

Mechano-Activated Self-Immolation of Hydrogels via Signal Amplification

Claudius Lupfer, Sebastian Seitel, Oliver Skarsetz, and Andreas Walther*

Abstract: Cellular organisms possess intricate mechano-adaptive systems that enable them to sense forces and process them with (bio)chemical circuits for functional adaptation. Inspired by such processes, this study introduces a hydrogel system capable of mechanically activated and chemically transduced self-destruction. Our judiciously designed hydrogels can mechanically generate radicals that are processed and amplified in a self-propagating radical de-crosslinking reaction, ultimately leading to mechanically triggered self-immolation. We put such systems to work in mechano-induced debonding, and in a bilayer actuator, where swelling-induced bending generates sufficient force for selective degradation of one layer, leading to autonomous self-regulation associated with unbending. Our work helps define design criteria for molecularly controlled adaptive and self-regulating materials with embodied mechano-chemical information processing, and showcases their potential for adhesives and soft robotics.

Sensing mechanical forces and adapting the functional state through precise molecular mechanism is a key domain of cellular mechano-adaptation.^[1] Mechano-adaptation typically occurs from two primary components, a force-sensing module and a coupled functional entity, e.g., the cytoskeleton, to which the force sensing event is transduced. Signal amplification often plays a key role to transduce and amplify few force-sensing events to a tangible functional outcome. Synthetic systems able to undergo transformations in response to mechanical forces have been known since the discovery of macromolecules.^[2] However, the design of synthetic materials with elaborate mechano-sensitivity to precisely engineer force detection and response has only recently become a viable option.

To this end, mechanochromic materials, which change their optical properties when mechanically actuated, have attracted considerable attention in recent years. These

materials serve various purposes, including monitoring structural integrity^[3,4] and sensing complex mechanical processes like cell/matrix interactions.^[5] A major challenge in the field of mechano-sensitive materials is to go beyond reporting of mechanical force and to use the mechano-activated system for distinct downstream processes. For instance, mechanical tension was used for the activation of functional groups,^[6] for drug release,^[7,8] or for transforming a non-conducting polymer to a semi-conducting one,^[9] thus granting a new functional property through the adaptation to a signal. Azo-compounds have emerged as reliable tool to generate mechanoradicals.^[10,11] In terms of mechanical effects, self-reinforcing hydrogels have been reported that polymerized a highly cross-linked network upon repeated mechano-radical generation using embedded monomers.^[12] To predict the correct reactivity and required forces to break mechanophores, Constrained Geometries Simulated External Forces (CoGEF) has been proven as a valuable tool.^[13,14]

One of the important aspects towards generating mechano-induced downstream effects is to consider how few mechano-events can be translated to many using signal processing networks in the context of global functional adaptation processes. To this end, important progress has been made in connecting chemical circuits to regulate materials, e.g., with transient life-cycles, or for transducing signals in materials.^[15-26]

Herein, we introduce a hydrogel system capable of complete auto-destruction by a mechano-activated self-immolation mechanism that uses a signal amplification scenario. The system uses radical-addition-fragmentation-chain-transfer (AFCT) to convert a single mechano-radical event into multiple chain breakage events. We will demonstrate how these events can be used for functional adaptation at the level of materials systems for pressure-induced debonding of adhesives as well as for self-regulating soft robotic devices.

Our hydrogel system is composed of dibenzocyclooctyne-terminated 4-arm star-poly(ethylene glycol) (PEG-DBCO, $M_n = 20 \text{ kg mol}^{-1}$, arm length = 113 units) that are crosslinked at the overlap concentration ($c = 62 \text{ g/L}$) with mixtures of azide-terminated diazo linkers (azoCL) and allyldithioether linkers (ADTE) via strain-promoted azide-alkyne click reaction (SPAAC) (Figure 1a). AzoCL was used for its ability to undergo specific homolytic cleavage upon mechanical strain, whereas ADTE has the capability to propagate the radical signal in the presence of free small molecule thiols, leading to an amplified self-immolation process.

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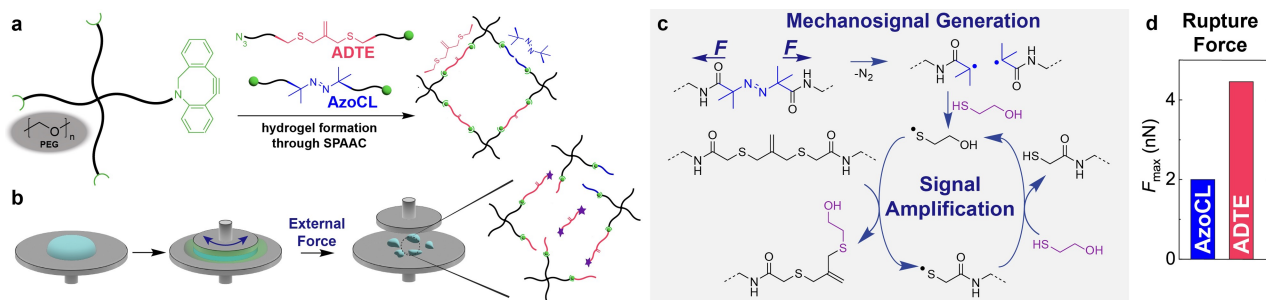


Figure 1. Design and mode of operation of mechano-immolative hydrogels. (a) Hydrogel formation using DCBO-functionalized star-PEG, and diazide terminated allyldithioether- (ADTE) and diazoalkane-based (azoCL) crosslinkers. (b) Experimental approach for measuring the degradation of mechano-immolative hydrogels via plate-plate oscillatory shear rheology. (c) Mechanism of immolation: Generation of mechano-radicals and subsequent signal amplification and concurrent network degradation through an addition-fragmentation chain transfer mechanism (AFCT) in the presence of a small molecule thiol, ME. (d) CoGEF calculations of the rupture forces for the two crosslinkers shows preferred breakage of azoCL.

Figure 1c displays mechanistic details of the mechano-signal generation and subsequent signal amplification. Initially formed mechano-radicals can undergo hydrogen transfer to the incorporated mercaptoethanol (ME), resulting in the formation of thiyl radicals. Both the carbon radicals and the thiyl radicals can react with the ADTE linker. Through a series of thiol-ene additions in the presence of thiyl radicals, the network undergoes rapid chain breakage. Each thiol-ene addition consumes one thiyl radical and generates another, leading to the conversion of the ADTE from a crosslinked state to a non-crosslinked state while generating a thiyl radical bound to the network. This cyclic process involves the repeated occurrence of thiol-ene addition and chain transfer from the released network thiyl to a free thiol, resulting in the replacement of crosslinking ADTEs with their non-crosslinking counterparts. We incorporated azoCL to ensure facile mechano-radical formation. CoGEF calculations indeed show that the force required to cleave the azoCL is 2.0 nN, which is lower than the 4.5 nN required for cleaving the ADTE (Figure 1d). This indicates preferential mechano-activation at the azoCL.

We used oscillatory shear rheology to monitor the gelation as well as the mechano-immolation (Figure 1b). Gelation of these hydrogel mixtures takes place rapidly at room temperature. The gel point, as defined as the crossover of the storage (G') and loss (G'') modulus, occurs typically within 20 seconds after mixing (ca. 10 s after placing it into the rheometer) and the gels reach a final G' of 2–4 kPa after ca. 10 minutes (Figure S1).

In terms of mechano-adaptive behavior, rheology allows to generate significant insight into the mechano-immolation process as a function of (i) the strain amplitude (γ), (ii) the auxiliary agent needed for signal amplification (ME), and (iii) the ratio of signal generator to signal transducer (ADTE:azoCL). Plotting the relative loss of G' by normalizing to G'_0 (at time=0) is an efficient way to describe the time-dependent and shear-induced mechano-immolative behavior. We considered a drop to 10% of G'_0 as the endpoint for comparing the time frame of the processes.

The first important parameter to consider is the strain amplitude used during the oscillatory rheology (Figure 2a). Hydrogels containing a ratio of ADTE:azoCL=9:1 (total

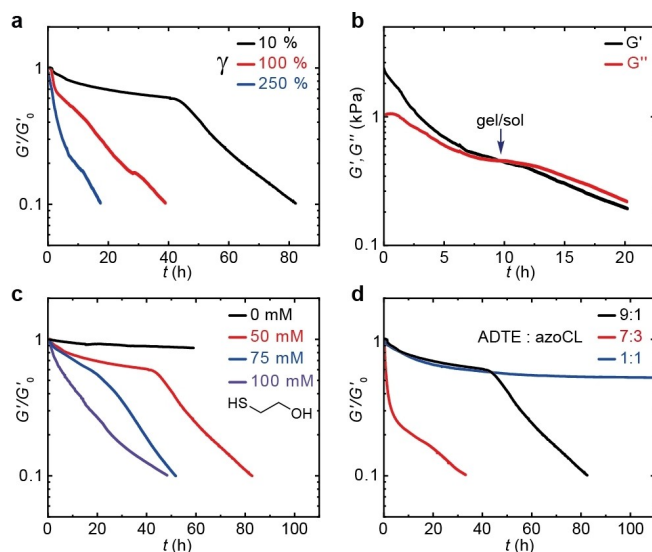


Figure 2. Rheological analysis of mechano-induced disintegration of hydrogels. (a) Screening of strain amplitude γ . (b) G'/G'' crossover and gel-to-sol transition during mechanoimmolation at $\gamma = 250\%$. (c) Influence of ME concentration. (d) Influence of the ratio of azoCL:ADTE. Unless otherwise specified: $\gamma = 10\%$, angular frequency = $1 \text{ rad}\cdot\text{s}^{-1}$, 6.2 wt% PEG-DBCO, 50 mM ME, ADTE:a-azoCL=9:1.

concentration of both linkers=6.8 mM) and 50 mM ME clearly show a quicker self-immolation for larger strain amplitudes. A strain amplitude of 250%, which is close to the yield point of the gel (Figure S2), leads to a twofold and fourfold faster immolation compared to strain amplitudes of 100% and 10%, respectively (Figure 2a). This can be explained by the fact that larger amplitudes exert more tension inside the hydrogel network and lead to larger fractions of bond rupture to initiate the self-propagating auto-immolation. The clear G'/G'' crossover during the mechano-immolation confirms the occurrence of a gel-to-sol transition and liquification during the process (Figure 2b).

Additionally, the presence and the concentration of ME is critical to the occurrence and speed of immolation (Figure 2c). Most importantly, mechano-degradation is com-

pletely absent when no ME is present. This confirms that the plain activation of some mechanoradicals during shearing is insufficient for a material response, but the signal amplification mechanism needs to be present. A continuous increase of ME from 50, 75, to 100 mM leads to an acceleration of the auto-immolation process proportional to the ME concentration.

A variation of the ratio of mechano-labile azoCL to immolative ADTE sheds important details on their functions (Figure 2d). For azoCL:ADTE=1:1—a system containing 5 fold more azoCL as compared to our standard system above— G' converges to only about 50 % of G'_0 . This suggests that the azoCL bonds are largely preserved during the radical-induced degradation, or at least undergo less facile radical-induced breakage compared to the ADTE units. This sets a limit for how many mechanolabile azoCL units can be implemented to still allow for efficient degradation based on small forces to fall below the percolation threshold of the network. However, the initial rate of degradation is roughly 10-fold faster when 30 % of radical-forming azoCL is employed compared to the standard conditions of 10 % azoCL (Figure 2d), whereas the total extent of degradation is similar as seen in the same total drop of G'/G'_0 . These non-linear correlations originate from differences in chemical susceptibility to degrade during the signal transduction and also from the different extents of mechano-activation as the gels soften during the immolation process.

Next, we will demonstrate how these mechano-immolation processes can be leveraged to create new functionalities in application settings for self-regulating soft robotic elements and mechano-induced debonding of adhesives. We first focus on a self-regulating soft robotic element by building a bilayer system composed of one layer of our mechano-immolative gels combined with one layer of a highly swelling polyelectrolyte (PE) layer based on poly(2-acrylamido-2-methylpropane sulfonic acid) (pAMPS; Figure 3a; please see Movie S1 for a synchronized depiction). We hypothesized that the rapid swelling of the PE layer would dominate the swelling of the system and that the resulting bending would induce sufficient force to initiate the mechano-immolation that would eventually destroy the mechano-immolative gel layer. This in turn would remove the bilayer geometry needed for actuation itself.^[17,27]

We first predicted force generation and the whole self-regulation process through finite element (FE) simulations (Figure 3b–d). Figure 3b describes the input parameters. These are (1) rapid volume expansion of the PE layer, and (2) continuous loss of the mechanical stiffness (E) of the mechano-immolative layer (details in Supporting Information). The simulations use the measured elastic moduli and the measured swelling behavior of the PE layer as inputs. The FE simulations predict a bending due to the PE layer swelling, and finally an unbending of the device due to loss of mechanical consistency in the mechano-immolative layer (Figure 3c). Most interestingly, we can learn something about the stress/force concentration in the device. The maximum force is exerted at the interface between the rapidly swelling PE layer and the rather non-swelling

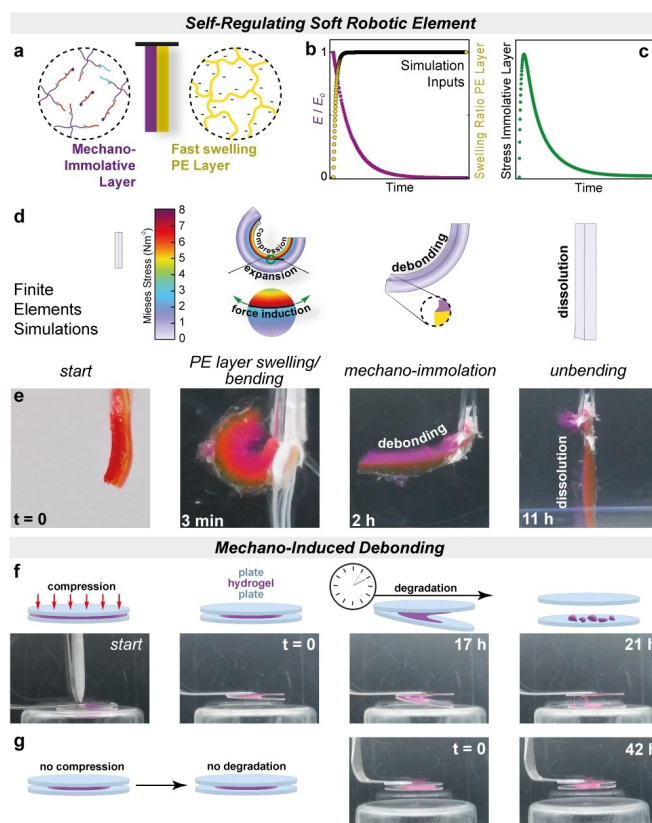


Figure 3. Functional material concepts using mechano-immolative hydrogels. (a) A self-regulating soft robotic bilayer element composed of a mechanoimmolative gel (6.2 wt% sPEG-DBCO; ADTE: a-azoCL=9:1, stained by incorporation of trace amounts of a fluorescent polymer) and a PE layer (25 wt% pAMPS crosslinked using methylene bis-acrylamide in a ratio of 30:1, stained with traces of fluorescein acrylate). (b) Finite element (FE) simulation inputs: (1) Swelling of PE layer, (2) exponential decrease of elastic modulus E of the mechano-immolative layer. (c) Computed Mises stress close to the interface in the mechano-immolative layer. (d) Snapshots of FE simulations of bilayer bending and unbending. (e) Experimental observation when immersing a bilayer (as prepared) into PBS buffer (pH = 7.4, 0.01 M phosphate, 0.138 M NaCl, 0.138 M KCl, at 50 mM ME), to trigger PE swelling. Bilayer bending due to swelling and subsequent unbending due to mechano-immolation, debonding, and dissolution of the mechano-immolative layer (see also Movie S1). (f) Pressure-triggered debonding of a mechano-immolative gel (6.2 wt% PEG-DBCO; ADTE: azoCL=9:1, 50 mM ME; stained by incorporation of trace amounts of a fluorescent polymer) after compressing the plate for 5 sec with forceps. (g) Control experiment shows no debonding in absence of mechanical triggers.

mechano-immolative gel layer. Compression at the top surface also occurs, but this is not the concentration point of maximum force. At the fully bent state, the mechano-immolative layer experiences maximum stress (Figure 3c,d).

The experimental implementation of the device conforms to the simulations but reveals additional features (Figure 3e). The bilayer indeed undergoes rapid bending due to the excessive swelling of the PE layer when the as-prepared bilayer is placed into PBS buffer (pH = 7.4). The difference in swelling between both layers leads to a high stress at the interface, which initiates the mechano-immola-

tion process. As time goes by, degradation proceeds, G' of the immolative layer drops, and the bilayer bends back towards a fully straight state. Interfacial debonding and even dissolution of this layer can be observed in the experiments (which however cannot be simulated). Additionally, during the relaxation process, the tip of the bilayer shows a distinct difference in swelling in both experiments and simulations, which again confirms the predominant buildup of stress at the interface of the two layers due to different swelling ratios (see circle highlight in Figure 3d). Since the whole concept of hydrogel bilayer bending requires the buildup of different swelling degrees at comparable mechanical stiffness of both layers,^[17,27] the relaxation confirms the loss of mechanical consistency in the mechano-immolative layer.

To further demonstrate system disintegration under external force in a different application setting, we constructed a pressure-sensitive adhesive element using a mechano-immolative hydrogel sandwiched between two glass plates. Upon compression and activation (strong compression for 5 sec with forceps), the hydrogel adhesive slowly debonds, leading to release of the lower glass plate (Figure 3f). In comparison, the same element without a pressure trigger exhibits no debonding and remains intact (Figure 3g). This demonstrates a simple on-demand mechano-debonding system.

In conclusion, we have introduced a mechano-adaptive hydrogel system that can sense small forces using specific azoCL units and transduce few force-triggered events into complete degradation using a signal amplification process brought about by the ADTE units in combination with an auxiliary thiol. We showed the critical importance of both components for the signal amplification process as mechano-immolation is absent if no auxiliary thiol is present, as well as the importance of mechanical strain to accelerate the behavior. Moreover, we demonstrated two different application scenarios for mechano-adaptive functions: self-regulating soft robotic elements, where actuation in one direction automatically triggers reverse actuation, and mechanically induced debonding for pressure-sensitive adhesives. We believe that the concepts underpinning this work are important for the future development of more autonomous materials systems with life-like functionalities. Ample opportunities exist to increase the capacity of the presented concept. While the small molecule was still present as an auxiliary agent, one can conceive to embed it covalently in future hydrogel systems, and even an operation in rubbery bulk materials may be possible. Additionally, more precise force sensing units could allow to engineer thresholds for when mechano-immolation is triggered, and more advanced signal-processing chemistries could speed up the processes.

Supporting Information

The authors have cited additional references within the Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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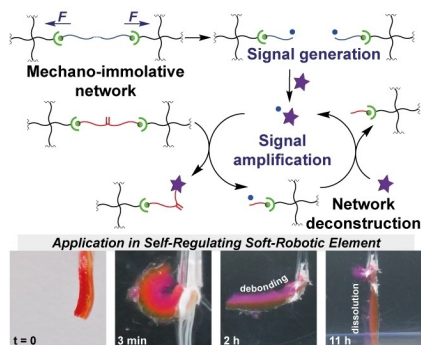
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Communications

Mechanochemistry

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Mechano-Activated Self-Immolation of Hydrogels via Signal Amplification



This study presents a hydrogel system that self-destroys after mechanical activation via the combination of a mechano-to-chemo signal translation and a chemical signal amplifier module to trigger many chain breaks following one single mechano event. Self-regulating soft robotic elements and mechano-induced debonding in adhesives can be realized.