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Editorial

Force ahead: Emerging Applications and Opportunities of Polymer Mechanochemistry

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The use of mechanochemical reactions in polymer science is a relatively new concept. Initially, the widespread introduction of polymers as commodity materials required the investigation of their behavior under mechanical action. One of the early experiments in this regard was performed by Staudinger and Heuer in 1934 who observed that the degradation of polystyrene and natural rubber led to a decreasing viscosity and hence attributed this to a decreasing molar mass. They speculated that this was caused by the mechanochemically induced depolymerization of the polymer backbone.[1] Kauzmann and Eyring confirmed Staudinger's hypothesis in 1940 and offered the first kinetic description of the mechanochemical bond scission process in polymers.[2] Besides degradation, it was found that mechanically produced macroradicals could be used for secondary polymerizations thus rendering mechanochemistry a versatile tool in polymer chemistry.[3,4]

Continuing this early work on polymer fragmentation and formation,[5] the past decade experienced rapid growth of polymer mechanochemistry employing designer polymers that bear force sensitive functional molecular motifs (mechanophores).[6,7] These mechanophores were placed in different polymer architectures and their mechanochemical actuation resulted in specific molecular transformations realizing a desired function. Exciting examples are the incorporation of chromogenic molecules as mechanophores that undergo a molecular transformation accompanied by alteration of absorption and/or emission, rendering them optical force probes (OFPs).[8] Thereby, the mechanical failure mechanisms in different architectures ranging from soft matter to high-performance polymers were studied with the aim to use the gained knowledge to design materials with better properties. Moreover, the incorporation of multiple, nonconjugated, fused four-membered carbon rings, reminiscent of the unusual ladderane membrane lipids of anaerobic ammonium-oxidizing bacteria in polymers, led to the formation of polyacetylene with extended π-conjugation along the polymer backbone after mechanical activation.[9] Besides changing the optical or electronic properties of polymer systems under force, transition metals were incorporated into the central region of linear polymers resulting in catalysts that were activated by applying elongational flow as mechanical stimulus.[10] More generally, polymer mechanochemistry was used to dynamically alter potential energy surfaces by force allowing access to products unavailable by traditional reaction pathways.[11]

Arguably, these seminal contributions had transformative character for the field and have sparked new developments and unprecedented applications in the field. In this Editorial, we present selected emerging trends, opportunities, and obstacles for the application of mechanochemical methods in polymer science. We highlight the trend toward bond scission quantification using OFPs and its associated difficulties. Moreover, we summarize which solutions polymer mechanochemistry contributes to a more sustainable usage of polymers. Lastly, we put focus on the emerging field of sonopharmacology where the principles of polymer mechanochemistry are employed for drug delivery and activation.

FROM MECHANOCHROMISM TO OPTICAL FORCE PROBES

The force-induced activation of a latent mechanophore can cause a change in its optical properties, rendering the mechanophore an OFP (Figure 1).[12] Such OFPs allow real-time in situ or postmortem monitoring of force-induced events from the molecular to the macroscopic scale, qualifying them ideal tools to investigate material mechanics. However, OFPs are not a one-size-fits-all solution for every polymer. The OFP type and its localization within a material determine the mechanical information that is accessible regarding spectral properties, force range, and spatiotemporal resolution in solution, the bulk, and at interfaces. Polymer materials differ,

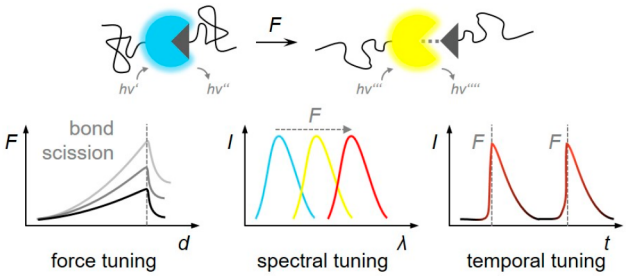

Figure 1. Optical force probe concept and exemplary tunable characteristics, such as scission force threshold, spectral properties, and temporal response for reversibility.

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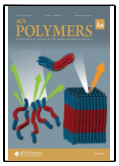

e.g., in their time-dependent mechanical properties (creep, stress-relaxation) or in their optical properties (intrinsic absorption or fluorescence). Tailoring OFPs to a specific demand of the material they are incorporated within is thus a necessary step to obtain meaningful and representative data.

While historically the first examples of OFPs (e.g., spiropyran) were designed by synthetic chemists and were employed qualitatively to visualize force-induced reactions in polymers,[8,13] recently a strong trend to quantitative measurements has been promoted by researchers applying OFPs as tools to investigate mechanical phenomena in soft matter.[14−16] Specifically the application of high-resolution microscopy methods, such as confocal laser scanning microscopy,[17,18] enabled the quantification of bond scission processes on the locally resolved sub-micrometer scale.[14,19] This information aided in developing and benchmarking computational models and polymer theory.

Prospectively, the popularity of OFPs in engineering and physics applications will continue to spur new developments, such as previously inaccessible spectral ranges,[20] broader force ranges,[21] instantaneous reversibility,[22] continuum and ratiometric OFPs,[23,24] or higher spatial resolution beyond the diffraction limit (Figure 1). It will be necessary at every instance to critically evaluate the quality of the obtained data and how they relate to the formulated scientific hypothesis. For example, Storm and co-workers investigated the conditions at which OFPs (which are intrinsically designed to contain bonds that cleave at an increased rate compared to other bonds) over- or underreport overall bond scission events in bulk materials.[25]

SUSTAINABLE POLYMER CHEMISTRY

Plastic waste constitutes one of the central and most visible arguments to develop sustainable approaches to materials. Since this topic is at the heart of chemistry, polymer chemists perform sustainability research in three general directions: (i) to prolong the life cycle of a given material, (ii) to achieve sustainable syntheses of polymers, and (iii) to efficiently degrade and/or recycle polymers (Figure 2). These directions

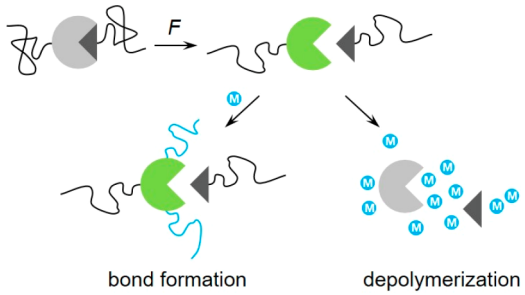

Figure 2. Mechanochemical approaches to sustainable polymer chemistry exemplarily shown for life cycle prolongation by secondary bond formation reactions using monomers (M) and for a circular economy by depolymerization to monomers.

are generally addressed by gating certain functions in polymers by external physicochemical stimuli. Using mechanical force in this context is complex but also potentially rewarding, since stress and strain are ubiquitous and continuously act on most polymers, particularly on structural materials.

One approach to prolong the lifecycle of polymers that is being fundamentally explored is self-healing.[26] Although the seminal report by Wudl and co-workers in 2002[27] and those that followed did not explicitly investigate mechanochemical reactions, it is plausible to assume that material fracture has led to the scission of chemical bonds—also at the functional group that provides the healing capability.[28] While the use of polymer mechanochemistry (e.g., by ultrasound) to initiate secondary bond formation reactions has been known since the 1980s,[3] it was not before 2013 when Craig and co-workers showed that *gem*-dibromocyclopropane (gDBC) mechanophores upon bond scission could be used to cross-link the resulting activated chains, thus strengthening the mechanically challenged material.[29] Other approaches followed that used the mechanochemical generation of transient[30] and persistent radicals[31−33] or nucleophiles.[34,35] Boulatov, Couty, and co-workers recently demonstrated for poly(styrene-*co*-butadiene) that such principles may even be implemented without distinct mechanophores.[36] This line of research in polymer mechanochemistry must overcome the same obstacles as other self-healing concepts to eventually make the leap into application. However, polymer mechanochemistry has the decisive advantage that it makes use of the stimulus that causes material failure in the first place to initiate a repair or reinforcement reaction on the molecular level. In contrast to other physicochemical stimuli, this may mitigate material failure at a microscopic stage where the necessity to initiate the healing process would not even be visible on the macroscale.

Exploiting mechanical force to initiate a bond formation reaction can reach far beyond repair and healing functions, as Kim, Borchardt, and co-workers succinctly summarized.[4] Specifically, researchers within the mechanochemical trituration community investigated ball milling processes for sustainable polymer syntheses,[4] postsynthetic modification,[37] or tuning of molar mass distributions.[38] Notably, this line of research might lead to a convergence of the methods of trituration and polymer mechanochemistry.

In addition, the degradation and recycling of polymers are important topics in sustainability research.[39] Modern concepts of degradation for a circular economy are generally concerned with the recovery of polymerizable monomers or chain fragments (i.e., depolymerization reactions). This also holds true for mechanochemical approaches and might contribute to the convergence of trituration and polymer mechanochemistry mentioned above[40] since the controlled mechanochemical degradation of polymers is being investigated using ball milling.[41] Other forms of force application have been investigated as well. Moore and co-workers showed that a polymer with a low ceiling temperature could be mechanochemically unzipped into its monomers by ultrasound.[42] Craig and co-workers even proved that such a degradation reaction could be activated inside of an extruder.[43] In addition, Yang and Xia synthesized a hydrolytically stable polymer that contained a cyclic ether and a cyclobutane mechanophore moiety based on their experience with ladderanes.[9] Mechanochemical ring-opening of the cyclobutanes produced poly(enol ether) derivatives that were found to be acid-degradable, thus gating the degradability with two stimuli, force and protons.[44] These examples showcase the dichotomy of the mechanochemically induced degradability of polymers. On the one hand, force application is easily scalable using ball mills or extruders and therefore promising on an industrial scale. On the other hand, such polymers cannot be safely used as structural materials that are required to withstand base and peak loads of stress and strain in their life cycles. The latter might be circumvented by serially connecting different stimuli

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that logically gate the programmed degradability. These stimuli must be orthogonal to the environmental stimuli the polymer is subjected to in its application; i.e., using light as the gating stimulus will not be promising in strongly light-exposed applications, such as in automotive parts.

SONOPHARMACOLOGY

Medical professionals use ultrasound as a tool for diagnostic and therapeutic purposes. Thereby, ultrasound overcomes several systematic limitations of pharmacotherapy, such as drug resistance, environmental toxicity, degradation, and most importantly off-target activity.[45] Since ultrasound is used as convenient tool to deliver shear forces in solution to polymer chains as well,[46] the development of polymers for biomedicine that are activated using the principles of polymer mechanochemistry is only consequential. Specifically, the mechanochemical release of bioactive molecules, being an imperative feature for drug delivery systems, has paved the way toward the emerging field of sonopharmacology.[47,48]

First steps in this direction were taken by the incorporation of strong covalent or supramolecular dedicated mechanophores as drug releasing and drug activating moieties (Figure 3).[49−54] However, it became clear very soon that the applied

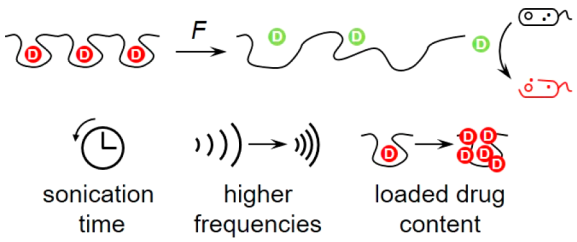

Figure 3. Principle of sonopharmacology for drug (D) activation (upper panel) and associated standing challenges for its successful future biomedical application, such as reduction in ultrasound doses by reducing sonication time, compatibilization with therapeutic and diagnostic ultrasound frequencies, or increase of loaded drug content (lower panel).

ultrasound doses were biomedically incompatible with regard to frequency, power intensity, and necessary sonication times. Recently, these issues were addressed twofold. On the one hand, the force-reactive molecular moieties were tailored such that they require less mechanical energy to break. On the other hand, mechanophores were incorporated into polymer structures for which the topology drastically increased the mechanochemical reactivity[55] and thereby decreased the necessary ultrasound doses. For example, this was achieved by designing mechanochemically responsive ultrahigh molar mass polyaptamers as supramolecular groups to inhibit the activity of bioactives,[50,56] gold nanoparticle assemblies,[50,57] genetically engineered proteins,[58] microgels,[59] and polymer brushes.[60] Consequently, sonication times using a classical immersion probe sonicator at 20 kHz could be reduced by 1−2 orders of magnitude, i.e., from hours to seconds.

However, ultrasound in biomedicine is rarely employed at the frequencies of polymer mechanochemistry due to cytotoxicity,[61] and hence, compatibilization with clinically employed therapeutic and diagnostic ultrasound has become one of the currently standing challenges. First examples of polymer mechanochemical reactions using either clinically employed high-intensity focused ultrasound (HIFU)[62] or low-intensity focused ultrasound (LIFU)[56] have been performed, but diagnostic or imaging ultrasound frequencies remain out of reach. Should research in sonopharmacology overcome limitations associated with ultrasound type and dosage, loaded drug content, as well as mechanochemical reactivity of the carrier polymer architecture (Figure 3), prospects for success in clinical settings can be expected in the future. Although the spatiotemporal resolution of ultrasound as an external trigger is lower than that of, e.g., light,[63] the drastically increased routinely achievable penetration depth of ultrasound (multiple cm) renders it a unique method for spatiotemporal control of drug action.[64]

Over the course of the past almost 90 years, polymer mechanochemistry has undergone dramatic developments. While the initial focus—of what could hardly be called a field at the time—was on studying and understanding polymer degradation, researchers soon developed methods to productively use generated mechanoradicals for functionalization and polymerization reactions. However, a true blooming of the field was initiated by the development of dedicated mechanophores that continue to give access to novel intricate functionalities that can be activated by force. In this Editorial, we have highlighted three selected areas, out of a wide variety of others, that present exciting and important challenges and opportunities of research for the polymer science community.

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