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Successive Mechanochemical Activation and Small Molecule Release in an Elastomeric Material

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Supporting Information

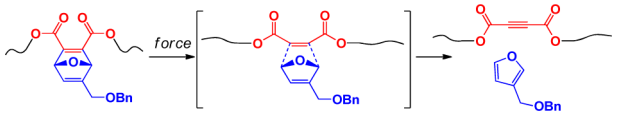
ABSTRACT: We have developed a mechanochemically responsive material capable of successively releasing small organic molecules from a cross-linked network upon repeated compressions. The use of a flex activated mechanophore that does not lead to main chain scission and an elastomeric polyurethane enabled consecutive compressions with incremental increases in the % mechanophore activation. Additionally, we examined the effect of multiple applications of compressive stress on both mechanophore activity and the mechanical behavior of the elastomeric matrix in which the mechanophore is embedded.

Advancements in polymer mechanochemistry have given rise to exciting new capabilities in areas including drug delivery, catalysis, sensory materials, and self-healing systems.[1] In particular, the development of mechanophores that react in the solid state (e.g., when incorporated into cross-linked networks) provides an entryway into materials capable of bearing load and responding to the physical stress with precise chemical output.[2−7] This is an attractive feature for materials designed for the release of therapeutics, catalytically active species, cross-linking agents, or other functional small molecules.[8]

One limitation of most mechanoresponsive materials that have been demonstrated, however, is that a single application of stress sufficient for mechanochemical activation results in macroscopic failure or permanent deformation, thus irreversibly altering the material or precluding additional cycles of mechanochemical transduction. One exception, recently reported by Craig and co-workers,[3c] involved mechanochemical activation of *gem*-dihalocyclopropanes embedded within poly(butadiene). Compression of the material up to 12 times resulted in a linear increase in the % activation of mechanophores, ultimately reaching 2.8%. Additional studies to correlate the load history and extent of mechanochemical activation, combined with a mechanophore able to release small molecules, could enable advancements in the areas described above. Challenges to developing such materials include the need to balance the force required to activate the mechanophore with that which results in macroscopic failure, and the incorporation of a mechanophore that can release the desired small molecules. Thus, we consider the primary design components of a mechano-responsive release platform to be (a) minimal change in the mechanical and material properties of the bulk matrix upon application of sufficient force and (b) release of the desired species in a manner that does not inherently degrade the macromolecular architecture.

We recently reported a mechanophore that has the unique capability of releasing a small organic molecule upon application of mechanical force (Scheme 1).[6] The mechanophore features an oxanorbornadiene that undergoes "flex activation," in which bond bending motions directed by the application of mechanical stress led to the scission of bonds orthogonal to the polymer backbone via retro-[4 + 2] cycloaddition. Our initial studies centered on examination of the mechanochemical activity of oxanorbornadiene mechanophores within cross-linked poly(methyl acrylate) (PMA) networks. Unfortunately, the compressive force necessary for mechanochemical transduction led to macroscopic failure of the sample. As a result, the amount of activated mechanophore was limited to that achieved in a single compression, and the relative inability of the polymer matrix to withstand mechanochemically relevant pressures limits its use in practical applications. Adaptation of this system to an elastomeric scaffold able to recover its initial shape after experiencing forces necessary for activation would enable multiple compression−activation cycles, thereby increasing the conversion of mechanophores in a dose-responsive fashion.

Scheme 1. Generalized Flex Activation in an Oxanorbornadiene-Based Mechanophore



To obtain a material with a lower elastic modulus than the cross-linked PMA networks previously employed, we incorporated the flex activated mechanophore into an elastomeric segmented polyurethane network. These networks comprise flexible polyether segments joined by short, hard diisocyanates and diol chain extenders, resulting in the phase separation between hard and soft segments responsible for their superior strength and elasticity.[9] Toward this end, diol **1** was first reacted with an excess of methylene diphenyldiisocyanate (MDI) to form a diisocyanate-capped mechanophore (Scheme 2). Polymerization and cross-linking were effected via addition of dihydroxy-terminated poly(ethylene glycol) and triol **2** to the reaction mixture, resulting in full gelation of the network

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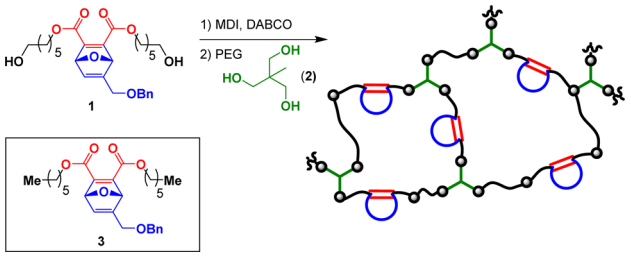
Scheme 2. Synthesis of Polyurethane Networks



within 48 h. After curing at 30 °C, solid materials were obtained with a mechanophore concentration of 6.7 wt % (0.13 mmol of mechanophore **1** per gram of material), based upon the feed ratios. Analysis of soluble noncross-linked (i.e., linear polymers) systems revealed excellent mechanophore stability during polymerization and curing (see Supporting Information). A control system was also prepared, in which mechanophore chain extender **1** was replaced by 1,6-hexanediol and mechanophore **3** was physically adsorbed into the material, thus enabling determination of the mechanical (as opposed to thermal or pressure-induced) activation.

The mechanochemical reactivity of each network cured at 30 °C was evaluated by subjecting each to compression in a hydraulic press at sustained pressures as indicated in Figure 1.

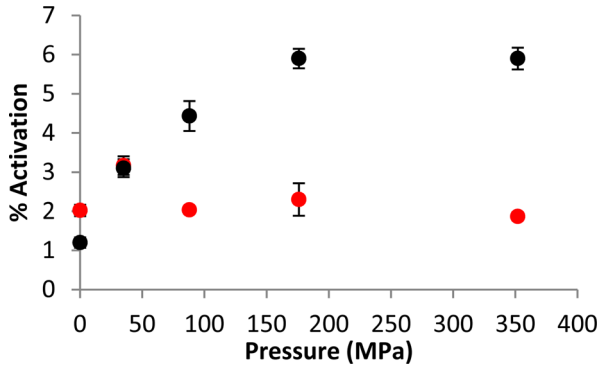


Figure 1. Plot of applied pressure versus activation of cross-linking (black) and control (red) mechanophore, as judged by GC-MS analysis of soak solutions after compression. Error bars represent standard deviations.

After 1 min of sustained stress, the sample was placed in CH_2Cl_2 to facilitate the diffusion of released small molecules. The CH_2Cl_2 solutions were then analyzed by GC-MS in the presence of an internal standard. Without applied stress, only a small amount of benzyl furfuryl ether was observed in the soak solution, corresponding to activation of roughly 1% of the incorporated mechanophores. As the pressure was increased in each subsequent experiment using fresh samples of the polyurethane material, we observed a monotonic increase in the % activation of the cross-linked mechanophore up to 176 MPa of applied pressure. At higher pressures, we observed consistent % activation but no additional increase. Importantly, the control network only gave ca. 2% activation, and we observed no increase in the % activation with increasing pressure. Collectively, these results confirmed the mechanical origins of the cycloreversion reaction.

We next explored the feasibility of using multiple compressions to achieve iterative increases in the % mechanophore activation from the same sample of material. Samples were compressed at 35 or 88 MPa for 1 min, and pressure was then released to reveal a flattened disc-like material. The sample was then folded before being subjected to another 1-min compression.[3c] The process, including folding between compressions, was repeated for each fresh sample until the target number of compressions was reached, at which point the sample was soaked in CH_2Cl_2 and the soak solution was analyzed by GC-MS. As shown in Figure 2, we observed a

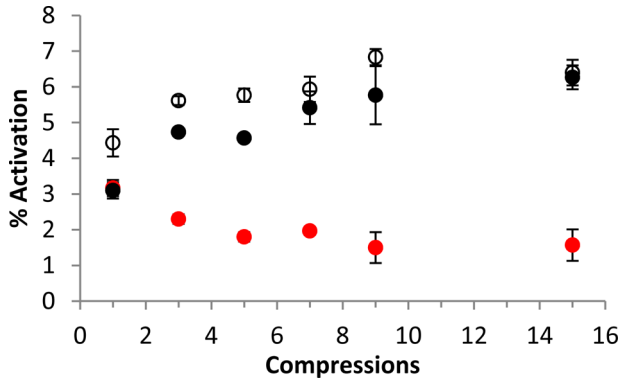


Figure 2. Plot of % activation of mechanophores versus number of successive compressions (1 min each) at 35 (●) and 88 MPa (○). Control network (red) was compressed at 35 MPa. Error bars represent standard deviations.

discernible positive correlation between the number of compressions and the % activation. The amount gained with each compression began to diminish, which we speculate is likely due to a strain softening effect (see below) that continued with the increasing number of compressions. For compressions at either 35 or 88 MPa, increases in activation were apparent up to 9 compression−activation cycles, reaching a maximum of 6−7% activation. This suggested to us that once a sufficient load history was imposed to cause this maximum % activation, the material had softened to the extent that additional mechanophore activation could not be achieved. In comparison, however, no increase in % activation was observed for >1 compression when using the previously reported PMA networks or the polyurethane control networks containing **3**.

To investigate the effects of load history on the physical properties of the material, we measured the flexural modulus after increasing numbers of compressions on the same sample.[10] These larger rectangular samples were not folded between compressions. Shown in Figure 3 are representative examples of the % of initial flexural modulus versus number of compressions at 35 and 88 MPa. As expected, the material softened more quickly under higher load (88 MPa), reducing to 68% of the initial flexural modulus after just one compression. For comparison, at 35 MPa the material retained 68% of its initial flexural modulus for up to nine compressions. In segmented polyurethanes, strain softening is generally attributed to the breakup of hard domains in response to applied force.[11,12] A possible explanation for the observed upper limit of mechanophore reactivity lies in both the random scission of chemical cross-links and destruction of the physical cross-links provided by hard domains. As previously reported, the mechanochemical reactivity of the oxanorbornadiene is directly related to cross-link density,[6] and it is possible that the lower limit of cross-link density sufficient for mechanochemical activation has been reached after strain-induced softening by ca. 30%.

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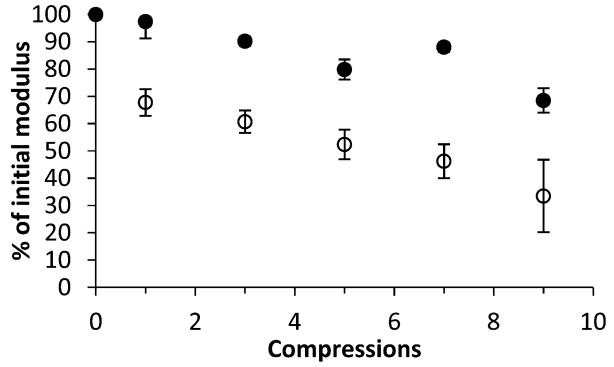

Figure 3. Changes in measured flexural modulus after compressions at 35 (●) and 88 MPa (○), plotted as percent of modulus of initial, uncompressed material. Error bars represent standard deviations.

Despite softening, a single sample of material clearly resisted permanent physical deformation even after multiple compressions, as shown in Figure 4. Notably, it has been demonstrated

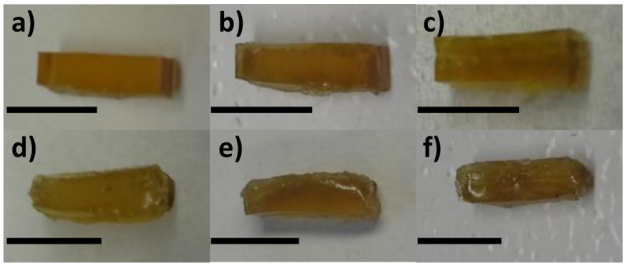

Figure 4. Polyurethane material after compressions at 35 MPa. (a–f) Images that were taken after 0, 1, 3, 5, 7, and 9 compressions, respectively, of the same sample piece. Scale bars = 5 cm.

that more efficient mechanochemical activation is associated with plastic deformation of the bulk material,[2a,e] a limit not reached under our experimental conditions as judged by the nearly identical physical measurements of samples when subjected to repeated compressions (see Supporting Information). Thus, the conditions experienced by the mechanophores may not be optimal for reaching high levels of activation; yet, a sequential increase in small molecule release was still achievable.

In summary, we have demonstrated the ability to use elastomeric polyurethane scaffolds combined with a flex activated mechanophore to achieve the force-activated release of small molecules over multiple load cycles. Mechanical analysis of the compressed material revealed the ability of the bulk polymer matrix to maintain its elasticity and shape after the application of force sufficient for mechanophore activation. This advancement is an important step toward realizing force-coupled capabilities, including reloadable sensory materials, refillable reservoirs of therapeutics or catalysts, and composites capable of healing fractures from repeated, low-level stresses.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization of all new compounds, physical dimensions of compressed samples, images of PMA networks before and after compression. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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