

# Acid-Triggered, Acid-Generating, and Self-Amplifying Degradable Polymers

Kali A. Serrano,<sup>†</sup> Shampa R. Samanta,<sup>†</sup> Brittany A. Walker,<sup>†</sup> Ephraim G. Morado,<sup>†</sup> Arif Z. Nelson,<sup>§</sup> Dung T. Trong,<sup>†</sup> Daniel J. Whitaker,<sup>†</sup> Paul V. Braun,<sup>†,‡,||,∇</sup> and Steven C. Zimmerman<sup>\*,†,||</sup>

<sup>†</sup>Department of Chemistry, <sup>‡</sup>Department of Materials Science and Engineering, <sup>§</sup>Department of Mechanical Science and Engineering, <sup>||</sup>Frederick Seitz Materials Research Laboratory, <sup>∇</sup>Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, USA

## **S** Supporting Information

**ABSTRACT:** We describe the 3-iodopropyl acetal moiety as a simple cleavable unit that undergoes acid catalyzed hydrolysis to liberate hydroiodic acid ( $pK_a \sim -10$ ) and acrolein stoichiometrically. Integrating this unit into linear and network polymers gives a class of macromolecules that undergo a new mechanism of degradation with an acid amplified, sigmoidal rate. This trigger-responsive self-amplified degradable polymer provides an accelerated rate of degradation and agent release.

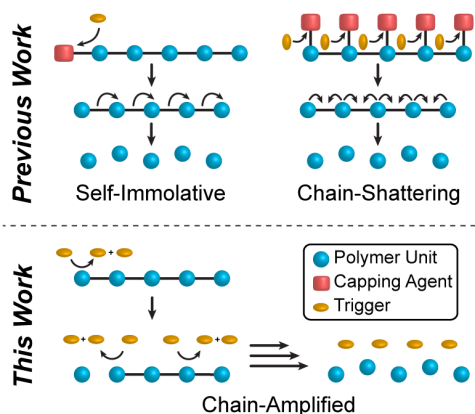
There is increasing demand for smart polymers that change their shape or properties or degrade in response to environmental stimuli.<sup>1</sup> Indeed, a renewed interest in degradable polymers, especially for biomedical and engineering applications has led to an extensive search for new mechanisms to breakdown polymers.<sup>2</sup> Most degradable polymers contain functional groups along their main chain that cleave independently by chemical or photochemical reaction, in which case, the degradation rate remains more or less constant until the trigger or cleavable functionality is consumed. The discovery of self-immolative polymers was particularly exciting be-

cause one triggering event is sufficient to activate an entire polymer chain to degrade.<sup>3,4</sup> These systems are stable under ambient conditions until a reactive unit at the polymer end is cleaved, triggering a cascade of fragmentation reactions which proceed sequentially along the polymer chain (Figure 1).

More recently, the development of chain-shattering polymers allows materials to spontaneously degrade along the main chain with a triggering event occurring at each monomer unit (Figure 1).<sup>5</sup> Both the self-immolative and chain-shattering approaches do have limitations in degradation rate and require a stoichiometric amount of the triggering agent. We were interested in a less studied approach that can be referred to as a chain-amplified degradation. In this mechanism, a catalytic species effects chain cleavage generating a full equivalent of the same agent such that there is an exponential degradation cascade (Figure 1).<sup>6</sup>

Herein, we describe simple acetal units derived from 3-iodopropanal that undergo acid catalyzed, self-amplified cleavage and demonstrate how they can be readily integrated into both degradable polymers and hydrogels. The acetal unit and acid trigger were chosen because pH gradients are ubiquitous in the environment and within biological systems. Furthermore, polymeric acetals (polyacetals) are well studied, with tunable reactivities and properties.<sup>7</sup> The simplest, polyoxymethylene (POM) is a widely used engineering thermoplastic, whereas more complex polyacetals are used in a range of applications from controlled release to drug delivery.

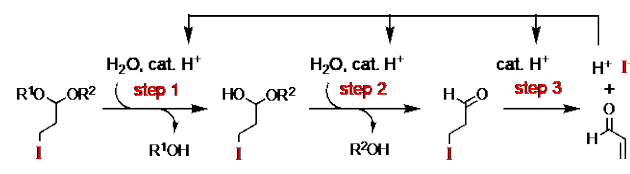
The acetal design was based on small molecules reported by Ichimura and coworkers<sup>8</sup> that produced *p*-toluenesulfonic acid ( $pK_a \approx -2.8$ ) in an amplified manner. With this starting point, a large number of monomeric units were prepared and tested, ultimately leading to the 3-iodo-1,1-dialkoxy moiety as having the most suitable properties. In particular, this unit is easily prepared and has good stability, but undergoes acid amplified degradation under mildly acidic conditions. In this mechanism, the acetal likely hydrolyzes to the hemiacetal and then further to the aldehyde, which subsequently undergoes



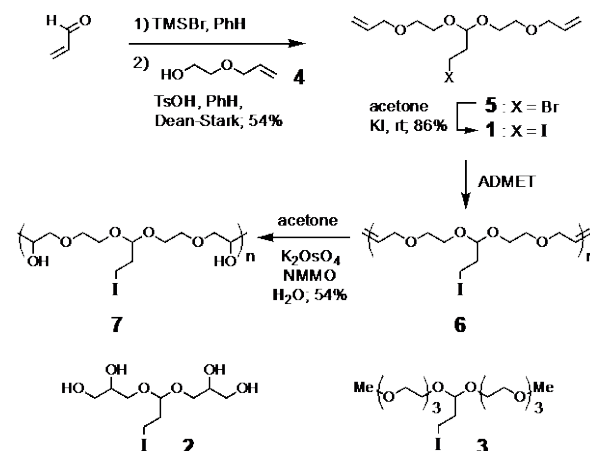
**Figure 1.** Schematic representation of polymer degradation mechanisms.

$\beta$ -elimination to generate stoichiometric amounts of hydroiodic acid with  $pK_a \approx -10$  and acrolein (Scheme 1). Each of the three steps is catalyzed by acid.

**Scheme 1. Mechanism of 3-iodopropyl acetal hydrolysis with stoichiometric formation of HI and amplified cleavage.**



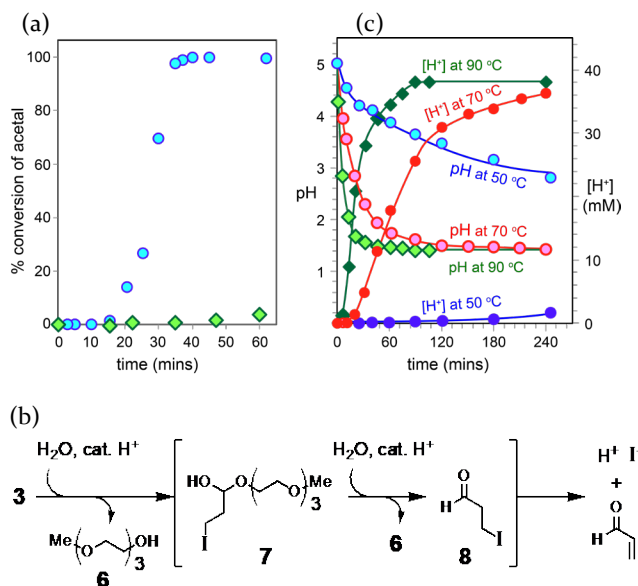
## Scheme 2



The key 3-iodopropyl acetals **1-3** used in this study are shown in Scheme 2. The synthesis of iodo-acetal monomer **1** was achieved by treatment of acrolein with TMSBr and acetalization with alcohol **4** to afford **5**.<sup>9</sup> Conversion of bromo acetal **5** to the iodo acetal **1** proceeded in good yield under standard Finkelstein conditions. Iodo acetals **2** and **3** were prepared in analogous fashion or by using HCl in place of TMSBr, the diol units in **2** obtained by dihydroxylation (see Supporting Information).

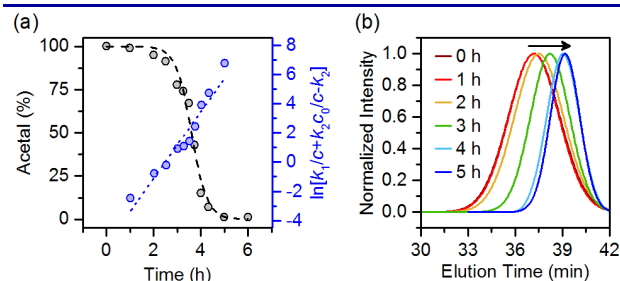
The ability of the 3-iodopropyl acetal unit to undergo acid amplified cleavage was examined by monitoring the hydrolysis of **3** under different conditions, monitoring the progress by <sup>1</sup>H NMR. Thus, a solution of **3** in D<sub>2</sub>O at pD = 5.5 at 70 °C showed an induction period of about 15-20 minutes at which time the acetal underwent a rapidly accelerating degradation (Figure 2a). The reaction was largely complete after about 45 min. Consecutive <sup>1</sup>H NMR spectra taken over 1 h were indeed consistent with the formation of hemiacetal **7**, further hydrolysis to aldehyde **8**, which subsequently undergoes  $\beta$ -elimination to generate hydroiodic acid (Figure 2b and Figure S1). The stoichiometric generation of the very strong acid HI ( $pK_a \approx -10$ ) can accelerate each of the previous steps and produce the nonlinearity observed for the process. Consistent with these observations, performing the same hydrolysis reaction in the presence of 0.1 M acetate buffer dramatically suppressed the rate of hydrolysis as seen in Figure 2a.

The acid amplified degradation of **3** was further characterized by measuring the pH over time. Thus, a 48 mM aqueous solution of **3** in nanopure water, which was slightly acidic (pH = 5.5) due to dissolved atmospheric CO<sub>2</sub>, was heated at three temperatures (50, 70, and 90 °C) and the pH measured at regular intervals (Figure 2c). The proliferation of H<sup>+</sup> was almost instantaneous at 90 °C, whereas an induction period of ~2 h and 5 min was observed at 50 °C and 70 °C, respectively. No lag time was observed at 50 °C when starting the reaction at pH 3 by adding *p*-toluenesulfonic acid monohydrate. Both higher temperature reactions rapidly leveled off at pH  $\approx$  1.5, the final [H<sup>+</sup>] value consistent with near quantitative conversion of **3** to HI. Final support for the autocatalytic, acid



**Figure 2.** (a) Proposed mechanism of acetal hydrolysis with stoichiometric formation of HI and amplified cleavage. (b) Percent conversion of **3** in D<sub>2</sub>O at initial pD = 5.5, with [3] = 48 mM at 70 °C in presence (green diamonds) and absence (blue circles) of 0.1 M acetate buffer. (c) Change in solution pH over time of a solution, [3] = 48 mM in nanopure water. Filled points, [H<sup>+</sup>]; open points pH. Blue, 50 °C, red 70 °C,

amplification mechanism came by using standard autocatalytic rate equations to fit the sigmoidal degradation curve seen at 70 °C (Figure S6, equation S4).



**Figure 3.** (a) Monitoring the disappearance of acetal functionality of **6** by  $^1\text{H}$  NMR as a 48 mM solution in  $\text{D}_2\text{O}/\text{CD}_3\text{CN}$  at 70 °C. Dashed line is fit of the data to equation S4 and dotted line is a guide to the eye. (b) GPC traces of the degradation of **7** in a 48 mM solution in  $\text{H}_2\text{O}$  over time at 70 °C.

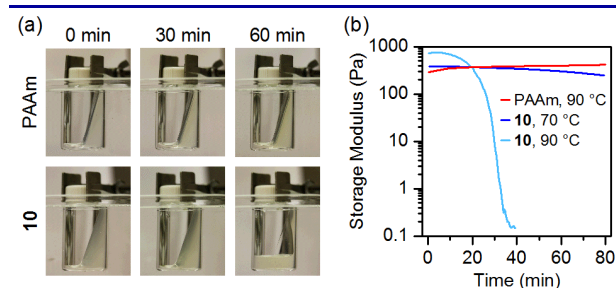
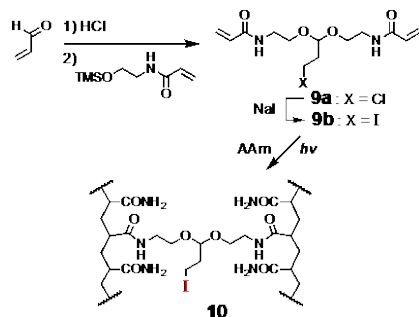
Monomer **1** underwent acyclic diene metathesis (ADMET) polymerization to give **6** by a step-growth mechanism. Thus, successful ADMET polymerization was accomplished by using Grubb's 1st generation catalyst providing polymer **6** with  $M_n \approx 10,000$ . Upjohn-dihydroxylation was then used to convert **6** to **7** which significantly increased its water solubility (Scheme 2). However, polymer **7** exhibits thermo-responsiveness in pure aqueous solution with an LCST above room temperature. Therefore, the hydrolysis of **7** was followed by  $^1\text{H}$  NMR spectroscopy in 40% (v/v)  $\text{CD}_3\text{CN}$  in  $\text{D}_2\text{O}$  ( $pD_0 = 5.5$ ) by monitoring the disappearance of the methine signal of the acetal moiety. At 70 °C, the hydrolysis of the acetal group was complete within 4 h with an induction period of  $\sim 2$  h, consistent with an autocatalytic degradation mechanism. A plot of % conversion of acetal vs. time showed a distinctive sigmoidal shape that is well fit by an autocatalytic model (Figure 3a).<sup>10</sup> Likewise, using the rate law for an autocatalytic reaction, an expression (equation S3) can be derived that allows the data to be linearized as shown in Figure 3a.

An autocatalytic, acid-amplified polymer degradation process should be accompanied by a sigmoidal decrease in molar mass of **7**. As seen in Figure 3b, a solution of **7** in water heated to 70 °C was monitored at regular time intervals using GPC. Due to self-amplified degradation, there are only small changes in the GPC traces in the first 2 h of the reaction, followed by a rapid increase in retention time over the next 2 h, and then much smaller changes in the last 2 h. These characteristic degradation profiles were also well-fit to standard autocatalytic rate equations (Figure S7).

Upon successful demonstration of the acid triggered self-amplified degradation behavior of the small molecule and linear polymer, we were interested in developing a degradable hydrogel containing the 3-iodopropyl acetal moiety. Treatment of **1** with HCl and acetalization with TMS-protected *N*-hydroxyethyl acrylamide gave **9a**, which was converted to acrylamide crosslinker **9b** con-

taining a central 3-iodopropyl acetal unit. Finally, degradable hydrogel **10** was synthesized using free radical polymerization using 3 mol% of **9b** as the crosslinker and acrylamide (AAm) as the monomer with diethoxyacetophenone (DEAP) as the photo-initiator (Scheme 3 and Supporting Information).

**Scheme 3. Synthesis of degradable hydrogel 10.**



**Figure 4.** (a) Visual observation of the degradation of **10** compared to polyacrylamide control at 90 °C. Pictures are of the gel in a scintillation vial submerged in an oil bath. (b) Storage modulus of **10** at 70 °C and **10** and the polyacrylamide hydrogel at 90 °C.

Hydrogel **10** was studied and compared to gels prepared with a nondegradable crosslinker (*N,N'*-methylenebisacrylamide) in the same mole ratio. Visual observation of hydrogel degradation over time shows that **10** has a delay period of  $\sim 30$  min and then degrades rapidly to give a solution, whereas the polyacrylamide control did not show any sign of degradation (Figure 4a). The degradation process was characterized using rheology. Thus, the storage modulus was measured and minimal degradation was seen from the polyacrylamide control (PAAm) at 90 °C and **10** at 70 °C. However, upon heating to 90 °C, **10** undergoes the rapid degradation that is characteristic of autocatalytic reactions (Figure 4b). This degradation profile was quantified using the standard autocatalytic rate equations described above and in the Supporting Information (Figure S8).

Given that small molecule acid amplifier **3**, polymer **7**, and hydrogel **10** each showed a sigmoidal degradation rate, we sought to compare the kinetics of the three systems. The sigmoidal reaction profile reflects the presence of both a non-autocatalytic mechanism, which is responsible for the initial formation of the products, ( $k_i$ ), and an

autocatalytic mechanism wherein one of the products accelerates the reaction, ( $k_2$ ). At 70 °C, **3** and **6** exhibit comparable  $k_1$  values (Table 1). However,  $k_2$  is slower by an order of magnitude, which can be attributed to diffusion differences between the small molecule **3** and polymer **6**. This effect is even more prevalent for **10** because the temperature must be increased to 90 °C to observe degradation on a reasonable time scale. Additionally, the increase of  $k_1$  in this case is due to increased hydrolysis rate at this high temperature.

**Table 1. Calculated rate constants for **3**, **6**, and **10** at various temperatures.**

	Temp (°C)	$k_1 \times 10^3$ (min <sup>-1</sup> )	$k_2$ (M <sup>-1</sup> min <sup>-1</sup> )
<b>3</b>	70	0.02 ± 0.01	74.4 ± 5.7
<b>7</b>	70	0.06 ± 0.07	8.5 ± 1.1
<b>10</b>	90	1.65 ± 0.09	12.6 ± 0.2

In conclusion, we demonstrated a new class of trigger-responsive self-amplified-degradable materials. The specific moiety developed here, the 3-iodopropyl acetal group, produces two products stoichiometrically: (1) hydroiodic acid, a very strong acid that accelerates further degradation, and (2) acrolein, a potent biocide and mercaptan scavenger. We anticipate that this acid amplifying motif could serve as a unique method for the controlled delivery of protic acid for various biological applications. These materials may also serve as benign carriers that undergo amplified release of biocidal acrolein in acidic solution. Investigations in these directions are currently in progress in our laboratory. We are further developing polymers for the self-amplified release of other reagents as well as other architectures that do not produce acrolein to expand the toolbox for potential applications.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, NMR spectra, additional characterization and kinetic data, and synthesis and degradation of a PEG-based hydrogel (PDF)

## AUTHOR INFORMATION

### Corresponding Author

\*sczimmer@illinois.edu

### ORCID

Kali A. Serrano: 0000-0003-3632-0615

Paul V. Braun: 0000-0003-4079-8160

Steven C. Zimmerman: 0000-0002-5333-3437

### Author Contributions

## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENT

The authors gratefully acknowledge support from the Dow Chemical Company, the National Science Foundation (NSF CHE-1709718), and the Department Defense/US Army W911NF-17-1-0351. K.A.S. acknowledges the National Science Foundation for support (DGE-1746047). We thank Professor Randy H. Ewoldt, Shuqi Lai, Eric S. Epstein, Hsuan-Chin Wang, and Yugang Bai for technical support and insightful discussions.

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