constant as it corresponds to the CH$_3$CH_2-O- in both the polymer and the depolymerization products).

Results and Discussion

Development of redox-responsive PEtG

Polymer systems that respond to oxidizing or reducing conditions have been actively sought for the past several years due to the practical interest in these stimuli.[49-51] For example, increased concentrations of the reducing agent glutathione are associated with the intracellular environment as well as with hypoxic tumor tissue, potentially allowing drug molecules to be selectively released from reduction-sensitive polymers in these environments.[52,53] Reactive oxygen species are also associated with a wide range of pathologies including inflammation and tissue injury.[54] While end-to-end depolymerization has previously been initiated by these stimuli,[19,30-32] oxidation-

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and reduction-sensitive PEtGs were chosen as initial targets to explore the versatility of the

chloroformate end-capping strategy for PEtG and the response of PEtG to these stimuli.

A phenylboronic acid pinacol ester was selected as the H_2O_2-sensitive end-cap.[55] As shown

in Figure 2a, in the presence of H_2O_2 this end-cap undergoes cleavage to the corresponding

phenol, which can then undergo a 1,6-elimination followed by loss of CO_2, releasing the PEtG

hemiacetal terminus and triggering depolymerization. The thiol-responsive pyridyl disulfide was

selected based on its well-established sensitivity to reduction by thiols as well as its successful

use as an end-cap for depolymerizable polycarbonates and poly(carbamate-thiocarbamate)s.[18,19]

Reductive cleavage of the disulfide reveals a thiol that can subsequently cyclize to form either a

cyclic thiocarbonate (Figure 2b) or a thiirane ring followed by loss of CO_2, releasing the PEtG

terminus.[56] Finally, an azobenzene moiety was also explored as a reduction-sensitive end-cap.

Recent work from our group has shown that the reduction of azobenzene end-caps with hydrazine

can trigger end-to-end depolymerization of polycarbamates and studies on small molecule model

compounds suggested that the reduction should also be possible with thiols.[57] As shown in Figure

2c, reduction leads an electron-rich hydrazobenzene that can undergo a 1,6-elimination, followed

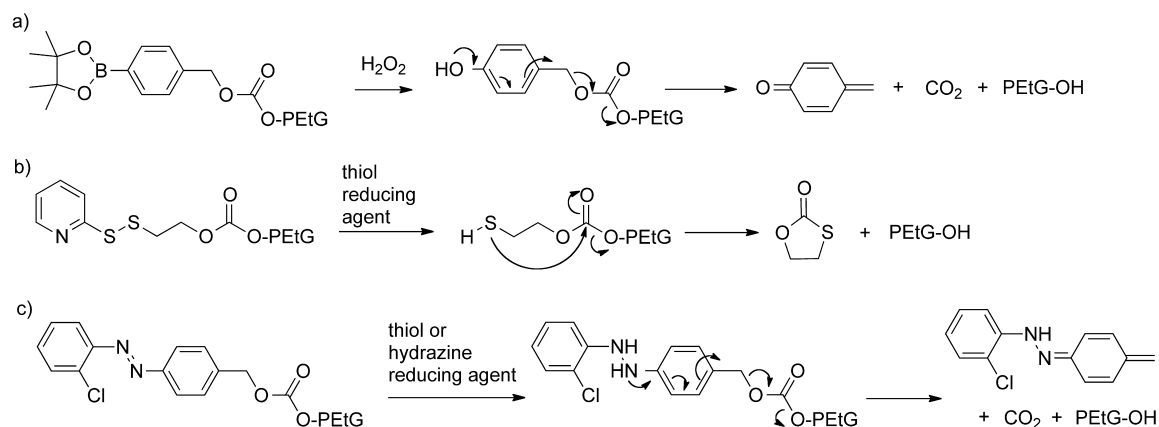by loss of CO_2 to release the polymer terminus.

Figure 2. Proposed triggering mechanisms for redox-responsive PEtG end-caps.

As shown in Scheme 1, alcohol derivatives of the boronate (**1**), disulfide (**2**)[44] and azobenzene

(**3**)[57] were reacted with phosgene in THF/toluene to afford the corresponding chloroformates **4** - **6**.

The disulfide end-cap was isolated as its HCl salt. Polymerization of freshly distilled ethyl

glyoxylate was initiated by the addition of NEt_3 and was conducted at -20 °C as previously

reported (Scheme 2).[24] The resulting PEtG was end-capped *in situ* by the addition of the

chloroformate and additional NEt_3 at -20 °C, and the reaction was allowed to slowly reach

ambient temperature and stirred overnight, affording **PEtG-boronate**, **PEtG-disulfide**, and

PEtG-azobenzene from chloroformates **4**, **5**, and **6** respectively. In addition to the

chloroformates **4** - **6**, benzyl chloroformate was used to provide a non-responsive control

carbonate end-capped PEtG (**PEtG-control**) as previously reported.[35]
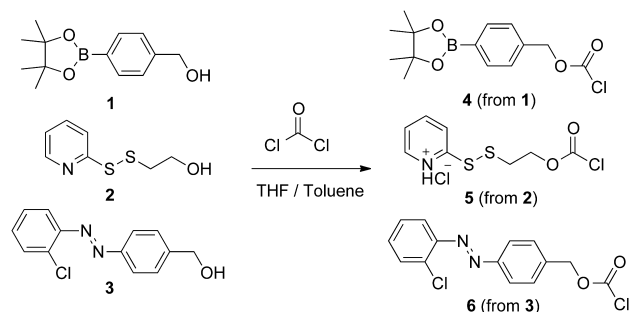
Scheme 1. Synthesis of chloroformate end-caps **4** - **6**.
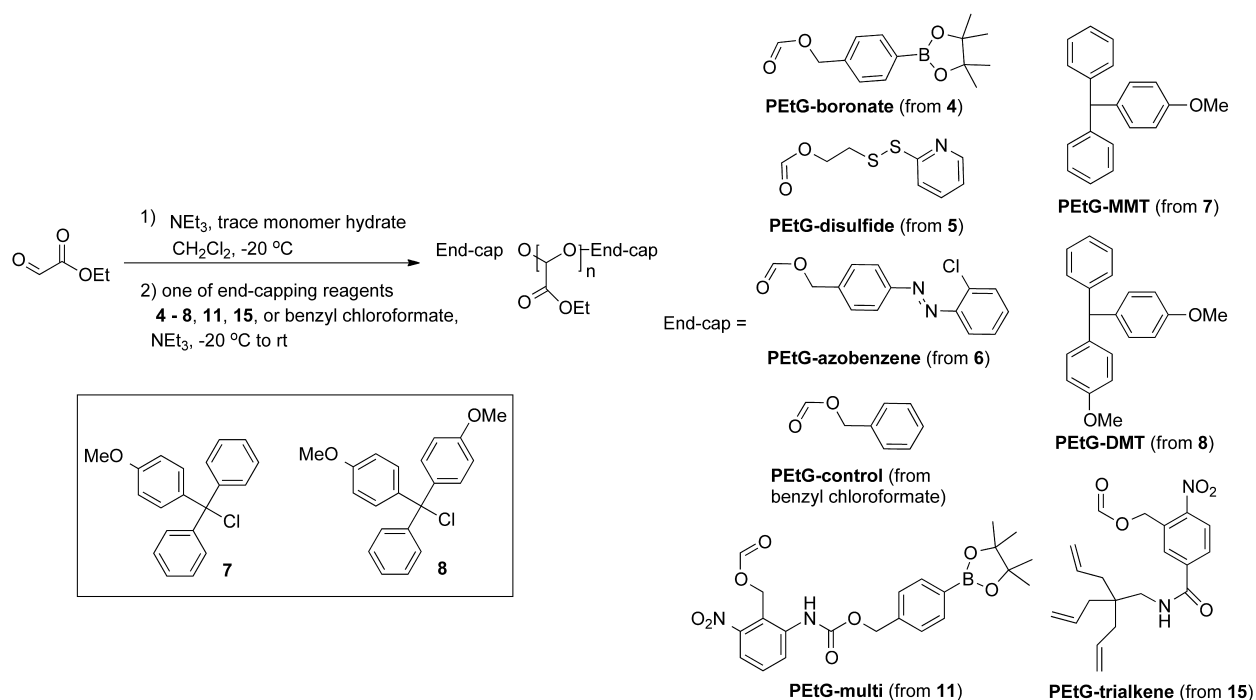
Scheme 2. Synthesis and end-capping of PEtG.

The end-capped polymers were characterized by SEC, NMR spectroscopy, DSC and TGA. As shown in Table 1, based on SEC the number average molar masses (M_n) of these polymers ranged from 24 - 250 kg/mol and their dispersities (*Đ*) ranged from 1.3 - 2.3. The variation in M_n between the different polymers likely results from the fact that these polymers were prepared from different batches of distilled monomer, as we have observed a strong dependency of M_n on

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the purity of monomer. This dependency arises from the initiation of the polymerization from trace ethyl glyoxylate hydrate (EtGH) that is present in the distilled monomer. Different batches of distilled monomer contain different amounts of this initiator. Although in principle, it should be possible to achieve a controlled polymerization of PEtG by adding a defined amount of initiator, this has not yet been achieved. In each case, NMR spectroscopy showed very small peaks consistent with the presence of the appropriate end-caps on the polymers. However, given the high degrees of polymerization (DP), these peaks were challenging to detect and accurately integrate, so DP was not determined by NMR spectroscopy. It was previously demonstrated that TGA provides an excellent indicator of successful end-capping as uncapped polymer is thermally unstable and depolymerizes below 100 °C in the solid state. Even small fractions of uncapped polymer can be detected by TGA.[24] As shown in Table 1 and Figure S46, the polymers had onset degradation temperatures (T_o) from 183 - 255 °C, confirming that they were well end-capped. In addition, through the preparation and analysis of two different batches of **PEtG-disulfide** (**a** and **b**) with a ~10-fold difference in M_n, it was confirmed that the PEtG molar mass did not have a significant effect on its thermal stability. Based on DSC, the T_g values were very similar for the different end-capped PEtGs, ranging from -7 to -1 °C.

Table 1. Molar mass and thermal properties of end-capped PEtGs and measured by SEC, TGA, and DSC.

Polymer	M_n (SEC) (kg/mol)	Dispersity ($Đ$)	T_o (ºC)	T_g (ºC)
PEtG-boronate	131	2.3	226	-1
PEtG-disulfide-a	250	1.7	183	-7
PEtG-disulfide-b	26	1.4	191	-7
PEtG-azobenzene	30	1.4	255	-1
PEtG-control	35	1.4	247	-3
PEtG-DMT	21	1.3	131	-10
PEtG-MMT	29	1.5	168	-1
PEtG-multi	41	1.6	164	-4
PEtG-trialkene	11	1.7	225	-7
PEtG-crosslinked	N/A	N/A	191	5

The depolymerization of the redox-responsive polymers and **PEtG-control** was then studied in the presence and absence of the corresponding stimuli. PEtG is not soluble in water, but it was possible to dissolve the polymers in 9:1 $CD_3CN:D_2O$ in order to study the depolymerization by ^{1}H NMR spectroscopy. First, the response of **PEtG-boronate** to H_2O_2 was studied. Prior to the

addition of H_2O_2, the spectrum had three broad peaks corresponding to the protons on the PEtG

backbone and pendant ester groups (Figure 3a). Following the addition of H_2O_2, the broad peak at

5.5 ppm corresponding to backbone methine protons rapidly decreased in intensity while two new

sharp peaks at 5.3 ppm and 5.1 ppm emerged. The sharp peak at 5.1 ppm corresponds to the

degradation product EtGH as described previously.[24] The new peak at 5.3 ppm can be attributed to

a peroxy hydrate of ethyl glyoxylate arising from the increased nucleophilicity of H_2O_2 compared

to water due to the α-effect.[58] The same product could be formed by the direct addition of ethyl

glyoxyate into the above degradation conditions, and was fully characterized by ^1H and ^{13}C NMR

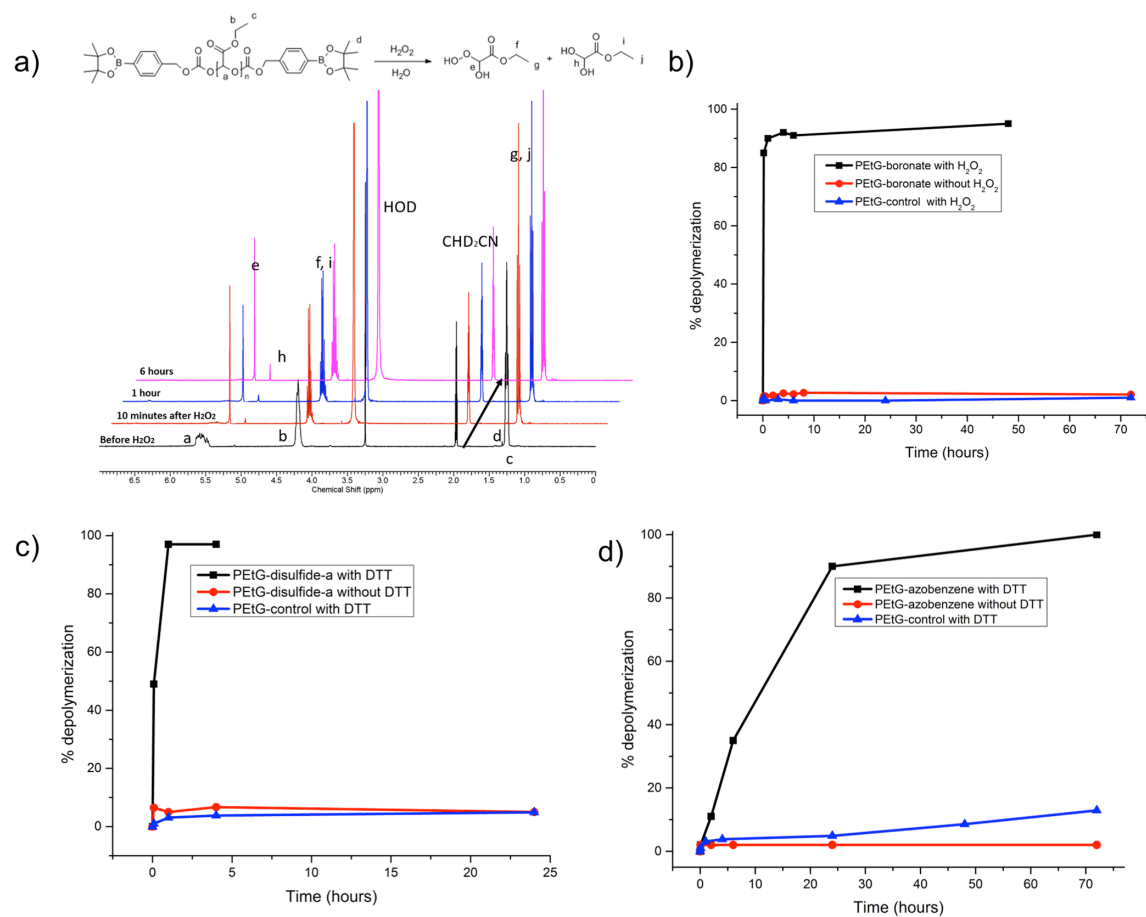spectroscopy and high resolution mass spectrometry (Figures S23-S25).

Figure 3. a) ^{1}H NMR spectra of **PEtG-boronate** in 9:1 CD$_3$CN:D$_2$O before addition of H$_2$O$_2$ and at various time points after H$_2$O$_2$ addition (spectra are offset to allow the progression over time to be clearly observed); b-d) Percent depolymerization versus time in the presence and absence of stimuli for b) **PEtG-boronate**, c) **PEtG-disulfide-a**, and d) **PEtG-azobenzene**. In each case, PEtG-control was also exposed to the stimulus to confirm specific cleavage of the end-cap.

The percent depolymerization, defined as the percentage of the monomer released as small molecule from the polymer, as a function of time for **PEtG-boronate** is shown in Figure 3b. It was noted that depolymerization was more rapid than previously observed following the cleavage of the UV light-sensitive 6-nitroveratryl end-cap from our previous work.[24] For example, 80% depolymerization had occurred in 10 minutes for **PEtG-boronate**, while 70% was observed after 24 h for the previous system. This difference can likely be attributed to the rapid trapping of the ethyl glyoxylate depolymerization product as the peroxy hydrate. However, the drawback of this trapping reaction is that high concentrations of H$_2$O$_2$ (~100 mM) were required in order to achieve complete depolymerization. Lower concentrations led to a plateau in the depolymerization because peroxide lost through peroxy hydrate formation was no longer available to cleave the end-cap. The required equivalents of H$_2$O$_2$ per polymer chain was similar to the DP based on SEC analysis (~1000). Control experiments showed that in the absence of H$_2$O$_2$, **PEtG-boronate** was stable, undergoing less than 3% depolymerization over 3 days in 9:1 CD$_3$CN:D$_2$O (Figure 3b and S29a). Furthermore, **PEtG-control** did not undergo any detectable depolymerization when treated with

100 mM H_2O_2 under the same conditions for 7 days (Figure 3b and S29b). These results confirm

the specificity of H_2O_2 for end-cap cleavage rather than backbone cleavage or side reactions.

The same procedure was used to study the depolymerization of **PEtG-disulfide-a**, except that

the reducing agent dithiothreitol (DTT) was used instead of the oxidizing agent H_2O_2. As shown

in Figure 3c and S30, depolymerization occurred rapidly following DTT addition, with more than

95% depolymerization observed over 1 h. Like H_2O_2, DTT is also a strong nucleophile, and

reacted rapidly with ethyl glyoxylate (Figure S26-S28), resulting in the requirement for high

(~110 mM) concentrations of DTT in order to achieve complete end-cap cleavage and

depolymerization. **PEtG-disulfide** without DTT and **PEtG-control** in the presence of 110 mM

DTT underwent only ~5% depolymerization over 24 h (Figure 3c and S31), again showing that

DTT could selectively trigger depolymerization through specific end-cap cleavage.

Hydrazine was initially investigated as a trigger for **PEtG-azobenzene** as it was successfully

used as a trigger in the context of polycarbamates and poly(ester amide)s.[45,57] When 100 mM

hydrazine was added to **PEtG-azobenzene** in 9:1 CD_3CN:D_2O solution, rapid depolymerization

was observed, but these conditions also resulted in complete depolymerization of **PEtG-control**,

suggesting that hydrazine induced non-specific cleavage of the terminal carbonate or the pendant

esters, which could subsequently trigger backbone cleavage and depolymerization.[59] This could

be caused by the basicity or nucleophilicity of hydrazine. Thus, DTT was investigated as a trigger.

As shown in Figures 3d and S32, 110 mM DTT could indeed induce depolymerization of

PEtG-azobenzene, albeit at a slower rate than for **PEtG-disulfide**. For example, ~35%

depolymerization of **PEtG-azobenzene** was observed after 6 h, whereas more than 95% of

PEtG-disulfide was depolymerized in 1 h. Therefore, end-cap cleavage was the rate-limiting step in this process. In the absence of DTT, ~2% depolymerization of **PEtG-azobenzene** was observed over 3 days (Figure 3d and S33) and ~14% of **PEtG-control** depolymerized over this time period in the presence of 110 mM DTT (Figure 3d and S31). This suggests that high concentrations of DTT can induce small amounts of non-specific backbone or terminal carbonate cleavage reactions over a period of days. Thus, the azobenzene moiety provides an additional reduction-sensitive end-cap with slower cleavage kinetics that may be useful for some applications, but it is not as selective a trigger as the boronate or carbonate.

Development of acid-responsive PEtG

Change in pH is also a stimulus of significant interest. For example, tumor tissue, as well as the endosomes and lysosome of cells are well known to have mildly acid pH (e.g., pH $5-7$) relative to the normal neutral physiological pH of 7.4, thereby providing a potential mechanism for selectively releasing therapies in these locations.[51,60] To the best of our knowledge, the use of mildly acidic conditions to trigger end-to-end depolymerization has not yet been reported. Alcohol protecting groups provide an ideal starting point for the development of acid-sensitive end-caps and our studies began by investigating linkages such as acetals that have been widely exploited in the context of stimuli-responsive polymers.[61-63] However, the direct end-capping of PEtG with acetal precursors such as vinyl ethers was unsuccessful and the insertion of spacers that would enable chloroformate preparation resulted in poor initiation of the depolymerization due to the requirement for a subsequent slow cyclization of a hydroxyl nucleophile to release the

PEtG hemiacetal terminus. Fortunately, it was found that triphenylmethyl (trityl) chlorides could be used to directly end-cap PEtG. Trityl groups have been investigated in the context of prodrugs and drug conjugates and can be cleaved in buffers at pH 5-7.[64] As shown in Scheme 2, the use of monomethoxytrityl chloride (**7**) and dimethoxyltrityl chloride (**8**) as end-capping reagents led to **PEtG-MMT** and **PEtG-DMT** respectively. As shown in Table 1, **PEtG-MMT** and **PEtG-DMT** had M_n values of 29 and 21 kg/mol and $Đ$ values of 1.5 and 1.3 respectively. ^{1}H NMR spectroscopic data were consistent with the incorporation of the end-caps at the PEtG terminus (Figures S11, S12). TGA confirmed complete end-capping, but while **PEtG-MMT** had a T_o of 168 °C, **PEtG-DMT** had a T_o of only 131 °C, which is much lower than all of the other end-capped PEtGs. TGA of **8** suggested that this can be attributed to the relatively poor thermal stability of the trityl moiety as **8** undergoes degradation with a T_o of only 78 °C (Figure S45).

The acid triggered depolymerizations of **PEtG-MMT** and **PEtG-DMT** were studied in 9:1 $CD_3CN:D_2O$. Normally it is ideal to adjust the pH using buffers, but the high acetonitrile content of the solvent mixture makes buffer salts insoluble, so instead varying concentrations of acetic acid were added to the $CD_3CN:D_2O$ solutions. As shown in Figure 4a and S34, **PEtG-MMT** underwent end-cap cleavage and complete depolymerization over ~48 days in the presence of 510 mM acetic acid, and with a slightly slower rate in 340 mM acetic acid. In the absence of acetic acid ~18% depolymerization was observed over this time period (Figure S35). Furthermore, the addition of 510 mM acetic acid to **PEtG-control** did not lead to any significant depolymerization over 48 days (Figure S36). Although PEtG is a polyacetal, these acetals are not sensitive to mildly acidic conditions as the adjacent electron-withdrawing ester groups make

them less susceptible to acidic cleavage in comparison with other polyacetals and
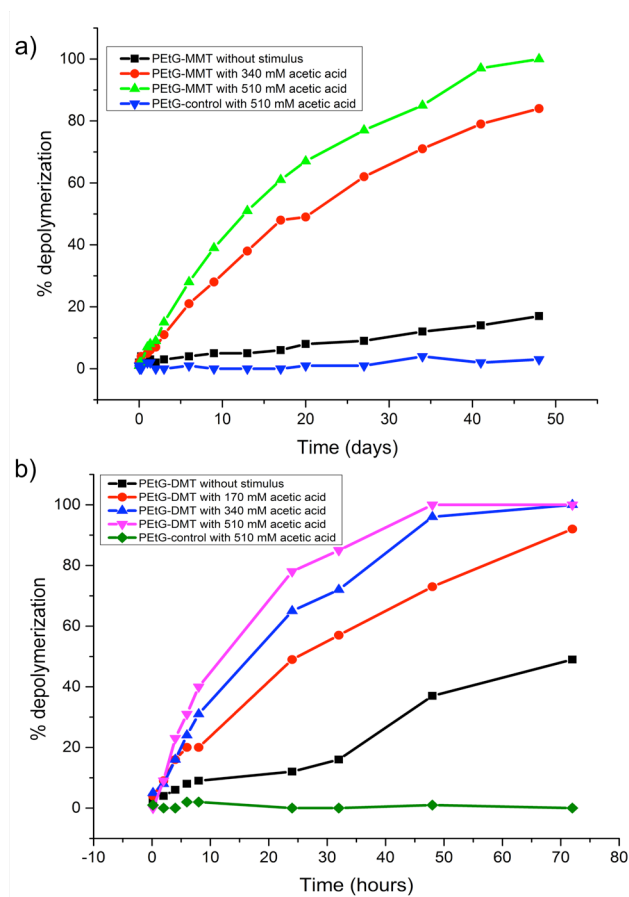
polyketals.[61,62,65]

Figure 4. Percent depolymerization versus time for a) **PEtG-MMT** and b) **PEtG-DMT** in the

absence and presence of varying concentrations of acetic acid.

The presence of two methoxy groups in the end-cap of **PEtG-DMT** was expected to lead to

more rapid cleavage and subsequent depolymerization under acidic conditions[66] and indeed this

was the case. As shown in Figure 4b and S37, complete end-cap cleavage and depolymerization

occurred over only 2 days in the presence of 340 mM or 510 mM acetic acid and at a slightly

slower rate in the presence of 170 mM acetic acid. However, ~50% depolymerization also

occurred for **PEtG-DMT** without added acetic acid (Figure S38). This observation is

characteristic of the typical trade-off with pH-sensitive groups where faster cleavage at mildly

acidic pH is commonly accompanied by faster cleavage under neutral conditions. Nevertheless,

the results show that pH-sensitive PEtGs can indeed be prepared and that the rate of triggering

can be tuned by altering the chemical structure of the end-cap. Although the acetic acid

concentrations employed in 9:1 $CD_3CN:D_2O$ during this study were quite high, the cleavage

would be expected to be faster and to occur at mildly acidic pH in a fully aqueous system.[66]

Development of multi-responsive end-caps

While the above work demonstrates that diverse stimuli can be used to trigger PEtG

depolymerization, for some applications it may be beneficial to develop a versatile end-capping

strategy that allows the polymer to respond to multiple stimuli, either individually or

simultaneously. To prepare an end-cap responsive to multiple stimuli, the previously reported

aniline **9**[46] was reacted with chloroformate **4** in the presence of Na_2CO_3 in THF/H_2O at 0 °C to

functionalize the aniline group selectively, affording compound **10** (Scheme 3). The benzylic

alcohol of **10** was then reacted with phosgene to provide the chloroformate-activated end-cap **11**.

The *o*-nitrobenzyl moiety on this end-cap provides sensitivity to UV light,[67] but also to Zn/acetic

acid[68] (Scheme S1). At the same time, the phenylboronic acid pinacol ester is responsive to H_2O_2.

After fragmentation via the mechanism shown in Figure 2a, the resulting aniline can undergo a

1,4-elimination to release the PEtG, triggering depolymerization (Scheme S1). In addition, using

this simple synthetic route, it should be possible to replace chloroformate **4** with other

chloroformates such as **5** and **6**, such that this route can be used to prepare PEtG responsive to

UV light, Zn/acetic acid and an additional stimulus, provided a chloroformate responsive to that

stimulus can be prepared. Chloroformate **11** was used to cap PEtG as described above (Scheme 2),

providing **PEtG-multi**, with an M_n of 41 kg/mol and *Đ* of 1.6 (Table 1). TGA confirmed that the

polymer was well end-capped and its thermal properties were similar to those of other PEtGs.
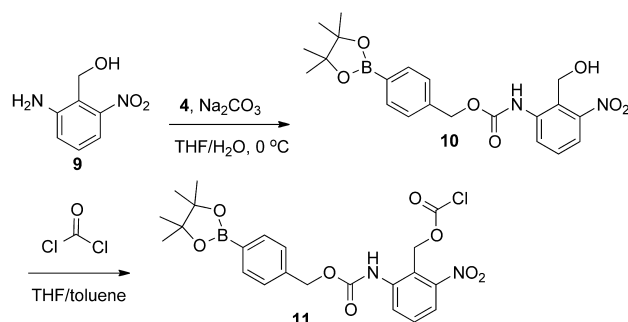
Scheme 3. Synthesis of multi-responsive end-cap **11**.

The depolymerization behaviour of **PEtG-multi** was studied in the presence and absence of

the relevant stimuli in 9:1 $CD_3CN:D_2O$. As shown in Figures 5 and S39, irradiation of

PEtG-multi for 20 min with UV light followed by incubation in the solvent resulted in ~50%

depolymerization over 2 days. The addition of 100 mM H_2O_2 alone and the combination

treatment of 20 min of UV light irradiation and 130 mM H_2O_2 led slightly faster rates of

depolymerization (Figure S40-S41). While the result using UV light as a stimulus was similar to

that previously observed for PEtG with a photoresponsive 6-nitroveratryl end-cap,[24] the rate of

depolymerization using H_2O_2 was significantly slower for **PEtG-multi** than for **PEtG-boronate**

(Figure 3b). Following oxidative cleavage of the phenylboronic acid pinacol ester in **PEtG-multi**

by H_2O_2, the molecule must undergo a 1,6-elimination, loss of CO_2, 1,4-elimination, and finally a

second loss of CO_2 prior to the release of the hemiacetal-terminated PEtG for depolymerization

(Scheme S1). On the other hand, **PEtG-boronate** only requires a single sequence of

1,6-elimination and loss of CO_2. While such elimination reactions can be very rapid under fully

aqueous conditions, as the solvent polarity is decreased (such as through addition of CD_3CN),

these reactions are known to be significantly slowed and this may be responsible for the slower

rate of complete end-cap cleavage and thus the overall depolymerization rate of **PEtG-multi**.[57,69]

Another possible explanation is that the reactive quinone methides or azoquinone methides

generated upon end-cap fragmentation can be trapped by the hydroxyl terminus of

depolymerizing PEtG (Scheme S2). This would generate benzyl ether capped polymers that can

still undergo elimination to continue depolymerization, but at a slower rate. This would explain

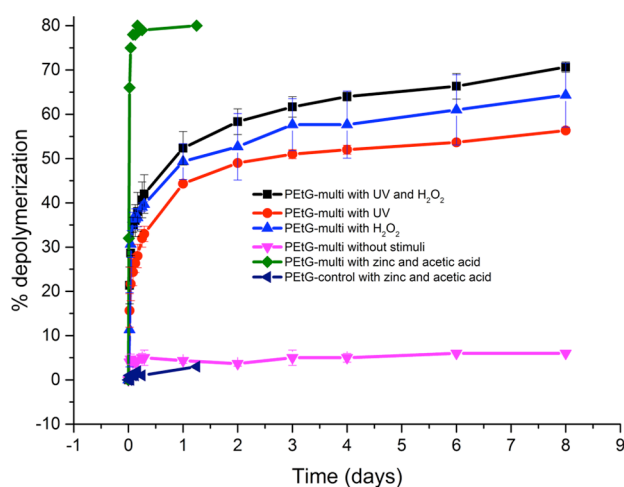the initial rapid phase of depolymerization, followed by the slower phase of depolymerization.

Figure 5. Depolymerization versus time for **PEtG-multi** following exposure to UV light, H_2O_2,

Zn/acetic acid, and combinations of these stimuli.

The addition of Zn (250 mM) and acetic acid (700 mM), conditions previously reported for

triggering dendrimer degradation,[68] afforded ~80% depolymerization within 6 h (Figure S42).

PEtG-control underwent less than 5% depolymerization when exposed to Zn (250 mM) and acetic acid (700 mM) for 30 h (Figure S43). Control experiments described above and previously reported[24] have already confirmed the stability of **PEtG-control** in the presence of UV light and H_2O_2. Furthermore, a control experiment where **PEtG-multi** was not exposed to any stimuli showed that less than 5% depolymerization occurred over 8 days (Figure S44). Overall, these results demonstrate that PEtG can be designed to respond to multiple different stimuli through careful engineering of the end-cap, but that the requirement for multiple sequential reactions can slow the initiation of depolymerization.

Development of a cross-linkable end-cap

Polyglyoxylates are of significant interest as coating materials as they undergo degradation through a surface erosion mechanism with the depolymerization time tunable based on the coating thickness.[35] In order to cure the coating and tune its physical properties, it was desirable to develop a curing process for the polymer. Thus, an end-cap that would allow for cross-linking was designed. Thiol-ene reactions have been extensively used to prepare cross-linked polymer networks in recent years,[70,71] so it was envisioned that an end-cap bearing a stimuli-responsive moiety as well as multiple alkenes would be ideal for subsequent cross-linking using a multivalent thiol.

Synthesis of the end-cap began from the previously reported benzoic acid derivative **12**[47] and amine **13**,[48] which were coupled using *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl) in the presence of 4-(dimethylamino)pyridine (DMAP) to afford the amide **14** (Scheme 4). This amide was then activated using phosgene in THF/toluene to provide

the chloroformate **15**. PEtG was synthesized and end-capped using **15** as described above to

afford **PEtG-trialkene** (Scheme 2) with the slight modification that due to the sterically bulky

nature of this end-cap it was necessary to keep the end-capping conditions at -20 $^{\circ}$C for 6 hours

instead of immediately allowing the solution to gradually warm to room temperature. This

ensured that the polymer had sufficient time to be end-capped at -20 $^{\circ}$C, as it would otherwise

depolymerize when warmed to room temperature. The M_n of **PEtG-trialkene** was 11 kg/mol ($Đ$

= 1.7), which is lower than that of the other polymers due to the end-capping challenges.

However, thermal analyses showed that it was well end-capped and had a T_g similar to that of the

other PEtGs.
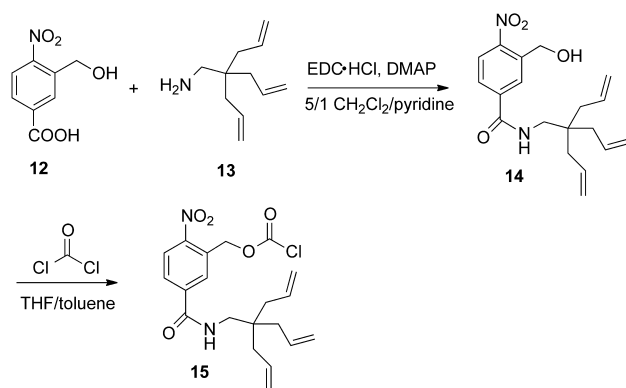
Scheme 4. Synthesis of cross-linkable end-cap **15**.

The cross-linking of **PEtG-trialkene** was performed using pentaerythritol

tetrakis(3-mercaptopropionate) (**16**) in toluene at 60 °C using 2,2'azobis(2-methylpropionitrile)

(AIBN) as an initiator to provide **PEtG-cross-linked** (Scheme 5). After the reaction, unreacted

polymer and small molecules were removed by extracting the gel 3 times with CH_2Cl_2. The

resulting gel content was 72%. Infrared spectroscopy was used to confirm the reaction, as the

peak at 1660 cm^{-1} corresponding to the C=C stretch of the alkene almost entirely disappeared

25

after cross-linking (Figure S53). In addition, the cross-linking resulted in an increase in the T_g from -7 ^{o}C for **PEtG-trialkene** to 5 ^{o}C for **PEtG-cross-linked**. The end-cap of **PEtG-trialkene** contains an *o*-nitrobenzyl moiety enabling it to respond to UV light irradiation, so the depolymerization of the network in response to UV light was explored. The **PEtG-cross-linked** network was immersed in 9:1 $CD_3CN:D_2O$, then irradiated with UV light (2.8 mW/cm^2). Prior to irradiation, only peaks corresponding to CD_2HCN and DOH were observed in the ^{1}H NMR spectrum, as the gel-like network was completely insoluble. After 5 h of UV irradiation, peaks corresponding to the expected depolymerization product EtGH were clearly observed, confirming that depolymerization of the network could be triggered (Figure S45). Only a small amount of particulate material remained, likely corresponding to the product of the reaction between the end-cap and cross-linker **16**. Thus, PEtG can be both incorporated into polymer networks to tune its properties and can also be depolymerized within network structures. It is anticipated that the structure and properties of the cross-linked networks can be optimized for different applications by varying the structure and ratio of the thiol cross-linking agent.
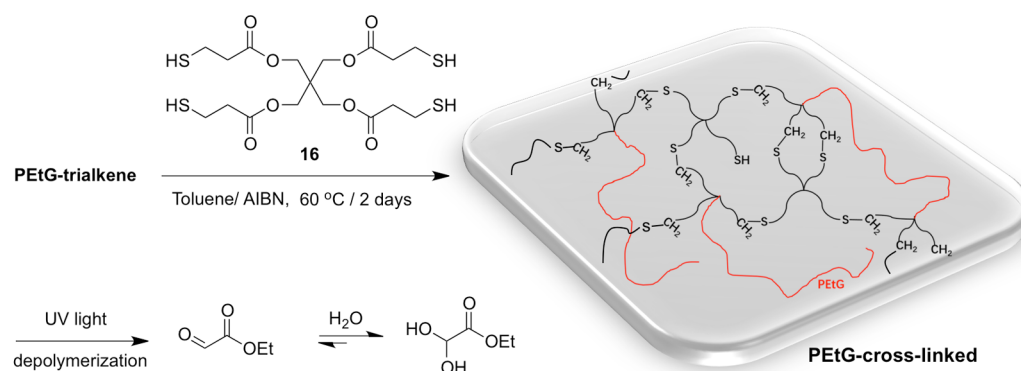
Scheme 5. Cross-linking of **PEtG-trialkene** and UV light triggered depolymerization of the resulting **PEtG-cross-linked**.

Mechanically triggered degradation of PEtG

It was recently demonstrated that high molar mass poly(*o*-phthalaldehyde) could be cleaved by the mechanical force induced by ultrasound.[27] Unlike conventional polymers such as PMMA, that simply undergo chain scission to produce lower molar mass polymers, chain cleavage of poly(*o*-phthalaldehyde) induced end-to-end depolymerization resulting in the conversion of polymers to monomers. Although not technically an end-capping strategy, we sought to determine whether this mechanism of chain scission would also apply to high molar mass PEtG.

In order to evaluate this, the response of high molar mass **PEtG-disulfide-a** ($M_n = 250$ kg/mol) and lower molar mass **PEtG-disulfide-b** ($M_n = 26$ kg/mol) to ultrasound was studied and compared. Dilute (1 mg/mL) solutions of the polymers in THF were prepared in order to avoid polymer chain entanglement and then pulsed ultrasound was applied at -20 °C (1 s on, 0.5 s off). The solutions were removed at various time points and analyzed by SEC. After 5 min, the M_n of **PEtG-disulfide-a** had decreased from 250 kg/mol to 113 kg/mol (Figure 6a and c). With additional sonication over 60 min the molar mass continued to decrease to 46 kg/mol and the intensity of the refractive index (RI) signal in SEC decreased to almost baseline values suggesting that the polymer had almost completely depolymerized. Over this time period, the reduction in M_n and RI signal intensity arose from the continual cleavage of high molar mass polymers by ultrasound, combined with the depolymerization of these cleaved chains to small molecules. On the other hand, neither the molar mass or RI signal intensity in SEC changed for **PEtG-disulfide-b** over 60 min of pulsed ultrasound (Figure 6b and c). This is consistent with the previously reported molar mass threshold of 30 kg/mol for polystyrene chain cleavage by
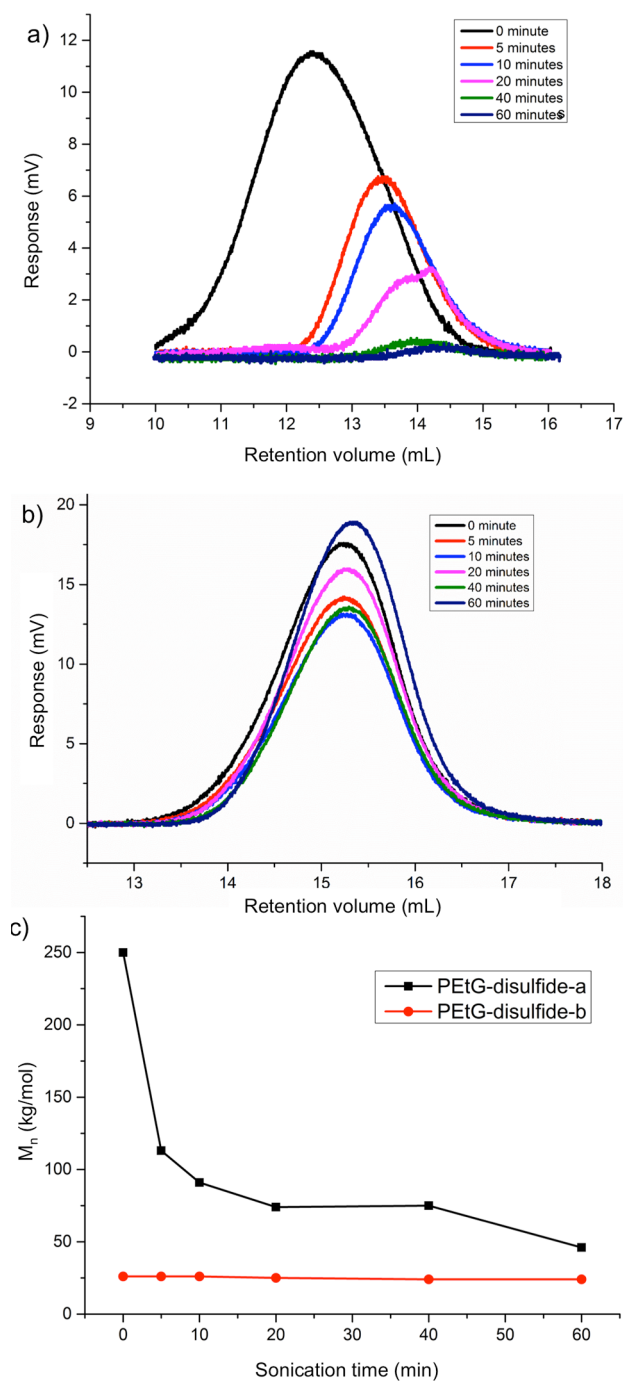
ultrasonication.[72]

Figure 6. a-b) SEC traces (RI detection) for a) **PEtG-disulfide-a** and b) **PEtG-disulfide-b**

following different sonication times; c) Changes in M_n for **PEtG-disulfide-a** and

PEtG-disulfide-b following different sonication times.

Unlike most mechanically-induced chain scissions, that involve the generation of macroradicals,[73] poly(*o*-phthalaldehyde) was demonstrated by trapping experiments to undergo heterolytic bond cleavage prior to depolymerization.[27] Because PEtG also has a polyacetal backbone, it was proposed to follow a similar mechanism. To confirm this, ultrasound was applied to **PEtG-disulfide-a** as described above, but in the presence of *tert*-butyldimethylsilyl chloride, an electrophilic trapping agent capable of reacting with the nucleophilic terminus of heterolytically cleaved PEtG. Depolymerization was significantly slowed in comparison to without the trapping agent, suggesting that a heterolytic cleavage mechanism also applies to PEtG (Figures S54-S55).

These results confirm that mechanical triggering with ultrasound is an additional stimulus that can be applied to initiate the depolymerization of PEtG. This should apply to PEtG with any end-cap, provided the molar mass is sufficiently high. Ultrasound is of particular interest for biomedical applications as ultrasonic radiation is routinely applied for medical imaging and there has been substantial interest in the development of drug delivery systems that are responsive to ultrasound.[74,75]

Conclusions

It was demonstrated that a phenylboronic acid pinacol ester, disulfide, and azobenzene could be converted into chloroformates and used to end-cap PEtG. This allowed PEtG to undergo depolymerization in response to H_2O_2 and DTT, while the non-responsive **PEtG-control** was stable under these conditions. Relatively high concentrations of H_2O_2 and DTT were required due to the trapping of these stimuli by the depolymerization product. It is possible that this drawback

will be mitigated in fully aqueous conditions, where water will be present at 10-fold higher concentration that in 9:1 $CD_3CN:D_2O$, but testing this will require the synthesis of water-soluble polyglyoxylates or water-dispersible block copolymers. It was also shown that acid-sensitive end-caps could be introduced to PEtG using trityl chlorides and that their sensitivity could be tuned by adjusting the number of electron donating methoxy substituents on the phenyl ring. Next, a new end-cap that was responsive to multiple stimuli including UV light, H_2O_2, and Zn/acetic acid was developed. It is envisioned that the backbone and synthetic method for this molecule can be applied to introduce other stimuli-responsive groups, providing a versatile strategy towards multi-responsive end-caps. Furthermore, it was demonstrated that a cross-linkable trialkene could be incorporated into a photo-responsive end-cap, allowing cross-linked networks of PEtG to be formed. Finally, the backbone of high molar mass PEtG could also be cleaved mechanically, thereby initiating depolymerization. Overall, these new end-caps significantly expand the utility of PEtG, by expanding the available stimuli from UV light to many other conditions, some of which are relevant to the physiological environments associated with disease states such as cancer and inflammation. It is also anticipated that these end-caps and triggering mechanisms will be useful for the growing field of stimuli-responsive backbone cleavable and end-to-end depolymerizable materials. Current work is focused on the incorporation of these triggering mechanisms into PEtG block copolymers and the study of their assemblies in aqueous solution.

Supporting information

Additional experimental procedures, NMR spectra, thermal data, depolymerization data, IR data

for cross-linking, proposed cleavage mechanisms for the multi-responsive end-cap. This material

is available free of charge via the Internet at http://pubs.acs.org.

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