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Moving mechanochemistry forward: programming force-induced responses into macromolecular systems

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Introduction

The action of mechanical force on polymer chains leads to covalent bond scission and polymer degradation. Staudinger and Heuer already realized this in 1934 and their insight remains highly relevant today, especially when considering the impetus to recycle commodity polymers.[1,2] The development of the concept of a mechanophore in contemporary polymer mechanochemistry has substantially improved the selectivity and increased the rate of bond scission and has thereby facilitated the mechanical control over structural and functional transformations in macromolecular systems.[3] While force-induced bond scission is often the primary focus in synthetic polymers, biopolymers such as polypeptides and poly(nucleic acids) possess well-defined three-dimensional structures and biological activities that can be modulated by mechanical force. Alongside the wealth of synthetic mechanophores and mechanoresponsive biomolecules, several methods to exert mechanical force have been developed, ranging from ultrasonication,[4] ball milling,[5] and single-molecule force spectroscopy (SMFS)[6,7] to computational approaches.[8,9] They have critically informed the design of new force-reactive molecular motifs. This editorial addresses the central question of which chemical functionalities can be activated by mechanical force. Four significant areas of polymer mechanochemistry are highlighted for which molecular structure–mechanics relationships and precisely controlled force-induced reactions govern the mechanochemical reactivity of macromolecular systems.

Synthetic mechanophores for productive bond scission in polymers

The productive bond scission of a synthetic mechanophore leads to the generation of a functional entity that undergoes a further chemical reaction, aiding in the initiation of, for example, self-repair functions. Such chemically reactive entities can either be stoichiometric or catalytic in nature. Mechanically induced formation of stoichiometrically reactive species occurs when the force cleaves a mechanophore, generating radicals or other reactive intermediates that can subsequently react with the surroundings. This concept was first demonstrated by Moore and colleagues for an azo-containing poly(ethylene glycol) (PEG) chain that was activated by ultrasound to generate radicals, suggesting potential routes for self-healing in bulk materials.[10] Subsequent studies explored various mechanophores. Weng, Boulatov, and coworkers established spirothiopyrans that, upon activation, underwent ring opening to trigger thiol-ene reactions that are useful for crosslinking or grafting.[11] The combination of spirothiopyran and anthracene–maleimide Diels–Alder adducts then enabled force-controlled crosslinking to result in a color change.[12]

Beyond stoichiometric intermediates, mechanophore activation can also release or activate catalytic species, including organocatalysts, metal complexes, acids, bases, or even biocatalysts. Sijbesma and colleagues pioneered this approach, embedding latent metal-based catalysts into polymer chains that were activated by ultrasonication. For example, silver(I) complexes of N-heterocyclic carbenes (Ag-NHC) released active ligands for transesterification, while Ru-NHC complexes catalyzed ring-closing metathesis (RCM) and ring-opening metathesis polymerization (ROMP).[13] More recently, Herrmann and coworkers demonstrated enzyme- and DNAzyme-based mechanocatalysis where mechanical force released enzymes from inhibitory complexes or DNAzyme precursors from polyaptamers.[14,15] Together, these

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stoichiometric and catalytic technologies may enable the future synthesis of adaptable macromolecular materials with multifunctional responses and autonomous self-repair or self-immolation.[16,17]

Synthetic mechanophores for sensing force-induced events

When mechanophores undergo force-induced reactions that alter their optical properties, they become optical force probes (OFPs). These OFPs enable real-time or *post factum* visualization and quantification of bond scission across length and time scales. Using changes in absorption, fluorescence, or chemiluminescence, each method offers distinct advantages and limitations in sensitivity and resolution.[18,19] Even though detecting microscopic damage in polymers before catastrophic failure is still a major challenge, particularly in soft and brittle materials, it has been impressively demonstrated that OFPs allow bond scission events to be measured and correlated to the macroscopic and microscopic mechanical properties of the polymer material. Creton, Sijbesma, and colleagues pioneered this concept using multi-network elastomers, using chemiluminescent (thus transient) dioxetane-based OFPs to visualize the impact of sacrificial bonds on reactivity.[20] The utilization of quantifiable, high-resolution confocal laser scanning microscopy (CLSM) in conjunction with non-transient OFPs, such as anthracene–maleimide Diels–Alder adducts, enabled microscale imaging of fracture zones and bond scission in hydrogels and elastomers.[21–23] Quantitative mapping of strain and fracture behavior could even be achieved under extreme conditions such as rapid decompression[24] or cyclic loading in high-strain regions.[25]

Despite these compelling demonstrations of the power of OFPs, it remains technically difficult to perform *in situ* measurements where mechanochemical events are recorded in real time while deforming the sample on the microscope. One reason is that high-resolution CLSM objectives have a working distance of only a few micrometers, meaning that the sample must remain stable in the *z*-direction to maintain accurate focus during measurements. First attempts toward real-time monitoring of OFP activation events were carried out by the teams of Weder, Schrettl, and Clough.[26,27] While it is possible to measure the number of bond scission events, establishing a quantitative relationship between the macroscopic force exerted on the polymer and the microscopic force experienced by individual mechanophores remains difficult. Single-molecule methods that correlate an applied force with an optical signal have been used for calibrating OFPs,[6] yet methods for monitoring force distributions at the required spatial resolution directly within a material are still lacking. Nevertheless, the application of OFPs as analytical tools has significantly enhanced our quantitative understanding of polymer mechanics. OFPs have enabled precise strain mapping and energy dissipation analysis, sparking new developments toward improving the design of high-performance, damage-resistant polymers.

Biopolymers as mechanoresponsive molecules, mechanophores, and optical force probes

In contrast to synthetic polymers discussed above, biological macromolecules have unique, precisely controlled structures. They are monodisperse with precise sequence control and the ability to fold into complex, hierarchically organized, three-dimensional structures. These properties have been harnessed to design stimulus-responsive hydrogels whose mechanical responses are regulated at the molecular level. Li and coworkers pioneered the concept of folded protein hydrogels consisting of crosslinked protein domains.[28] These hydrogels exhibit tunable elastic moduli depending on the conformation of the proteins, *e.g.*, folded *versus* unfolded,[28] or ligand-free *versus* ligand-bound states.[29,30] Furthermore, the use of reversible protein–protein interactions as dynamic crosslinking motifs enables control over viscoelastic properties, such as stress relaxation.[31,32] These approaches highlight the unique molecular tunability of biological interactions and demonstrate how mechanical properties of bulk materials can be programmed through the responsive behavior of their biomolecular building blocks. As SMFS is applied to an increasingly diverse range of biological macromolecules, the library of structural motifs available as building blocks and crosslinking units with defined structure–mechanics relationships has grown substantially.

Both proteins and poly(nucleic acids) (DNA and RNA) have been developed into mechanophores, *e.g.*, for the force-induced dissociation and release of binding partners, or into OFPs. Release has been triggered by ultrasound[14,33–35] or upon stretching of hydrogels,[16] and a wide variety of interactions have been shown to be mechanosensitive, such as DNA duplexes,[35–37] aptamer–ligand interactions,[33,34] enzyme–inhibitor complexes,[14,16] as well as protein–protein interactions.[31] For example, Herrmann and coworkers crosslinked hydrogels with thrombin and its inhibitor hirudin.[16] After force-induced dissociation, thrombin catalyzed the polymerization of fibrin, thereby strengthening the hydrogel. In contrast, the hydrogel was softened when it contained thrombin-cleavable peptide crosslinks.

Current designs of biopolymer-OFPs frequently rely on DNA hairpins,[37,38] equipped with a Förster resonance energy transfer (FRET) reporter system, or on engineered fluorescent proteins.[14,39–43] For example, OFPs using fluorescent proteins exploit protein unfolding to switch off fluorescence and visualize damage at the fiber–matrix interface in composite materials.[40,41] As the deactivation of a small subset of fluorescent proteins in a large population of active ones can be difficult to detect, alternative designs use pairs of fluorescent proteins, or [pairs] of fluorescent proteins and organic fluorophores, to establish a FRET readout. Activated OFPs can then be discriminated from intact ones based on

their emission of donor or acceptor fluorescence. This more sensitive readout of OFP state has, for example, allowed for the visualization of fracture in a glassy polyacrylamide network[39] and for differentiating adhesive and cohesive failure in bio-glues.[43] Overall, while biopolymers often respond to mechanical stimuli at lower forces than synthetic mechanophores, they offer greater tunability through sequence design and the possibility of using different pulling geometries.[44–46] These features make mechanoresponsive biopolymers a powerful and complementary addition to the existing mechanophore toolkit.

Biomedical applications of mechanophores

A recent advancement in ultrasound polymer mechanochemistry is the controlled release of bioactive molecules with promising applications in drug delivery. Ultrasound serves as an efficient means of transmitting shear forces to polymer chains,[4] making it a logical choice for activating mechanochemically responsive macromolecular systems in medicine. In particular, the force-triggered release[47,48] of active pharmaceutical ingredients (APIs) relevant to pharmacotherapy has led to the emergence of sonopharmacology as a new research direction.[49]

As a first step, tailored, strongly covalent or supramolecular mechanophores were utilized as API-releasing and -activating moieties.[33,50–54] However, these motifs generally encompass only a single mechanophore (and therefore a single drug) in multi-kilodalton polymer chains, and require the prolonged application of cytotoxic ultrasound that produces inertial cavitation at frequencies of 20 kHz.[55] This problem could be alleviated to a certain extent when using multi-mechanophore-containing polymer structures with ultrahigh molar masses, such as microgels, polymer brushes,[56,56] polymer-coated microbubbles,[57,58] or gas vesicles.[59] Thereby, the ability to use higher frequencies in the kHz range was unlocked for polymer mechanochemistry, but with the associated price of increased power intensities of high-intensity focused ultrasound (HIFU). While HIFU is biomedically applicable in certain scenarios with a limiting mechanical index (MI, a metric for ultrasound biosafety) of <1.9,[60] it is still capable of producing inertial cavitation. It severely heats the irradiated tissue, thus limiting its realistic application to living organisms. Recent results show that the development of ultrahigh molar mass polyaptamers as supramolecular protecting groups of APIs[33,34] enables the use of lower ultrasound doses, even at MHz frequencies used for ultrasound imaging. These developments have recently culminated in the first demonstration of mechanochemistry carried out *in vivo* by Herrmann and coworkers.[61] These foundational investigations set the stage for future successes of this approach in clinical settings.

Future directions

The scope and potential of polymer mechanochemistry continue to expand as it converges with several other vibrant research fields. In the effort to increase sustainability, the application of mechanical force, especially through ball milling, has emerged as a promising strategy for solvent-free, energy-efficient degradation, depolymerization, and recycling of commodity polymers.[62] Harnessing mechanochemical bond scission pathways, synthetic mechanophore research allows polymer breakdown processes to be optimized with enhanced selectivity and minimized by-product formation. In the future, this approach may lead to scalable, greener recycling methodologies, helping to address the challenges of global plastic and microplastic waste.

Equally compelling is the alignment between polymer mechanochemistry and mechanobiology. The shared use of protein and DNA/RNA OFPs and force-activated biomolecules in both disciplines[6,38,45,46] opens opportunities for cross-fertilization. Innovations in synthetic and biopolymer mechanophores for precisely sensing force-induced events could inform the development of biosensors and mechanoresponsive therapeutics in living organisms, while insights into biomechanical structure–function relationships could inspire the design of next-generation synthetic materials with biologically relevant force thresholds and responses. This synergistic relationship holds promise for advancing both fields through a deeper understanding of force sensing and transduction across synthetic and biological systems.

Lastly, the intersection between soft actuators and robotics offers exciting future possibilities. For example, mechanically responsive polymers and biopolymer-based hydrogels with programmable viscoelasticity can provide new paradigms for self-healing, adaptable and shape-morphing, or force-sensing components in soft robotic systems.[16,17,30] The integration of mechanophores into robotic actuators could enable autonomous sensing and real-time feedback to enhance durability and function. These developments suggest a future where polymer mechanochemistry not only serves as a fundamental tool in materials science but also as a central enabler for building sustainable technologies, responsive biomedical devices, and intelligent soft machines.

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