

Communication

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Mechanically Triggered Small Molecule Release from a Masked Furfuryl Carbonate

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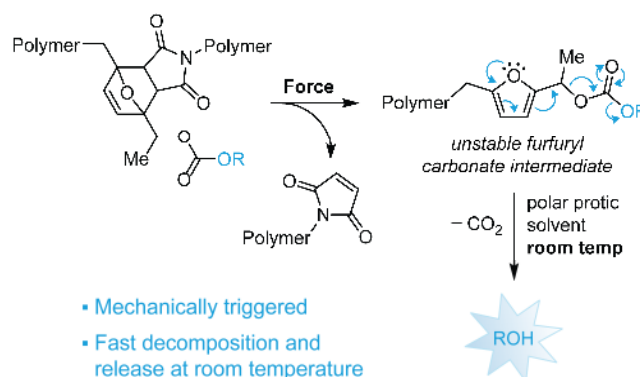
Supporting Information Placeholder

ABSTRACT: Stimuli-responsive polymers that release small molecules under mechanical stress are appealing targets for applications ranging from drug delivery to sensing. Here, we describe a modular mechanophore design platform for molecular release via a mechanically triggered cascade reaction. Mechanochemical activation of a furan–maleimide Diels–Alder adduct reveals a latent furfuryl carbonate that subsequently decomposes under mild conditions to release a covalently bound cargo molecule. The computationally guided design of a reactive secondary furfuryl carbonate enables the decomposition and release to proceed quickly at room temperature after unmasking via mechanical force. This general strategy is demonstrated using ultrasound-induced mechanical activation to release a fluorogenic coumarin payload from a polymer incorporating a chain-centered mechanophore.

Mechanical to chemical transduction is a powerful strategy for achieving materials with stimuli-responsive properties. The emerging field of polymer mechanochemistry aims to harness mechanical forces in polymers to promote productive chemical transformations in stress-responsive molecules known as mechanophores.¹ Mechanical force is delivered to mechanophores through covalently attached polymer chains using a variety of techniques including solution-phase ultrasonication,² tension/compression in solid materials,³ atomic force microscopy,⁴ laser-induced stress waves,⁵ and high intensity focused ultrasound.⁶ Mechanically coupled chemical activation has been demonstrated for covalent bond transformations to engender a wide range of functional responses including changes in color or fluorescence,^{3a,7} chemiluminescence,⁸ switching of electrical conductivity,⁹ activation of catalysts,¹⁰ and generation of reactive functional groups.¹¹

Polymers that release small molecules under stress are particularly appealing targets for a number of applications including catalysis, sensing, self-healing, and drug delivery.¹² However, mechanophores capable of releasing functional small molecules are still limited. An oxanorbornadiene mechanophore was demonstrated to release a benzyl furfuryl ether molecule from polymeric materials under compression,¹³ while a *gem*-dichlorocyclopropanated indene mechanophore was shown to generate HCl.¹⁴ In addition, mechanochemical chain scission of poly(*o*-phthalaldehyde) results in an unzipping reaction above its ceiling temperature to regenerate monomer.¹⁵ Metal ion release from the mechanical dissociation of ferrocene was also recently demonstrated.¹⁶ Nevertheless, a more modular and general mechanophore design platform capable of the triggered release of functional organic molecules would enable new opportunities for polymer mechanochemistry.

Scheme 1. Mechanically Triggered Reaction Cascade Resulting in Small Molecule Release.



Cascade reactions initiated by external stimuli offer a unique approach for controlling molecular release. For example, retro-Diels–Alder reactions have served as thermal triggers for the depolymerization of self-immolative polymers. Boydston and coworkers reported a 1,2-oxazine linker,¹⁷ while Gillies and coworkers reported a furan–maleimide adduct that initiated a depolymerization reaction at elevated temperatures by invoking the thermal decomposition of a furfuryl carbonate intermediate.¹⁸ The photogating concept has also been used to control cascade reactions. Branda and coworkers designed a diarylethene photoswitch that allowed electronic conjugation between a remote electron donating group and a labile carbonate group to be modulated with light, resulting in carbonate fragmentation upon photochemical electrocyclozation.¹⁹ We recently extended the concept of mechanochemical gating²⁰ to regulate a photochemical transformation in which a mechanically facilitated retro-Diels–Alder reaction unmasked a diarylethene photoswitch.²¹

Here we report a mechanophore platform based on a furan–maleimide Diels–Alder adduct that leverages the instability of a judiciously designed furfuryl carbonate for small molecule release via a mechanically gated reaction cascade. As illustrated in Scheme 1, mechanochemical activation of the kinetically stable adduct results in a retro-Diels–Alder reaction, revealing a metastable furfuryl carbonate that quickly decomposes in polar protic media to release carbon dioxide and a covalently bound alcohol molecule. The secondary furfuryl carbonate structure is a key design feature that significantly increases the rate of decomposition and small molecule release, enabling the transformation to proceed spontaneously under mild conditions, but only after the prerequisite mechanochemical cycloelimination reaction. We describe the computationally

supported design and reactivity of the furfuryl carbonate, and as a proof-of-concept, demonstrate the mechanically triggered release of a model fluorogenic coumarin probe via ultrasound-induced mechanochemical activation of a polymer chain-centered mechano-phore.

We initially set out to investigate the effect of substitution on the decomposition reaction of furfuryl carbonates. Activation energies for the reaction of a series of three model furfuryl carbonates (**FC1**–**FC3**) were calculated at the M06-2X/6-311+G** level of density functional theory (DFT) to gauge the effect of substitution on the rate of decomposition (Figure 1a, see the SI for details). The activation energy for the fragmentation of **FC1**, which is analogous to Gillies' design,¹⁸ was calculated to be 29.4 kcal/mol, suggesting very slow reaction at room temperature. Addition of a methyl group at the 5-position of the furan (**FC2**) reduces the reaction barrier to 25.8 kcal/mol, although this is still insufficient for rapid release. In fact, model compounds with analogous structures to **FC1** and **FC2** were synthesized and the half-lives for decomposition at room temperature were estimated to be on the order of several weeks (Figures S1 and S2). DFT calculations indicate that substitution with an α -methyl group, however, results in a pronounced decrease in activation energy for **FC3** ($\Delta G^\ddagger = 22.0$ kcal/mol) as might be expected

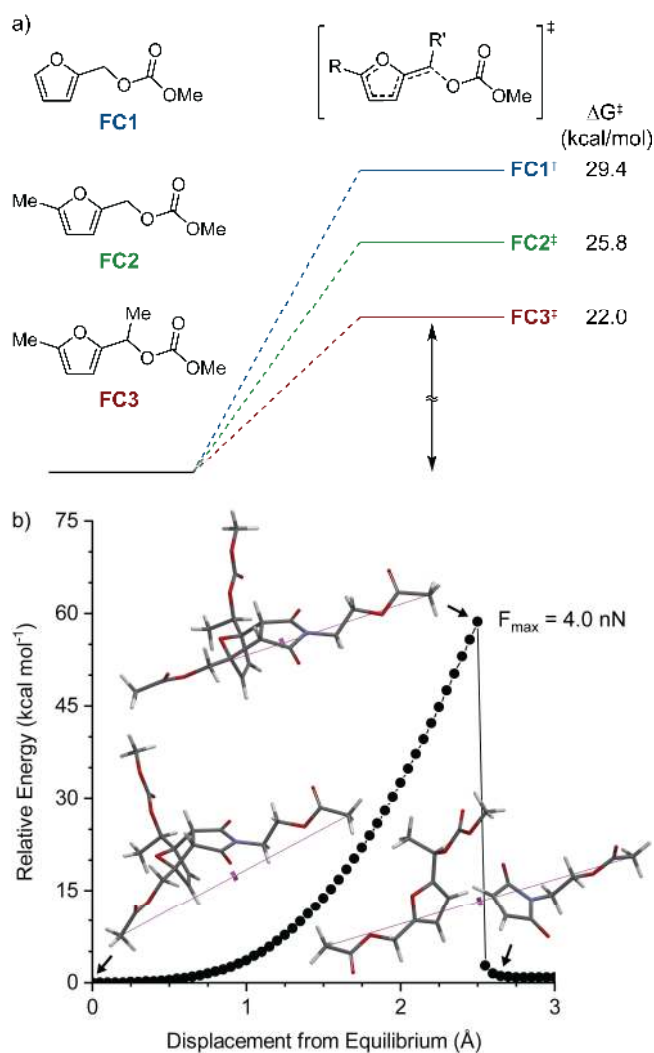


Figure 1. Density functional theory (DFT) calculations of (a) activation energies for carbonate fragmentation from a series of furfuryl carbonates at the M06-2X/6-311+G** level of theory, and (b) mechanical elongation of a truncated furan-maleimide Diels-Alder adduct using the constrained geometries simulate external force (CoGEF) method at the B3LYP/6-31G* level of theory.

from stabilization of the putative furfuryl cation intermediate suggested by the mechanism in Scheme 1. We therefore identified the general structure of furfuryl carbonate **FC3** as a promising target for mechanically triggered small molecule release from a furan-maleimide Diels-Alder adduct using the 5-position of the furan for polymer attachment. Additional DFT calculations using the simple constrained geometries simulate external force (CoGEF) technique²² indicate that mechanical elongation of an appropriately substituted furan-maleimide adduct generates the expected furfuryl carbonate (Figure 1b, see the SI for details). The retro-Diels-Alder reaction occurs with an estimated rupture force of 4.0 nN, which is comparable to rupture forces calculated with the CoGEF method for other active furan-maleimide mechanophores.²³ While these forces are typically overestimated compared to experiments,²⁴ they provide a useful framework for predicting relative mechanochemical activity.

We synthesized fluorogenic furfuryl carbonate model compound **1** with an analogous structure to computational model **FC3** and investigated its reactivity experimentally (Figure 2). The coumarin payload exhibits enhanced photoluminescence (PL) upon release, allowing reaction progress to be tracked using fluorescence spectroscopy in addition to NMR spectroscopy. Furfuryl carbonate **1** is relatively stable in chloroform and acetonitrile (Figures S3 and S4); however, the addition of methanol to an acetonitrile solution of **1** leads to fast decomposition at room temperature and clean formation of hydroxycoumarin **2** and furfuryl ether **3** (Figure 2a). The generation of furfuryl ether **3** under these conditions is consistent with a mechanism involving initial fragmentation of the carbonate group to form a furfuryl cation, which is subsequently attacked by methanol followed by proton transfer. Figure 2b shows the decomposition of furfuryl carbonate **1** in a 3:1 (v/v) mixture of acetonitrile-*d*₃ and methanol monitored by ¹H NMR spectroscopy. Signals corresponding to **1** fully disappear in a few hours with the concomitant formation of two new sets of resonances that match the spectra of the isolated hydroxycoumarin and furfuryl methyl ether products. The generation of hydroxycoumarin **2** from a room temperature solution of furfuryl carbonate **1** in MeCN:MeOH (3:1) was also monitored over time using fluorescence spectroscopy (Figure 2c). Excitation at 330 nm revealed an emission peak around 380 nm that increased in intensity over time and matches the emission spectrum of hydroxycoumarin **2** (Figure S5). Approximately 98% of the theoretical yield of hydroxycoumarin **2** is released over about 6 h (Figure 2d). The conversion of furfuryl carbonate **1** and the generation of hydroxycoumarin **2** follow exponential decay under these conditions with the reaction half-life estimated from NMR measurements to be $t_{1/2} = 79$ min. We note that decomposition of furfuryl carbonate **1** occurs even faster in a water/acetonitrile mixture ($t_{1/2} < 10$ min), indicating the potential of this system for molecular release in aqueous environments (Figure S6).

Having identified a suitable furfuryl carbonate structure for small molecule release we next set out to synthesize a furan-maleimide Diels-Alder adduct and incorporate it into a polymer to study its mechanochemical behavior. Polymers containing a chain-centered mechanophore are mechanically activated in solution using ultrasonication, which produces elongational forces that are maximized near the chain midpoint.² Furan-maleimide adduct (\pm)-**4** equipped with two α -bromoester initiating sites and a modular alcohol functional group for cargo attachment was prepared on gram scale in four steps from commercially available reagents (Scheme 2, see the SI for details). Starting from a racemic mixture of α -methylfurfuryl alcohol resulted in four diastereomeric Diels-Alder adducts. Although both *endo* and *exo* isomers exhibited mechanochemical reactivity in an initial screening as expected from previous studies of furan-maleimide mechanophores,²³ here we focus on one particular *endo* racemate shown in Scheme 2. The absolute configuration of the Diels-Alder adduct was confirmed by single crystal X-ray diffraction. Precursor (\pm)-**4** was converted to

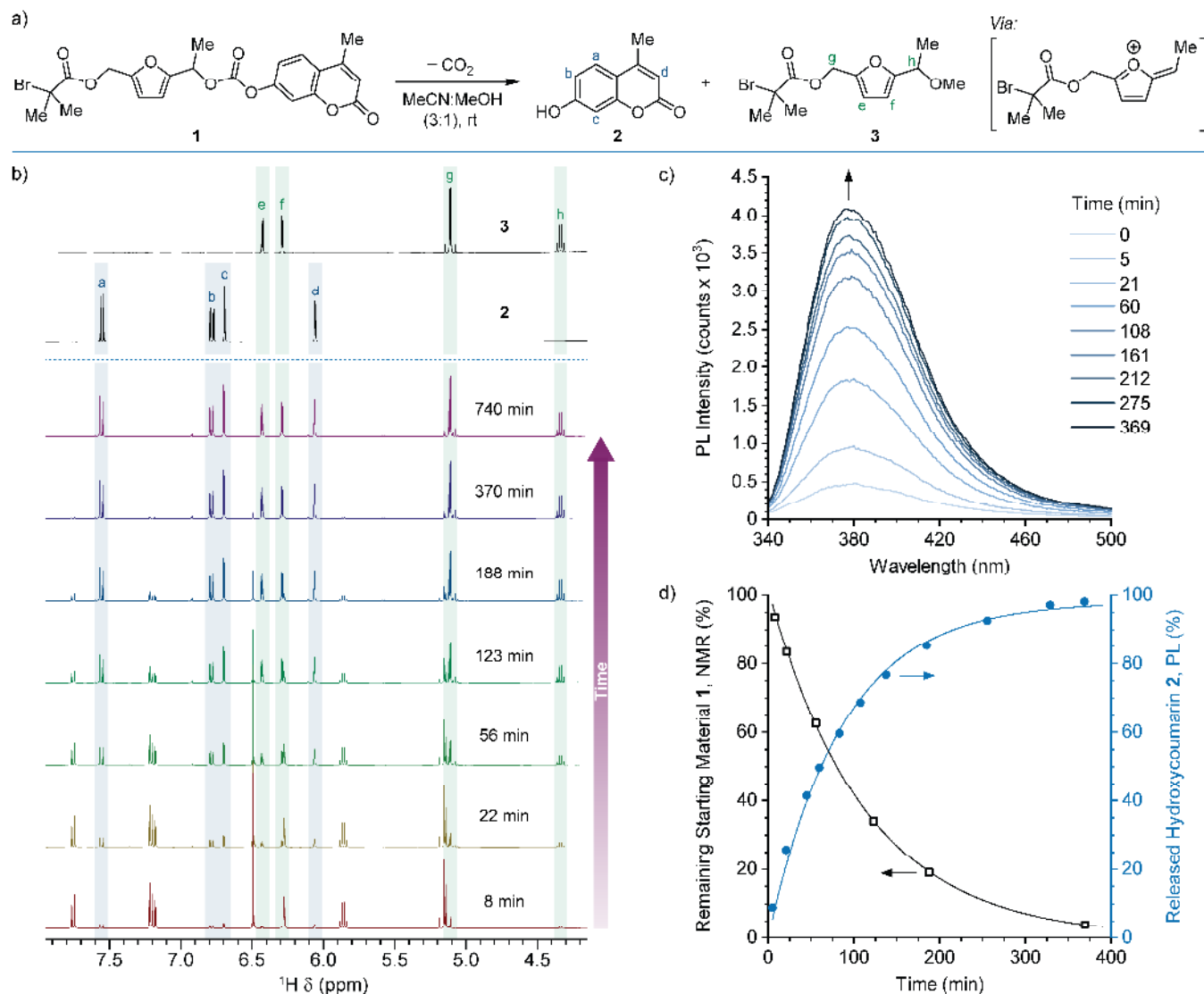
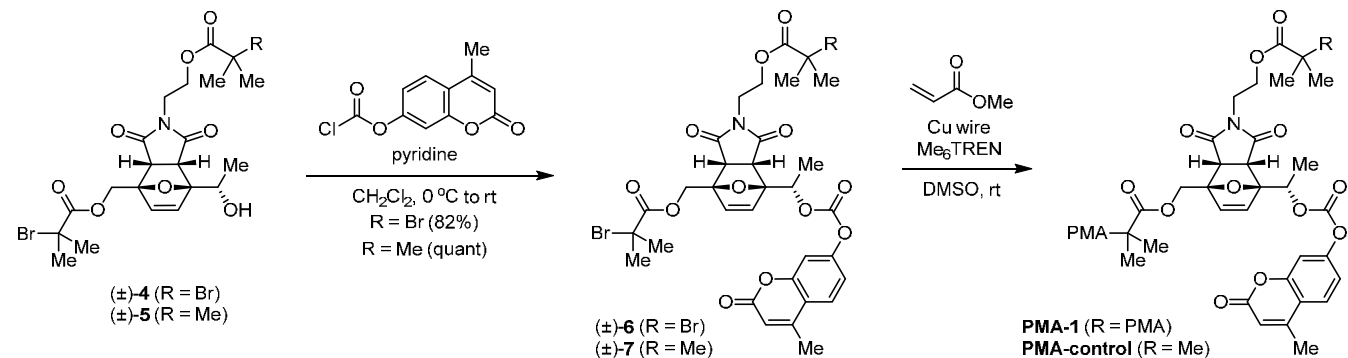


Figure 2. Characterization of the room temperature decomposition reaction of furfuryl carbonate **1**. (a) Decomposition of **1** in 3:1 MeCN:MeOH generates fluorescent hydroxycoumarin **2** and furfuryl methyl ether **3** via a putative furfuryl cation intermediate. (b) ¹H NMR spectra (3:1 MeCN-*d*₃:MeOH) demonstrating the clean conversion of **1** to products ($[1]_0 = 12$ mM). (c) Photoluminescence spectra ($[1]_0 = 6.1$ μM in 3:1 MeCN:MeOH, $\lambda_{\text{ex}} = 330$ nm) monitoring the generation of hydroxycoumarin **2** over time. (d) Quantification of data from panels b and c illustrating the time-dependent conversion of furfuryl carbonate **1** and the generation of hydroxycoumarin **2** as measured by NMR and fluorescence spectroscopy, respectively.

mechanophore bis-initiator (\pm)-**6** via installation of the fluorogenic coumarin payload by reaction with the corresponding chloroformate, and then subsequently employed in the controlled radical

polymerization of methyl acrylate using Cu wire/Me₆TREN in DMSO to afford the chain-centered polymer **PMA-1** ($M_n = 100$ kg/mol; $D = 1.06$). Chain-end functional control polymer **PMA-**

Scheme 2. Synthesis of Poly(Methyl Acrylate) (PMA) Containing a Chain-Centered Mechanophore Equipped with a Fluorogenic Coumarin Probe and a Chain-End Functional Control Polymer.



control ($M_n = 86$ kg/mol; $D = 1.14$) was synthesized similarly starting from (\pm)-**5** containing a single α -bromoester initiating group (see the SI for details).

Mechanically triggered molecular release from **PMA-1** was evaluated using pulsed ultrasonication (1s on/2s off, 0 °C, 20 kHz, 8.2 W/cm²) in the same polar protic solvent mixture employed in the small molecule model studies (3:1 MeCN:MeOH). Aliquots were periodically removed from the sonicated polymer solution and measured with gel permeation chromatography (GPC) to determine changes in molecular weight and fluorescence spectroscopy to monitor the generation of hydroxycoumarin **2** (Figure 3). The M_n decreased steadily over 150 min of ultrasonication, with the GPC chromatograms exhibiting characteristic features of midchain scission (Figure 3a and Figure S7). Photoluminescence measurements also showed a predictable increase in intensity indicating the successful release of hydroxycoumarin **2**, reaching approximately 64% of the theoretical yield after 150 min (Figure 3a). By fitting

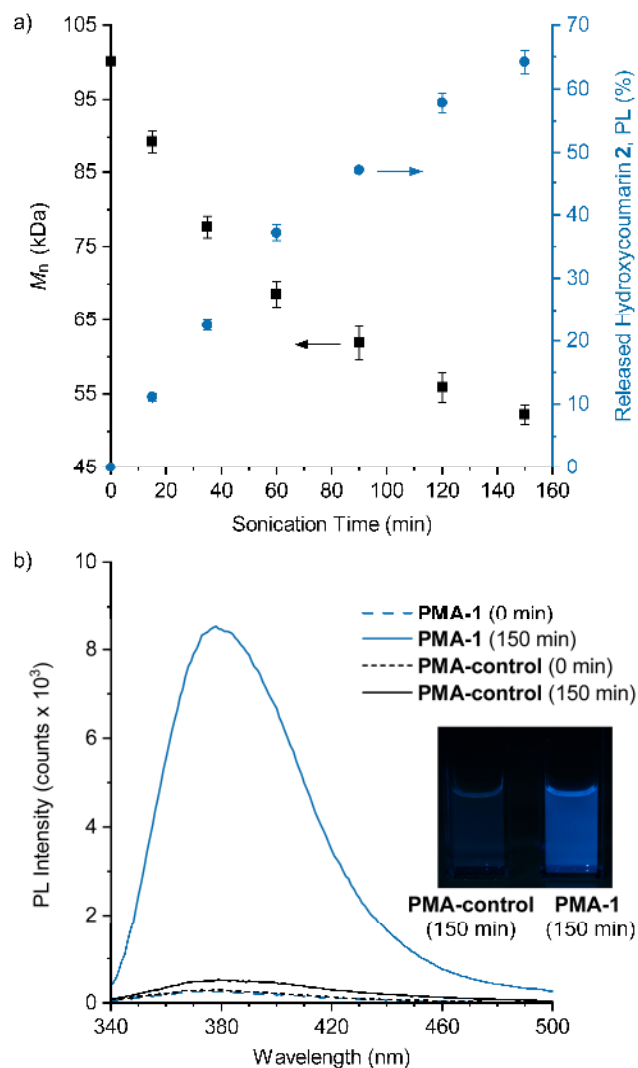


Figure 3. Characterization of mechanically triggered small molecule release. (a) Time-dependent evolution of number-average molecular weight (M_n) monitored by GPC-MALLS and release of hydroxycoumarin **2** monitored using fluorescence spectroscopy for **PMA-1** subjected to ultrasound-induced mechanochemical activation (2 mg/mL polymer in 3:1 MeCN:MeOH). $\lambda_{\text{ex}} = 330$ nm. (b) Fluorescence spectra of **PMA-1** and **PMA-control** before and after ultrasonication for 150 min. The inset shows photographs of sonicated solutions excited with 365 nm UV light after 6x dilution and addition of 5% water.²⁵ Error bars represent standard deviation from three replicate experiments.

the time-dependent PL data to a first-order rate expression, the extent of release is projected to plateau at a maximum value of approximately 87% (Figure S8). The reduced efficiency compared to the small molecule decomposition study likely stems from the inherent competition between mechanophore activation and nonspecific chain scission, resulting in part from a distribution in the position of mechanophores in the polymer backbones.²⁶ The fluorescence data presented in Figure 3 was acquired after incubating each aliquot at room temperature for approximately 20 h to ensure complete decomposition of the mechanically generated furfuryl carbonate. However, PL measurements taken immediately after sample removal from the sonicated solution exhibit appreciable fluorescence, indicating that a significant degree of release occurs quickly even at lower temperatures (Figure S9). Importantly, chain-end functional control polymer **PMA-control** subjected to the same ultrasonication conditions exhibits negligible changes in fluorescence compared to **PMA-1** (Figure 3b). These results indicate that ultrasound-induced release of hydroxycoumarin **2** from **PMA-1** is indeed a mechanically triggered cascade reaction process.

In summary, we have demonstrated a mechanophore platform for release of small molecules via a mechanically triggered cascade reaction. The strategy relies on the mechanochemically activated retro-Diels–Alder reaction of a furan–maleimide adduct, which reveals a latent furfuryl carbonate that subsequently decomposes in polar protic solvents to release a covalently bound cargo molecule. The computationally guided design of a reactive α -methylfurfuryl carbonate enabled small molecule release via a well-defined decomposition reaction that proceeds efficiently under mild conditions. Ultrasound-induced mechanical activation of a chain-centered furan–maleimide mechanophore loaded with a fluorogenic coumarin probe illustrates the power of this approach for a wide range of mechanically triggered cascade reactions. We anticipate that this general strategy will be useful for the mechanically triggered release of functional molecules in drug delivery, stress sensing, depolymerization, and other applications.

ASSOCIATED CONTENT

Supporting Information

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

Experimental details, synthetic procedures, DFT calculations, GPC chromatograms, fluorescence data, NMR spectra, and crystallographic data (PDF).

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Notes

The authors declare no competing financial interests.

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