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Self-Immolative Polymers Containing Rapidly Cyclizing Spacers: Toward Rapid Depolymerization Rates

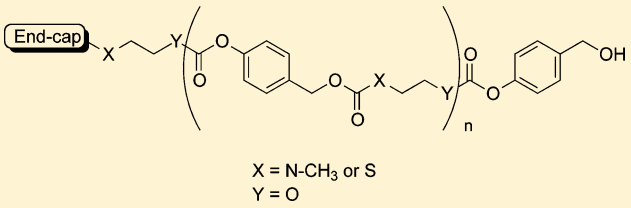
Eric K. Y. Chen,[†] Ryan A. McBride,[‡] and Elizabeth R. Gillies*[,†,‡]

[†]Department of Chemistry, Western University, 1151 Richmond St., London, Canada N6A 5B7

[‡]Department of Chemical and Biochemical Engineering, Western University, 1151 Richmond St., London, Canada N6A 5B9

Supporting Information

ABSTRACT: Self-immolative polymers containing 4-hydroxybenzyl alcohol alternating with either *N*-methylaminoethanol or 2-mercaptoethanol spacers were synthesized and demonstrated to controllably depolymerize in response to the cleavage of a stabilizing end-cap from the polymer termini. These new polymers depolymerized at much higher rates than the previously reported polymer containing an *N*,*N*′-dimethylethylenediamine spacer, with the time scales for complete depolymerization reduced from days to hours. Herein, we report the design and synthetic strategies for incorporating both stronger nucleophilic and electrophilic sites to induce faster cyclization reactions, which are known to be the rate-limiting steps in the depolymerization of this class of self-immolative polymers. These modifications and results demonstrate that the proposed structure-to-property relationships translate to the development of new polymer backbones for applications that require rapid depolymerization rates.



INTRODUCTION

In recent years, biodegradable polymers have emerged as materials of significant interest for a wide range of applications from biomedical devices to more environmentally friendly substitutes for traditional plastics. Thus far, much research has focused on the development and application of materials such as polyesters, which undergo degradation by backbone cleavage at random sites via hydrolytic mechanisms in a variety of environments.[1−4] To address the limited control over the degradation of these materials, new classes of polymers that degrade in response to more specific stimuli such as light or changes in pH[5−7] or redox potential[8−11] have also been developed. When incorporated into devices such as drug delivery vehicles[12−16] such materials offer the possibility to induce degradation at specific times or locations where the stimulus is applied, affording additional control over the polymer degradation process. However, many stimuli-mediated cleavage events are typically required for the complete degradation of the polymer backbone. For many applications it would be desirable to have mechanisms to amplify these stimuli.

Self-immolative materials have been developed over the past decade to introduce new levels of control and amplification in degradation processes.[17,18] These materials are inspired by and derived from self-immolative spacers.[19−22] In prodrug chemistry, upon the introduction of a stimulus that reveals a reactive functional group, these moieties undergo intramolecular reactions to release the drug in its active form.[23,24] Self-immolative materials typically comprise a "trigger moiety" or end-cap, as well as multiple self-immolative monomer units covalently linked in an iterative manner. Upon cleavage of the end-cap by a stimulus, they undergo a cascade of intramolecular reactions, resulting in complete degradation of the material.[17,18] The first self-immolative materials were dendritic in nature and were prepared by careful stepwise synthesis procedures.[25−27] They have since been reported as promising systems for the simultaneous delivery of multiple drug molecules[28,29] and as sensors capable of high degrees of chemical amplification.[30,31]

More recently, self-immolative linear polymers have been developed as a means of providing high degrees of amplification in a limited number of synthetic steps. While no longer monodisperse, linear polymers may provide some advantages over high-generation dendrons, which require lengthy syntheses and are challenging or sometimes impossible to prepare due to steric constraints. The first reported self-immolative linear polymer was composed entirely of monomer units that underwent rapid 1,6-elimination reactions to break down the polymer into fluorescent monomer units.[32,33] This polymer was used as a sensor to amplify the response to the enzymatic cleavage of the end-cap.[32] Subsequently, our group showed that it was possible to introduce spacers that underwent intramolecular cyclization reactions in alternation with elimination reactions to provide polymers that underwent depolymerization by alternating cyclization and 1,6-elimination reactions.[34] Incorporation of the cyclization spacers enabled control over the depolymerization kinetics. It was also possible to prepare polymers that degraded entirely by intramolecular cyclization reactions.[35] Amphiphilic block copolymers derived

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from such polymers were shown to form micelles that were capable of encapsulating and releasing nile red upon depolymerization.[34] Subsequently, materials that depolymerized by 1,6-elimination reactions were used to form capsules for stimuli-triggered release,[36] and end-capped poly(phthaldehyde)s were shown to induce changes in the shape of patterned plastics when exposed to chemical signals.[37] These examples demonstrate the diverse applicability of this new class of materials.

In order to develop ideal materials for various applications, it is critical to have access to self-immolative polymers that depolymerize in a controlled manner at different rates. However, the number of different self-immolative polymer backbones that are currently available is very limited. While the poly(phthaldehyde)s[37] and polymers based entirely on 1,6-elimination spacers[32] depolymerize very rapidly, on the order of minutes, the current polymers containing the cyclization spacers[34,35] depolymerize much more slowly, over a period of several days, owing to the slow cyclization kinetics of the *N*,*N*′-dimethylethylenediamine-based monomer. To address this gap and significantly broaden the spectrum of accessible depolymerization rates, it was proposed that the cyclization spacer could be tuned to achieve different cyclization rates. This has been achieved in part through our development of a new series of cyclization spacers based on 4-aminobutyric acid,[38] and their incorporation into linear self-immolative polymers is currently in progress. Here we describe a different approach involving changes to the *N*,*N*′-dimethylethylenediamine spacer structure aimed at altering the electrophilicity and nucleophilicity of the sites involved in the cyclization reaction to ultimately achieve faster depolymerization. The design and synthesis of two new self-immolative polymers are reported, along with depolymerization studies on the resulting materials.

EXPERIMENTAL SECTION

General Procedures and Materials. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Anhydrous DMF and toluene were obtained from a solvent purification system using aluminum oxide columns. Dichloromethane, pyridine, and triethylamine were distilled from calcium hydride. Unless otherwise stated, all reactions were performed under a N_2 atmosphere using flame-dried glassware. Column chromatography was performed using silica gel (0.063−0.200 mm particle size, 70−230 mesh). Thin layer chromatography (TLC) was performed using Macherney-Nagel Polygram SIL G/UV_{254} plates. ^{1}H NMR spectra were obtained at 600 MHz, and ^{13}C NMR spectra were obtained at 150 MHz using a Varian Inova spectrometer. NMR chemical shifts are reported in ppm and are calibrated against residual solvent signals of $CDCl_3$ (δ 7.26, 77). Coupling constants are expressed in hertz (Hz). High-resolution mass spectrometry (HRMS) was performed on a Finnigan MAT 8400 mass spectrometer using either electron impact (EI) or chemical ionization (CI). Size exclusion chromatography (SEC) was carried out at a flow rate of 1 mL/min in DMF with 10 mM LiBr and 1% (v/v) triethylamine at 85 °C using a Waters 2695 separations module equipped with a Waters 2414 differential refractometer and two PLgel 5 μm mixed-D (300 mm × 7.5 mm) columns from Polymer Laboratories connected in series. The calibration was performed using polystyrene standards. Dialyses were performed using Spectra/Por regenerated cellulose membranes with a 3500 g/mol molecular weight cutoff (MWCO).

Synthesis of Compound ***5***. Alcohol **4**[39] (0.87 g, 5.0 mmol, 1.0 equiv) and pyridine (0.6 mL, 7.5 mmol, 1.5 equiv) were dissolved in 15 mL of anhydrous CH_2Cl_2 and added dropwise to a solution of 4-nitrophenyl chloroformate (1.5 g, 7.5 mmol, 1.5 equiv) in 40 mL of anhydrous CH_2Cl_2, and the reaction mixture was stirred at room temperature until completion (∼2 h) as determined by TLC. The reaction was then washed with 1 M HCl followed by brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The material was purified by column chromatography (1:3 EtOAc:cyclohexane) to give activated carbonate **5** (1.27 g, 75%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.23 (d, J = 8.2, 2H), 7.35 (d, J = 8.2, 2H), 4.35 (t, J = 5.5, 2H), 3.56, (br, m, 2H), 2.92 (s, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 155.7, 155.4, 152.3, 145.2, 125.1, 121.7, 79.9, and 79.8 (rotamers), 66.8, 47.5, and 47.0 (rotamers), 35.1 and 35.0 (rotamers), 28.2. HRMS: calcd $[M]^+$ ($C_{15}H_{20}N_2O_7$): 340.1271. Found: (EI) 340.1191.

Synthesis of Compound ***7***. Activated carbonate **5** (0.80 g, 2.4 mmol, 1.0 equiv), phenol **6**[40] (0.68 g, 2.9 mmol, 1.2 equiv), DIPEA (0.30 μL, 2.9 mmol, 1.5 equiv), and DMAP (0.03 g, 0.24 mmol, 0.1 equiv) were dissolved and stirred at room temperature in 30 mL of anhydrous CH_2Cl_2 for 15 h. The reaction was then washed with 1 M HCl followed by brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. Compound **7** was then used in the next step without further purification (0.76 g, 73%). ^{1}H NMR ($CDCl_3$): δ 7.34 (d, J = 8.6, 2H), 7.14 (d, J = 8.6, 2H), 4.73 (s, 2H), 4.35 (br, m, 2H), 3.56 (br, m, 2H), 1.48 (s, 9H), 0.95 (s, 9H), 0.10 (s, 6H).

Synthesis of Compound ***8***. Fully protected monomer **7** (0.75 g, 1.7 mmol, 1.0 equiv) was stirred at room temperature in 10 mL of 1% HCl in ethanol until the reaction was complete (∼1.5 h) as determined by TLC. The reaction was neutralized with minimal 1 M $NaHCO_3$ as determined with pH paper. The reaction was then diluted with 30 mL of CH_2Cl_2 and washed with water followed by brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The material was purified by column chromatography (1:3 EtOAc:cyclohexane) to give **8** (0.44 g, 80%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.38 (d, J = 8.6, 2H), 7.17 (d, J = 7.2, 2H), 4.68, (s, 2H), 4.34 (br, m, 2H), 3.56 (br, m, 2H), 2.95 (s, 3H), 2.04 (br, s, 1H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 155.4, 153.6, 150.3, 138.8, 128.0, 121.0, 80.0, and 79.9 (rotamers), 66.5, 64.5, 47.8, and 47.4 (rotamers), 35.6 and 35.2 (rotamers), 28.4. HRMS: calcd $[M]^+$ ($C_{16}H_{23}NO_6$): 325.1525. Found: (ESI) 325.1534.

Synthesis of Compound ***9***. Compound **8** (0.25 g, 0.77 mmol, 1.0 equiv), 4-nitrophenyl chloroformate (0.19 g, 0.92 mmol, 1.2 equiv), and pyridine (0.18 mL, 2.3 mmol, 3.0 equiv) were dissolved and stirred at room temperature in 5 mL of anhydrous CH_2Cl_2 until the reaction was complete (∼2 h) as determined by TLC. The reaction mixture was then washed with 1 M HCl followed by brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The material was purified by column chromatography (1:3 EtOAc:cyclohexane) to give **9** (0.32 g, 87%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.27 (d, J = 9.4, 2H), 7.47 (d, J = 8.4, 2H), 7.38 (d, J = 9.4, 2H), 7.23 (d, J = 8.4, 2H), 5.28 (s, 2H), 4.36 (br, m, 2H), 3.57 (br, m, 2H), 2.95 (s, 3H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 155.7, 155.3, 153.3, 152.3, 151.4, 145.3, 132.0, 130.0, 125.2, 121.7, 121.3, 79.9, and 79.7 (rotamers), 70.0, 66.5, 47.7, and 47.2 (rotamers), 35.4 and 35.1 (rotamers), 28.3. HRMS: calcd $[M + H]^+$ ($C_{23}H_{27}N_2O_{10}$): 491.1666. Found: (CI) 491.1769.

Synthesis of Monomer ***11***. Protected monomer **7** (0.80 g, 1.8 mmol, 1.0 equiv) was dissolved and stirred at room temperature in 6 mL of 1:1 (v/v) TFA:CH_2Cl_2 for 2 h. The reaction was neutralized with minimal 1 M $NaHCO_3$ as determined with pH paper and then diluted with 20 mL of CH_2Cl_2. The organic layer was washed with water and then brine, dried over $MgSO_4$, and filtered, and the solvents were removed *in vacuo* to provide compound **10**. This compound was then redissolved in 15 mL of anhydrous CH_2Cl_2 and cooled to 0 °C. Triphosgene (0.22 g, 0.73 mmol, 0.4 equiv) was slowly added to the reaction, followed by DIPEA (1 mL, 0.73 mmol, 4 equiv). The reaction was stirred at 0 °C for 1 h and then let warm to room temperature. The reaction was then washed with 1 M HCl followed by brine to give the chloroformamide **10** after solvent removal *in vacuo*. To the reaction flask was added a solution of 18 mL of 2:1:1 THF/H_2O/1 M Na_2CO_3 (9 mL of THF, 9 mL of H_2O, and 0.44 g of Na_2CO_3) to fully convert the trifluoroacetate to the corresponding benzyl alcohol. The reaction was then diluted with 30 mL of CH_2Cl_2 and washed with brine. The organic layer was dried over $MgSO_4$ and

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filtered, and the solvent was removed *in vacuo*. The material was purified by column chromatography (1:1 EtOAc:cyclohexane) to give activated monomer **11** (0.32 g, 61%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.41 (d, J = 8.6, 2H), 7.21−7.15 (m, 2H), 4.71 (s, 2H), 4.48−4.41 (m, 2H, rotamers), 3.90−3.74 (m, 2H, rotamers), 3.26 and 3.16 (s, 1.3:1, 3H, rotamers), 1.69 (br, s, 1H). ^{13}C NMR ($CDCl_3$): δ 153.4, 150.3, and 150.1 (rotamers), 150.0 and 149.1 (rotamers), 139.1 and 139.0 (rotamers), 128.0 and 127.9 (rotamers), 120.84 and 120.81 (rotamers), 65.4 and 65.3 (rotamers), 64.2, 51.2, and 49.8 (rotamers) 39.6 and 37.6 (rotamers). HRMS: calcd $[M]^+$ ($C_{12}H_{14}ClNO_5$): 287.0561. Found: (CI) 287.0570.

Synthesis of Polymer ***2***. Monomer **11** (0.25 g, 0.87 mmol, 20 equiv), end-cap **8** (0.014 g, 0.044 mmol, 1.0 equiv), DIPEA (0.038 mL, 0.22 mmol, 5.0 equiv), and DMAP (0.0005 g, 0.0044 mmol, 0.1 equiv) were stirred in minimal anhydrous toluene (1 mL) at 90 °C for 6 h. The reaction was allowed to cool down to room temperature. Dilution with CH_2Cl_2, washing with 1 M HCl and then 1 M Na_2CO_3, then drying the organic layer with $MgSO_4$, filtering, and evaporating typically provided yields of 85−90% of polymeric/oligomeric material. However, to remove the small molecule byproducts as well as fractionate the higher MW polymers from the lower MW oligomers, the reaction mixture was instead diluted with 0.5 mL of DMF and then dialyzed overnight against DMF. The fraction contained in the membrane was then diluted with an equal volume of H_2O and lyophilized to give polymer **2** (0.085 g, 36%). ^{1}H NMR spectroscopy indicated a degree of polymerization of ∼20 by integrating methylene peaks against the Boc end-cap. ^{1}H NMR ($CDCl_3$): δ 7.45−7.31 (m, 41H), 7.24−7.04 (m, 45H), 5.19−5.06 and 4.72−4.63 (m, 26 and 15H, respectively, rotamers), 4.51−4.28 (m, 42H), 3.85−3.51 (m, 43H), 3.30−2.86 (m, 66H), 1.47 (s, 9H, Boc). SEC: M_n = 3200 g/mol, PDI = 1.26.

Synthesis of Compound ***13***. TBS protected mercaptoethanol[41] (2.0 g, 10.4 mmol, 1.0 equiv) and pyridine (1.2 mL, 16.0 mmol, 1.5 equiv) were dissolved in 50 mL of anhydrous CH_2Cl_2 and stirred at 0 °C. Triphosgene (1.04 g, 3.45 mmol, 0.4 equiv) was slowly added to the reaction, which was stirred at 0 °C for 1 h and then 3 h at room temperature. The reaction mixture was then washed three times with 1 M HCl followed by water and then brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. Compound **13** was then used in the next step without further purification (2.12 g, 80%). ^{1}H NMR ($CDCl_3$): δ 3.83 (t, J = 6.4, 2H), 3.11 (t, J = 6.4, 2H), 0.90 (s, 9H), 0.08 (s, 6H).

Synthesis of Compound ***15***. Thiochloroformate **13** (1.0 g, 4.0 mmol, 1.0 equiv), 4-nitrophenyl-activated 4-hydroxybenzyl alcohol **14**[28] (1.15 g, 4.0 mmol, 1.0 equiv), pyridine (1.8 mL, 24.0 mmol, 6.0 equiv), and DIPEA (1.0 mL, 8.0 mmol, 2.0 equiv) were dissolved in 75 mL of anhydrous THF and stirred at 50 °C for 6 h. Another equivalent of thiochloroformate **13** (1.0 g, 4.0 mmol, 1.0 equiv) was added, and the reaction was stirred at 45 °C for 15 h. The reaction was then diluted with 200 mL of CH_2Cl_2 and washed with 1 M HCl followed by brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The material was purified by column chromatography (1:6 EtOAc:cyclohexane) to give **15** (2.0 g, 65%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.35−8.31 (m, 2H), 7.52−7.42 (m, 4H), 7.31−7.28 (m, 2H), 5.25 (s, 2H), 3.80 (t, J = 6.4, 2H), 3.04 (t, J = 6.4, 2H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 171.1, 155.2, 150.8, 150.6, 145.6, 133.9, 129.8, 125.4, 121.7, 120.9, 67.9, 62.0, 33.8, 25.8, 18.3, −5.4. HRMS: calcd $[M + H]^+$ ($C_{23}H_{30}NO_8SSi$): 508.1461. Found: (CI) 508.1449.

Synthesis of Monomer ***16***. Compound **15** (0.50 g, 0.98 mmol, 1.0 equiv) was stirred at room temperature in 10 mL of 1% HCl in ethanol until the reaction was complete (∼1.5 h) as determined by TLC. The reaction was neutralized with minimal 1 M $NaHCO_3$ as determined with pH paper. The reaction was then diluted with 30 mL of CH_2Cl_2 and washed with water followed by brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The material was purified by column chromatography (1:19 EtOAc:CH_2Cl_2) to give monomer **16** (0.31 g, 80%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 8.35−8.31 (m, 2H), 7.53−7.44 (m, 4H), 7.33−7.30 (m, 2H), 5.28 (s, 2H), 3.85 (br, m, 2H), 3.10 (t, J = 6.0, 2H), 2.19 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 171.0, 155.1, 150.8, 150.6, 145.6, 133.6, 129.8, 125.4, 121.7, 120.9, 68.2, 61.6, 33.8. HRMS: calcd $[M + H]^+$ ($C_{17}H_{16}NO_8S$): 394.0597. Found: (CI) 394.0595.

Synthesis of Polymer ***3***. Monomer **16** (0.100 g, 0.25 mmol, 20 equiv), end-cap **17**[42] (0.0024 g, 0.013 mmol, 1.0 equiv), DIPEA (0.01 mL, 0.063 mmol, 5.0 equiv), and DMAP (0.0002 g, 0.0013 mmol, 0.1 equiv) were stirred in minimal anhydrous toluene (0.3 mL) at −15 °C for 8 h. The reaction was allowed to warm up to room temperature and stirred for another 15 h. The reaction mixture was then diluted with 0.5 mL of DMF and dialyzed overnight in DMF. The membrane content was then diluted with an equal volume of H_2O and lyophilized to give polymer **3** (0.035 g, 51%). ^{1}H NMR spectroscopy indicated a degree of polymerization of ∼15 by integrating methylene peaks against the dithiopyridyl end-cap. ^{1}H NMR ($CDCl_3$): δ 8.49−8.43 (m, 1H), 8.24−8.18 (m, 2H), 8.08−8.04 (m, 1H), 7.51−7.31 (br, m, 30H), 7.23−7.16 (br, m, 30H), 5.30−5.20 (m, 30H), 4.47−4.39 (br, m, 30H), 3.27−3.19 (br, m, 30H). SEC: M_n = 5040, PDI = 1.67.

Synthesis of Compound ***20***. Activated carbonate **5** (0.70 g, 2.2 mmol, 1.0 equiv), phenol **19**[43] (0.33 g, 2.4 mmol, 1.1 equiv), DIPEA (0.30 μL, 2.9 mmol, 1.6 equiv), and DMAP (0.03 g, 0.24 mmol, 0.1 equiv) were dissolved in 30 mL of anhydrous CH_2Cl_2 and stirred at room temperature for 15 h. The reaction was then washed with 1 M HCl followed by brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The material was purified by column chromatography (1:4 EtOAc:cyclohexane) to give **20** (0.58 g, 82%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.32 (d, J = 8.2, 2H), 7.15 (d, J = 8.2, 2H), 4.42 (s, 2H), 4.36−4.30 (m, 2H), 3.57−3.51 (m, 2H), 3.36 (s, 3H), 2.93 (s, 3H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 155.6, 153.4, 150.3, 136.0, 128.6, 120.8, 79.8, 73.8, 66.4, 58.0, 47.6, and 47.3 (rotamers), 35.4 and 35.0 (rotamers), 28.2. HRMS: calcd $[M]^+$ ($C_{17}H_{25}NO_6$): 339.1682. Found: (EI) 339.1677.

Synthesis of Compound ***23***. Alcohol **17**[42] (0.24 g, 1.2 mmol, 1.0 equiv), carbonate **22**[34] (0.62 g, 1.5 mmol, 1.2 equiv), DIPEA (0.35 mL, 1.9 mmol, 1.5 equiv), and DMAP (0.015 g, 0.12 mmol, 0.1 equiv) were dissolved in 20 mL of anhydrous CH_2Cl_2 and stirred at 35 °C until reaction was complete (∼4 h) as determined by TLC. The reaction was then washed with 1 M HCl followed by brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The material was purified by column chromatography (1:3 EtOAc:cyclohexane) to give **23** (0.40 g, 69%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.52−8.47 (m, 1H), 7.73−7.62 (m, 2H), 7.34 (d, J = 8.6, 2H), 7.16−7.09 (m, 3H), 4.73 (s, 2H), 4.51 (t, J = 6.6, 2H), 3.15 (t, J = 6.6, 2H), 0.95 (s, 9H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 159.3, 153.3, 149.74, 149.67, 139.3, 136.9, 126.9, 120.8, 120.5, 119.9, 65.9, 64.2, 36.9, 25.8, 18.3, −5.4. HRMS: calcd $[M]^+$ ($C_{21}H_{29}NO_4S_2Si$): 451.1307. Found: (EI) 451.1307.

Synthesis of Compound ***24***. Compound **23** (0.40 g, 0.89 mmol, 1.0 equiv) was stirred at room temperature in 10 mL of 1% HCl in ethanol until the reaction was complete (∼1.5 h) as determined by TLC. The reaction was neutralized with minimal 1 M $NaHCO_3$ as determined with pH paper. The reaction was then diluted with 30 mL of CH_2Cl_2 and washed with water followed by brine. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. The material was purified by column chromatography (1:3 EtOAc:cyclohexane) to give **24** (0.24 g, 80%) as a clear oil. ^{1}H NMR ($CDCl_3$): δ 8.45 (d, J = 4.7, 1H), 7.71−7.67 (m, 1H), 7.64 (dt, J = 7.1, 1.2, 1H), 7.36 (d, J = 8.8, 2H), 7.14 (d, J = 8.8, 2H), 7.11−7.08 (m, 1H), 4.66 (s, 2H), 4.49 (t, J = 6.4, 2H), 3.13 (t, J = 6.4, 2H), 2.44 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 159.3, 153.3, 150.2, 149.7, 138.9, 137.1, 128.0, 120.94, 120.90, 119.9, 66.0, 64.4, 36.9. HRMS: calcd $[M]^+$ ($C_{15}H_{15}NO_4S_2$): 337.0442. Found: (EI) 337.0438.

Monomer Cyclization Kinetics Studies. *Compound* ***18***[34] *by UV−vis Spectroscopy.* 3 mL of preheated isopropanol was added to a quartz cuvette containing compound **18** (1.50 mg), and the resulting mixture was incubated at 37 °C over a period of 8 days. Absorbance measurements at 282 nm were made at regular intervals throughout the cyclization process with the initial time point (t = 0) defined at the time of isopropanol addition. As the cyclization did not reach completion over this time period, the relative concentrations of compound **18** and 4-hydroxybenzyl alcohol throughout the cyclization

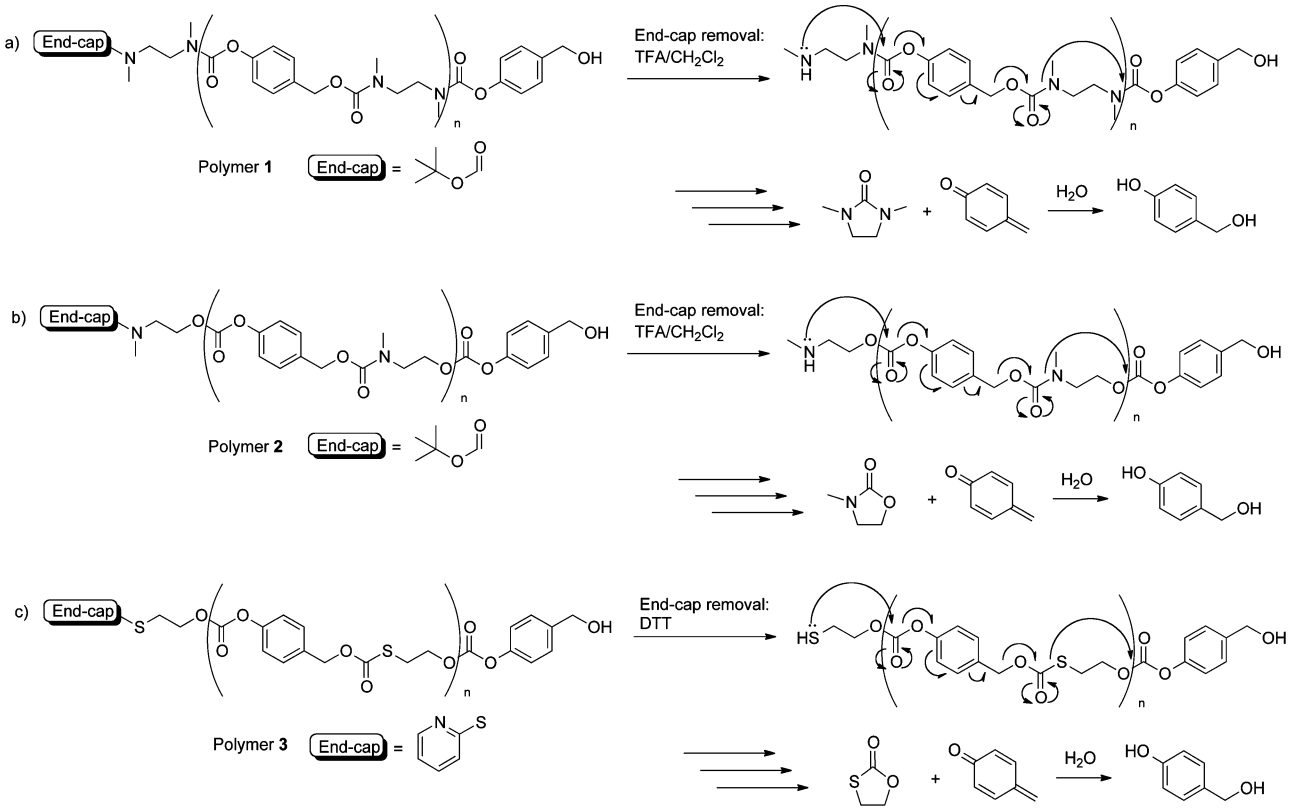

Figure 1. Chemical structures, proposed depolymerization mechanisms, and expected depolymerization products of (a) previously reported polymer **1**,[34] (b) target polymer **2**, and (c) target polymer **3**.

process were calculated using the experimentally determined extinction coefficients of 28.8 and 1466 M^{-1} cm^{-1} at 282 nm for compound **18** and 4-hydroxybenzyl alcohol in isopropanol, respectively. The rate constant and half-life were determined by regressing the natural logarithm of the concentration of compound **18** onto time.

Compound **21** was obtained by dissolving compound **20** (0.020 g, 0.060 mmol) in 6 mL of 1:1 (v/v) TFA:CH_2Cl_2 and stirring at room temperature for 2 h. The solvent and TFA were removed *in vacuo*. *Compound **21** kinetics by ^{1}H NMR spectroscopy*: Compound **21** (20 mg) was dissolved in 0.5 mL of 0.1 M pH 7.4 phosphate buffered D_2O:acetone-d_6 (3:2) at 37 °C, and a ^{1}H NMR spectrum was obtained as rapidly as possible (<3 min.). By the time the spectrum could be acquired, complete cyclization was observed (Figure S14). *Compound **21** by UV−vis spectroscopy:* 3 mL of preheated isopropanol was added to a quartz cuvette containing compound **21** (0.75 mg), and the resulting mixture was incubated at 37 °C over a period of 500 min. Absorbance measurements at 282 nm were made at regular intervals throughout the cyclization process with the initial time point (t = 0) defined at the time of isopropanol addition. The mean absorbance at 282 nm in the plateau region from 400 to 500 min was taken to correspond to 100% cyclization, and the percent cyclization was calculated based on this value. The rate constant and half-life were determined by regressing the natural logarithm of percent monomer remaining onto time.

*Compound **24** Kinetics by ^{1}H NMR Spectroscopy*. Compound **24** (20 mg) was dissolved in 0.5 mL of 0.1 M pH 7.4 phosphate buffered D_2O:acetone-d_6 (3:2) at 37 °C, and the solution was purged with argon for 10 min. DTT (0.027 g, 0.18 mmol) was added, and a ^{1}H NMR spectrum was obtained as rapidly as possible (<3 min.). By the time the spectrum could be acquired, complete cyclization was observed (Figure S18).

Polymer Degradation Studies. Polymer **2** (30 mg) was dissolved in 1 mL of 1:1 TFA:CH_2Cl_2 and stirred at room temperature for 2 h to remove the Boc end-cap. The solvent was removed *in vacuo*, diluted with 1 mL of H_2O, and lyophilized to remove residual TFA. The deprotected polymer was then taken up in 0.5 mL of 0.1 M pH 7.4 phosphate buffered D_2O:acetone-d_6 (3:2), and the solution was incubated at 37 °C. The extent of depolymerization was quantified using ^{1}H NMR by integrating the methylene peak of the 3-methyloxazolidin-2-one cyclic product relative an internal DMF standard in the sample. Polymer **3** (30 mg) was dissolved in 0.5 mL of 0.1 M pH 7.4 phosphate buffered D_2O:acetone-d_6 (3:2), and the solution was purged with argon for 10 min. DTT (0.009 g, 0.058 mmol) was added to remove the end-cap. The extent of depolymerization was quantified using ^{1}H NMR by integrating the methylene peak of the 1,3-oxathiolan-2-one cyclic product relative to an internal DMF standard in the sample. Polymer degradation data was treated by nonlinear regression and fit to a modified Avrami equation of the following form:

$$P = P_0 e^{-(kt)^{\alpha}} \quad (1)$$

where P is the percent polymer remaining, P_0 is the initial percentage of polymer, k is the effective first-order rate constant, and α is an adjustment factor. Nonlinear least-squares regression was performed using a Gauss−Newton algorithm contained within the R stats package.

RESULTS AND DISCUSSION

Design. The chemical structure of our previously reported polymer **1** based on alternating 4-hydroxybenzyl alcohol and *N*,*N*′-dimethylethylenediamine moieties is shown in Figure 1a.[34] Cleavage of the end-cap reveals a terminal amine that cyclizes to *N*,*N*′-dimethylimidazolidinone, revealing a phenol which undergoes a 1,6-elimination reaction. This releases a quinone methide that under aqueous conditions is rapidly trapped by water to regenerate 4-hydroxybenzyl alcohol. CO_2 is lost from the polymer terminus to reveal an amine, which

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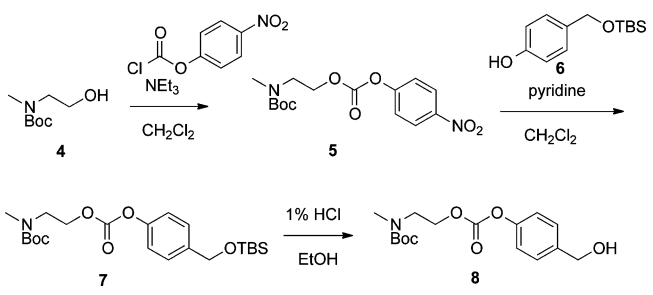
allows this series of steps to repeat until end to end degradation is complete. In this depolymerization, the 1,6-elimination is rapid, making the cyclization step, which exhibits a half-life of 35 min under the depolymerization conditions, the rate-limiting step. For the current work, it was proposed that this cyclization rate could be altered by modifications to the *N,N′*-dimethylethylenediamine spacer. More specifically, in the context of this cyclization reaction, both the nucleophilic and electrophilic sites can be modified by the choice of heteroatom.

The structure of the target polymer **2** is shown in Figure 1b. It was proposed that the cyclization of the *N,N′*-dimethylethylenediamine spacer is slowed by the requirement of the amine to cyclize on a carbamate, a relatively poor electrophile. Replacement of one of the amino groups of *N,N′*-dimethylethylenediamine with an oxygen would convert this carbamate to a carbonate, a more electrophilic site. A second modification was also proposed and is depicted in the structure of target polymer **3** in Figure 1c. As the pK_a of a protonated amine is in the range of 9−10, in aqueous conditions at pH 7.4 the nucleophilicity of the amine is attenuated by partial protonation. Thus, it was proposed that replacement of the amine with a thiol would also provide faster cyclization rates as thiols typically have pK_as in the range of 7−8 and are even good nucleophiles in their neutral form. For polymer **2**, a *tert*-butyloxycarbonyl (Boc) end-cap was selected. Though not cleavable under physiological conditions, this end-cap is readily accessible as a synthetic intermediate in the synthesis of the required monomer for polymerization. In addition, it possesses the advantage that it can be cleanly removed, and the resulting intact polymer isolated by a separate treatment with trifluoroacetic acid (TFA), allowing the depolymerization rate to be studied separately from the end-cap cleavage. For polymer **3**, a disulfide end-cap was selected. It can be selectively cleaved under reducing conditions. The conditions can be readily created chemically using reducing agents such as dithiothreitol (DTT) and are also relevant to biomedical applications as the intracellular environment and diseased tissues such as tumors are more reducing than the healthy extracellular environment, potentially allowing for site-specific delivery of molecules.[44−46]

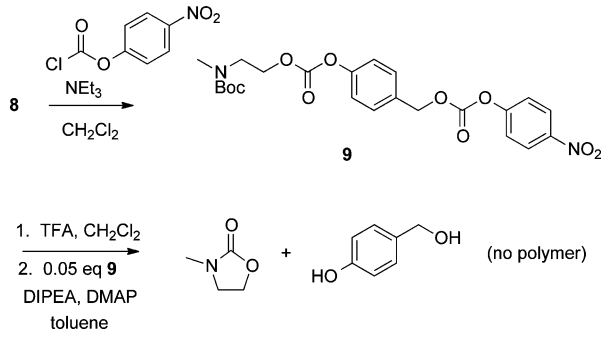
Synthesis of Polymer 2. The first attempted synthesis of polymer **2** was based on the route used for the preparation of the analogous polymer based on *N,N′*-dimethylethylenediamine,[34] with minor modifications. Boc-protected 2-methylaminoethanol (**4**)[39] was prepared as the starting material instead of mono-Boc-protected *N,N′*-dimethylethylenediamine. As shown in Scheme 1, activation of **4** with 4-nitrophenyl chloroformate afforded **5**, which when reacted with *tert*-butyldimethylsilyl (TBS)-protected 4-hydroxybenzyl alcohol (**6**),[40] gave the carbonate **7**. Upon TBS deprotection in acidic ethanol, the alcohol **8** was obtained.

Scheme 1. Synthesis of Compound 8



As shown in Scheme 2, compound **8** was then activated with 4-nitrophenyl chloroformate to obtain the protected monomer **9**. After removal of the Boc protecting group on **9** by TFA treatment, attempts to polymerize the resulting amine salt in the presence of a small amount of **9** as an end-cap provided the first indications that cyclization of this carbonate-based monomer was indeed faster than the previously investigated carbamate. Whereas polymerization of the analogous carbamate monomer yielded mainly polymeric material with only traces of cyclization products, polymerization of deprotected **9** under various conditions yielded mostly cyclic product 3-methyloxazolidin-2-one, 4-hydroxybenzyl alcohol, and only trace amounts of oligomers.

Scheme 2. Activation, Deprotection, and Attempted Polymerization of Compound 8



It was hypothesized that intermolecular polymerization reactions would be favored over intramolecular monomer cyclization if the distal electrophile were more reactive as the intramolecular cyclization on the other portion of the molecule should occur independently of this electrophile. Thus, alternative synthetic strategies toward such monomers were investigated. For example, the conversion of **8** to a chloroformate by activation with triphosgene instead of 4-nitrophenyl chloroformate was investigated. Unfortunately, it was difficult to isolate pure chloroformate monomer and preliminary investigations into the polymerization of this chloroformate revealed that the undesired intramolecular cyclization reaction was still occurring. As step-growth polymerizations are sensitive to impurities, this strategy was not viable.

To completely inhibit potential monomer cyclization, we sought to reverse the roles of the monomer termini by activating the amino terminus as the electrophilic site such that it could not cyclize, while leaving the benzyl alcohol moiety free to act as the nucleophile in the polymerization. As shown in Scheme 3, compound **7** was treated with TFA to remove the Boc protecting group. Under these conditions, the TBS group protecting the hydroxy terminus was converted into a trifluoroacetate, providing **10**, as indicated by the benzylic methylene chemical shift in the NMR spectrum. This functional group conversion was unexpected but did not hinder our synthesis as the trifluoroacetate acted as a temporary base-sensitive protecting group. Activation of the amine on **10** with 4-nitrophenyl chloroformate to form the corresponding carbamate was investigated, but the resulting monomer was unreactive under various polymerization conditions. However, activation of **10** with triphosgene followed by bicarbonate work-up gave conversion to the chloroformamide **11**, which was isolated in 61% yield.

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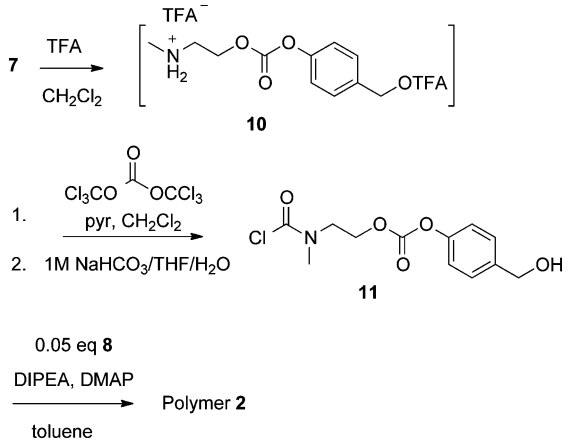
Scheme 3. Completion of the Monomer Synthesis and Synthesis of Polymer 2



Monomer **11** was polymerized in toluene in the presence of 0.05 equiv of end-cap **8** as well as *N*,*N*-diisopropylethylamine (DIPEA) and catalytic 4-(dimethylamino)pyridine (DMAP) to provide polymer **2** (Scheme 3). Size exclusion chromatography (SEC) analysis of the crude polymer **2** revealed a broad distribution of molecular weights and some low molecular weight oligomers, as expected based on the step-growth polymerization mechanism. To fractionate the polymer for degradation studies, dialysis in *N*,*N*-dimethylformamide (DMF) was performed using a membrane with a molecular weight cutoff (MWCO) of 3500 g/mol. The resulting material had a number-average molecular weight (M_n) of 3200 g/mol and a polydispersity index (PDI) of 1.26 (Figure 2a). Based on ^{1}H NMR spectroscopy, the monomer to end-cap ratio corresponded approximately to the target ratio of 20:1.

Synthesis of Polymer **3**. With the expectation that the cyclization of any monomer bearing a free thiol moiety would be problematic during the synthesis of polymer **3** as the free amine was in the synthesis of polymer **2**, the synthetic strategy toward polymer **3** involved a masked thiol. As shown in Scheme 4, TBS-protected mercaptoethanol **12**[41] was converted to the thiochloroformate **13** by reaction with triphosgene and then reacted with 4-nitrophenyl carbonate-activated 4-hydroxybenzyl alcohol **14**,[28] expecting regioselectivity based on the more reactive thiochloroformate center. This reaction indeed gave the protected monomer **15** in good yield, which after TBS deprotection provided monomer **16**.

Monomer **16** was polymerized in toluene in the presence of 0.05 equiv of end-cap **17**[42] as well as DIPEA and catalytic DMAP to provide polymer **3** (Scheme 4). Unexpectedly, some cyclic product 1,3-oxathiolan-2-one was observed (40−45%), presumably from cyclization of the terminal alcohol in **16** on the adjacent thiocarbonate, but this could be suppressed to some degree by cooling the polymerization reaction to −15 to 0 °C. Polymer **3** was purified by dialysis in DMF using a membrane with a MWCO of 3500 g/mol. The resulting polymer had an M_n of 5040 g/mol and a PDI of 1.67 (Figure 2b). Analysis by ^{1}H NMR spectroscopy revealed a monomer to end-cap ratio of 15:1, similar to the monomer feed ratio of 20:1.

Probing the Monomer Cyclization Rates. In our previous work, the cyclization rate of the *N*,*N*′-dimethylethylenediamine from polymer **1** was studied by ^{1}H NMR spectroscopy using compound **18** as a model compound

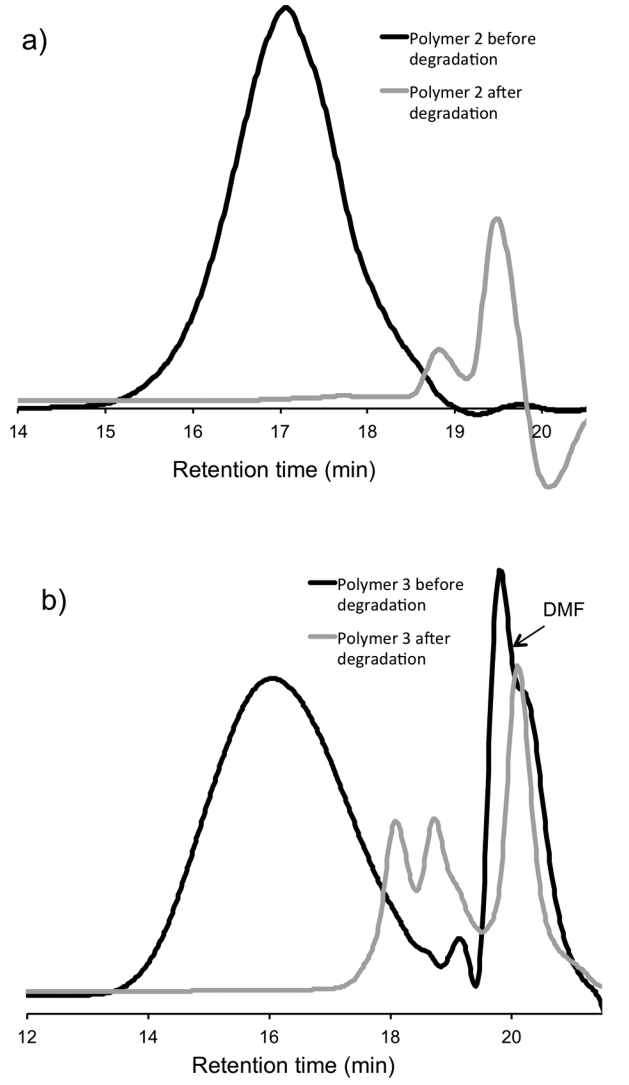
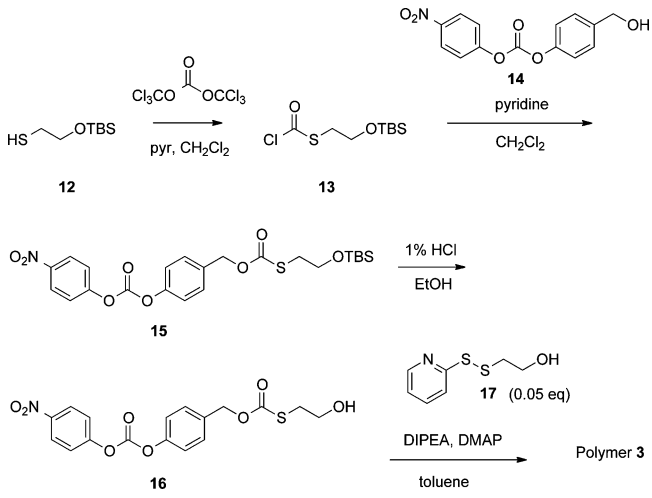


Figure 2. SEC traces of (a) polymer **2** before and after degradation and (b) polymer **3** before and after degradation (detection based on differential refractive index).

Scheme 4. Monomer Synthesis and Synthesis of Polymer 3



(Scheme 5).[34] In 0.1 M pH 7.4 phosphate buffered D_2O:acetone (3:2) at 37 °C the cyclization half-life was

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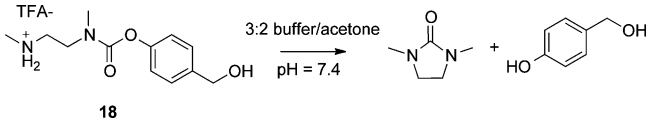
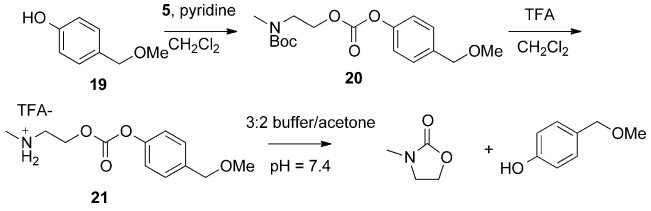
Scheme 5. Cyclization of Compound 18 To Form *N,N′*-Dimethylimidazolidinone and 4-Hydroxybenzyl Alcohol



found to be 35 min.[34] In order to investigate the cyclization rate of the *N*-methylaminoethanol spacer, a model compound was prepared. While compound **10** could be used in principle, the presence of the trifluoroacetate at the benzylic position was undesirable as this moiety might exert modest electronic effects. Thus, as shown in Scheme 6, the methyl ether **19**[43] was reacted

Scheme 6. Synthesis of Compound 21 and Its Cyclization To Form 3-Methyloxazolidin-2-one



with the activated carbonate **5** to provide compound **20**. Treatment with TFA afforded the model compound **21**. Upon dissolution in the same buffer:acetone mixture described above, by the time a ^{1}H NMR spectrum could be obtained, complete cyclization to the 3-methyloxazolidin-2-one was already complete, indicating that this cyclization was very rapid under these conditions (Figure S23). It was verified by ^{1}H NMR spectroscopy in $CDCl_3$ that no cyclization had occurred during the Boc deprotection (Figure S25), but only upon transfer of the material to the aqueous buffer system.

In order to further probe these rapid cyclization kinetics, UV−vis spectroscopy was used as there is not a significant delay time required in order to lock and shim the sample as is required for NMR spectroscopy. As in our previous work with rapidly cyclizing 4-aminobutyric acid derivatives,[38] it was found that the cyclization product 4-hydroxybenzyl alcohol could be detected at 282 nm, where the starting compounds **18** and **21** have minimal absorbance (Figure S26). Unfortunately, due to the absorbance of acetone at this wavelength, it was not possible to use it as a cosolvent to compare with the above NMR results. The replacement of acetone with isopropanol made UV−vis spectroscopy possible, but the cyclization rate in 0.1 M pH 7.4 phosphate buffered D_2O:isopropanol (3:2) at 37 °C was still too rapid to measure accurately by this method, and intermediate ratios created isopropanol−buffer miscibility issues. The use of isopropanol alone slowed the cyclization rate substantially. This can be attributed partly to the absence of buffer, which would result in the amine existing primarily in its protonated form as isolated from the TFA deprotection reaction. Such reactions have been found to be highly sensitive to pH as protonation greatly decreases the nucleophilicity of amines.[38] In addition, the rates of similar cyclization reactions have been found to be highly solvent dependent in our hands and the increased hydrophobicity of isopropanol relative to water may slow the cyclization reaction, which possesses a polar transition state. However, the use of isopropanol as a solvent allowed a rate constant of 9.12×10^{-3} min^{-1} and a corresponding half-life of 76.0 min to be measured (Figure 3). To compare with the previous carbamate, the cyclization

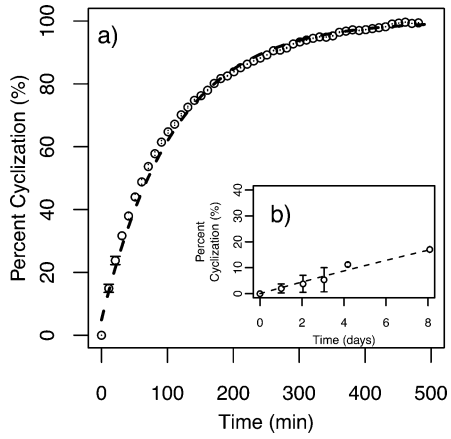
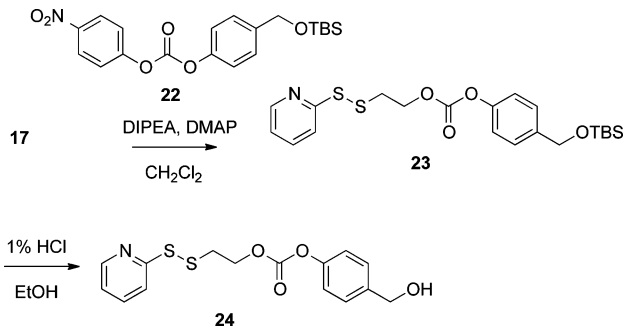


Figure 3. First-order cyclization profiles of (a) compound **21** and (b) compound **18** in isopropanol at 37 °C as measured by the change in absorbance at 282 nm. Experimentally measured data (○) and regression fits (- - -). All kinetic studies were performed in triplicate; depicted data points correspond to the mean value ± 1 standard deviation.

rate of **18** in pure isopropanol was also measured. It was found that over a period of 8 days only ∼17% of **18** had undergone cyclization. Fitting this partial cyclization data to a first-order model yielded a rate constant of 2.72×10^{-2} day^{-1} and a corresponding half-life of 26.7 days, suggesting that compound **21** cyclizes ∼500-fold faster than **18**. This result confirmed that changing the electrophilic site from a carbamate to a carbonate did indeed greatly increase the rate of cyclization.

As none of the above synthetic intermediates described above could be used to probe the cyclization rate of the thiol on the phenyl carbonate, a model compound was also prepared for this purpose. As shown in Scheme 7, end-cap **17** was reacted

Scheme 7. Synthesis of Model Compound 24



with the activated 4-hydroxylbenzyl alcohol derivative **22**[34] to provide **23**. TBS deprotection using HCl in ethanol provided compound **24**. NMR spectroscopy in 0.1 M pH 7.4 phosphate buffered D_2O:acetone (3:2) at 37 °C was investigated first as a method for probing the cyclization rate of compound **24**. Upon addition of DTT, by the time a ^{1}H NMR spectrum could be obtained, complete cyclization to 1,3-oxathiolan-2-one had occurred (Figure S28). This demonstrated that this cyclization was very rapid under these conditions. Unfortunately, in attempts to further investigate the cyclization rate by UV−vis spectroscopy, it was found that the absorption spectrum was

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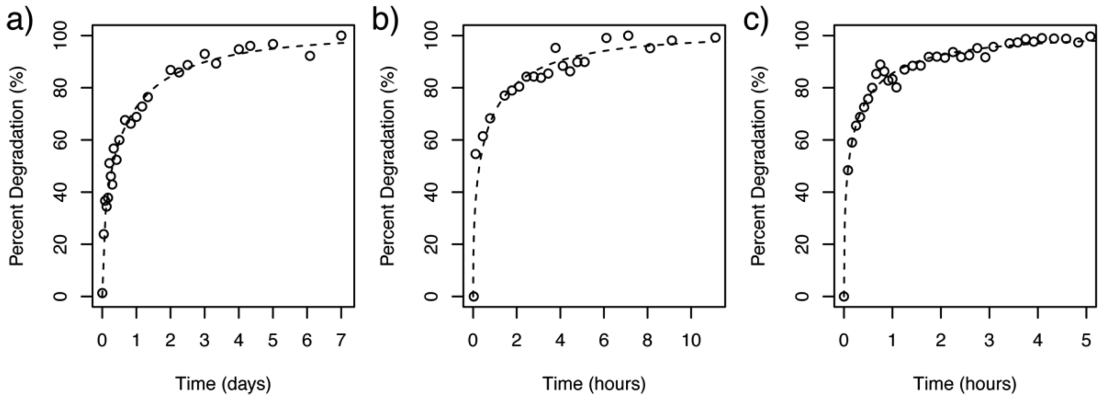

Figure 4. Kinetics of polymer depolymerization in 0.1 M pH 7.4 phosphate buffered D_2O:acetone (3:2) at 37 °C as measured by ^1H NMR spectroscopy for (a) polymer **1**, (b) polymer **2**, and (c) polymer **3**. The data were fit to a modified Avrami equation[47] (dashed lines) to assess the degradation kinetics and demonstrate the mixed zero and first-order behavior.

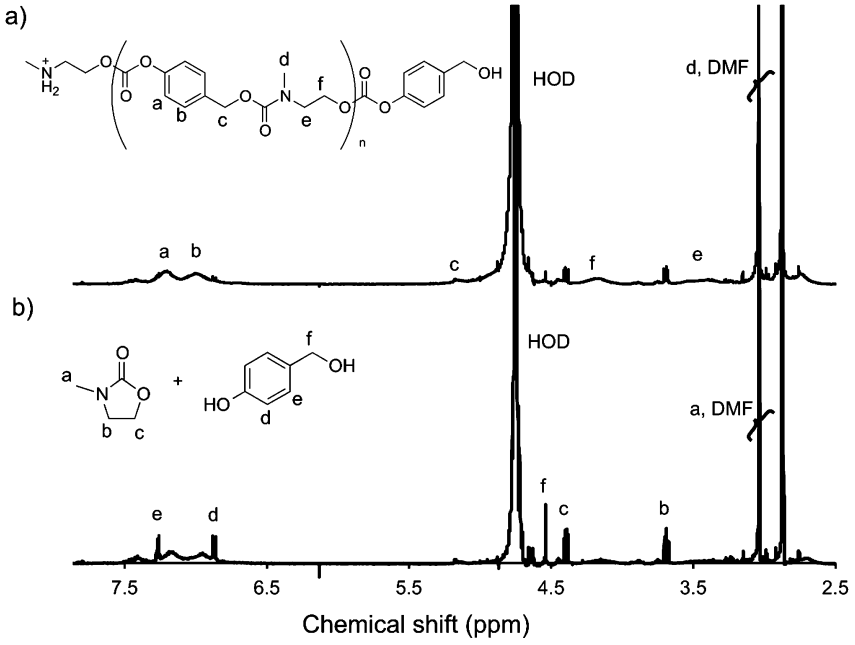

Figure 5. ^1H NMR spectra of polymer **2**: (a) immediately following dissolution in 0.1 M pH 7.4 phosphate buffered D_2O:acetone (3:2) at 37 °C; (b) after 600 min under the same conditions.

dominated by the thiopyridyl group, preventing the detection of any significant change in absorbance upon cyclization. While it might have been possible to exchange this disulfide for one that did not absorb at 282 nm, a quantitative study of the cyclization kinetics for this monomer would always be complicated by the fact that disulfide reduction must occur first in situ prior to cyclization and it would not be possible to separate these steps based on UV−vis spectroscopy. It should be noted that the incorporation of a disulfide capping moiety in compound **24**, allowing for in situ uncapping, was required for this model compound because unlike the amine, which can be preventing from cyclizing when prepared in the form of its TFA salt, storage of the unprotected thiol derivative for any time period under any conditions leads to rapid intramolecular cyclization. Because of these factors, an exact half-life for the thiol cyclization was not measured, but based on the NMR study, it can be inferred that it was also significantly faster than that of the previous *N*,*N*′-dimethylethylenediamine spacer.

Polymer Degradation. In order to compare the depolymerization rates of polymers **2** and **3** with the previously reported polymer **1** and to identify the degradation products, the depolymerization was studied by ^1H NMR spectroscopy in 0.1 M pH 7.4 phosphate buffered D_2O:acetone (3:2) at 37 °C. The Boc group of polymer **2** was first removed by treatment with 1:1 TFA/CH_2Cl_2, then the solvents were removed, and the resulting polymer was dissolved in the buffer:acetone mixture, being careful that residual TFA did not change the pH from 7.4. The degree of degradation was quantified by the integrations of 3-methyloxazolidin-2-one and 4-hydroxybenzyl alcohol peaks relative to that of an internal DMF standard. As shown in Figure 4, in comparison to polymer **1**, which required ∼7 h to reach 50% degradation and several days for complete degradation, polymer **2** was more than 50% degraded within an hour and complete degradation occurred over a period of 3−4 h. Following depolymerization, no polymeric material was detected by SEC (Figure 2a), suggesting that complete depolymerization had occurred. In addition, as shown in Figure 5, the products detected by ^1H NMR spectroscopy were as expected based on the proposed degradation mechanism. Overall, these results demonstrate that the faster monomer

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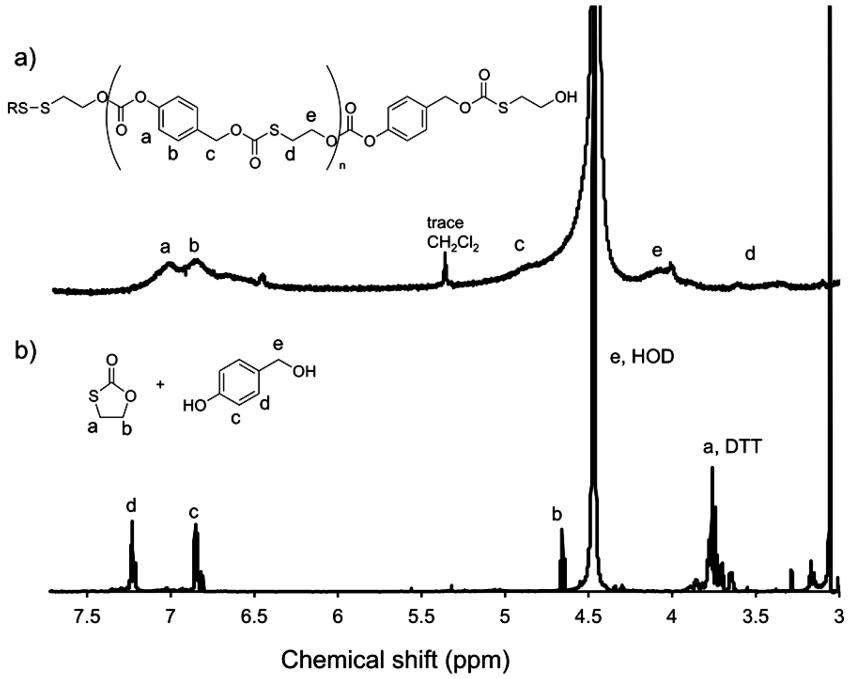

Figure 6. ^{1}H NMR spectra of polymer **3**: (a) prior to DTT addition in 0.1 M pH 7.4 phosphate buffered D_2O:acetone (3:2) at 37 °C; (b) after 240 min under the same conditions.

cyclization kinetics did translate into faster polymer degradation. A control experiment was also performed by incubating polymer **2** with the Boc group intact in the buffer:acetone mixture. Only trace depolymerization was detected over a period of several hours (Figure S29).

The degradation of polymer **3** was also studied by ^{1}H NMR spectroscopy in 0.1 M phosphate buffered D_2O:acetone (3:2) at 37 °C. In this case, argon was bubbled through the NMR sample to remove oxygen, and then dithiothreitol (DTT) was added to reductively trigger the cleavage of the disulfide end-cap. The degree of degradation was quantified by the integrations of 1,3-oxathiolan-2-one and 4-hydroxybenzyl alcohol peaks relative to that of an internal DMF standard. As shown in Figure 4c, this polymer underwent 50% degradation in less than 30 min and complete degradation within 1−2 h, an even faster rate than polymer **2**. Again, no remaining polymeric material was detected by SEC after degradation (Figure 2b). Comparison of the SEC trace for this degraded polymer with that of the undegraded material suggested that a small fraction of the material may have been comprised of relatively low MW cyclic oligomers that were not end-capped and thus did not depolymerize upon end-cap cleavage. However, unlike in our previous study where ∼20 wt % of cyclic oligomers was observed in polymers composed entirely of aliphatic cyclization-based spacers,[35] this cyclic fraction appears to be very small in the current work. Furthermore, a control polymer to which DTT was not added did not exhibit significant degradation over this time period (Figure S30). Although the cyclization half-life of the 2-mercaptoethanol spacer had not been explicitly measured, it had been anticipated that it would be faster than that of the *N*-methylaminoethanol spacer based on increased nucleophilicity of the thiol at pH 7.4. This depolymerization result confirmed this hypothesis.

The depolymerization kinetics was further analyzed by fitting the data to different kinetic models. While the cyclization of an individual monomer unit is a first-order process, during the initial stages of the depolymerization process, the concentration of polymer termini does not change significantly, introducing a zero-order component to the degradation process. However, when polymer chains become completely depolymerized, the concentration of polymer termini does decrease, introducing a first-order component to the depolymerization process. Because of the polydispersity of the materials, it is expected that there should be both zero- and first-order processes occurring simultaneously throughout the process. Consistent with this expected mechanism, the fitting of the kinetic data to zero- or first-order models provided poor fits. However, fitting of the data to a modified Avrami equation (1) provided a good fit in all cases (Figure 4). This rate equation has previously been used in thermogravimetric analysis modeling to describe the depolymerization of linear polymers under isothermal conditions, a process that is mechanistically similar to the proposed depolymerization process for polymers **1**−**3**.[47] The α values obtained from the fits were 0.52, 0.46, and 0.43 for polymers **1**, **2**, and **3**, respectively, suggesting that the kinetics were indeed between zero and first order. The obtained rate constants were 6.8×10^{-2} h^{-1}, 2.6×10^{-2} min^{-1}, and 7.8×10^{-2} min^{-1} for polymers **1**, **2**, and **3**, respectively. While the nature of eq 1 means that the precise values of these rate constants are not directly comparable to those obtained from conventional zero- or first-order kinetic models, they do provide quantitative support for the observation that the replacement of the electrophilic carbamate site with a carbonate provided a substantial increase in the depolymerization rate of the polymer and the additional replacement of the nucleophilic amine with a thiol provided a modest further enhancement in the rate.

■ CONCLUSIONS

In conclusion, two new self-immolative linear polymers based on alternating cyclization and elimination reactions were successfully designed and synthesized. Synthetically, it was

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necessary to alter the strategy toward monomer and polymer preparation in order to avoid possibilities for the premature occurrence of rapid cyclization reactions. It was demonstrated that by tuning the electrophilicity and nucleophilicity of the sites involved in the cyclization reaction, the cyclization reactions could be accelerated, resulting in faster depolymerization relative to the previously reported polymers. By replacing the electrophilic carbamate site with a carbonate, the cyclization half-life of the spacer was reduced 500-fold, as measured by UV−vis spectroscopy in isopropanol, and the corresponding polymer degradation rate was increased more than 20-fold in 0.1 M pH 7.4 phosphate buffered D_2O:acetone (3:2). The rate was further increased by also replacing the nucleophilic amine with a thiol. The proposed degradation mechanism was supported by fitting the kinetic data to a modified Avrami equation. Overall, these new polymers fill an important gap in the depolymerization rates of the currently available self-immolative polymers and thus significantly expand the availability of these materials for diverse applications. This work also demonstrates that the depolymerization rate of these materials can be tuned through rational design.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of compounds **5**, **7**, **8**, **9**, **11**, **13**, **15**, **16**, **20**, **23**, and **24** and polymers **2** and **3**; NMR spectra of compounds **21** and **24** prior to and following cyclization; UV−vis spectra of compounds **18**, **24**, and 4-hydroxybenzyl alcohol; NMR spectra of polymers **2** and **3** in D_2O:acetone without end-cap removal. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail egillie@uwo.ca.

Notes

The authors declare no competing financial interest.

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