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Journal:	*Polymer Chemistry*
Manuscript ID	PY-MRV-05-2018-000720.R1
Article Type:	Minireview
Date Submitted by the Author:	06-Jun-2018
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Polymer Chemistry

MINIREVIEW

Empowering mechanochemistry with multi-mechanophore polymer architectures

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The development of multi-mechanophore polymers (MMPs) has empowered new methodologies for observing, quantifying, and exploiting mechanochemical transformations. For example, techniques such as single molecule force spectroscopy and pulsed ultrasound can be used to induce and observe up to hundreds of chemical reactions within a single polymer, enabling mechanistic insights into mechanochemical reactivity. At the same time, MMPs allow for the substantial mechanochemical remodeling of polymers and associated change in material properties. This minireview presents synthetic approaches that have been used to make MMPs, methods that have been developed to probe and characterize their reactivity, and changes in properties that have been observed through their mechanochemical response.

1. Introduction

In recent years, the molecular-level engineering of force-reactive functional units (mechanophores) has become an attractive route for creating new stress-responsive polymeric materials.[1] The basis for this approach comes from the observation that distributed forces within polymer materials can lead to covalent bond scission of overstressed subchains.[2] The careful design and placement of mechanophores within the overstressed regions within polymers has led to the creation of polymers that are capable of a wide range of constructive responses to mechanical stimuli, such as mechanochromism,[3] stress-strengthening,[4] and small-molecule release.[5] In addition to providing access to new types of materials, the mechanophore strategy has been used to trap force-free transition state and high energy intermediate structures and bias chemical reactions down their classically forbidden pathways.[6-8] This allows for the characterization of reaction dynamics and products that are less accessible by traditional means. Understanding the force-coupled reactivity of these mechanophores also provides the opportunity for gaining fundamental insights of how force is distributed within polymer networks and other macromolecular structures. These and other advancements in polymer mechanochemistry are of great interest to both materials scientists and synthetic chemists alike.

Central to the success of the mechanophore approach is the ability to embed the force-responsive functional group of interest within a polymer chain such that it will experience adequate force for activation.[9] To date, the most widely

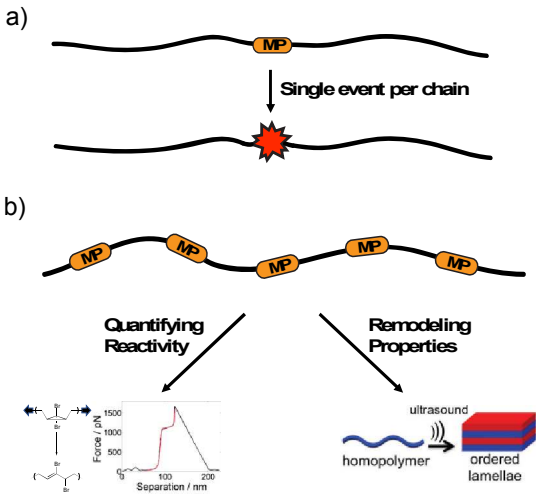

Fig. 1 a) Cartoon sketch of a chain-centered mechanophore polymer. b) Cartoon sketch of a multi-mechanophore polymer. Having multiple mechanophores along the polymer backbone allows for enhanced quantification methods such as SMFS (left) and the rapid remodeling of polymer architectures (right). Adapted with permission from refs. 37 and 39. Copyright (2010 and 2012) American Chemical Society.

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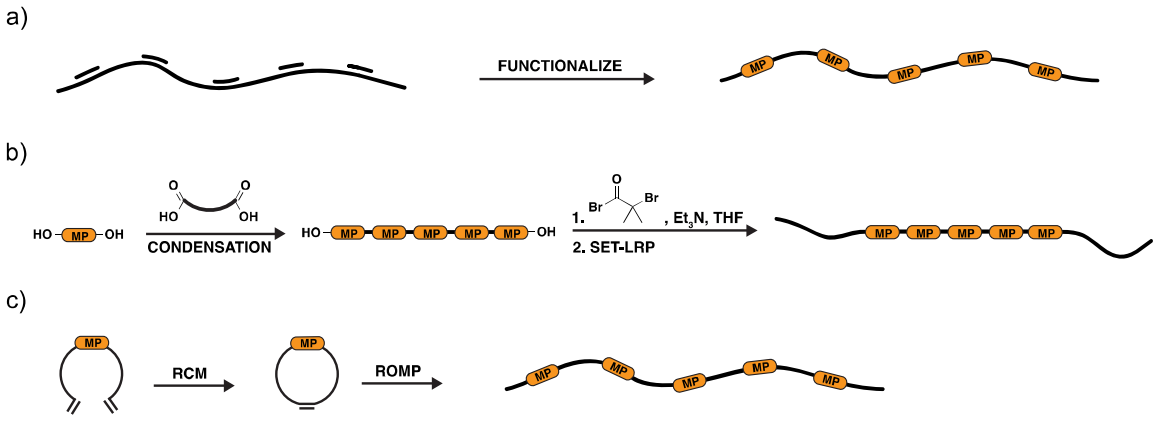

Fig. 2 Cartoon representations of the reported approaches for synthesizing MMPs: a) post-polymerization modification, b) polycondensation, with optional chain extension by CRP, and c) ring-closing metathesis followed by entropy driven ROMP.

employed strategy for that purpose involves the synthesis of chain-centered mechanophores (Fig. 1a), in which a single mechanophore is embedded in the central portion of a linear polymer strand.[10] One motivation for this strategy is that the primary tool for screening new mechanophores is pulsed ultrasound, a technique that generates the greatest amount of force at or near the center of polymer strands.[11] In addition, it has become quite easy to synthesize high molecular weight, mechanophore-centered polymers via living/controlled radical polymerization (CRP) methods.[12-14] There are, however, several drawbacks to the single mechanophore architecture that limit its utility for applications in stress-responsive mechanical properties or for probing reaction mechanisms. Chief among these is the low mechanophore content, which makes it more challenging to quantify reactivity and characterize mechanically generated products.[15] It is also more difficult to produce meaningful changes in polymer properties if at most only one very small fraction of the polymer strand (~0.1 - 1.0%) is responding to the mechanical input.

Another challenge with the single chain-centered approach is the difficulty of precisely controlling the position of the mechanophore in the middle portion of the chain. This was demonstrated recently by Kean et al., who used a coumarin dimer probe to show how even fairly narrow molecular weight distributions of mechanophore-bearing polymers synthesized by CRP can affect the probability of chain-centered mechanophore activation.[16] Although qualitative successes have been realized by comparative kinetics studies,[17, 18] this lack of fidelity in mechanophore placement potentially compromises the usefulness of single-mechanophore polymers for quantitative analysis of sonicated polymers.

Lastly, even as the force distribution along linear polymer backbones during pulsed ultrasound becomes better understood (although many questions remain),[11, 19-27] it is often difficult to know *a priori* where the areas of localized stress will be for other types of materials and for other methods of mechanical input.[28-30] If a certain macromolecular architecture channels force to regions other than the center of the chain, then a chain-centered mechanophore that is highly reactive in pulsed ultrasound might remain mechanically inactive simply because it is in the wrong place to couple to the applied tension.

The aforementioned challenges have led to the development of a multi-mechanophore strategy (Fig. 1b) for creating mechanophore-rich polymer architectures, which is the focus of this mini-review. The chain-centered mechanophore approach was the first to be widely adopted and has historically been the most popular. Recently, however, more groups are beginning to use multi-mechanophore containing polymers (MMPs), and thus the advantages of MMPs are emerging. The purpose of this mini-review is to summarize: 1) the considerations for designing MMPs and useful synthetic methods for their production, 2) the methods that have been enabled by MMPs, and 3) the new types of stress-responsive materials that are possible because of MMPs. General considerations about mechanochemical coupling, including the role of loading/strain rate and influence of molecular structure on the mechanical susceptibility of a reaction, are alluded to in passing but not discussed in detail here. We focus on recent developments within our own lab, but other work will be highlighted where appropriate. We begin by discussing some general approaches and considerations for synthesizing MMPs.

2. Synthesis of MMPs

There are several key considerations that should be taken into account when designing the synthesis of MMPs. Having the functional group of interest (mechanophore) coupled to the polymer backbone is of central importance, because the backbone is the vehicle through which force is channeled to the mechanophore.[31] Methods that would decouple the functional group from the backbone, such as radical addition of functionalized acrylates or other olefins, are therefore typically ineffective for making useful MMPs. Techniques that allow for a wide range of chemical functionalities along the polymer backbone are advantageous, such as the polymerization of macrocylic monomers.[32] Because force

transduction occurs through the polymer backbone, considering the structural identity of the backbone and the relative position of the mechanophore along the backbone is crucial. It is also important to know the strength (mechanical as well as thermodynamic[33]) of the bonds that comprise the polymer backbone, as these bonds could compete with the mechanical reactivity of the mechanophore. Lastly, the molecular weight and polydispersity of MMPs can influence their mechanical reactivity, so these characteristics should be considered. In this section, we present three popular approaches for the synthesis of MMPs, summarized in Fig. 2: post-polymerization modification (Fig. 2a), step-growth polymerization (Fig. 2b), and entropy driven ring-opening metathesis polymerization (ED-ROMP) (Fig. 2c).

2.1. Post-polymerization modification

The first reported MMPs were synthesized via the post-polymerization modification of commercially available polymers (Fig. 2a). Lenhardt et al. incorporated multiple *gem*-dichlorocyclopropanes (*g*DCCs) along the backbone of *cis*-polybutadiene by reacting the butadiene polymer with aqueous NaOH in $CHCl_3$ under phase-transfer conditions, resulting in a *g*DCC-PB copolymer through dichlorocarbene addition to the nascent backbone alkenes.[20] This approach of modifying polybutadiene backbones was then extended to other *gem*-dihalocyclopropanes (*g*DHC).[8, 28, 34-39] Advantages in this particular example stem from the use of commercially available polymers that are available in high molecular weights and very low dispersities, and a relative inexpensive and scalable post-polymerization reaction. The method also allows for extremely high mechanophore content. For example, Wu et al. synthesized *gem*-dibromocycloproane (*g*DBC)-containing polymers with >98% mechanophore content.[39] The post-polymerization approach requires the presence of functional groups along the polymer backbone that can be chemically transformed into a mechanophore of interest. Thus far, only *g*DHC mechanophores have been incorporated into MMPs in this manner, with polybutadiene as the dominant backbone of choice. It should be possible, however, to synthesize more diverse architectures via post-polymerization modification by adding to other types of functional groups, such as other alkenes or alkynes. Klukovich et al., for example, were able to modify a polynorbornene backbone with different *g*DHCs in order to quantify the importance of backbone structure on mechanochemical activation.[36] Another consideration in using post-polymerization modification is that an abundance of reactive groups along a polymer strand often limits polymer stability. For example, the lingering olefins along a polybutadiene backbone are susceptible to crosslinking. Finally, backbones rich in other types of reactive functional groups are rare for the same reasons that backbones rich in mechanophores are rare – many highly effective polymerization strategies (including CRP) are not compatible with their synthesis.

2.2. Step-growth polymerization

A general strategy for building functional groups along polymer backbones includes step-growth polymerization methods, such as polycondensation, in which the necessary reactive groups can be appended to both sides of a functional monomer. For example, a wide range of mechanophore-rich polyesters have been synthesized by functionalizing the stress-responsive monomer with reactive "handles" (-OH or -COOH terminated) for condensation reactions.[40, 41] One of the challenges with this method is the need to synthesize polymers of sufficiently high molecular weights, because the extent of mechanical activation often depends on the molecular weight or contour length of the polymer.[42] Using methodology reported by Moore and Stupp,[43] Kean et al. were able to use carbodiimide mediated polyesterification to generate high-molecular weight polyesters (>150 kDa) bearing multiple cyclobutane mechanophores.[44] When desired molecular weights cannot be achieved through step-growth methods alone, macromonomers can be extended through conventional chain growth polymerization. For example, the ends of polycondensation polymers can be functionalized with bromoisobutyrate initiators, from which chain extension under single-electron transfer living radical polymerization conditions[12] gives acrylate-polyester-acrylate triblock copolymers with a mechanophore-rich central block (Fig. 2b).[40] This method is particularly attractive because the central block of linear polymers is often the site of greatest activity, especially in sonicated polymers where forces tend to accumulate around the center of the chain.[45, 46] Though not discussed further here, it should be noted that step-growth methods can also be used to generate polyurethane-based MMPs.[47, 48]

Other drawbacks of step-growth methods are the standard issues with any step-growth polymerization: the need for high conversion and long reaction times.[49] Additionally, it is sometimes desirable to construct polymers where the mechanophores are closely connected to one another without a linker between them,[38] which would require the synthesis of monomers with multiple mechanophores already present in each.

2.3. ED-ROMP

Advances in various ring-opening polymerizations, such as ring-opening metathesis polymerization (ROMP),[50] have offered an attractive route for incorporating main-chain functionality in polymers.[51-54] Due to the functional group tolerance of Grubb's ruthenium-based catalysts, ROMP has proven to be a successful means for generating a variety of MMPs. ED-ROMP has been particularly useful in this regard (Fig. 2c),[32, 55] especially considering the variety of methods available for synthesizing the macrocylic monomers, such as ring-closing metathesis (RCM) of terminal alkenes[56] or the chemical modification of other macrocycles.[57] It is important to carefully consider the size of the macrocycle and the reaction conditions (catalyst, solvent, concentrations, etc.), as these factors influence the complex ring-chain equilibria and therefore the success of the polymerization.[32] Given the fast

initiating properties of modern, commercially available catalysts (e.g. Grubbs 2nd generation), mechanophore-rich, high-molecular weight polymers can even be synthesized, characterized, and tested all in a single day. This method also provides an easy way to embed multiple functionalities along the polymer backbone in a random and quantitative manner. Further, ROMP only requires a single monomer and catalyst, so extremely high mechanophore content can be achieved. Similar to the post-polymerization of polybutadiene, the residual olefins are a potential problem with this method, especially if not all unreacted catalyst is properly removed.[58]

3. MMPs empowering mechanochemical methodology

The synthetic effort required to produce multi-mechanophore polymers is often rewarded in improved functionality. For example, having multiple mechanophores that can react in a single polymer strand allows for easier detection of mechanically triggered events, making more quantitative analyses possible. Quantifying reactivity with the single-mechanophore approach is more challenging primarily due to a lack of information. One common approach, for example, is to infer the mechanochemical reactivity of scissile mechanophores from the rate of polymer chain scission in pulsed sonication experiments.[17] Although this appears to be straightforward and can be informative, there are a variety of factors that impact reactivity and could potentially skew the interpretation of the molecular weight data, such as the initial molecular weight and the position of the mechanophore along the backbone (dispersity of the half-strands on either side).[16, 59] As a result, successful studies typically require a series of experiments that span a range of initial molecular weights.

Because multiple mechanochemical transformations occur within a single polymer, MMPs have empowered two techniques for quantifying mechanochemistry: single-molecule force spectroscopy (SMFS) and pulsed ultrasound. In this section, we highlight how these quantitative analyses have allowed us to: 1) probe the fundamental (mechano)chemistry (reaction rates, transition state dynamics, mechanisms, etc.) of a variety of reaction classes, 2) better understand the factors (force-free reactivity, reaction conditions, polymer architecture, etc.) that govern the rates of mechanochemical transformation, and 3) use the obtained information for better understanding mechanophore behavior within solid-state materials (quantifying stress distributions, percent mechanophore activation, etc.).

3.1. Single-molecule force spectroscopy

For many years, SMFS has been used to understand the behavior of chemical bonds under load, and the general theory and methodology is reviewed elsewhere.[60-63] In recent years, SMFS has proven to be a valuable tool for studying polymer mechanochemistry, because it provides information about the forces required for covalent bond rupture.[64, 65] Historically, however, its use has been limited to studying only a single event per chain. Recording only one reaction per polymer limits the utility of the SMFS measurements on two fronts: (1) a single event per chain often makes it difficult to unambiguously assign which bond within the polymer was broken, and (2) many successful SMFS measurements are required in order to obtain the statistical power necessary to derive quantitative information, limiting experimental throughput. MMPs provide a solution to both of these longstanding challenges in SMFS. By introducing multiple, non-scissile mechanophores into the polymer backbone, a single force curve can capture hundreds or thousands of mechanochemical (polymer-extending) events and provide a statistically significant sample for data analysis (Fig. 3), whereas an event that leads to polymer chain scission is far from sufficient on its own, and therefore would require

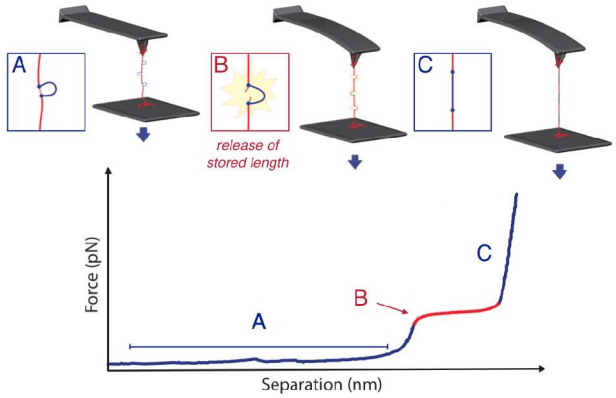

Fig. 3 Cartoon representation of a SMFS experiment using a MMP. A) Reducing entropic degrees of freedom as the MMP starts to uncoil while the mechanophore remains unreacted. B) The activation of multiple non-scisscile mechanophores leads to a characteristic plateau in the force-separation curve that is reflective of the release of stored length from the mechanophore. C) Enthalpic distortions rapidly ensue once all mechanophores have reacted, eventually leading to sufficient forces for chain scission or polymer detachment.

hundreds of subsequent replicate measurements to made to achieve the same statistical power. Furthermore, the presence of many events creates a structural signature that often can be unambiguously assigned to the desired transformation; in contrast, the scission of a polymer chain at a mechanophore looks identical in the force curve to polymer chain detachment from the tip of an AFM.

The use of MMPs is SMFS was first demonstrated by Wu et al., who observed extensions of ~28% in the contour length of active, stress-bearing *g*DBC polymer chain segments, matching the expected extension due to rearrangement of the *g*DBCs to dibromoalkenes (Fig. 4). The transition plateau can be modeled as a series of independent, individual (and experimentally unresolvable) force-coupled reactions, from which the force-coupled kinetics of ring opening can be extracted. Alternatively, SMFS can be implemented in a constant force mode ("force clampling"), and the growth in contour length can be fit with a first order rate law.[66] Importantly, the presence of up to hundreds of independent events in a single force curve means that accurate kinetics can be derived from a single chain extension profile. As discussed

above, this presents an enormous practical advantage, as it is often difficult to achieve high force (> 1 nN) attachments to a polymer analyte in SMFS, and so many polymers detach before the critical forces for covalent activation are achieved; "successful" pulls are typically rare events. A comparable data set from single-event polymers (even if single events could be resolved) would require hundreds of these rare events to be captured, severely limiting experimental throughput. Although "successful" pulls can be considered rare events, one can improve the prevalence of such pulls by incorporating functional groups along the polymer backbone that help the polymer adhere to the tip of the atomic force microscope, such as epoxides.[36] In addition, observations within our own lab indicate that polymers with higher molecular weights tend to provide more opportunities for achieving "successful" pulls. Finally, we note that some traditionally scissile mechanophores can be incorporated into designs that are non-scissile with respect to maintaining the polymer backbone, for example by tethering them within larger macrocycles.[41, 64, 67]

The details of the kinetic analyses are provided elsewhere,[39] but the critical point here is that the measurement precision enabled by MMPs allows the activation length for polymer-embedded mechanochemical reactions to be inferred in a way that reveals a range of structure-activity effects. For example, SMFS analysis has been

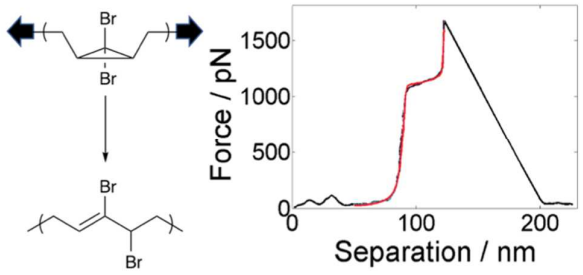

Fig. 4 A representative force-separation curve for the electrocyclic ring-opening of *g*DBC. The red line is a theoretical fit to the experimental data. Adapted with permission from ref. 39. Copyright (2010) American Chemical Society.

used to probe the effects of molecular lever-arms (Fig. 5a) and pulling regiochemistry (Fig. 5b), to quantify rates of classically forbidden reactions (Fig. 5c), and to investigate a host of other structure-activity relationships discussed elsewhere.[1]

The degree to which an applied force couples to the reaction pathway of a mechanophore is one major determining factor of the rates of mechanochemical transformations, as discussed elsewhere.[1] This chemo-mechanical coupling can be influenced by changing the atomic structure of the mechanophore or the macromolecular structure of the polymer backbone. Depending on the nature of the mechanophore, certain chemical functionalities along the polymer backbone can act as phenomenological levers that effectively enhance the chemo-mechanical coupling and can lead to an increase in reaction rates. Building off of the work of Klukovich,[36] Wang et al. recently used SMFS to quantify the effect of a polymer lever-arm on the ring-opening reaction of benzocyclobutene (Fig. 5a).[68] He found that the installation of an *α*-*E*-alkene "lever" lowered the force required for ring-opening by ~500 pN in comparison to the force required when no *α*-*E*-alkene is present. The use of lever-arms in polymer mechanochemistry is an ongoing endeavor,[57] and SMFS serves as a valuable tool for quantifying their effectiveness in altering the rates of force-induced reactions.

SMFS analysis of structure-activity relationships on the single-molecule level can also help aid the understanding of mechanophore reactivity in solid-state materials. Gossweiler and coworkers were able to quantify the force required for inducing the well-known spiropyran-to-merocyanine isomerization (~240 pN on the time scale of 10^{-2} s), explaining why the spiropyran mechanophore has been so valuable for making and studying mechanochromic polymer-based materials.[5, 56] In addition, they were able to quantify the effects of pulling regiochemistry on the force-induced isomerization (Fig. 5b). The force gap between the two regioisomers studied was small (only ~20 pN under the conditions of the experiments), but, based on prior

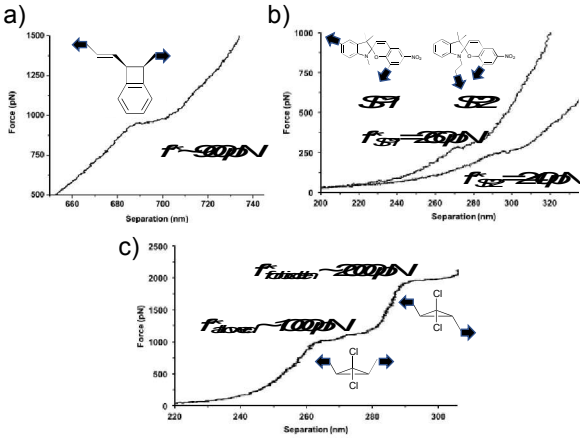

Fig. 5 Representative force-separation curves for the electrocyclic ring-opening reactions of: a) an alkene-functionalized benzycyclobutene mechanophore,[68] b) two spiropyran regiosomers,[56] and c) two *g*DCC stereoisomers embedded within the same polymer (blue=allowed pathway, red=forbidden pathway).[6] The average plateau force is given in each curve as *f**.

observations, other regioisomers should allow for a wide range of activation forces to be realized.[69] A fundamental understanding of the mechanical reactivity for this range of mechanochromic force probes at the single-molecule level (using SMFS) could allow for the accurate mapping of force distributions within more complex networks.

The single-molecule analysis of MMPs has recently been used to probe interesting chemical transformations that are otherwise difficult to access, such as reactions that are classically considered forbidden. Using SMFS, Wang et al. quantified for the first time the level of "forbiddenness" for three different pericyclic reactions that are governed by the Woodward-Hoffman symmetry rules, including the force-induced ring-opening of *g*DCC mechanophores (Fig. 5c).[6] By pulling on different stereoisomers of *g*DCC within the same polymer, they were able to access and directly compare both the symmetry-allowed and symmetry-forbidden ring-opening

pathways. By understanding how force accelerated the forbidden reactions relative to their allowed analogs, they were able gain otherwise inaccessible mechanistic insights into the nature of "classically forbidden" reactions, such as the geometry of transition state structures and how electronic factors bias certain pathways over others.

In principle, each of the observations summarized in this section could be obtained by SMFS on single mechanophore polymers. But we note that because of the high forces required (hundreds to thousands of pN), achieving the required high-force attachments is a relatively rare event. Operationally, it is much easier to acquire several force curves of MMPs than the >100 force curves necessary to get comparable statistics on single event polymers. In addition, the extension plateau is a less ambiguous signature of a specific mechanochemical response than relatively small (~nm) individual features associated with single-event SMFS experiments.[64, 70] In fact, when the single events release enough length to be detected individually, MMPs offer even more unique sawtooth plateaus from which additional dynamic and structural information can be inferred, as demonstrated recently in studies of cinnamate dimers by Boulatov and Zhang.[41]

make it the most popular strategy for probing force-coupled chemistries. Although the technique has proven to be useful, characterizing the reactive fate of a single mechanophore within a polymer (typically ≥ ~50 kDa) often requires involved and/or indirect labeling or trapping experiments.[7, 19]

Having multiple events per chain facilitates more extensive characterization, making the already-popular technique of pulsed ultrasound even more powerful. For example, the first observation of multiple activation events in a single polymer chain was of multiple ring-opening events in a *g*DCC-rich MMP triggered by pulsed ultrasound.[20] In contrast to the typical yield of < 1 event per polymer, 35% of the *g*DCC units in the polymer (molecular weight = 310 kDa) had activated after only 4.5 minutes of sonication, equaling ~690 events per chain. After 4 hours of sonication, ~1650 ring opening events per chain occurred, allowing for easy detection and characterization by NMR (Fig. 6a). The ability to characterize reactants and products in MMPs with conventional spectroscopic methods makes it easy to compare the relative reactivity of different mechanophores, including those that convert to the same product. For example, in the *g*DCC study described above, a copolymer of *cis* and *trans* *g*DCC was sonicated and the relative amounts of each stereoisomer that remained after sonication revealed directly that the *cis* isomer is the more reactive.

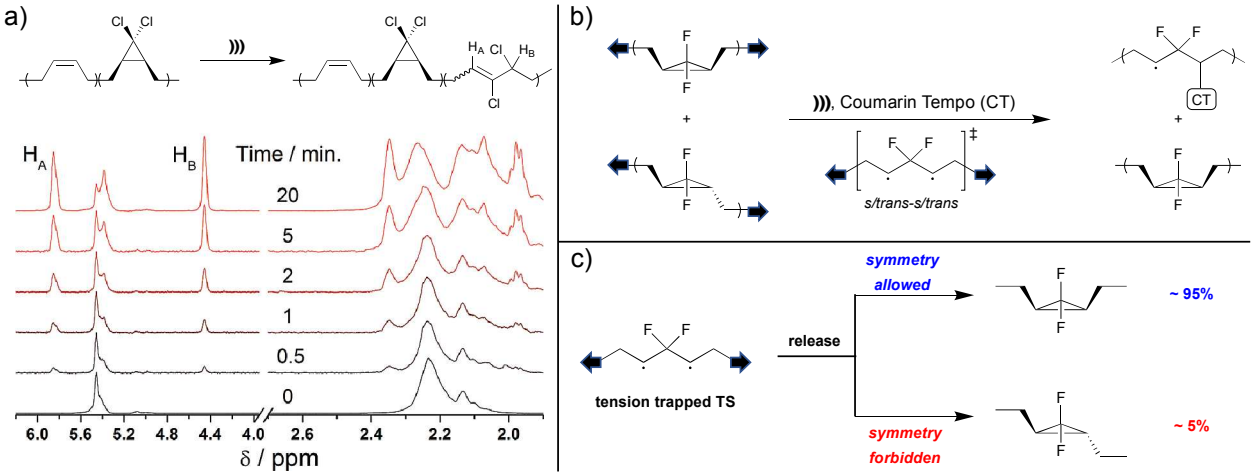

Fig. 6 a) The ring-opening of multiple *g*DCCs per scission event allows for easy detection of reaction progression by ^{1}H NMR.[20] b) Tension trapping of the *g*DFC, diradical transition state with CT. If not trapped, the complex isomerizes to *cis* *g*DFC, regardless of the stereochemistry of the nascent mechanophore.[8] c) Determining the branching ratio of the tension-trapped *g*DFC via sonication.[72]

3.2. Pulsed ultrasound

The use of pulsed ultrasound to study mechanochemical transformations has been central to the modern development of polymer mechanochemistry. Whereas early studies of pulsed ultrasound focused on how the forces that are generated can lead to polymer degradation,[26] more recent work has coupled the tension generated along the polymer backbone to other mechanochemical reactions. The theory and developments of this technique in the context of mechanochemistry are reviewed elsewhere,[11, 15] and its relatively easy experimental setup and sample preparation

Perhaps the greatest advantage of the ability to characterize reaction products is when they are unexpected and/or unprecedented in force-free reactivity. In our lab, for example, we have used sonication to facilitate the "tension trapping" of transition states and high-energy intermediates in sufficient quantities so that their generation and subsequent chemical transformations can be characterized. Lenhardt et al. used pulsed ultrasound to trap the 1,3-diradicaloid transition state of *gem*-difluorocyclopropane (*g*DFC) isomerization (Fig. 6b).[8] This trapping, confirmed by computation, was initially unexpected, and its occurrence was only revealed because of

an unexpected trans-to-cis isomerization that was apparent in the ^{19}F NMR; this serendipitous observation might never have been made in a single mechanophore polymer. In addition, strong supporting evidence for the trapped diradicaloid species came from the bimolecular addition of a coumarin-TEMPO (CT) radical trap. The trapping efficiency is relatively low (only a few percent of the diradicaloid species), and again would have been very difficult if not impossible to observe in a single mechanophore polymer because of competing addition to chain-end radicals generated by chain scission.[71] A similar advantage is observed in experiments to quantify the minor contributions of net cis-to-trans isomerization (ca. 4.5%), which revealed the branching of conrotatory vs. disrotatory ring closing from the tension trapped diradicaloid once released (Fig. 6c).[72]

Because of the high strain rates achieved, the forces generated by pulsed ultrasound are high enough that polymer chain scission typically competes with mechanophore activation.[22, 71] Characterizing the extent of mechanophore activation per scission event offers information about the mechanical strength of the bonds comprising the polymer backbone.[33, 59] The more easily a bond breaks, the less mechanophore activation occurs per scission event, because the chain scission event temporarily drops the tension along the polymer chain and limits the extent of mechanophore activation. This offers an opportunity to quantify the relative reactivity of scissile weak bonds within a polymer (bonds that lead to polymer scission when ruptured) that are difficult to probe by SMFS (precisely because they are scissile). For example, Lee et al. recently quantified the relative strength of three weak scissile bonds (C-N, C-S, and C-O) by characterizing the extent of *g*DCC ring-opening per scission event for polymers that contained both *g*DCC mechanophores and the weak bond of interest (Fig. 7a).[33] The extent of *g*DCC ring-opening as a function of chain scission reveals the relative mechanical strengths of the scissile, weak bonds. A similar analysis was used to quantify the relative mechanical strengths of bonds within more topologically complex polymers, such as a poly(catenane).[73]

Comparing the extent of mechanophore activation to polymer chain scission appears to be a more sensitive and robust approach for quantifying the relative reactivity of mechanophores in comparison to other methods that are used for single-mechanophore pol ymer systems. For example, another approach is to compare the relative rates of polymer scission for polymers of differing mechanophore content - mechanically weaker mechanophores lead to faster rates of polymer degradation. Although this method has been applied successfully to some systems,[17] it is not as sensitive as the competition within MMPs.[38] In addition, it is difficult to compare the rates of polymer degradation obtained in different labs and/or on different days, because the rates are fairly sensitive to variations in sonication conditions.[22] In contrast, Lenhardt and coworkers recently demonstrated that the competition-based approach used for *g*DCC based MMPs gives consistent results across a fairly wide range of sonication conditions, including temperature, solvent, sonication power, and polymer concentration. Changing sonication conditions altered the rate of molecular weight degradation (polymer scission), but had no effect on the relative extent of mechanophore ring-opening reactions versus chain scission (Fig. 7b), highlighting the robust nature of the competition-based approach for quantifying the relative reactivity of mechanophores.

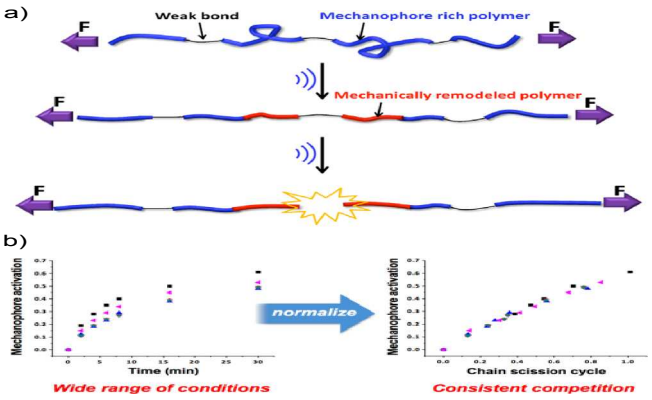

Fig. 7 a) Cartoon representation of the competition between polymer chain scission and mechanophore activation in a typical sonication experiment. Reprinted with permission from ref. 33. Copyright (2015) American Chemical Society. b) Changing sonication conditions affects the rate of mechanophore activation (left), but does not affect the competition between mechanophore activation and polymer chain scission (right). Reprinted with permission from ref. 59. Copyright (2015) American Chemical Society.

4. Empowering new stress-responsive materials

Finally, MMPs allow for the rapid and extensive remodeling of polymer architectures in response to mechanical forces, representing a new class of stress-responsive polymer properties. With the single-mechanophore approach, the potential to remodel properties in a significant way remains limited. Although changes in the photophysical properties of a polymer can be achieved by a single mechanophore,[10] it is more difficult to amend other properties (e.g. mechanical and electrical) with only a single event per chain. Having multiple reactive sites per polymer provides an opportunity for more extensive transformations to take place. Some of these transformations require added reaction partners while others do not, depending on the identity of both the mechanophore and the polymer scaffold.

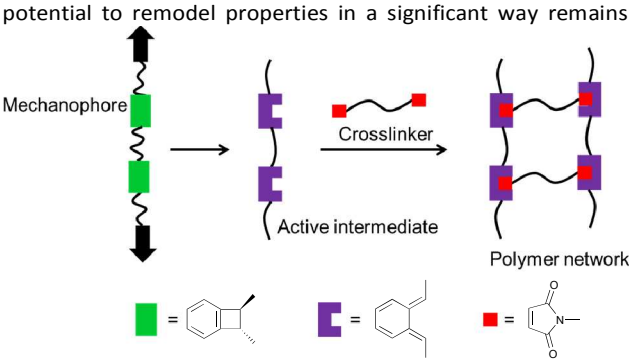

Fig. 8 Schematic representation of activated cross-linking for BCB. Adapted with permission from ref. 4. Copyright (2015) American Chemical Society.

Recent studies have shown that polymer toughness can drastically increase *in situ* when sonicating MMPs in the presence of a highly reactive cross-linking reagent of

complementary chemistry. For example, the mechanically generated products of the ring opening of *g*DBC, benzocyclobutene (Fig. 8), and diester substituted fused cyclobutanes can be captured through specifically tailored cross-linking chemistry, allowing the rate of bond-forming reactions along a given polymer backbone to outpace the rate of bond breaking during pulsed sonication experiments.[4, 35, 44] Similar behavior has been observed in bulk materials under destructive shear forces, with the resulting mechanochemical remodeling leading to orders of magnitude increases in bulk modulus. In all cases, the extent of the observed property changes are only possible because of the high mechanophore content of the MMPs.

In addition to extensive cross-linking, the mechanochemical remodeling of MMPs can result in the release of stored length upon mechanophore activation (Fig. 9a). The stored length per mechanophore is often small (e.g., ~1.5 Å per *g*DBC, 4 Å per bicyclo[3.2.0]heptane, 7 Å per bicyclo[4.2.0]octane), but sufficiently high mechanophore content has been demonstrated to lead to overall chain extensions of up to ~30% of the nascent contour length. The ability to tune stored length through fused rings has made cyclobutane-based mechanophores an increasingly popular force-responsive unit, enhanced by the fact that the mechanically generated olefins can undergo further chemistry, depending on the nature of the substitutents.[17, 64, 74, 75]

Boulatov et al. recently employed this strategy in the synthesis of MMPs that incorporated two isomers of macrocyclic cinnamate dimer (Fig. 9b).[41] The position of the polymer attachments and the size of the macrocycles were carefully chosen to maximize the amount of "stress relief" and to tailor the photophysical properties of the diene products. Using the aforementioned techniques of SMFS and pulsed ultrasound, they observed dramatic increases in the single-chain toughness of the MMP. After subsequent activation of the two isomers, the contour length of a single polymer strand more than doubled, resulting in a 600 kcal mol^{-1} increase in the strain energy that can be absorbed by the chain before fragmenting. In addition to increasing single-chain toughness, the mechanically generated products are chromophores that are optically repairable. These mechanophores therefore represent a promising route towards polymers that have multiple, desirable responses to stress without the need of additional reagents.

The release of stored length in MMPs not only enhances polymer toughness, but it can also generate radical changes in polymer architecture. When Ramirez and co-workers sonicated a homopolymer of *g*DCC, the result was the formation of block copolymers comprised of the unreacted mechanophore and the 2,3-dichloroalkene products, an observation which yielded insights into the force distribution experienced by sonicated polymers.[37] Data from differential scanning calorimetry and small-angle X-ray scattering revealed the microphase-separation of the block copolymers into an ordered lamellar morphology (Fig. 9c), demonstrating how the sonication of high-content MMPs can lead not only to molecular order, but ordered supramolecular morphologies.

An even more dramatic transformation of polymer properties and architecture using MMPs was recently reported by Chen et al., who used the forces generated by pulsed ultrasound to mechanochemically unzip polyladderenes (Fig. 10).[76] The base polymer comprises repeating units of fused multiple cyclobutanes/cyclobutenes (ladderenes) synthesized via ROMP to generate the polyladderene architecture. Similar to the Ramirez study, sonication resulted in the formation of

block copolymers consisting of unreacted and reacted mechanophore (~37% activation after 2 hours of sonication). In this case, mechanophore activation involves the rapid unzipping of continuous stretches of the ladderene repeat to yield large blocks of polyacetylene that self-assembled into semiconducting nanowires. In addition to the intense change in electronic properties, the unzipping released an abundance of stored length, roughly 10 Å per monomer. The increased length came from the complete unravelling of the ladderene subunits and the mechanically induced *cis*-to-*trans* isomerization of the nascent olefin in the ladderene. The combination of released length, enhanced single molecule toughness, and change in electronic properties is one of the

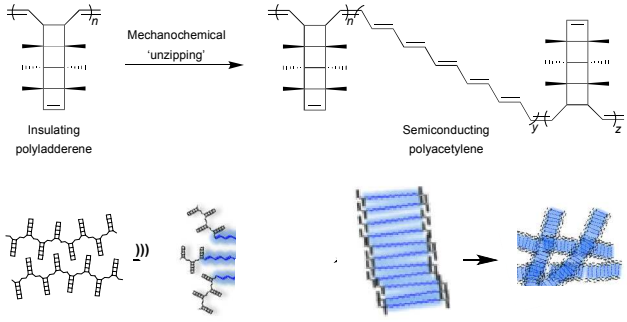

Fig. 9 a) Cartoon sketch demonstrating the release of stored length from cyclic mechanophores. b) The release of stored length from a macrocyclic cinnamate dimer in response to an applied force. c) Cartoon representation of the formation of ordered morphologies arising from the sonication of homopolymers comprised of *g*DCC mechanophores. Reprinted with permission from ref. 37. Copyright (2012) American Chemical Society.

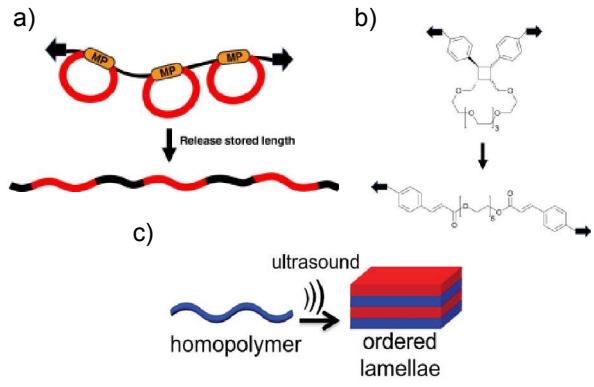

Fig. 10 Top: the mechanochemical unzipping of polyladderene leads to a large release of stored length accompanied by pronounced changes in electronic properties. Bottom: the unveiled blocks of polyacetylene spontaneously aggregate in solution to form semiconducting nanowires. Figure adapted from ref. 76.

most potent demonstrations to date of the potential of MMP remodeling.

5. Conclusions and future outlook

The creative use of mechanophore-rich architectures has enabled new methods and brought access to new properties to the field of polymer mechanochemistry. Aside from the simple scale of mechanophore synthesis, the subsequent polymerization strategies of MMPs are only modestly more involved than those required in chain-centered mechanophore polymers, and in our experience the benefits derived from using MMPs far outweigh the marginal cost in effort to produce them. Looking ahead, however, we note that gains in synthetic methodology have potential advantages, especially if MMPs could be obtained through addition polymerizations, and radical polymerizations in particular. For example, the radical addition polymerization of cyclobutene would yield cyclobutane mechanophores along the polymer backbone.[77]

In terms of properties, a broad question for the future involves understanding circumstances in which the greatest extent of mechanochemical remodeling might be obtained. In the case of polyladderene, for example, less than 50% of mechanophores reacted, and enhanced activation could lead to even more dramatic changes in properties. It is likely, and perhaps necessary, that in the pursuit of this objective MMPs will serve as both a probe of the fundamental relationships that dictate mechanophore activation and the target of efficient remodeling.

To that end, new scalable mechanophore designs might help the dramatic energy absorbing properties of single MMP molecules be optimized and translated to bulk materials. Mechanophores that release large amounts of stored length at forces of interest are therefore desirable, as are synthetic methods that maximize the mechanophore content and minimize the mechanically inert content of MMP backbones.

Additional opportunities include a systematic understanding of how forces are correlated along individual polymer changes – if a given mechanophore reacts, what is the probability that its neighbor on the same backbone also reacts, and what structural features of the polymer and dynamic features of the material and loading environment influence that correlation? Ramirez[37] and Chen[76] both observed that pulsed ultrasound led to continuous stretches of activated mechanophores, but it is not clear whether the activation of one mechanophore effectively increased the reactivity of its neighbor(s), or whether, as expected, the correlation is due entirely to the force distribution along the polymer backbone. One can envision new stress-responsive MMP architectures in which the activation of a single, highly reactive mechanophore leads to a reaction cascade of its originally less reactive neighboring mechanophores, thereby amplifying desired responses at lower forces and in a more region-specific manner along the polymer backbone. Such ideas will require increasingly precise quantitative insights into mechanophore reactivity, and here again MMPs should be quite useful. We note for example the potential to combine the SMFS and pulsed-ultrasound methodologies to achieve greater insights especially into the latter, testing physical models of transient force distributions during sonication using well-defined MMP architectures whose force-dependent reactivity has been quantified by SMFS.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This material is based on work supported by the US Army Research Laboratory and the Army Research Office under Grant W911NF-15-0143 and by the National Science Foundation (CHE-1508566). The authors thank G. Gossweiler for his assistance with figures and Y. Xia for help in creating Fig. 10.

References

1. C. L. Brown and S. L. Craig, *Chem. Sci.*, 2015, **6**, 2158-2165.
2. K. Tashiro, G. Wu and M. Kobayashi, *Polymer*, 1988, **29**, 1768-1778.
3. R. Gostl, J. M. Clough and R. P. Sijbesma, in *Mechanochemistry in Materials*, The Royal Society of Chemistry, 2018, DOI: 10.1039/9781782623885-00053, pp. 53-75.
4. J. Wang, I. Piskun and S. L. Craig, *ACS Macro Letters*, 2015, **4**, 834-837.
5. G. R. Gossweiler, G. B. Hewage, G. Soriano, Q. Wang, G. W. Welshofer, X. Zhao and S. L. Craig, *ACS Macro Letters*, 2014, **3**, 216-219.
6. J. Wang, T. B. Kouznetsova, Z. Niu, M. T. Ong, H. M. Klukovich, A. L. Rheingold, T. J. Martinez and S. L. Craig, *Nat Chem*, 2015, **7**, 323-327.
7. C. R. Hickenboth, J. S. Moore, S. R. White, N. R. Sottos, J. Baudry and S. R. Wilson, *Nature*, 2007, **446**, 423-427.
8. J. M. Lenhardt, M. T. Ong, R. Choe, C. R. Evenhuis, T. J. Martinez and S. L. Craig, *Science*, 2010, **329**, 1057.
9. J. Ribas-Arino, M. Shiga and D. Marx, *Journal of the American Chemical Society*, 2010, **132**, 10609-10614.
10. S. L. Potisek, D. A. Davis, N. R. Sottos, S. R. White and J. S. Moore, *Journal of the American Chemical Society*, 2007, **129**, 13808-13809.
11. P. A. May and J. S. Moore, *Chemical Society Reviews*, 2013, **42**, 7497-7506.
12. G. Lligadas, B. M. Rosen, M. J. Monteiro and V. Percec, *Macromolecules*, 2008, **41**, 8360-8364.
13. D. Konkolewicz, Y. Wang, P. Krys, M. Zhong, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Polymer Chemistry*, 2014, **5**, 4396-4417.
14. D. Konkolewicz, Y. Wang, M. Zhong, P. Krys, A. A. Isse, A. Gennaro and K. Matyjaszewski, *Macromolecules*, 2013, **46**, 8749-8772.
15. S. Akbulatov and R. Boulatov, *ChemPhysChem*, 2017, **18**, 1422-1450.

16. Z. S. Kean, G. R. Gossweiler, T. B. Kouznetsova, G. B. Hewage and S. L. Craig, *Chem Commun (Camb)*, 2015, **51**, 9157-9160.
17. M. J. Kryger, A. M. Munaretto and J. S. Moore, *Journal of the American Chemical Society*, 2011, **133**, 18992-18998.
18. R. Stevenson and G. De Bo, *Journal of the American Chemical Society*, 2017, **139**, 16768-16771.
19. K. L. Berkowski, S. L. Potisek, C. R. Hickenboth and J. S. Moore, *Macromolecules*, 2005, **38**, 8975-8978.
20. J. M. Lenhardt, A. L. Black and S. L. Craig, *Journal of the American Chemical Society*, 2009, **131**, 10818-10819.
21. K. S. Suslick and G. J. Price, *Annual Review of Materials Science*, 1999, **29**, 295-326.
22. M. M. Caruso, D. A. Davis, Q. Shen, S. A. Odom, N. R. Sottos, S. R. White and J. S. Moore, *Chemical Reviews*, 2009, **109**, 5755-5798.
23. A. L. Black, J. M. Lenhardt and S. L. Craig, *Journal of Materials Chemistry*, 2011, **21**, 1655-1663.
24. E. W. Flosdorf and L. A. Chambers, *Journal of the American Chemical Society*, 1933, **55**, 3051-3052.
25. M. V. Encina, E. Lissi, M. Sarasúa, L. Gargallo and D. Radic, *Journal of Polymer Science: Polymer Letters Edition*, 1980, **18**, 757-760.
26. G. J. Price and P. F. Smith, *Polymer International*, 1991, **24**, 159-164.
27. G. J. Price and P. F. Smith, *Polymer*, 1993, **34**, 4111-4117.
28. J. M. Lenhardt, A. L. Black, B. A. Beiermann, B. D. Steinberg, F. Rahman, T. Samborski, J. Elsakr, J. S. Moore, N. R. Sottos and S. L. Craig, *Journal of Materials Chemistry*, 2011, **21**, 8454-8459.
29. M. N. Silberstein, L. D. Cremar, B. A. Beiermann, S. B. Kramer, T. J. Martinez, S. R. White and N. R. Sottos, *Journal of the Mechanics and Physics of Solids*, 2014, **63**, 141-153.
30. M. N. Silberstein, K. Min, L. D. Cremar, C. M. Degen, T. J. Martinez, N. R. Aluru, S. R. White and N. R. Sottos, *Journal of Applied Physics*, 2013, **114**, 023504.
31. P. Dopieralski, P. Anjukandi, M. Ruckert, M. Shiga, J. Ribas-Arino and D. Marx, *Journal of Materials Chemistry*, 2011, **21**, 8309-8316.
32. S. Strandman, J. E. Gautrot and X. X. Zhu, *Polymer Chemistry*, 2011, **2**, 791-799.
33. B. Lee, Z. Niu, J. Wang, C. Slebodnick and S. L. Craig, *Journal of the American Chemical Society*, 2015, **137**, 10826-10832.
34. A. L. B. Ramirez, A. K. Schmitt, M. K. Mahanthappa and S. L. Craig, *Faraday Discussions*, 2014, **170**, 337-344.
35. A. L. B. Ramirez, Z. S. Kean, J. A. Orlicki, M. Champhekar, S. M. Elsakr, W. E. Krause and S. L. Craig, *Nat Chem*, 2013, **5**, 757-761.
36. H. M. Klukovich, T. B. Kouznetsova, Z. S. Kean, J. M. Lenhardt and S. L. Craig, *Nat Chem*, 2013, **5**, 110-114.
37. A. L. Black Ramirez, J. W. Ogle, A. L. Schmitt, J. M. Lenhardt, M. P. Cashion, M. K. Mahanthappa and S. L. Craig, *ACS Macro Letters*, 2012, **1**, 23-27.
38. J. M. Lenhardt, J. W. Ogle, M. T. Ong, R. Choe, T. J. Martinez and S. L. Craig, *Journal of the American Chemical Society*, 2011, **133**, 3222-3225.
39. D. Wu, J. M. Lenhardt, A. L. Black, B. B. Akhremitchev and S. L. Craig, *Journal of the American Chemical Society*, 2010, **132**, 15936-15938.
40. Z. S. Kean, A. L. B. Ramirez and S. L. Craig, *Journal of Polymer Science Part A: Polymer Chemistry*, 2012, **50**, 3481-3484.
41. H. Zhang, X. Li, Y. Lin, F. Gao, Z. Tang, P. Su, W. Zhang, Y. Xu, W. Weng and R. Boulatov, *Nature Communications*, 2017, **8**, 1147.
42. P. A. May, N. F. Munaretto, M. B. Hamoy, M. J. Robb and J. S. Moore, *ACS Macro Letters*, 2016, **5**, 177-180.
43. J. S. Moore and S. I. Stupp, *Macromolecules*, 1990, **23**, 65-70.
44. Z. S. Kean, Z. Niu, G. B. Hewage, A. L. Rheingold and S. L. Craig, *Journal of the American Chemical Society*, 2013, **135**, 13598-13604.
45. J. Frenkel, *Acta Physicochim. USSR*, 1944, **19**, 51-76.
46. S. Koda, H. Mori, K. Matsumoto and H. Nomura, *Polymer*, 1994, **35**, 30-33.
47. K. Imato, T. Kanehara, S. Nojima, T. Ohishi, Y. Higaki, A. Takahara and H. Otsuka, *Chem Commun (Camb)*, 2016, **52**, 10482-10485.
48. Y. Chen, H. Zhang, X. Fang, Y. Lin, Y. Xu and W. Weng, *ACS Macro Letters*, 2014, **3**, 141-145.
49. J. K. Stille, *Journal of Chemical Education*, 1981, **58**, 862.
50. M. A. Hillmyer, W. R. Laredo and R. H. Grubbs, *Macromolecules*, 1995, **28**, 6311-6316.
51. R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413-4450.
52. O. A. Scherman, H. M. Kim and R. H. Grubbs, *Macromolecules*, 2002, **35**, 5366-5371.
53. J. M. Pollino, L. P. Stubbs and M. Weck, *Macromolecules*, 2003, **36**, 2230-2234.
54. A. Leitgeb, J. Wappel and C. Slugovc, *Polymer*, 2010, **51**, 2927-2946.
55. P. Hodge and S. D. Kamau, *Angewandte Chemie International Edition*, 2003, **42**, 2412-2414.
56. G. R. Gossweiler, T. B. Kouznetsova and S. L. Craig, *J Am Chem Soc*, 2015, **137**, 6148-6151.
57. J. Wang, T. B. Kouznetsova, Z. S. Kean, L. Fan, B. D. Mar, T. J. Martínez and S. L. Craig, *Journal of the American Chemical Society*, 2014, **136**, 15162-15165.
58. R. H. Lambeth, S. J. Pederson, M. Baranoski and A. M. Rawlett, *Journal of Polymer Science Part A: Polymer Chemistry*, 2010, **48**, 5752-5757.
59. J. M. Lenhardt, A. L. Black Ramirez, B. Lee, T. B. Kouznetsova and S. L. Craig, *Macromolecules*, 2015, **48**, 6396-6403.
60. B. Cheng and S. Cui, in *Polymer Mechanochemistry*, ed. R. Boulatov, Springer International Publishing, Cham, 2015, DOI: 10.1007/128_2015_628, pp. 97-134.
61. K. C. Neuman and A. Nagy, *Nat Methods*, 2008, **5**, 491-505.
62. T. Hugel and M. Seitz, *Macromolecular Rapid Communications*, 2001, **22**, 989-1016.
63. A. Janshoff, M. Neitzert, Y. Oberdörfer and H. Fuchs, *Angewandte Chemie International Edition*, 2000, **39**, 3212-3237.
64. M. F. Pill, K. Holz, N. Preußke, F. Berger, H. Clausen-Schaumann, U. Lüning and M. K. Beyer, *Chemistry – A European Journal*, 2016, **22**, 12034-12039.
65. M. Grandbois, M. Beyer, M. Rief, H. Clausen-Schaumann and H. E. Gaub, *Science*, 1999, **283**, 1727.
66. T. B. Kouznetsova, J. Wang and S. L. Craig, *ChemPhysChem*, 2017, **18**, 1486-1489.

67. Z. S. Kean, A. L. B. Ramirez, Y. F. Yan and S. L. Craig, *Journal of the American Chemical Society*, 2012, **134**, 12939-12942.
68. J. Wang, T. B. Kouznetsova, Z. Niu, A. L. Rheingold and S. L. Craig, *The Journal of Organic Chemistry*, 2015, **80**, 11895-11898.
69. G. I. Peterson, M. B. Larsen, M. A. Ganter, D. W. Storti and A. J. Boydston, *ACS Applied Materials & Interfaces*, 2015, **7**, 577-583.
70. D. Schütze, K. Holz, J. Müller, M. K. Beyer, U. Lüning and B. Hartke, *Angewandte Chemie International Edition*, 2015, **54**, 2556-2559.
71. M. J. Paulusse Jos and P. Sijbesma Rint, *Journal of Polymer Science Part A: Polymer Chemistry*, 2006, **44**, 5445-5453.
72. J. Wang, M. T. Ong, T. B. Kouznetsova, J. M. Lenhardt, T. J. Martínez and S. L. Craig, *The Journal of Organic Chemistry*, 2015, **80**, 11773-11778.
73. B. Lee, Z. Niu and S. L. Craig, *Angewandte Chemie International Edition*, 2016, **55**, 13086-13089.
74. J. Wang, T. B. Kouznetsova, R. Boulatov and S. L. Craig, *Nature Communications*, 2016, **7**, 13433.
75. M. J. Kryger, M. T. Ong, S. A. Odom, N. R. Sottos, S. R. White, T. J. Martinez and J. S. Moore, *Journal of the American Chemical Society*, 2010, **132**, 4558-4559.
76. Z. Chen, J. A. M. Mercer, X. Zhu, J. A. H. Romaniuk, R. Pfattner, L. Cegelski, T. J. Martinez, N. Z. Burns and Y. Xia, *Science*, 2017, **357**, 475.
77. X.-P. Chen, B. A. Sufi, A. B. Padias and H. K. Hall, *Macromolecules*, 2002, **35**, 4277-4281.

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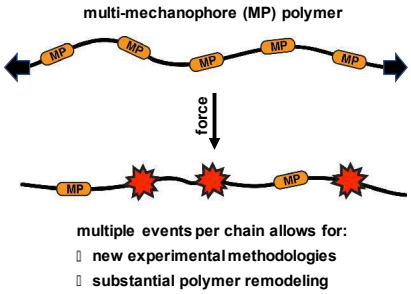

Multi-mechanophore polymers provide advantages in characterization and function relative to chain-centered, single mechanophore polymers.