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Alternating Sulfone Copolymers Depolymerize in Response to Both Chemical and Mechanical Stimuli

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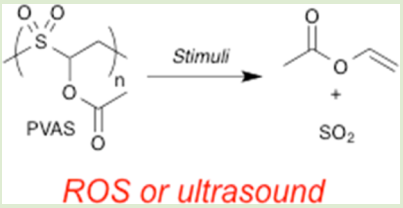
Supporting Information

ABSTRACT: This work describes the depolymerization of poly(vinyl acetate-*alt*-sulfur dioxide) as initiated by chemical and mechanical stimuli. In recent years, macromolecules that are able to depolymerize in response to specific stimuli have been highly sought because of their ability to amplify signal for sensing and drug delivery. Examples include self-immolative polymers from alkoxyphenol derivatives and polyaldehydes. We show here that alternating copolymers of sulfur dioxide and vinyl acetate are able to undergo similar depolymerization into their monomer components in response to various chemical and mechanical stimuli. Certain vinyl monomers such as vinyl acetate are able to polymerize with sulfur dioxide in a perfectly alternating manner, and the resulting copolymer possesses a low ceiling temperature. We show that this polymer is able to break down into its monomer components when subjected to UV/acetone, various reactive oxygen species (ROS), and ultrasonication. In the case of UV, the acetone reacted via a Norrish reaction to produce free radicals that caused clean monomer production. For ROS, the polymer showed reactivity to both oxidizing and radical-containing ROS. Through kinetic studies, these polymers were shown to proceed via a two-part, first-order kinetic model with a fast initiation phase and a slow depolymerization phase. Finally, the polymers were subjected to probe ultrasonication, and depolymerization occurred as well. Most tellingly, the polymer again showed a fast initiation step and continued to depolymerize even after ultrasonication stopped. This class of polymers shows potential for drug delivery in response to both endogenous chemical and externally applied mechanical cues.



Interest in stimulus-responsive polymers and materials has increased in recent years, primarily owing to a wealth of potential applications in medicine and devices. For medicine in particular, efforts have focused on changing the structure of assemblies and particles in response to both endogenous molecules and externally applied energy sources to release drugs, activate contrast agents, or initiate fluorescent signal. To attain necessary sensitivities, recent efforts have focused on amplification, in which single activation events can cause massive changes in chemical and physical structure. Examples for biomedical application include amphiphiles that change their self-assembly properties, charge-switching polymers for gene delivery, and phase changes in polymers with appropriate lower critical solution temperatures. In order to obtain activity at sites of interest, such polymers have been designed to react to stimuli specific to a diseased region. For example, many new sensing and imaging agents have been designed to respond to the presence of elevated reactive oxygen species (ROS) as indicators of inflammation, cell signaling, and cancer.[1−4] In addition, technologies have been developed that can initiate therapy at a specific location due to response to an external energy source that can be focused to a specific location.

A recent development has been the creation of polymers that spontaneously break down, or depolymerize, into their original monomer components only after activation by a specific stimulus. Such polymers have a low (e.g., < RT) ceiling temperature (T_c), which is the temperature above which depolymerization proceeds at a faster rate than polymerization. If the active chain end is capped, the polymer will be stable above its T_c, but if the chain end is activated, the polymer will equilibrate back to the original monomer. Polymers with low T_c were originally developed as photoresists,[5−7] but more recent examples have focused on sensing and drug delivery. For example, end-capped poly(phthalaldehyde) derivatives have been demonstrated both as substrates to generate amplified sensors capable of generating a visible response to the presence of various chemical analytes, as well as the focus of more detailed studies of the kinetics of depolymerization.[8−16] In addition, polyquinonemethides, coined "self-immolative polymers" by Shabat, have been developed into both linear and branched depolymerizable units, while polymers capable of tandem reactions of cyclization and release have shown excellent potential for drug delivery based on the degradation of linear polymers, branched polymers, and particles.[17−20] The key to both of these approaches has been the use of specific end-capping groups that, when reacted with a chemical or photochemical trigger, produce a functional group that can act as an active chain end to initiate the depolymerization process. While a versatile and tunable method of obtaining sensitivity to various stimuli, this method still requires a single reaction to trigger each depolymerization event, rather than breakage along the main chain.

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Here, we show that poly(vinyl acetate-*alt*-sulfur dioxide) (PVAS) exhibits an ability to depolymerize in response to ROS and ultrasonic waves. Alternating polymers containing sulfur dioxide and vinyl groups were originally developed as photoresists due to their ability to fragment into vaporizable fragments in response to deep-UV and X-ray irradiation.[21−24] Similarly, other alternating sulfone polymers were designed for radiation sensing.[25,26] The key property of PVAS for depolymerization is the perfectly alternating sulfur dioxide and vinyl acetate, which not only reduces the bond strength along the main chain (through substitution of C−C for C−S bonds),[27,28] but also increases the entropy associated with depolymerization through the release of additional small molecules.[7] Unless the chain propagation pathway is removed through chemical modification,[29] the depolymerization is able to proceed without encountering a stable C−C−C−C bond network.

Alternating copolymerization with sulfur dioxide has been shown for terminal alkenes, vinyl carbonates, and vinyl acetate.[7] In this work, vinyl acetate was cooled to −70 °C, followed by condensation of SO_2 into the polymerization mixture. *t*-Butylhydroperoxide (TBHP) initiator was added, and the reaction was stirred for 2 h, followed by precipitation into methanol and warming to room temperature. The polymer was then purified by reprecipitation. True alternation was observed through analysis of ^{1}H NMR spectra, which showed the presence of C**H**(OAc)-SO_2 protons at 6.47 ppm but no C**H**(OAc)−CH_2 bonds (Figure 1).

While degradation of PVAS as film has been studied previously,[7] here, the depolymerization behavior of PVAS was confirmed via photogeneration of radicals using UV light. Acetone is known to absorb UV light and generate radicals via a Norrish reaction.[30] When PVAS in acetone was irradiated with UV light in the range of 320−390 nm, the PVAS showed clean degradation into free VA monomer (Figures 2 and S1). In comparison, PVAS irradiated at 365 nm showed little degradation. This decrease is attributed to the decreased overlap between the UV irradiation and the absorbance spectrum of acetone (λ_{max} ∼ 265 nm, λ_{onset} ∼ 310 nm). Similarly, when PVAS was irradiated in other solvents with a lower UV cutoff, almost no conversion to the monomer was observed in THF, while a very small amount of degradation was observed in DMSO (Figure S2). Thus, depolymerization in this case appears to proceed through activation of monomer by radical formation. The degradation of PVAS by UV/acetone was intensity-dependent as well, in which irradiation at 32−34 mW led to 60% depolymerization in 1 min, while at 18−20 mW, the polymer showed little degradation after 1 min irradiation, but 80% depolymerization after 5 min. More importantly, the release of free monomer was confirmed by comparing the ^{1}H NMR spectra of the polymer and its degraded product (Figure S1).

To analyze the behavior of PVAS as a potential scaffold for drug delivery in response to endogenous ROS, the reactivity of PVAS was tested against various biologically relevant ROS. ROS can act as a radical (e.g., superoxide, hydroxyl radical), an oxidative species (e.g., hypochlorite), or both. To test ROS reactivity, solutions of PVAS were incubated with various ROS in acetone/water, and the reaction was monitored by ^{1}H NMR spectroscopy. Figures S3 and S4 show the relative reduction in the C**H**$_2$-S signal at 6.47 ppm by ^{1}H NMR spectroscopy and the appearance of a peak corresponding to CH_2=C**H**(OAc) at 7.25 ppm on addition of oxidative analytes within 20 min of

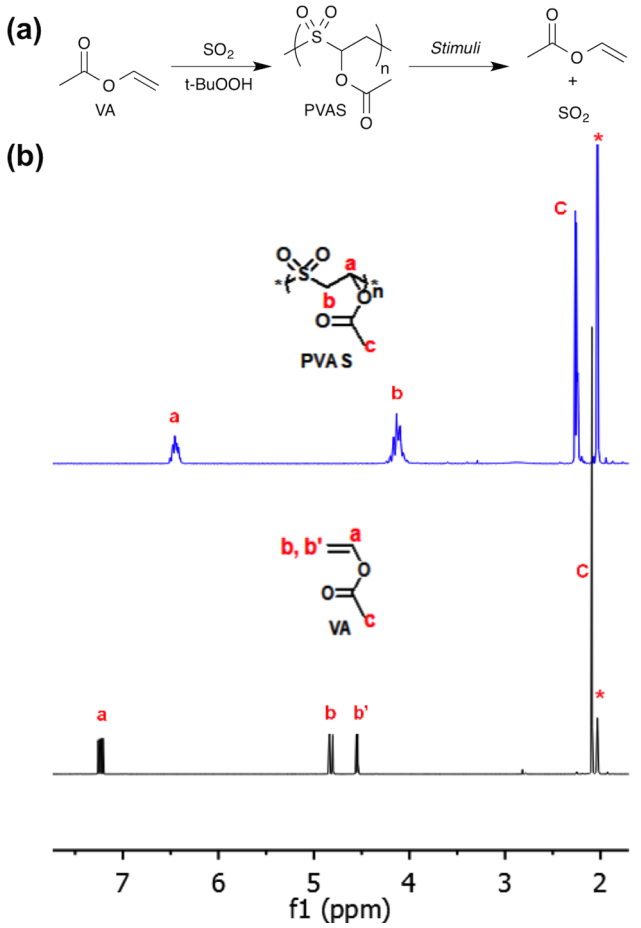

Figure 1. (a) Scheme of synthesis of PVAS from vinyl acetate and sulfur dioxide and depolymerization back into these components. (b) ^{1}H NMR spectra of PVAS and VA. Protons are assigned as shown; * indicates the solvent peak (acetone-d_6).

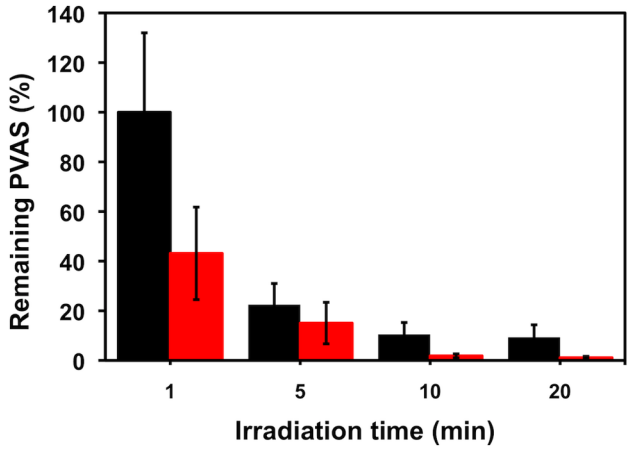

Figure 2. Conversion of PVAS into vinyl acetate under 320−390 nm UV light in acetone-d_6: Black bars, 18−20 mW; Red bars, 32−34 mW. Error bars represent the standard deviation of three trials.

addition. Reactions were observed for $Ca(OCl)_2$, $FeCl_2/H_2O_2$, KO_2, and NaOCl after 20 min, with greater levels observed after 24 h incubation (Figure 3). PVAS was not reactive to water, weak oxidizers such as hydrogen peroxide, or weak reducing agents such as glutathione (Figure S3). This reactivity profile indicates that PVAS is most sensitive to strongly

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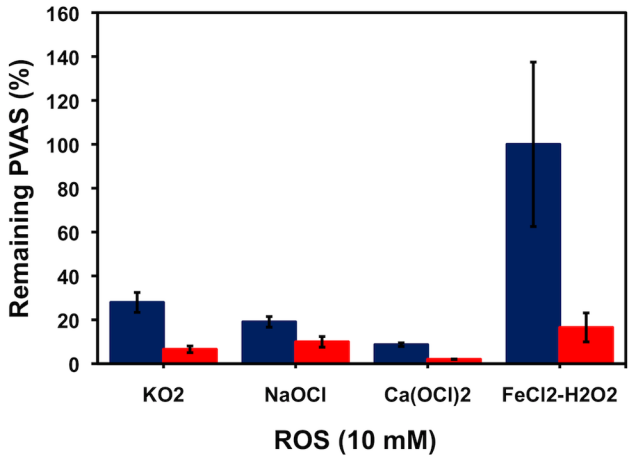

Figure 3. Conversion of PVAS to VA for various ROS at 10 mM. Blue bars indicate 20 min incubation; red bars indicate 24 h incubation. Error bars represent the standard deviation of three trials.

oxidizing agents. The major impurities appear to be the formation of acetaldehyde and acetic acid, which is expected from hydrolysis of VA. There are also peaks present that correspond to the initiation process, most likely due to an elimination side reaction. At basic pH, this elimination product appears to dominate, as alkenes tend to form adjacent to the sulfone, as characterized by ^{1}H NMR spectroscopy (Figures S5 and S6).

To be useful for amplified response to various stimuli, depolymerization of large polymers must be possible using small amounts of ROS. However, since in practice obtaining clear ^{1}H NMR spectra required large concentrations (>5 mg/mL) of PVAS to obtain reliably measurable product peaks (Figure S7). However, although PVAS did not have a strong UV−vis absorbance, the released sulfur dioxide had clear peaks at 260 and 330 nm (Figure S8). Using UV−vis absorbance measurements, the release of SO_2 was measured at varying concentrations of KO_2 addition (Figure 4a). PVAS showed degradation over background at 200 μM KO_2. In addition, PVAS showed good reactivity with sodium hypochlorite, with sensitivity down to about 2 mM (Figure S9a).

One important question about the mechanism of depolymerization is whether the generation of monomer is based on direct reaction with ROS or from initiation of depolymerization after ROS is generated. To test the kinetics of this process, PVAS was mixed with potassium superoxide in DMSO, and UV−vis spectra were taken at various time points, showing the increase in sulfur dioxide absorbance (Figure 4b). The depolymerization appears to follow two phases. In the initial phase, absorbance increases quickly, following first-order kinetics (Figure S10). This is likely to be the initial reaction of the superoxide at different places in the polymer chain, which would be pseudo first order with superoxide. The second phase also follows first-order kinetics, but with an apparent rate of about 1 order of magnitude slower, which corresponds to depolymerization. A similar reaction profile was observed for reaction with sodium hypochlorite (Figure S9b). Without superoxide, the polymer remains intact (Figure S11). While a specific rate constant could not be calculated due to difficulties in preparing a calibration curve with SO_2, this evidence indicates that both superoxide and hypochlorite are able to initiate depolymerization of PVAS.

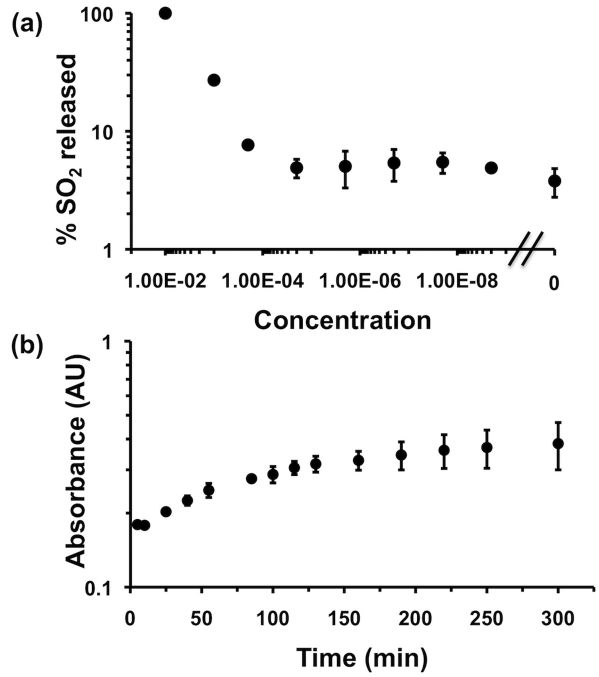

Figure 4. (a) Sulfur dioxide release from PVAS after 20 min, incubated with varying concentrations of KO_2, as measured at 260 nm. Error bars represent the standard deviation of two trials. (b) Absorbance at 260 nm vs time for PVAS incubated with 200 μM KO_2. Error bars represent the standard deviation of two trials.

Finally, the reactivity of PVAS was demonstrated against mechanical activation by ultrasonication. Ultrasonication generates transient solvent cavities that collapse to produce shear forces capable of breaking higher molecular weight polymers. Weaker chemical bonds are more susceptible to breakage, and carbon−sulfur bonds have lower bond dissociation energies than carbon−carbon or carbon−oxygen bonds.[27,28] Most polymers simply break into smaller fragments until a critical molecular weight (~30 kDa) is reached, but no further. However, if PVAS could undergo depolymerization by mechanical activation, the polymer would continue to disintegrate even after ultrasound was removed. To show that PVAS was susceptible to ultrasonication degradation, PVAS was dissolved in acetone-d_6 and subjected to probe sonication under argon (see SI for more details). The polymer solution was probe sonicated for 30 min only, and the generation of monomer was measured for a total of 4 h. As shown in Figure 5, a monomer was generated quickly during the sonication process, but even after sonication was finished, the monomer peaks continued to increase over time. Since the temperature of the sonication solution did not increase by more than 2 °C for the entire experiment, the temperature stayed well within the previously reported limits of T_c (−20 °C) and decomposition temperature (140 °C).[7] Thus, PVAS not only undergoes chain scission but also continues to generate free monomer after sonication is finished, indicating a depolymerization mechanism.

To further support a mechanically activated depolymerization mechanism, similar sonication experiments were run in DMSO, and the polymer molecular weight was monitored by DMSO GPC. Prior to sonication, the GPC trace of the polymer is bimodal, with one peak at about 1 MDa (vs PMMA) and another at 14 kDa and no peaks in the small molecule regime (Figure S13). Upon sonication, the peak molecular weight of

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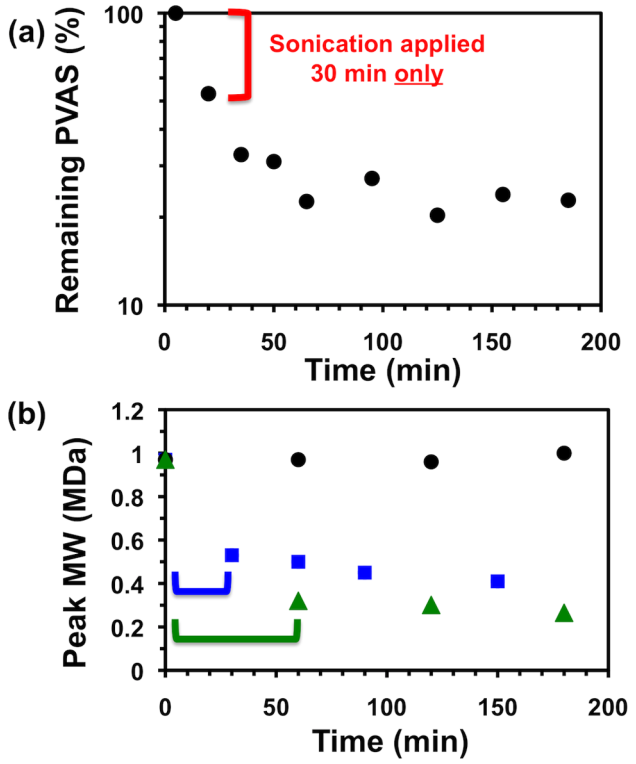

Figure 5. (a) Remaining PVAS vs time for probe sonication in acetone-d_6. Sonication was applied for the first 30 min only. (b) Peak molecular weight for larger molecular weight fraction vs time in DMSO, as measured by GPC (vs PMMA): blue squares, sonication applied for the first 30 min only; green triangles, sonication applied for the first 60 min only; black circles, no sonication applied.

the higher species decreases significantly as a function of sonication time (Figure S14). More tellingly, each molecular weight continues to decrease after sonication as well, indicating a depolymerization mechanism (Figure 5b). At the same time, a peak in the small molecule regime, presumably free monomer, increases, while the 14 kDa peak does not change significantly (Figures S15 and S16). Without sonication, none of these peaks change over the same time period (Figure S17). Since it is well-known from the mechanochemistry literature that larger molecular weight polymers are more susceptible to mechanical activation than smaller,[16,31] these experiments support a hypothesis of mechanical activation rather than ROS-generated activation. This mechanism of ultrasonic activation may find use in drug delivery applications in which therapy can be initiated within tissue but controlled slow release follows.

In conclusion, poly(vinyl acetate-*alt*-sulfur dioxide) (PVAS) was found to undergo depolymerization in response to ROS and ultrasound. PVAS is most reactive to superoxide, followed by hypochlorite, then hydroxyl radical. Kinetic studies of the hypochlorite-induced depolymerization showed that the reaction proceeded through a two-part mechanism in which monomer is generated rapidly first, then slowly. The PVAS shows reactivity to superoxide with a detection limit of 200 μM. Finally, PVAS shows reactivity to ultrasonication through an initiation/depolymerization mechanism. Current studies are focusing on adapting the alternating copolymers of sulfur dioxide as ROS-sensitive drug delivery vehicles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental methods, ^{1}H NMR spectra, sonication setup, GPC spectra, and UV−vis spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.5b00396.

(PDF)

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Notes

The authors declare no competing financial interest.

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