

Communication

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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 acidsensitive 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 polymers¹ 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 diselenum¹¹ and other cleavable functionalities¹²) on the polymer backbone that cleave under an external trigger, thus leading to the fragmentation of the polymer main chain (Figure 1). By embedding appropriate functionalities, polymers that degrade in response to heat,¹³⁻¹⁴ light,¹⁵ force,¹⁶ acid⁹ and redox species¹² 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, 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, including: 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





59 60 Mechanically gated degradable polymers retain most of all of their backbone in response to either stimulus alone, whereas combined exposure leads to a much greater extent of fragmentation.

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 (qDCC)mechanophore.²⁹ The concept of mechanochemical gating was further exploited by Robb and co-workers to regulate photochromism³⁰ and small molecule release,³¹ and Otsuka has similarly used photochemistry to gate mechanochemical reactivity. 27 In these latter examples, the "AND gating" is limited to a single event per chain. 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 is 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 non-scissile gate, leading to many 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 gDCC-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 (gDCC 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, D = 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 (¹H NMR, Figure 2c) without main chain scission. Thus, the main chain of **P1** is resistant to acidic degradation.

If, however, **P1** (M_n = 154 kDa, D = 1.53, 34 mol% **4**, 66 mol% gDCC-COD) is first subjected to pulsed ultrasonication (1 mg mL⁻¹ in THF, 1s on/1s off, ice bath, N₂) for 240 min, ¹H NMR indicates that the product **P4** comprises pristine and activated CB and gDCC mechanophores on the backbone (Figure 3a). The ¹H NMR integrations show that 58% of CB and 85% of the gDCC internal standard



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) ¹H NMR spectrum of P1 and P3.

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Figure 3. a) Mechanical conversion of **P1** into **P4**; ¹H 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 gDCC over sonication time.

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 We hypothesize that the increased *E* content from the ketal-fused CB here is 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.



8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 $\delta(\text{ppm})$



4. a) Schematic illustration Figure of generated fragments and furanone after TFA treatment of ${\bf P4}$ and its $^{1}{\rm H}$ NMR spectrum in $CDCl_3$. The molar ratio of furanone to E alkene species is 1/2. b) Overlay of normalized GPC traces of ${\bf P4}$ polymer before (maroon) and after (green) TFA treatment. Blue trace is PS standard (M_n = 1000 Da). c) GPC overlay of treated Р4 with TFA polymer various

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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 high molecular weight fragment **P3'** (blue dots).

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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, ¹H 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 gDCC 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 gDCC 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% gDCC activation per average scission event, which is comparable to previous results on C-C bond containing polymers³⁴ and suggests that the ketal is mechanically robust relative to conventional hydrocarbon This experimental result is supported polymers. computationally by CoGEF⁴² 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 gDCC containing polymer P3', along with activated gDCC fragments/oligomers that are consistent with acid catalyzed hydrolysis of the ketals. The ¹H NMR spectrum of the P4 + TFA products shows activated CB and gDCC 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 ¹H 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 ¹H 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 $f \sim 2000$ pN, which is about 200 pN lower than observed for a similar CB molecular gate fused to an eightmembered ring.²⁹ We attribute this minor difference in force to the greater ring strain in the fused CB in the present bicyclic design (see ESI, Section V.). 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 (e.g., combinations of degradable functionalities with other photo/chemical gates) could be applied to scale, it might lead to new degradable polymer systems that are increasingly (if not perfectly) 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 regulate the stressrelieving 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 Р2 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, $k = 16 \text{ s}^{-1}$). Note that very short survival times might be easily

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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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REFERENCES

1. Leja, K.; Lewandowicz, G. Polymer Biodegradation and Biodegradable Polymers - a Review. *Pol J Environ Stud* **2010**, *19*, 255-266.

2. Zhang, Q.; Ko, N. R.; Oh, J. K. Recent Advances in Stimuli-Responsive Degradable Block Copolymer Micelles: Synthesis and Controlled Drug Delivery Applications. *Chem Commun (Camb)* **2012**, *48*, 7542-7552.

3. Bawa, K. K.; Oh, J. K. Stimulus-Responsive Degradable Polylactide-Based Block Copolymer Nanoassemblies for Controlled/Enhanced Drug Delivery. *Mol. Pharm.* **2017**, *14*, 2460-2474.

4. Siracusa, V.; Rocculi, P.; Romani, S.; Rosa, M. D. Biodegradable Polymers for Food Packaging: A Review. *Trends Food Sci. Technol.* **2008**, *19*, 634-643.

5. Schneiderman, D. K.; Hillmyer, M. A. 50th Anniversary Perspective: There Is a Great Future in Sustainable Polymers. *Macromolecules* **2017**, *50*, 3733-3749.

6. Kricheldorf, H. R. Syntheses of Biodegradable and Biocompatible Polymers by Means of Bismuth Catalysts. *Chem. Rev.* **2009**, *109*, 5579-5594.

Kenley, R. A.; Manser, G. E. Degradable Polymers Incorporating a Difunctional Azo Compound into a Polymer
Network to Produce Thermally Degradable Polyurethanes. *Macromolecules* 1985, 18, 127-131.

43 8. Mutlu, H.; Geiselhart, C. M.; Barner-Kowollik, C. Untapped
44 Potential for Debonding on Demand: The Wonderful World of Azo45 Compounds. *Materials Horizons* 2018, *5*, 162-183.

9. Paramonov, S. E.; Bachelder, E. M.; Beaudette, T. T.;
Standley, S. M.; Lee, C. C.; Dashe, J.; Frechet, J. M. Fully Acid-Degradable Biocompatible Polyacetal Microparticles for Drug Delivery. *Bioconjug Chem* 2008, *19*, 911-919.

Tachibana, Y.; Baba, T.; Kasuya, K.-i. Environmental
Biodegradation Control of Polymers by Cleavage of Disulfide
Bonds. *Polym. Degrad. Stab.* 2017, 137, 67-74.

 Xia, J.; Li, T.; Lu, C.; Xu, H. Selenium-Containing Polymers: Perspectives toward Diverse Applications in Both Adaptive and Biomedical Materials. *Macromolecules* 2018, *51*, 7435-7455.
 Song, C.-C.; Du, F.-S.; Li, Z.-C. Oxidation-Responsive

12. Song, C.-C.; Du, F.-S.; Li, Z.-C. Oxidation-Responsive Polymers for Biomedical Applications. *J. Mater. Chem. B* **2014**, *2*, 3413-3426.

13. Peterson, G. I.; Church, D. C.; Yakelis, N. A.; Boydston, A. J. 1,2-Oxazine Linker as a Thermal Trigger for Self-Immolative Polymers. *Polymer* **2014**, *55*, 5980-5985.

14. Yardley, R. E.; Kenaree, A. R.; Gillies, E. R. Triggering Depolymerization: Progress and Opportunities for Self-Immolative Polymers. *Macromolecules* **2019**, *52*, 6342-6360.

15. Ayer, M. A.; Schrettl, S.; Balog, S.; Simon, Y. C.; Weder, C. Light-Responsive Azo-Containing Organogels. *Soft Matter* **2017**, *13*, 4017-4023.

16. Diesendruck, C. E.; Peterson, G. I.; Kulik, H. J.; Kaitz, J. A.; Mar, B. D.; May, P. A.; White, S. R.; Martinez, T. J.; Boydston, A. J.; Moore, J. S. Mechanically Triggered Heterolytic Unzipping of a Low-Ceiling-Temperature Polymer. *Nat. Chem.* **2014**, *6*, 623-628.

17. Li, Y.; Maciel, D.; Rodrigues, J.; Shi, X.; Tomas, H. Biodegradable Polymer Nanogels for Drug/Nucleic Acid Delivery. *Chem. Rev.* **2015**, *115*, 8564-8608.

18. Cai, Z.; Wan, Y.; Becker, M. L.; Long, Y. Z.; Dean, D. Poly(Propylene Fumarate)-Based Materials: Synthesis, Functionalization, Properties, Device Fabrication and Biomedical Applications. *Biomaterials* **2019**, *208*, 45-71.

19. Hernandez, H. L.; Kang, S. K.; Lee, O. P.; Hwang, S. W.; Kaitz, J. A.; Inci, B.; Park, C. W.; Chung, S.; Sottos, N. R.; Moore, J. S.; Rogers, J. A.; White, S. R. Triggered Transience of Metastable Poly(Phthalaldehyde) for Transient Electronics. *Adv. Mater.* **2014**, *26*, 7637-7642.

20. Tan, M. J.; Owh, C.; Chee, P. L.; Kyaw, A. K. K.; Kai, D.; Loh, X. J. Biodegradable Electronics: Cornerstone for Sustainable Electronics and Transient Applications. *Journal of Materials Chemistry C* **2016**, *4*, 5531-5558.

21. Fuhrmann, A.; Gostl, R.; Wendt, R.; Kotteritzsch, J.; Hager, M. D.; Schubert, U. S.; Brademann-Jock, K.; Thunemann, A. F.; Nochel, U.; Behl, M.; Hecht, S. Conditional Repair by Locally Switching the Thermal Healing Capability of Dynamic Covalent Polymers with Light. *Nat. Commun.* **2016**, *7*, 13623.

22. Asadirad, A. M.; Boutault, S.; Erno, Z.; Branda, N. R. Controlling a Polymer Adhesive Using Light and a Molecular Switch. *J. Am. Chem. Soc.* **2014**, *136*, 3024-3027.

23. Kaur, B.; Raza, R.; Stashick, M. J.; Branda, N. R. Using Light to Control the Inhibition of Karstedt's Catalyst. *Organic Chemistry Frontiers* **2019**, *6*, 1253-1256.

24. Al-Atar, U.; Fernandes, R.; Johnsen, B.; Baillie, D.; Branda, N. R. A Photocontrolled Molecular Switch Regulates Paralysis in a Living Organism. *J. Am. Chem. Soc.* **2009**, *131*, 15966-15967.

25. Erno, Z.; Asadirad, A. M.; Lemieux, V.; Branda, N. R. Using Light and a Molecular Switch to 'Lock' and 'Unlock' the Diels-Alder Reaction. *Org Biomol Chem* **2012**, *10*, 2787-2792.

26. Warford, C. C.; Carling, C. J.; Branda, N. R. From Slow to Fast--the User Controls the Rate of the Release of Molecules from Masked Forms Using a Photoswitch and Different Types of Light. *Chem Commun (Camb)* **2015**, *51*, 7039-7042.

27. Kida, J.; Imato, K.; Goseki, R.; Aoki, D.; Morimoto, M.; Otsuka, H. The Photoregulation of a Mechanochemical Polymer Scission. *Nat. Commun.* **2018**, *9*, 3504.

28. Nourmohammadian, F.; Wu, T.; Branda, N. R. A 'Chemically-Gated' Photoresponsive Compound as a Visible Detector for Organophosphorus Nerve Agents. *Chem Commun (Camb)* **2011**, *47*, 10954-10956.

29. Wang, J.; Kouznetsova, T. B.; Boulatov, R.; Craig, S. L. Mechanical Gating of a Mechanochemical Reaction Cascade. *Nat. Commun.* **2016**, *7*, 13433.

30. Hu, X.; McFadden, M. E.; Barber, R. W.; Robb, M. J. Mechanochemical Regulation of a Photochemical Reaction. *J. Am. Chem. Soc.* **2018**, *140*, 14073-14077.

31. Hu, X.; Zeng, T.; Husic, C. C.; Robb, M. J. Mechanically Triggered Small Molecule Release from a Masked Furfuryl Carbonate. *J. Am. Chem. Soc.* **2019**, *141*, 15018-15023.

32. Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. Template-Directed Ring-Closing Metathesis: Synthesis and Polymerization of Unsaturated Crown Ether Analogs. Angew Chem Int Ed Engl 1997, 36, 1101-1103.

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33. Lenhardt, J. M.; Black, A. L.; Craig, S. L. Gem-Dichlorocyclopropanes as Abundant and Efficient Mechanophores in Polybutadiene Copolymers under Mechanical Stress. J. Am. Chem. Soc. 2009, 131, 10818-10819.

Lenhardt, J. M.; Ramirez, A. L. B.; Lee, B.; Kouznetsova, T. 34. B.; Craig, S. L. Mechanistic Insights into the Sonochemical Activation of Multimechanophore Cyclopropanated Polybutadiene Polymers. Macromolecules 2015, 48, 6396-6403.

Wang, J.; Kouznetsova, T. B.; Niu, Z.; Ong, M. T.; Klukovich, 35 H. M.; Rheingold, A. L.; Martinez, T. J.; Craig, S. L. Inducing and 10 Quantifying Forbidden Reactivity with Single-Molecule Polymer Mechanochemistry. Nat. Chem. 2015, 7, 323-327. 11

Klukovich, H. M.; Kouznetsova, T. B.; Kean, Z. S.; Lenhardt, 36. 12 J. M.; Craig, S. L. A Backbone Lever-Arm Effect Enhances Polymer 13 Mechanochemistry. Nat. Chem. 2013, 5, 110-114. 14

Kean, Z. S.; Niu, Z.; Hewage, G. B.; Rheingold, A. L.; Craig, 37. S. L. Stress-Responsive Polymers Containing Cyclobutane Core Mechanophores: Reactivity and Mechanistic Insights. J. Am. Chem. Soc. 2013, 135, 13598-13604.

17 Neary, W. J.; Kennemur, J. G. Polypentenamer 38. 18 Renaissance: Challenges and Opportunities. ACS Macro. Lett. 2018, 19 8,46-56.

20 39. Lee, B.; Niu, Z.; Wang, J.; Slebodnick, C.; Craig, S. L. Relative Mechanical Strengths of Weak Bonds in Sonochemical 21 Polymer Mechanochemistry. J. Am. Chem. Soc. 2015, 137, 10826-22 10832. 23

Sha, Y.; Zhang, Y. D.; Xu, E. H.; Wang, Z.; Zhu, T. Y.; Craig, 40. S. L.; Tang, C. B. Quantitative and Mechanistic Mechanochemistry in Ferrocene Dissociation. ACS Macro. Lett. 2018, 7, 1174-1179.

Wang, Z.; Craig, S. L. Stereochemical Effects on the 41. Mechanochemical Scission of Furan-Maleimide Diels-Alder Adducts. Chem Commun (Camb) 2019, 55, 12263-12266.

Beyer, M. K. The Mechanical Strength of a Covalent Bond 42. Calculated by Density Functional Theory. J. Chem. Phys. 2000, 112, 7307-7312.

Gossweiler, G. R.; Kouznetsova, T. B.; Craig, S. L. Force-43. Rate Characterization of Two Spiropyran-Based Molecular Force Probes. J. Am. Chem. Soc. 2015, 137, 6148-6151.

Barbee, M. H.; Kouznetsova, T.; Barrett, S. L.; Gossweiler, 44. G. R.; Lin, Y.; Rastogi, S. K.; Brittain, W. J.; Craig, S. L. Substituent Effects and Mechanism in a Mechanochemical Reaction. J. Am. Chem. Soc. 2018, 140, 12746-12750.

ТОС		
	Mechanically gated ketal, Acid resilient backbone	
	TFA TFA Mechanically unveiled ketal, Acid sensitive backbone TFA	
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