Mechanically Gated Degradable Polymers

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Supporting Information Placeholder

ABSTRACT: Degradable polymers are desirable for the replacement of conventional organic polymers that persist in the environment, but they often suffer from the unintentional scission of the degradable functionalities on the polymer backbone, which diminishes polymer properties during storage and regular use. Herein, we report a strategy that combats unintended degradation in polymers by combining two common degradation stimuli—mechanical and acid triggers—in an "AND gate" fashion. A cyclobutane (CB) mechanophore is used as a mechanical gate to regulate an acid-sensitive ketal that has been widely employed in acid degradable polymers. This gated ketal is further incorporated into the polymer backbone. In the presence of acid trigger alone, the pristine polymer retains its backbone integrity, and delivering high mechanical forces alone by ultrasonication degrades the polymer to an apparent limiting molecular weight of 28 kDa. The sequential treatment of ultrasonication followed by acid, however, leads to a further 11-fold decrease in molecular weight to 2.5 kDa. Experimental and computational evidence further indicate that the ungated ketal possesses mechanical strength that is commensurate with the conventional polymer backbones. Single molecule force spectroscopy (SMFS) reveals that the force necessary to activate the CB molecular gate on the timescale of 100 ms is approximately 2 nN.

Degradable polymers, including biodegradable polymers[1] and stimuli-degradable polymers,[2-3] are highly desirable targets for the purpose of alleviating plastic pollution that results from poor recycling and improper disposal of typically 'long-lived' synthetic organic polymers.[4-5] Typical degradable polymers contain degradable functionalities (e.g. ester,[6] azo,[7-8] ketal,[9], disulfide,[10] diselenum[11] and other cleavable functionalities[12]) on the polymer backbone that cleave under an external trigger, thus leading to the fragmentation of the polymer main chain (Figure 1). Depending on the reactivities of the embedded functionalities, polymers that degrade in response to heat,[13-14] light,[15] force,[16] acid[9] and redox species[12] have been created. These degradable polymers have proven to be useful in drug delivery,[3, 17] biomedical surgery,[18] and designing transient electronics.[19-20] Despite exhibiting desirable degradability in response to mild triggers (e.g., orthoester or ketal containing polymers degrade in the presence of catalytic amount of acid), the instability that originates from the same degradable functionality increases the risk of diminished polymer properties under storage or in regular service. Therefore, polymers that are increasingly resistant to unintended degradation under storage or use conditions, while still responding to mild triggers for degradation, would be advantageous.

One strategy to achieving higher fidelity in triggered degradation is to combine existing degradation methods in an "AND gate" fashion (Figure 1), so that either stimulus alone leads to less degradation than the two in combination. The concept of gated function has been widely applied in regulable molecular systems. For example, regulation of chemical reactions underlies photochemically controlled self-healing and adhesion in polymers,[21-22] photo-regulable catalytic activity,[23] paralysis in living organs,[24] chemical or mechanochemical reactions,[25-27] and chemically controlled photochromism[28].

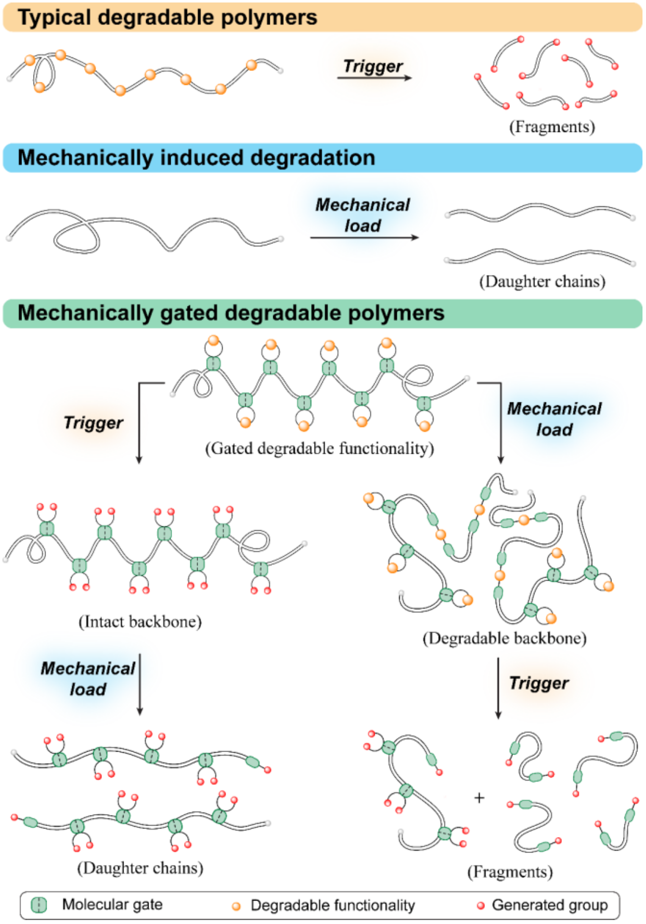
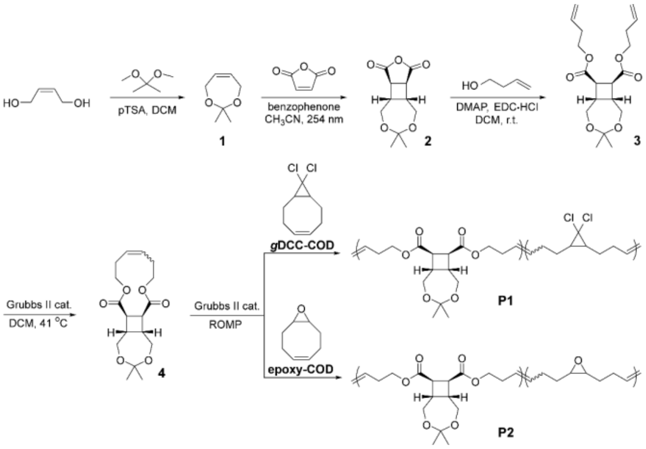


Figure 1. Typical degradable polymers contain degradable functionalities on the backbone and decompose to fragments/oligomers under an external trigger. Subjection of polymer to mechanical force produces fragmented daughter chains. Mechanically gated degradable polymers retain intact backbone in the presence of an external trigger and chain cleaves after subsequent mechanical load, while sequential treatment of mechanical load and an external trigger allows polymers to fragment.

Scheme 1. Synthesis of mechanically gated degradable polymers P1 and P2.



Mechanical force is a common trigger for degrading polymer molecular weight, and we were inspired by the recent use of a cyclobutane as a mechanochemical gate for the tandem activation of a *gem*-dichlorocyclopropane (*g*DCC) mechanophore.[29] The concept of mechanochemical gating was further exploited by Robb and co-workers to regulate a photochromic reaction[30] as well as small molecule release.[31] Here, we demonstrate that a similar mechanochemical gating concept (Figure 1) is also a viable strategy for degradable polymers. Broadly, we envisioned polymers in which a chemically triggered degradable functionality would be gated in a side-chain loop by a mechanophore that is positioned along the polymer main chain. Thus, application of the chemical trigger alone would not lead to molecular weight degradation. On the other hand, subjecting the polymer to high mechanical loads would open the gate, leading to chemically degradable functionalities along the main chain. Because mechanochemical gating allows many degradable functionalities to be exposed per mechanical chain scission event, the combination of mechanical and chemical triggers would lead to greater degradation than either stimulus alone.

Our synthetic design is described in Scheme 1. Cyclic alkene **1** with acid-cleavable ketal group is subjected to photo [2+2] cycloaddition with maleic anhydride to provide cyclobutane (CB) containing molecule **2**. Esterification of **2** yields diene **3**, and subsequent ring-closing metathesis gives polymerizable macrocycle **4**. Further entropy-driven ring-opening metathesis polymerization (ED-ROMP)[32] of **4** with *g*DCC-COD and epoxy-COD co-monomers gives polymers **P1** and **P2**, respectively. These co-monomers were chosen for their respective demonstrated utility as internal standards of mechanochemical activity (*g*DCC in **P1**)[33-35] and as a means to promote high forces of adhesion to cantilevers in single molecule force spectroscopy (SMFS) studies (epoxide in **P2**).[36]

To verify that our design is resilient to acid alone, a THF solution of **P1** (M_n = 129 kDa, Đ = 1.49; 1.2 mg mL^{-1}) was treated with trifluoroacetic acid (TFA) at room temperature overnight to yield **P3**. GPC analysis reveals that the retention time shifts slightly from 13.38 min to 13.48 min, and multi-angle light scattering shows a decrease in number average molecular weight (M_n) to 120 kDa (Figure 2b), which is attributed to the cleavage of the ketal (^{1}H NMR, Figure 2c) without main chain scission. Thus, the main chain of **P1** is resistant to acidic degradation.

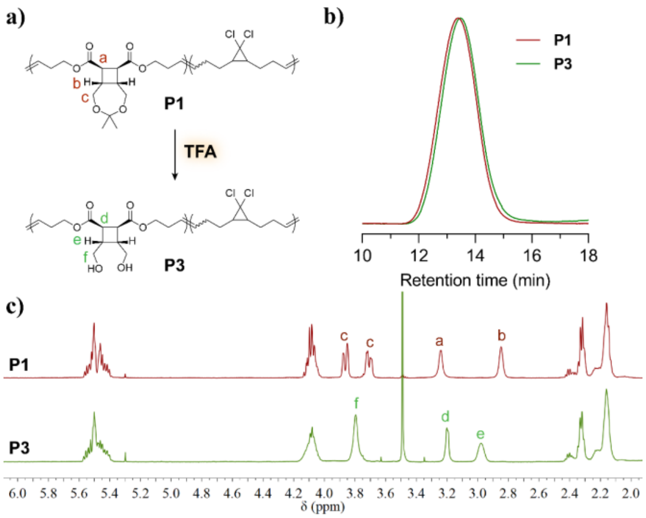


Figure 2. a) Treatment of **P1** polymer with TFA cleaves the ketal functionality but preserves the polymer backbone; b) Normalized GPC traces of **P1** and **P3**; c) ^{1}H NMR spectrum of **P1** and **P3**.

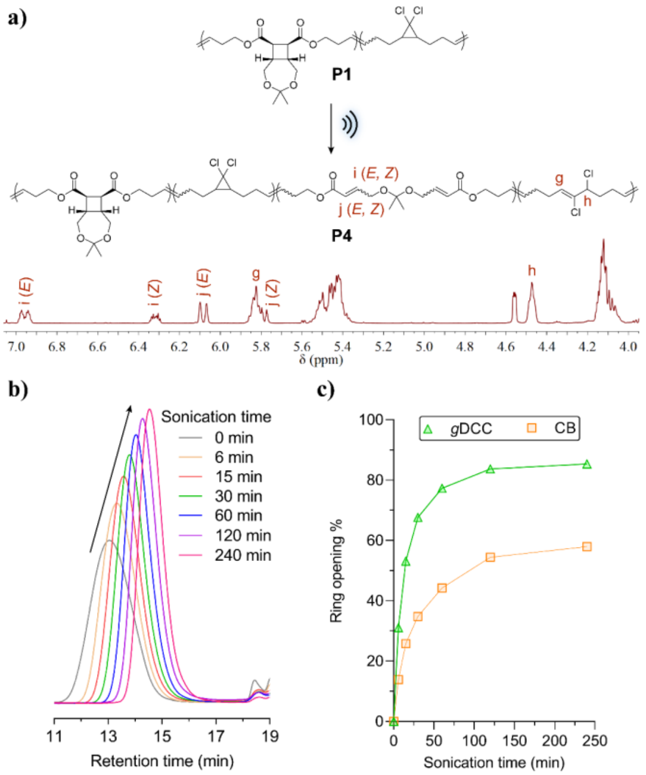


Figure 3. a) Mechanical conversion of **P1** into **P4**; ^{1}H NMR spectrum of **P4** after 30 min sonication. The relative integration of *i*(*E*) and *i*(*Z*) protons gives *E*:*Z* = 2:1; b) GPC traces of **P4** as a function of sonication time; c) Ring-opening percentage of CB and *g*DCC over sonication time.

If, however, **P1** (M_n = 154 kDa, Đ = 1.53, 34 mol% **4**, 66 mol% *g*DCC-COD) is first subjected to pulsed ultrasonication (1 mg mL^{-1} in THF, 1s on/1s off, ice bath, N_2) for 240 min, ^{1}H NMR indicates that the product **P4** comprises pristine and activated CB and *g*DCC mechanophores on the backbone (Figure 3a). The ^{1}H NMR integrations show that 58% of CB and 85% of the *g*DCC internal standard are activated under these conditions. Notably, activation of CB produces E/Z alkenes in a ratio of ~ 2/1 that is substantially higher than 1.14/1 observed previously with a similar cyclohexane-fused CB mechanophore.[37] The increased *E* content from the ketal-fused CB here is presumably due to the more strained seven-member ring,[38] relative to the cyclohexyl ring reported previously, that is fused to the CB. Following initial C1-C2 bond scission, the greater ring strain in the current design might promote the rate of C3-C4 bond scission, so that it occurs more quickly relative to C1-C4 bond rotation in the diradical intermediate. Such dynamic competition has previously been implicated in determining the product stereochemistry, with rapid C3-C4 scission facilitating the formation of *EE* product.

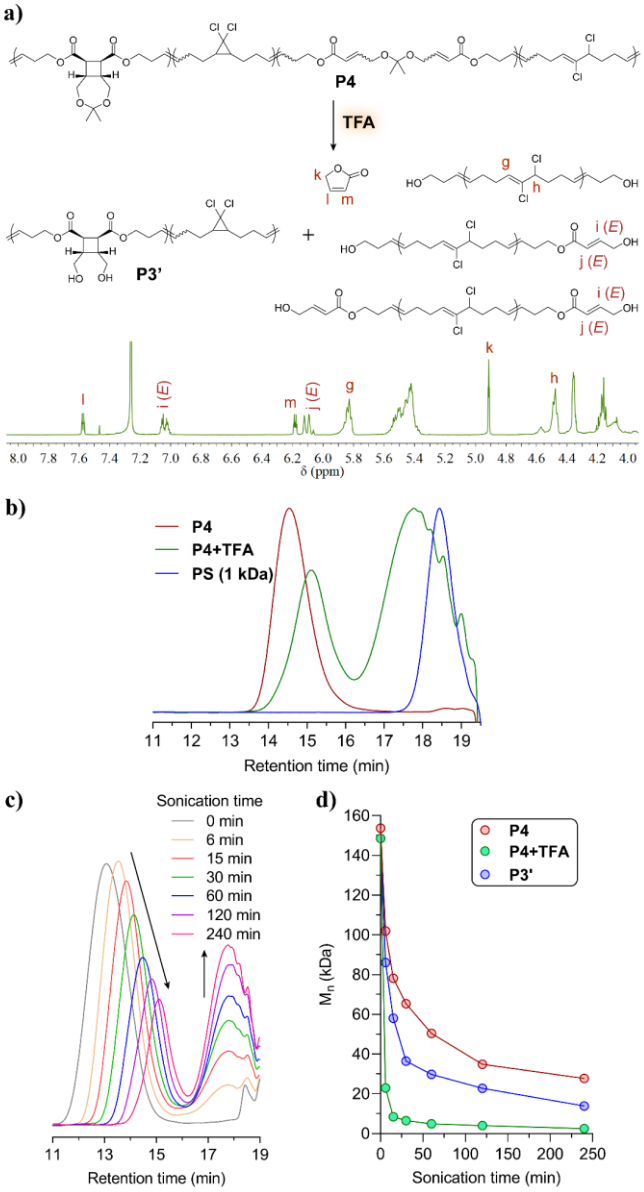


Figure 4. a) Schematic illustration of generated fragments and furanone after TFA treatment of **P4** and its ^{1}H NMR spectrum in CDCl$_3$. The molar ratio of furanone to *E* alkene species is 1/2. b) Overlay of normalized GPC traces of **P4** polymer before (maroon) and after (green) TFA treatment. Blue trace is PS standard (M_n = 1000 Da). c) GPC overlay of TFA treated **P4** polymer with various sonication times. The arrows indicate the shift of polymer peak and increase of oligomer peak over sonication time. d) Comparison of M_n for **P4** before (red dots) and after (green dots) TFA treatment and M_n of high molecular weight fragment **P3'** (blue dots).

With increasing sonication time, GPC traces show a continuous shift to longer retention time (Figure 3b), as expected for typical polymer chain scission under pulsed ultrasonication. Meanwhile, ^{1}H NMR indicates the activation of both CB and *g*DCC mechanophores due to sonication, with more ring opening observed for *g*DCC than CB (Figure 3c). The greater activity of *g*DCC relative to CB is consistent with prior reports on similar substrates.[29] The activation of CB results in unveiled ketals along the polymer backbone. To assess the mechanical stability of the ketals, we followed the procedure of previous studies that have shown that mechanically weak bonds on polymer backbones lead to less activation of *g*DCC internal standard per chain scission event.[39-41] After 15 min sonication, where the M_n reaches to half of initial value (from 154 kDa to 78 kDa, Figure 4d), the activation of *g*DCC reaches 53%. This gives 54% *g*DCC activation per average scission event, which is comparable to previous results on C-C bond containing polymers[34] and suggests that the ketal is mechanically robust relative to conventional hydrocarbon polymers. This experimental result is supported computationally by CoGEF[42] calculations that show that it is the C-O bond adjacent to the ester group, rather than the ketal, that breaks at high extension (Figure S19).

The mechanically activated **P4** was then treated with TFA. As seen in Figure 4a, TFA treatment of **P4** generates CB and *g*DCC containing polymer **P3'**, along with activated *g*DCC fragments/oligomers that are consistent with acid catalyzed hydrolysis of the ketals. The ^{1}H NMR spectrum of the **P4** + TFA products shows activated CB and *g*DCC proton signals and, remarkably, signals from furanone. The formation of furanone is attributed to quantitative conversion of the mechanically generated *Z* alkene, as supported by ^{1}H NMR integration. The GPC of the **P4** + TFA products is bimodal, with a higher molecular weight (MW) peak (**P3'**) that is shifted to longer retention times (lower MW) than untreated **P4**, and a new peak at even longer (~17-19 min) retention times that corresponds to low MW fragments and oligomers of ~1 kDa (Figure 4b). As sonication time increases, the GPC peak of **P3'** consistently shifts to longer retention time and the relative RI intensity of the oligomer region increases (Figure 4c). After 4 h of mechanical treatment followed by acid degradation, the gated system reaches an ultimate M_n of 2.5 kDa, in comparison to 28 kDa for the mechanical treatment alone and effectively no backbone degradation for acid treatment alone. Interestingly, the order of the combined treatment matters; reaction with TFA followed by 4 h of mechanical treatment leads to M_n = 22 kDa (Figure S2), because treatment with TFA converts the CB into a scissile “weak bond” whose activation now breaks the polymer main chain. That scission event prevents the activation of multiple CB mechanophores in the daughter fragments, and the associated ^{1}H NMR spectra are consistent with a single CB activation per chain scission event (Figure S5).

The gated cyclic ketal provides additional extension of the polymer upon mechanical activation of the CB gate, and so the design is well suited for quantitative studies of kinetics using previously reported SMFS techniques.[43-44] A representative force-extension curve of **P2** (48 mol% **4**, 52 mol% epoxy-COD) is shown in Figure 5a. The mechanical activation of CB and subsequent release of reserved length give a characteristic plateau transition at *f* ~ 2000 pN, which is about 200 pN lower than observed for a similar CB molecular gate fused to an eight-membered ring.[29] We attribute this minor difference in force to the influence of differential ring strain and stereochemistry in the fused bicyclic structures of the two systems. Despite our best efforts, we were unable to obtain a force-extension curve in which the polymer completed the ring-opening transition. An analysis of the polymer survival times in the plateau region (Figure 5b) is consistent with an effective (but approximate) rate constant for chain detachment of 16 s^{-1} at the plateau force of ca. 2000 pN. The competition with chain detachment limits the average fractional extension observed to only ~1.5%, far less than the 34% extension expected from modeling (see Supporting Information).

In summary, we have demonstrated that gated backbones provide access to polymers that are efficiently degraded by combinations of triggers used commonly in polymer degradation (here, mechanical force and acid), but that are resistant to degradation from either trigger alone. If similar concepts could be applied to scale, it might lead to new degradable polymer systems that are increasingly robust and more reliably maintain their properties during regular service. Beyond degradability, we also envision that the cleavable, gated ketal functionality provides a mechanism to chemically regulated the stress-relieving behavior (turning extensible mechanophores into scissile mechanophores). We are currently applying this concept to the study of stress-relief and fracture behavior in mechanophore-enriched polymer networks.

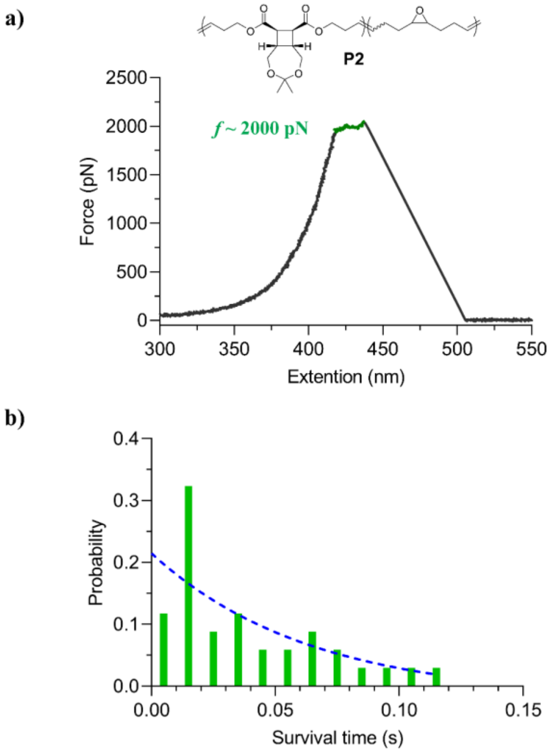


Figure 5. a) Representative force-extension curve of **P2** polymer (pulling velocity: 300 nm/s). b) Probability distribution of survival time at transition force (green histogram) and corresponding one-phase fitting (blue dotted line, k = 16 s^{-1}). Note that very short survival times might be easily missed by visual inspection, artificially limiting the population of the lowest bin.

ASSOCIATED CONTENT

Supporting Information. Synthetic procedures, sonication details, SMFS analysis and additional SMFS curves, CoGEF modeling. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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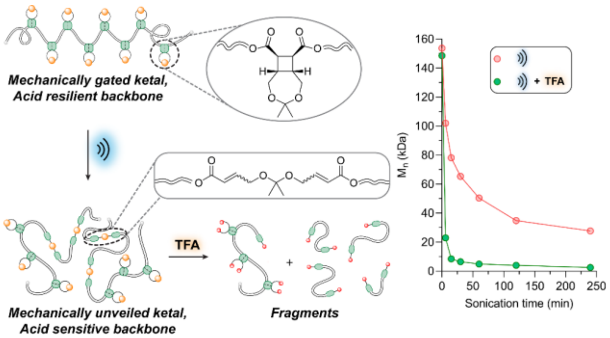
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Sonication time (min)