The many flavors of mechanochemistry and its plausible conceptual underpinnings.

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Numerous apparently-dissimilar observations discussed under the term 'Mechanochemistry' probably share a similar physical mechanism enabling mechanical motion to drive otherwise endergonic reactions. This Review discusses what studying reactions in stretched polymers and model macrocycles has taught us about this mechanism.

Abstract. Mechanochemistry described diverse phenomena in which mechanical load of some form affects chemical reactivity. The fuzziness of this definition means that it covers processes as seemingly disparate as operation of motor proteins, organic synthesis in ball milling, reactions at a propagating crack, chemical actuation, polymer fragmentation in fast solvent flows and in mastication. In some manifestations of mechanochemistry, macroscopic motion powers otherwise endergonic reactions. In others, spontaneous chemical reactions drive mechanical motion. Neither requires thermal or electrostatic gradients. Although distinct manifestations of mechanochemistry are conventionally treated as conceptually independent, the continuing evolution of the field from a collection of empirical observations to a rigorous discipline requires identifying the underlying common principles. In chemistry, the velocity of a flask moving in space has no effect on the rate of the reaction in it. In mechanochemistry, the rate at which a material is deformed affects which and how many bonds break. The unifying feature of mechanochemical phenomena may be coupling between inertial motion at the micro- to macroscales and changes in chemical bonding enabled by transient build up and relaxation of strains, from macroscopic to molecular. This dynamic coupling across multiple length and timescales also greatly complicates conceptual understanding of its manifestations.

INTRODUCTION

Little consensus exists on what mechanochemistry is, with several thoughtful reviews[1,2] devoting many paragraphs to enumerating observations that are or are not mechanochemistry. The mechano prefix references mechanical (inertial) motion, i.e., collective translation of between ~10^9 atoms comprising an organelle transported by kinesin or the elongational solvent flow generated by a collapsing cavitation bubble, to >10^{17} atoms of a milling ball. Yet, perhaps the simplest and best-known example of mechanical motion causing a chemical reaction powers a diesel engine, whereby nearly adiabatic compression of a fuel/air mixture by inertial motion of the piston ignites it, i.e., induces a reaction. Including this type of energy transduction in mechanochemistry holds little value. In other words, coupling (or, in the IUPAC definition, "direct absorption of mechanical energy"), whether isothermal or not, alone does not make mechanochemistry. A more detailed if unwieldy definition of "chemistry in which the change of the thermodynamic state variables and functions of a given chemical system, including at least one solid phase, can be ascribed to the effects of non-hydrostatic mechanical stresses, and of the resulting plastic strain."[3] applies to mechanochemistry of extended solids but excludes molecular mechanochemistry, which often occurs in solutions. The latter may be the easiest to define unambiguously as rearrangements of chemical bonds driven by dissipation of transient molecular strain generated by mechanical (inertial) motion (Figure 1).

Based on distinct sets of experimental approaches, interpretational frameworks and scientific priorities, contemporary mechanochemistry is made up of 3 partly overlapping subfields: bio, polymer and powder

mechanochemistries. These study, respectively (1) the operation of motor proteins[4-8] and certain enzymes;[9] (2) reactions of stretched polymer chains, both synthetic[10-18] and biological;[19-21] (3) reactions caused by grinding, ball milling or similar manipulation of powders of metals,[22] inorganic salts,[3,23-28] metal-organic[3,29-32] and organic[33-41] compounds, including polymers.[42,43] Remodeling of contacting crystalline surfaces in relative motion and other tribochemical phenomena[44] seem to overlap most with powder mechanochemistry.[1] A few reactions recur across the subfields, suggesting a common physical origin. For example, polymer chains fracture in milled powders, extruded melts, sonicated solutions, films between moving surfaces, or AFM experiments. Several organic and coordination compounds dissociate upon grinding as powders and when incorporated in polymer chain stretched in an elongational flow. Motor proteins, a few synthetic organic molecules,[45-47] photoactuating polymers[10,48-50] and crystals all convert structural changes during an exergonic reaction into microscopic motion. We suggest that a few observations outside the main subfields, including reactions of molecules deformed by an STM tip[51-54] or by hydrostatic pressure[55] and reactions of certain polymers at interfaces[56] represent models of molecular mechanochemistry.
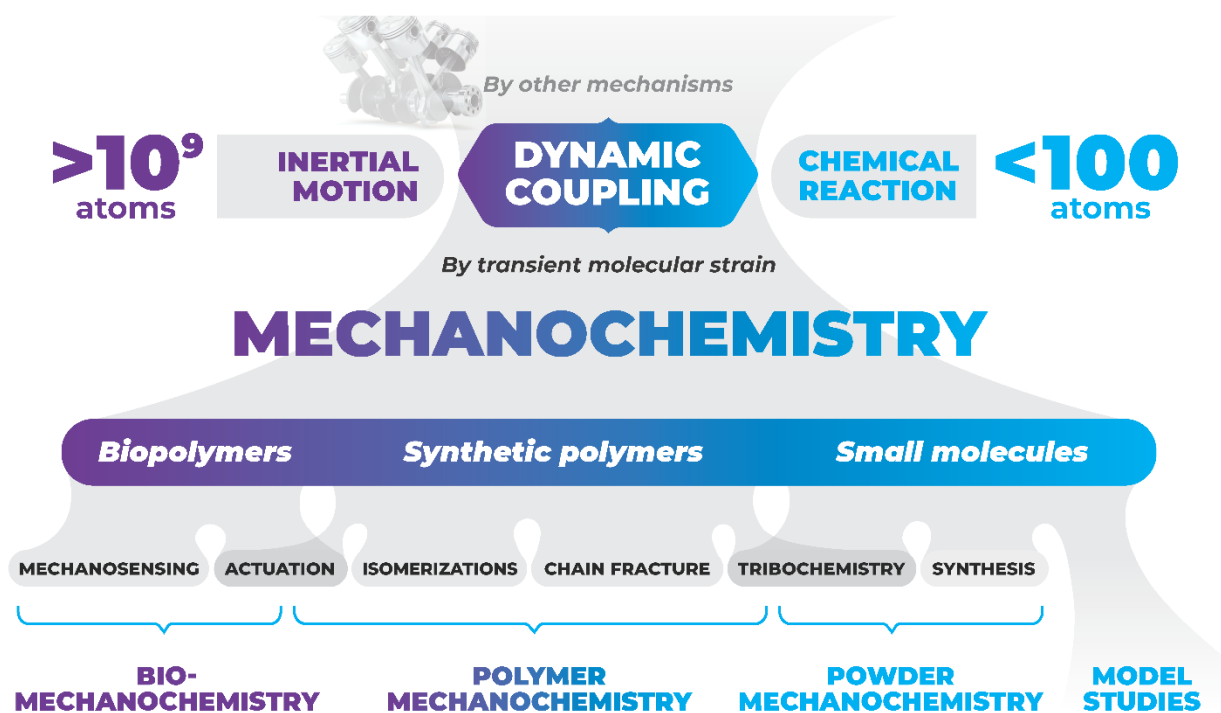

Figure 1. **A proposed taxonomy of molecular mechanochemistry**. As this review will argue, to date reactions in polymers and model compounds provide the clearest evidence of the role of transient molecular strain in enabling mechanochemistry and suggest a plausible strategy for developing a comprehensive conceptual framework of mechanochemistry by exploiting the capacity of force to quantify strain across the many lengthscales of mechanochemistry.

Reported mechanochemical transformations span a continuum from simple conformational transitions over small (<10 kcal/mol) activation barriers through disruption of weak (van-der-Waals, π, ionic and hydrogen) interactions and coordination bonds to scissions of covalent bonds. Mechanochemistry of weak interactions is reversible and usually require smaller strains than covalent mechanochemistry to occur at a detectable rate (with a few important exceptions[57]). Biomechanochemistry (or sometimes mechanobiochemistry) is dominated by rearrangements of such non-covalent bonds, which affect the tertiary and quaternary structures of biopolymers, stabilities of their complexes and may result in load-

dependent catalytic efficiencies, for example of ATPases. Fundamental studies in polymer mechanochemistry has focused primarily on irreversible scissions of covalent bonds, whereas mechanochemistry of weak interactions is increasingly exploited to improve mechanical properties of polymers. Powder mechanochemistry includes abundant examples of the formation and scission of both covalent and non-covalent bonds.

The majority of contemporary literature in mechanochemistry describe the search for new mechanochemical reactions and new applications of such reactions, particularly in synthesis and material science. The rarer studies of the molecular mechanisms of mechanochemical reactions illustrate the importance of integrating experimental and computational approaches, both in synthetic[58-60] and biological[57,61] polymers, for gaining potentially generalizable insights into the perturbations of the molecular geometry and electronic structure of the reactive sites responsible for mechanochemistry. The additional challenges of atomistic modeling of milling experiments probably explain the lack of such integrated approaches in powder mechanochemistry.[62] Finally, very little work has been reported on identifying the physical steps responsible for coupling of macro- or microscopic motion to chemical reactions, and on developing quantitatively predictive descriptions of this coupling.[27,63,64] The reason is probably the limitations of experimental and computational tools to study dynamics and energy flows across multiple length- and timescales.

At the most basic level, mechanochemistry appears to represent a chemical mechanism of relieving externally imposed strain. When this strain is imposed on a bulk material, the competition between chemical (mechanochemistry) and physical (mechanophysics[1]) dissipation mechanisms greatly complicates molecular interpretation of the resultant behavior. For example, considerable uncertainty exists even about which macroscopic parameters affect mechanochemical reactions in milled solids. At the other extreme, mechanochemistry of isolated synthetic macromolecules is amenable to quantitative predictions, at least at modest rates of stretching. Indeed, of all subfields of mechanochemistry, polymer mechanochemistry comes closest to having a coherent atomistic theoretical foundation based on the idea of local restoring force as a measure of kinetically significant molecular strain (see next section).

At least 4 attributes of synthetic polymers make them particularly suited for advancing conceptual understanding of mechanochemistry. First, polymer mechanochemistry is attainable in isolated molecules, making it considerably easier to interrogate experimentally and model computationally than mechanochemistry of bulk solids or interfaces. Second, synthetic polymers present numerous opportunities to vary mechanochemical response incrementally by changing the composition and topology of the chains, the properties of reactive sites and their number per chain. Third, incorporating small reactants into polymer chains provides a direct means of comparing mechanochemistry of the same reactive site under different loading scenarios and in different physical states (e.g., milled powders, sonicated solutions, single-molecule experiments). Fourth, the type of molecular strain responsible for reactions in stretched polymers is reproducible in individual monomers using molecular design rather than coupled macroscopic motion, vastly expanding the range of experimental and computational tools that can be brought to characterize the resulting reactivity.

The breadth and diversity of contemporary mechanochemistry makes comprehensive reviews of the field untenable, but numerous narrower accounts published recently include compilations of mechanochemical reactions of small molecules,[32] biopolymers[19], and synthetic polymers;[11,65,66] the effect of polymer architectures on their mechanochemistry;[12,15,67] experimental[68-72] or computational[73-75] methodology; laboratory and industrial applications, including organic[34-36,38-40,76,77] and materials[30,78,79] synthesis, polymer modifications and recycling,[43] and emerging technologies.[14,80,81]

To complement this vast literature, the current review aspires to present mechanochemistry from the perspective of developing a unifying description of it based on a few fundamental physical principles. While the path to such description remains to be identified, the likely starting point is the existing approach to quantifying mechanochemical reactivity in stretched (bio)polymers, discussed in the next section. We next review covalent polymer mechanochemistry to illustrate the utility of this framework in guiding the search for new mechanochemical reactivity and rationalizing existing observations. The penultimate section discusses additional challenges of quantifying mechanochemical reactivity of molecular powders compared to polymers. The final section describes the strategy of reproducing mechanochemical reactivity without the complexities of coupled motion (model studies) and its role in validating the force-based formalism. For reasons of space, we prioritize recent experimental work and include only computational studies validated against experiment or that can be compared with experiment. We recognize that in the absence of a theoretical framework of mechanochemistry, our conceptual perspective and experimental observations chosen to support it are subjective and we refer the reader to numerous reviews cited above for different takes on mechanochemistry.

FORCE-BASED APPROACH TO QUANTIFYING MECHANOCHEMICAL REACTIVITY

A qualitative connection between molecular mechanochemistry and the well-established increased reactivity of many small strained molecules relative to their strain-free analogs[13,82] was long noted.[83-86] Because molecular strain, unlike its macroscopic analog, is a qualitative concept, its quantitative effects on reactivity are discussed in terms of strain energy, i.e., the enthalpy (or free energy) of the strained molecule relative to its (often hypothetical) strain-free reference. The activation energy of a reaction of a strained molecule is lower than that of its strain-free analog by a fraction of this strain energy. This fraction is easy to predict for diverse small-molecule reactions, underlying the utility of the strain-energy approach.

The extensive (i.e., size-dependent) nature of energy makes this approach entirely unsuitable for quantifying mechanochemical reactivity. For example, the strain energy of a stretched macromolecule increases rapidly with its size, whereas the kinetic stability of a reactive site in such a chain is independent of this size.[87,88] Consequently, this chain strain energy does not allow the kinetic stabilities of its constituent monomers to be predicted. The same is likely true for reactions in a mechanically deformed organic crystal.[89] Replacing strain energy with its gradient offers a workaround, at least for molecules that are strained primarily along a single molecular axis. While the extreme aspect ratios of macromolecular geometries create such a unique molecular axis, an increasing number of dissociation reactions that proceed both in stretched polymers and in milled powders of the equivalent small molecules suggest that mechanical load strains even non-macromolecular substrates anisotropically.

Reversibly deforming an object (e.g., by stretching a single macromolecule or compressing a single crystal) increases its energy and creates restoring force. These two quantities are related: force is the gradient of excess (strain) energy along the force vector, i.e., force quantifies how sensitive the strain energy is to a miniscule change in the distortion. While energy is extensive and scalar, force is intensive and vectoral, which offers two advantages for describing mechanochemistry. First, it makes force, in theory, suitable for relating dynamics across the range of the underlying lengthscales. For example, the stress tensor quantifying the load on bulk material could be expressed as a distribution of restoring forces of its constituent molecules.[90,91] If these molecules are polymers, their single-chain forces determine the restoring force of each strained monomer comprising each chain. This restoring force of each monomer determines its kinetic stability. Hence, in theory, force allows the kinetic and thermodynamic stability of an average molecule in a deformed organic material (or an average monomer in a loaded polymer) to be expressed as a function of the macroscopic load (e.g., stress

4

tensor). Second, the directional (vectoral) nature of force accommodates the expectation that deforming a molecule along different axes should affect its kinetic stability differently and that for each axis, stretching should have a different effect from compression.

The known mechanochemical reactions or organic molecules are thermally activated, i.e., their kinetics follow the transition state theory (TST). The spectacular success of TST owes much to temperature and pressure being both rigorously defined molecular quantities and macroscopic parameters routinely controlled and measured in the lab.[92] Force, at least as a measure of strain, is neither.[93] This explains why the existing force-based models of reaction kinetics of a stretched polymer[94,95] are empirical, albeit rationalizable in the theoretical language of chemical kinetics. These models also enable quantum-chemical calculations of kinetic stabilities of stretched polymers[57,73-75,96] and systematization and rationalization of the results of single-molecule force experiments. Conversely, treating force as an abstract quantity devoid of molecular interpretation hinders analysis of constraints, accuracy, predictive capacities and limits of applicability of these models or generalizing them beyond stretched macromolecules. It also seeds confusion of what force is, as exemplified by recurred characterizations of mechanochemical reactions in the literature as "force-catalyzed".

Consequently, the current force-based approach to quantifying mechanochemical reactivity is best understood within a specific physical model of a reacting polymer chain, which exploits the localized nature of chemical reactions, i.e., that reactive sites contain just a few atoms (a polymer may have multiple reactive sites, but as long as each acts independently only one needs to be considered).[16] The atomistic intractability of polymer mechanochemistry arises from interactions among billions of atoms comprising the rest of the polymer chain and the surroundings that stretch the chain and determine the molecular strain of the reactive site. However, because these interactions are not directly affected by the localized reactions, their effect on the reaction can be captured by a simple model, leaving only a small fraction of the molecular degrees of freedom of a stretched polymer requiring the expensive explicit quantum-mechanical description.[87,97]

The result is a reacting stretched macromolecule approximated by a short segment of the chain containing the reactive site with a pair of its terminal atoms bridged and pushed away by a massless compressed harmonic spring. Unlike a stretched molecule alone, this hybrid can exist in stationary states (nuclear configurations in internal mechanical equilibrium), which means that its ensemble properties are amenable to statistical-mechanical treatment[97] and consequently, its reaction probability are available from the energy difference of two such states using the TST. This energy difference reflects the changes both in chemical bonding, molecular geometry and electronic structure of the reacting molecular segment and in the length of the compressed spring needed to remain in mechanical equilibrium with the changing molecular geometry.

While the energies of the molecular fragment are determined by the Schrodinger equation, the change in the strain energy of a very soft spring is simply its restoring force, f, times the change in the spring length, or, equivalently, in the ensemble-average separation of the two atoms connecting the molecular fragment to the spring in the two states, $\langle \Delta q(f) \rangle$ at the same force (eq. 1). Eq. 1 allows the activation energy of a reaction in a polymer stretched to force f, to be estimated at varying degrees of approximation. Assuming that both the energy and the dimensions of the molecular segment are independent of the applied force gives the most simplistic estimate of the activation energy changing linearly with force, $\Delta\Delta G^{\ddagger} \propto f$. In theory assuming that the molecular dimensions but not the energy depend on the applied force should improve the estimate by accounting for the Hammond effects.[98] In practice, the difficulty of estimating the force-dependence of $\langle \Delta q \rangle$ without optimizing force-coupled geometries makes this approach unreliable.[99-101] The most demanding and accurate approach calculates

5

the geometry and the energy of each kinetically-relevant conformer of the molecular fragment in each state for each value of f. It remains the only approach shown to reproduce single-molecule force measurements,[102-104] so far the most stringent experimental validation of mechanochemical computations. For 4 reactions magnitudes and causes of errors of different approximations of eq. 1 and practical workarounds were analyzed.[105,106]

$$\Delta G^{\ddagger}(f) = \underbrace{G_{TS}(f) - G_R(f)}_{molecular\ fragment} - \underbrace{f\langle\Delta q(f)\rangle}_{spring} \qquad (1)$$

Although practical implementation of this model poses numerous questions (e.g., What's the shortest chain segment below which the model no longer represents the reacting chain?[16]), it defines the physical basis of both the force and how it affects the activation energy. It shows that force is always associated with a specific internal coordinate of the reactive site (e.g., internuclear distance) and is the gradient of strain energy of the whole system (e.g., a stretched macromolecule and its surroundings) along this coordinate. Force reflects the contribution to the activation barrier of changes in the strain energy of non-reactive degrees of freedom. Importantly, the model shows that at any force the kinetic and thermodynamic stabilities of any reactive site are independent of the physical mechanism generating this force. These mechanisms include constraining the chain end-to-end distance as in single-molecule force spectroscopy (SMFS), cumulative interactions of multiple backbone atoms with molecules of a flowing solvent (in polymer mechanochemistry), transient compressive loads in powder mechanochemistry and AFM tip or suitably designed macrocycles in model studies.

POLYMER MECHANOCHEMISTRY

Polymer mechanochemistry studies how stretching a polymer chain changes the kinetic and/or thermodynamic stabilities of its constituent monomers, and how to exploit such changes to improve existing and create new materials,[10,12] devices and processes[14,80] and to advance our fundamental understanding of chemical reactivity.[11,13] Mechanochemical reactions of polymers are ubiquitous. Simply stretching an elastic band can break some of its C-C and C-S bonds in microseconds. These bond scissions are mechanochemical because they do not occur unless the band is stretched or "mechanically loaded".

Experimental techniques of polymer mechanochemistry

Fundamental studies of polymer mechanochemistry require experimental tools to measure the rates and products of diverse reactions as a function of the restoring force of the reactive site. Such tools do not yet exist. The existing techniques, dominated by single-molecule force spectroscopy (SMFS) and ultrasonication of polymer solutions, allow either some control over the force stretching a single polymer chain, or spectroscopic characterization of the products of mechanochemical reactions but not both. Only reactions accelerated in stretched chains are detectable and quantitation of reaction kinetics requires a number of assumptions of unknown validity.

In SMFS of covalent mechanochemistry, a single macromolecule is anchored covalently to an AFM tip at one end and a slide at the other, although the nature of the anchoring bonds is not always known. SMFS of biopolymers also uses optical and magnetic tweezers.[71] Retracting the slide from the tip, usually at a constant linear velocity of $0.01 - 1\ \mu m/s$, stretches the chain, deflecting the tip. An empirical equation converts this deflection to force, which is recorded as a function of the chain extension, estimated from the tip/slide separation. As the chain is stretched its further elongation requires increasingly high force. An abrupt flattening of the force-to-extension slope with increasing force ("plateau") therefore signals a mechanochemical reaction that increases the chain contour length and whose activation energy barrier

has been reduced by force to 15 – 18 kcal/mol. Competing reactions (e.g., detachment of the chain from the slide) limit the maximum achievable force to <3 nN, making reactions with barriers >18 kcal/mol at 3 nN unobservable by SMFS.

Molecular interpretation of the plateau forces is complicated by the likelihood that they systematically underestimate the restoring force of the stretched chain and deviate from the ensemble values each by unknown increments. The former reflects SMFS only measuring the longitudinal, f_z, component of the restoring force of a stretched chain: the more the axis of the chain backbone deviates from the vertical (z) axis defined by the AFM tip movement, the larger the difference between measured and true force is. This deviation results from the lateral offset of the chain attachment locations at the tip and the slide.

The second complication reflects the single-molecule nature of SMFS. A plateau results from the stochastic behavior of just a few monomers, which may deviate arbitrarily far from that of the ensemble. Mechanochemical reactions that elongate the chain by >1.5 nm per monomer make the reaction of each monomer observable and single-molecule effects quantifiable (Figure 2) and suggest that at present measuring enough force/extension curves to approach the ensemble behavior is practically impossible. Simultaneously, statistical tools to extract ensemble parameters from even well-sampled force distributions are lacking. Analyses of curves without resolvable transitions of individual monomers are further complicated by the uncertainty of the number of the reacted monomers and hence the elongation-per-monomer that suggests the nature of the product. Consequently, molecular interpretations of SMFS results require detailed quantum-chemical calculations of the reaction mechanisms and kinetics and demonstrating that they reproduce measured force/extension curves and/or distributions of the transition forces and elongations of individual monomers. Single-molecule effects have long been recognized and exploited in SMFS of biopolymers[107] but the slower kinetics and higher forces usually needed to affect covalent polymer reactions have precluded similar experiments in covalent mechanochemistry.

Most reported mechanochemical reactions of synthetic polymers have been demonstrated only in sonicated polymer solutions. Sound waves at 20 – 500 kHz frequency passing through a liquid create μm-size cavitation bubbles (Figure 3a) whose sudden collapse transiently generates elongational flows capable of stretching polymer chains in the immediate vicinity of the bubble. Unlike SMFS, ultrasonication probes ensemble behavior and the compositions of sonicated solutions are characterizable by size-exclusion chromatography, NMR and optical spectroscopies. The popularity of ultrasonication in experimental polymer mechanochemistry is motivated by its high throughput and technical simplicity, requiring low-cost equipment, no specialized technical expertise and little material.
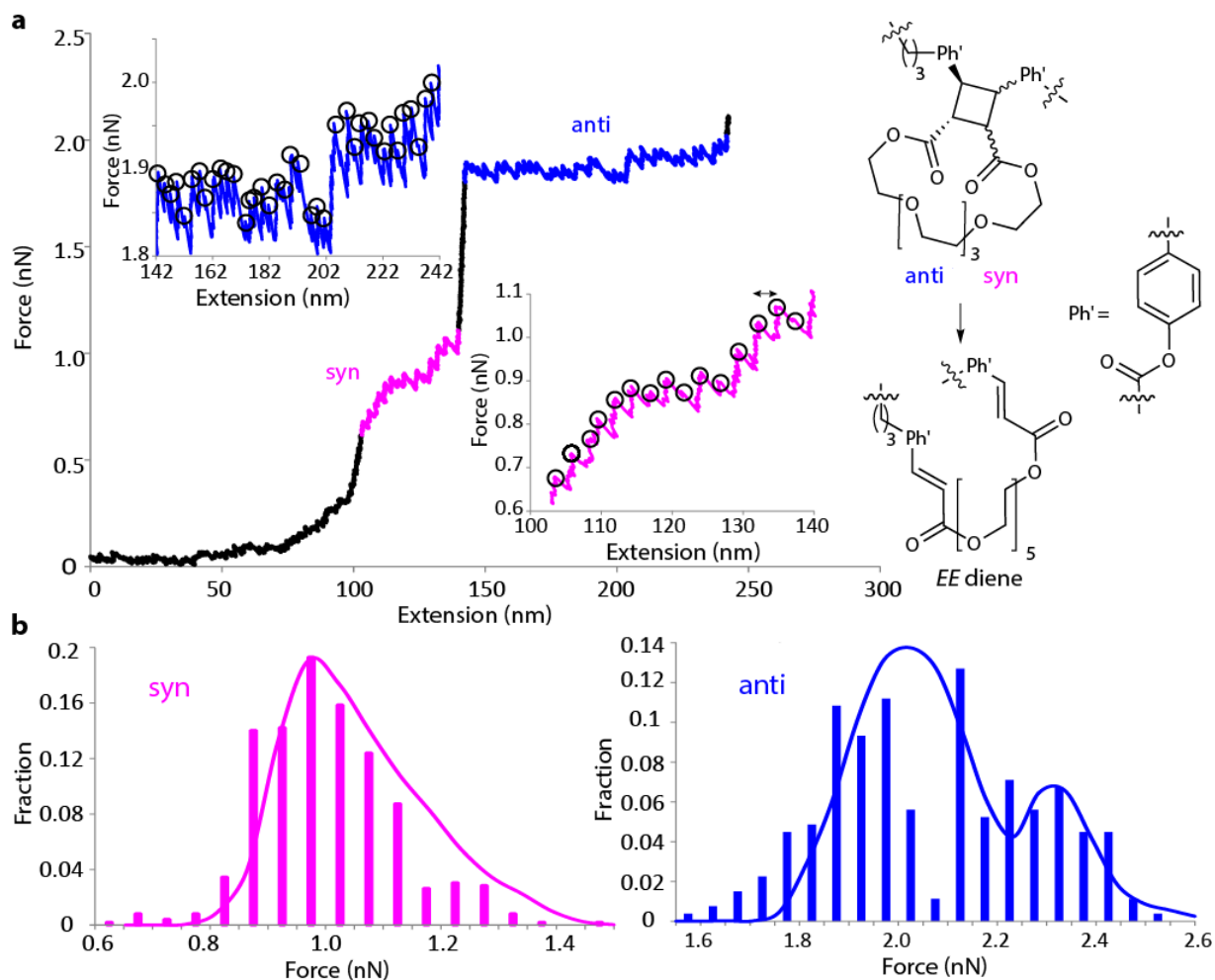
Figure 2. **An example of an output of a SMFS measurement on a mechanochemically active macromolecule**, a copolymer of two isomeric macrocyclic cinnamate dimers. (a) A typical force/extension curve with the two plateau regions highlighted, corresponding to mechanochemical dissociation of the syn- (purple) or anti- (blue) isomers. The magnified plateaus in the insets illustrate their saw-tooth pattern with each circled local force maximum corresponding to dissociation of a single dimer. This saw-tooth pattern reflects the inertial motion of the AFM tip as it slowly adjust to the new chain length. The chain detaches at 2.2 nN, terminating the force/extension curve. (b) The measured (bars) and computed (solid lines) distributions of the dissociation force (color matched to their corresponding plateaus). The measured values derive from 30 force/extension curves and reflect dissociation of 740 dimers. The computed distribution for the same set of polymer lengths studied experimentally is based on force-dependent activation free energies of dissociation calculated at the uMPW1K/6-31+G(d) level of DFT. The broad and complex shapes of the distributions reflect a combination of the stochastic nature of the plateaus, the dependence of the transition force of the length of the stretched segment and potentially randomly varying fraction of the chain restoring force measured experimentally. Adopted from [104] ; reproduced with permission.

Identification of mechanochemical products by NMR spectroscopy of sonicated solutions is often complicated by significant line broadening in such samples and the poor sensitivity when the reaction is limited to a single monomer per polymer chain. Mechanochemical products that are labile on the timescale of a sonication experiment (~10 min) are never characterized, only the products of their subsequent non-mechanochemical reactions. Mechanochromic reactions are often characterized only by UV-vis or fluorescence spectroscopy. While this approach confirms the generation of the expected product, it offers little or no information about side products, particularly if they are non-absorbing and

non-emitting. Sonication may produce complex product mixtures, of which the reported species are a single, not necessarily dominant, component.

Quantitative molecular interpretation of ultrasonication experiments is largely precluded by our ignorance of the microscopic conditions of a reacting chain: how much, how fast and for how long it is stretched, what fraction of the backbone is stretched and what fraction of the dissolved chains is stretched at any time. The intractable complexity of mechanochemistry in sonicated solutions reflects convolution of three dynamic processes: cavitation bubble collapse, chain unfolding and stretching, and mechanochemical reaction. We understand well collapse of an isolated cavitation bubble,[108] stretching of an isolated chain in steady-state planar elongational flows[109] and reaction kinetics of a slowly stretched chain.[88] We don't know how to extend this understanding to experiments dominated by interacting bubble clouds (Figure 3a),[110] which may implode synchronously and produce highly non-uniform elongational flows that evolve rapidly on the timescale of chain unfolding, and the reacting chains that may never reach internal mechanical equilibrium before fracture. Nor do we know the contributions of localized heating[16] and sonolytically generated radicals.[111]
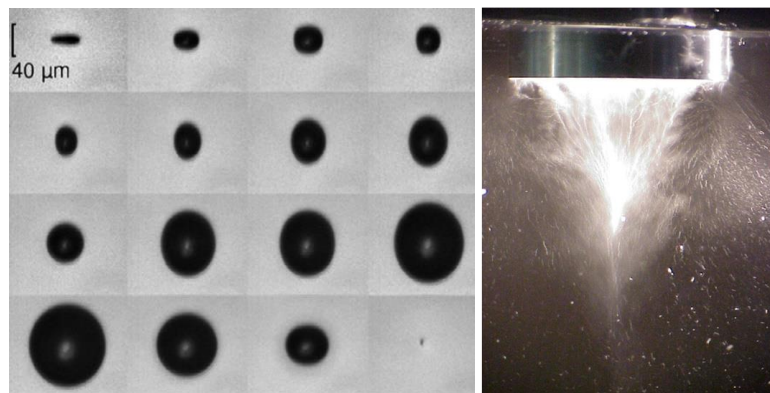

Figure 3 **Acoustic cavitation in liquid**. (a) A time lapsed sequence of micrographs of an isolated cavitation bubble from growth through collapse; sound frequency ~44 kHz, sound pressure amplitude ~159 kPa; the maximum bubble diameter ~100 μm and the total time ~15 μs. Note that bubble implodes >20-times faster than it grows driven by inertial motion of bubble walls. Several micrographs of the static bubble at maximum inflation are omitted. (b) A cloud of cavitation bubbles generated by an immersed ultrasound horn in a liquid. Adopted from [108]. Reproduced with permission.
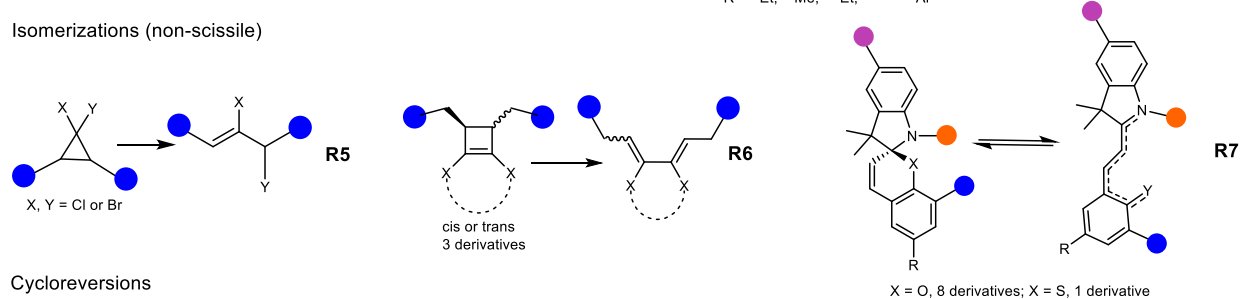
Covalent reactions in stretched polymer chains.

The simplest mechanochemical reaction in polymers is fracture of an overstretched chain by homolysis of a backbone bond. Hundreds of such reactions were demonstrated in solutions, melts and solids of diverse polymers in diverse loading scenarios.[84,112-115] The expected radicals were observed by EPR in solids and frozen solutions, and trapped by reactions with stable organic radicals, such as TEMPO. In elongational flows, however generated, backbone bonds closest to the chain center of mass manifest greatest dissociation probability.[16] A polymer backbone comprised of different bonds often break preferentially at the more liable bond, i.e., mechanochemical fragmentations are moderately chemoselective. This selectivity appears highest in chains containing a single dissociatively labile backbone bond (e.g., **R1**,[116] Figure 4 and refs. [117-119]) close to the chain center. Chain fragmentations by heterolytic dissociation of a covalent backbone bond are rarer,[112,119,120] and the solvent role in governing the balance of homolytic vs. heterolytic cleavage remains unknown. An overstretched chain containing a N-Pd (**R2**,[121] Figure 4) backbone fractures solvolytically, as probably do mechanochemical dissociations of other X-M backbone bonds (X is C, N or P, and M is Pd, Ag or Cu, Pt, Ru, **R3**, [122-125] Figure

4 and ref. [121,126-128]). Overstretched proteins containing backbone S-S bonds may fracture by nucleophilic displacement at S in the presence of a suitable nucleophile,[60] which is the only reported example of bimolecular kinetics in polymer mechanochemistry.
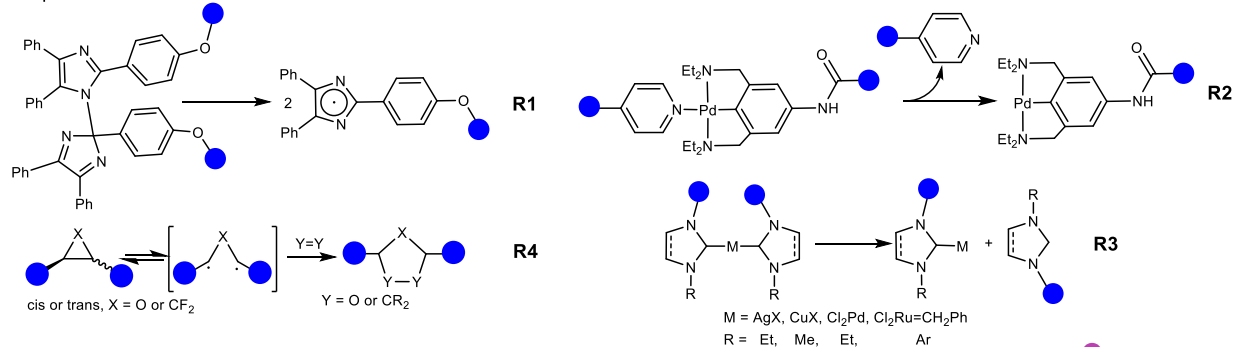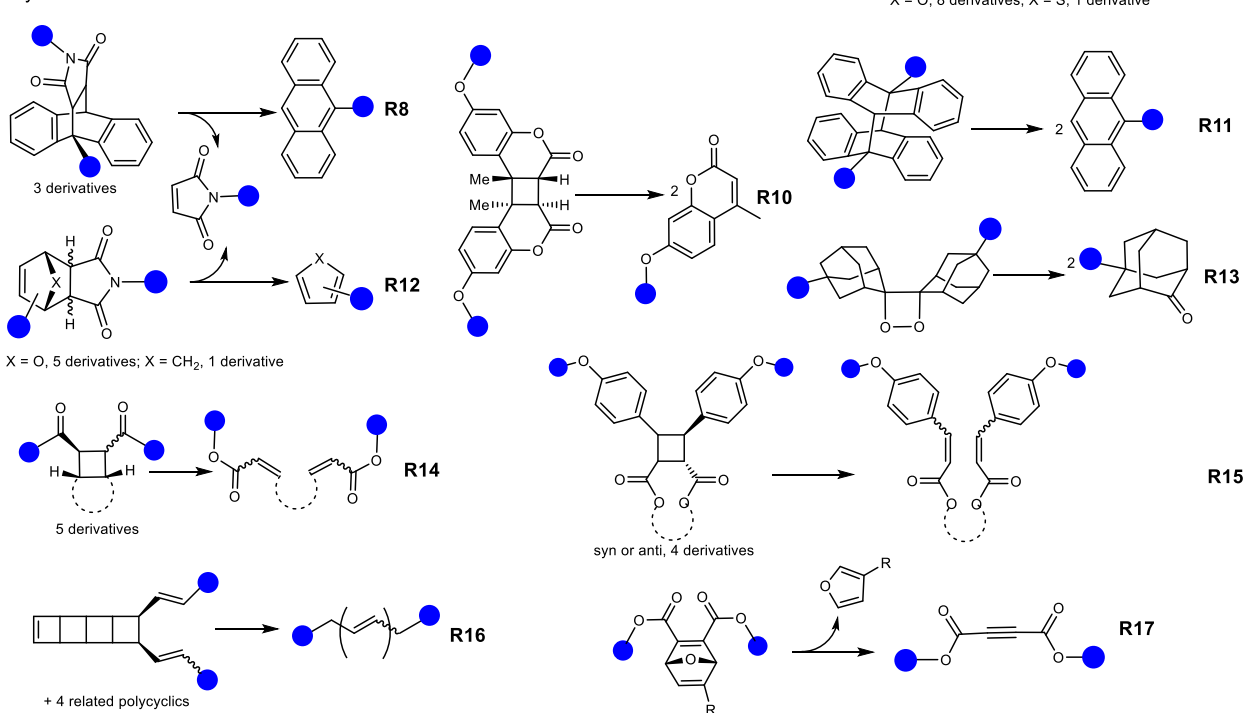

Figure 4. **Illustrative examples of covalent reactions accelerated in stretched polymers**. The circles represent the rest of the polymer, which may contain additional reactive moieties. The biradical intermediate in **R4** was trapped by O_2 or an olefin. In **R7** the orange and magenta circles signify the alternative attachment points of the 2nd polymer arm (see Figure 5).

Mechanochemical homolysis of backbone bonds that are part of a cyclic repeat unit[129,130] does not fracture the chain and may occur reversibly (**R4**).[131,132] Such chains still fracture mechanochemically and irreversibly by homolysis of acyclic backbone bonds.[16,133] Covalent backbones containing hexaarylbiimidazole (**R1**[116]) and analogous moieties[117] reform upon mechanochemical fracture, as do some coordination polymers,[127,134,135] potentially allowing dynamic de-crosslinking and molecular-level damage recovery.

Whereas every reported example of polymer mechanochemical reaction involves an accelerated dissociation of at least one covalent bond, ~35 such reactions are more complex than simple bond dissociations, comprising 2 additional categories: isomerizations[59,136-138] (**R5-7**, Figure 4) and cycloreversions[58,104,139-150] (**R8-16**). While a few reactions were documented in multiple related compounds (e.g., dihalocyclopropanes, **R5**[103,138,151-153], spiropyrans, **R7**;[154-157] and ladderanes, **R15**[58,146,147,149]), many are represented by a single example. Reactions of either category probably proceed by a variety of mechanisms, most of which are unknown and likely distinct from strain-free paths,[16,58,59,101,157,158] and our grouping is based on structural differences between the reactant and the (sometimes inferred) product rather than specific mechanistic insights.

Isomerizations do not fracture chains, exemplified by irreversible ring opening of dihalocyclo-propanes[103,138,151-153] (**R5**) and cyclobutenes[59,138] (**R6**), and reversible ring opening of spiropyrans[154-157,159,160] (**R7**) and related polycyclic chromophores.[161,162] Cycloreversions are usually scissile and the reported examples are dominated by dissociations of Diels-Alder adducts of maleimide with anthracene[157,160,163-165] (**R8**), furan[166-170] or cyclopentadiene[171] (**R12**), and of cyclobutanes[172,173] or related hydrocarbon cores (**R11**[174]) and their heteroanalogs (**R13**[144,175,176] and ref. [177]). Cycloreversions of cyclobutanes fused to another ring (**R13-15**[58,59,103,104,145-149]) are non-scissile as is a single example of non-scissile dissociation of a Diels-Alder adduct (**R16**[150]).

The reported mechanochemical reactions are dominated by ring-openings of strained 3- and 4-member rings and of labile heterocyclic 5- and 6-member rings, probably reflecting the preference for studying polymer mechanochemistry in sonicated solutions. The highly transient nature of chain elongation in the vicinity of a collapsing cavitation bubble[108] and the correspondingly high loading rates[16] reduce selectivity for site-specific reactions over chain fracture by backbone bond homolysis. Strained small rings or larger fused heterocycles are sufficiently labile and sensitive to tensile strain to outcompete chain fracture under these conditions, while many other reactions are not, even if they are detectable in loaded solids or by SMFS (e.g., **R11**, **R16** and thiol/disulfide exchange in proteins[60,178]). The resulting limited diversity of documented reactions in synthetic polymer probably skews our understanding of mechanochemical reactivity and limits opportunities to exploit it creatively.

Selected themes of contemporary research in polymer mechanochemistry

The bulk of contemporary literature on polymer mechanochemistry documents new examples of reactions accelerated in stretched polymers and is reviewed regularly. Of the rest, 3 themes are most relevant to developing a conceptual foundation of mechanochemistry:

1. Elucidating basic principles governing mechanochemical reactivity, including mechanistic studies and the effect of chain topology and the placement of the polymer "attachment points" on mechanochemical kinetics.
2. Developing reaction cascades in which a mechanochemical step controls the subsequent (usually non-mechanochemical) reactions that form new covalent bonds or release small molecules.

3. Identifying approaches to combining multiple productive responses to tensile load in a single reactive moiety (so-called multimodal mechanophores).
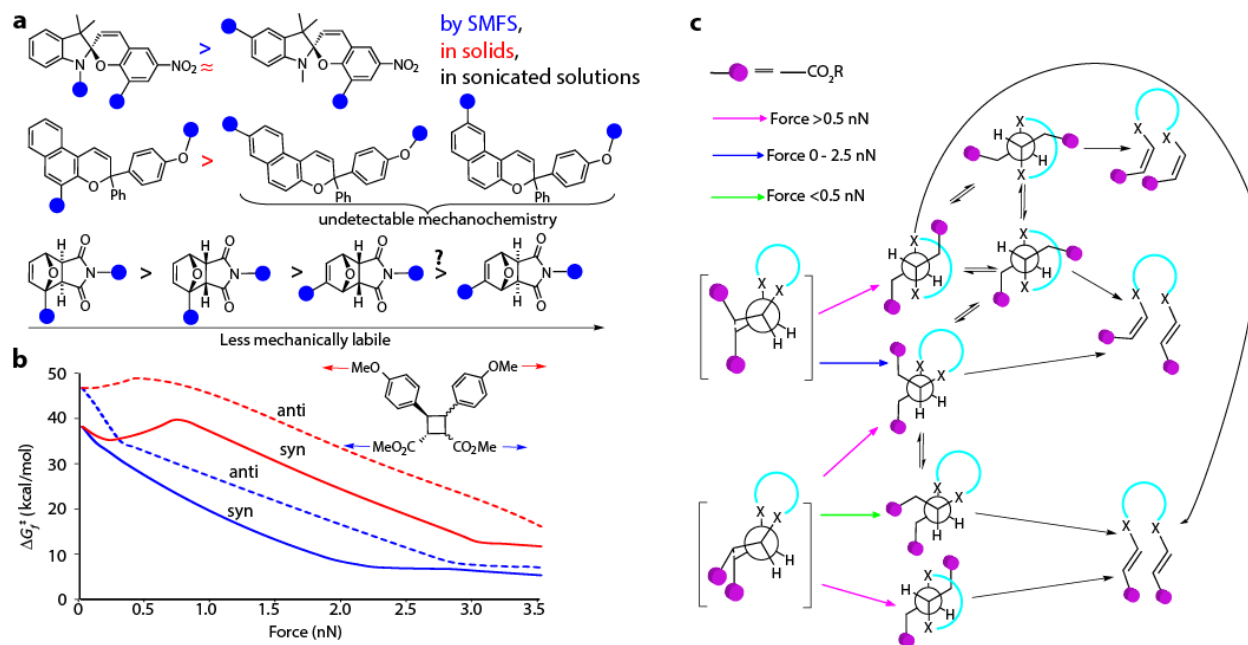

Figure 5 **Summary of mechanistic and structure/activity studies in polymer mechanochemistry**. (a) Relative mechanochemical lability of the reported connection isomers of spiropyran,[154] naphthopyran[161] and maleimide/furan adducts.[141,169] For the latter the two reported studies arrived at contradictory conclusions about the relative reactivities. (b) Calculated $\Delta G^{\ddagger}$/force relationships for two different pulling axis of syn and anti cinnamate dimers.[104] Adopted from [104]; reproduced with permission. (c) Calculated mechanism of mechanochemical dissociation of the cyclobutane core; combined data from refs. [103,104,145]. X are either terminal substituents or connections to a fused ring (blue circle). Mechanochemical isomerizations around the formed C=C bonds contributes negligibly to the product distribution.

Structural factors governing mechanochemical reactivity. Most reactive sites in Figure 4 have several pairs of atoms at which they can be connected to the rest of a polymer backbone. Isomerization force of spiropyrans varied by ~70 pN in SMFS[154] across the three "attachment" isomers, but they were indistinguishable in loaded bulk polymers.[155] Only one out of 3 studied isomeric naphthopyrans generated detectable mechanochromism in solids.[161] Whether these results reflect unfavorable kinetics or thermodynamics is unknown. Slight differences in kinetic stabilities of isomeric furan/maleimide adducts were inferred in sonicated solutions.[141,169] Conversely, DFT calculations of the dissociation kinetics and mechanisms of cinnamate dimers,[104] validated against SMFS measurements, revealed that the strong dependence of the mechanochemical mechanisms on the pulling axis yields large kinetic differences, suggesting that the choice of attachment atoms can be an exploitable molecular-design parameter for tuning mechanochemical behavior.

While polymer mechanochemistry remains primarily a study of linear polymers, increasing evidence suggests the importance of chain topology.[67,157,164,179-182] In sonicated solutions cyclic[180] and star polymers[67] fragment slower than linear polymers of the same composition and mass, an observation attributed to the shorter maximum end-to-end distance (spanning length) achievable in non-linear polymers. Conversely, comb polymers appear free from self-limiting fragmentation kinetics of linear polymers.[157] Empirically, fragmentation of a linear polymer reduces the rate of subsequent fragmentation 4-8 fold because the probability of a linear chain to become overstretched in an

12

elongation flow decreases rapidly with its contour length.[16] For a comb polymer, the equivalent number is <2 because it and its fragmentation products have the same spanning length.[157] Finally, spontaneous fragmentation of certain brush polymers at liquid/air or liquid/solid interfaces is thought to reflect chain overstretching not by coupled mechanical motion but interactions between the polymer and the solvent that minimize surface tension energy.[56]

Mechanochemical reaction mechanisms. Detailed mechanistic studies of mechanochemical reactions are rare. Best studied is [2+2] cycloreversion of the dicarboxycyclobutane core,[103,104,145,155] noteworthy both for its emerging use as a mechanochemically "gating" reaction (see the next subsection) and for yielding new C=C bonds with stereochemistry uncorrelated to that of the cyclobutane reactant (Figure 5c). DFT calculations benchmarked against SMFS measurements[103,104] suggest that the observed product distributions reflect relative stabilities of different conformers of the biradical intermediate produced in the rate-determining dissociation of the 1st bond, i.e., that stretching decouples the rate and product determining steps. These stabilities are very sensitive to the applied force and the size of the ring (if any) fused to cyclobutane, but are independent of the relative spatial arrangement of the cyclobutane substituents. As a result, depending on dissociation force and the size of the fused ring, cyclobutanes with *E* configuration of the non-scissile bonds may yield mostly *Z* olefins and vice versa. Conversely, cyclobutanes fused to short rings dissociate primarily to *E,Z* dienes. An alternative mechanism involving unusual ballistic dynamics was proposed for related cycloreversion of ladderanes.[58] This alternative is ruled out for dicarboxycyclobutanes by experimental trapping of the biradical intermediate.[145]

The reported[183] complex reaction surface for isomerization of dichlorocyclopropane (**R5**, Figure 4) may contribute to the limited success so far in reproducing the experimentally observed selectivity of isomerization computationally.[138,151] Recent experiments[59] suggest that mechanistically mechanochemical isomerization of cis-cyclobutene derivatives (**R6**), particularly the competition of the formally symmetry-allowed and symmetry-forbidden reaction paths,[59,138,158] may be more complex than originally thought. Several computational studies of nucleophile-assisted scission of a backbone S-S bond in stretched disulfides suggest increased mechanistic complexity[60,178] compared to strain-free reaction.

Mechanochemical reaction cascades. A cascade is a sequence of two or more reactions initiated mechanochemically. Both intra- and intermolecular cascades are known, all but two consisting of a single mechanochemical reaction each (Figure 6). The other two combine two mechanochemical reactions that occur either simultaneously[103] or sequentially.[59]

The longest-known examples of cascades are polymer grafting in ball-milled polymer mixtures containing an unsaturated polyolefin, e.g., polyisoprene.[84,184] The poorly understood mechanism probably involves additions of mechanochemically generated macroradicals to sp^2 C on adjacent chains. Although such grafting creates new covalent bonds, the mass of the average product chain in such mixtures decreases,[1] suggesting that mechanochemical chain fracture dominates. Mechanochemical chain fracture also initiates radical polymerizations of styrene[185] and acrylate[116,186] and yields a Ru catalyst for ROMP of norbornene.[128] Polymerizations enabled by dissociations of rare labile backbone bonds rather than dominant backbone bonds are more practical because they would occur at loads too low to cause catastrophic material failure. However, the slow solid-state diffusion limits all such polymerizations to materials swollen with monomer, reducing the utility of these self-reinforcing or self-growing materials.

More practical are reaction cascades crosslinking a loaded material because they require a limited concentration of a bifunctional small molecule,[137,145,156,187] a mixture of two polymers[157] or a

copolymer[132] of monomers with complementary reactivities. One such cascade was demonstrated in a melt,[137] while the others only in sonicated solutions.[132,145,156,157,187] In all reported examples, mechanochemical isomerization creates multiple sites per chain that react spontaneously with complementary functional groups of either the bifunctional solute or adjacent macromolecules, by cycloaddition,[187] S_N2 displacement,[137] or thiol-ene additions.[145,156,157] This reduces the solubility and increasing the average chain size and the bulk modulus of elasticity of the polymer. Being bimolecular, crosslinking is very sensitive to the steady-state concentration of the mechanochemically generated reactant, and the mechanochemical kinetics, which is hard to control, particularly in solids and melts. One workaround is to generate both reactants mechanochemically:[157] one reversibly at low load and the other at a higher load (mixed-polymer crosslinking in Figure 6). This maximizes the concentration of one crosslinking reactant while ensuring that crosslinking only occurs at sufficiently high load, limiting it to overloaded volumes of material at the highest probability of failure.
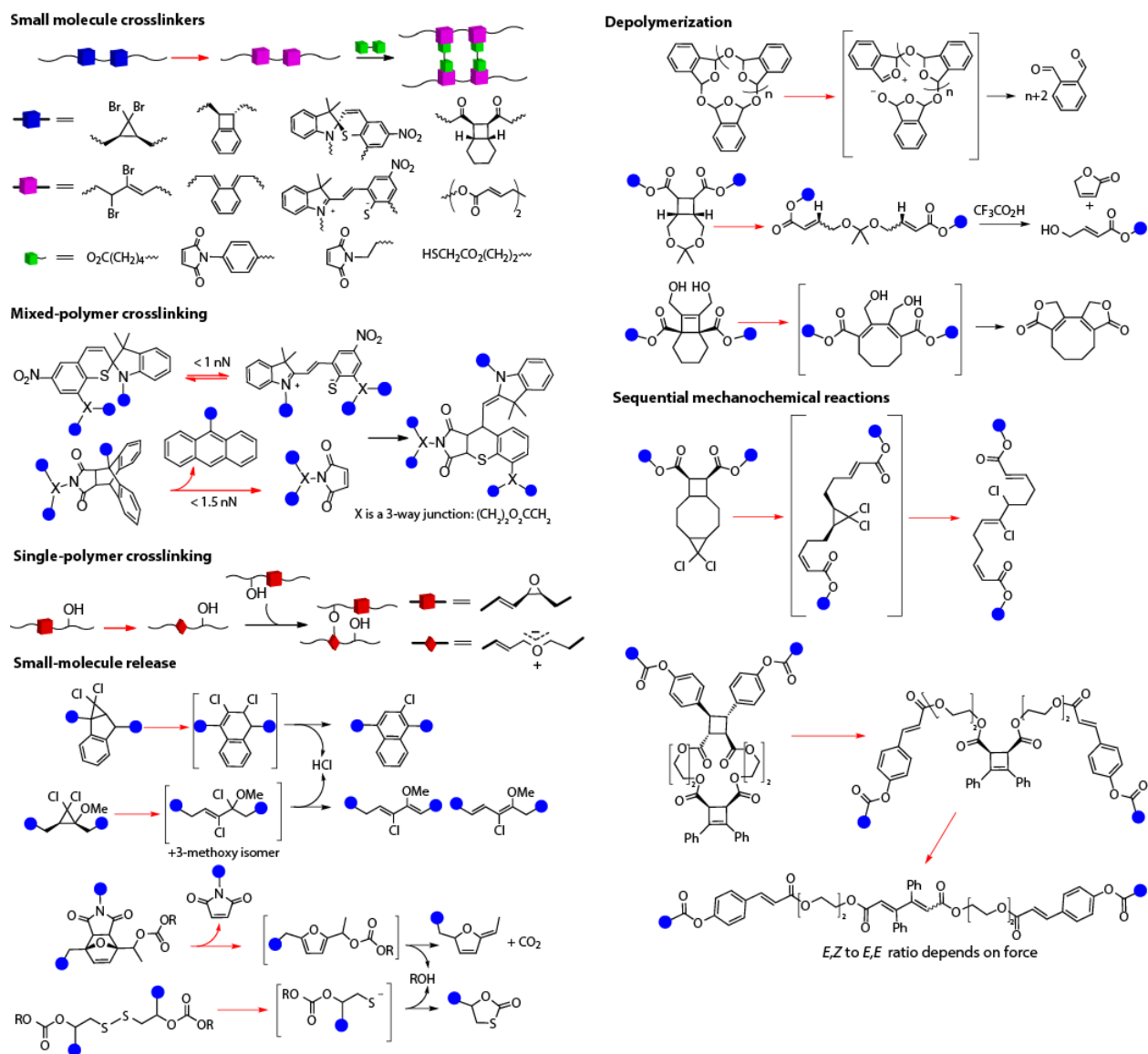

Figure 6. **Selected mechanochemical reaction cascades.** The red arrows designate mechanochemical step; blue dots are the rest of polymer chain, which may or may contain additional copies of the shown reactive sites. Square brackets identify postulated intermediates.

Whereas the reaction sequences described above increase the average molecular size and the density of covalent bonds of a polymer material, 8 cascades were designed to achieve the opposite, either releasing HCl[153,188] or alcohols,[168,189] or triggering depolymerization. [120,190-192] In all but 2 closely-related cascades,[190,191] the product of the mechanochemical step was too unstable to be isolated or characterized and spontaneously rearranged non-mechanochemically. The remaining 2 cascades required the exposure of the mechanochemical product to acid or base to proceed. Two cascades were demonstrated in solids,[153,192] while the rest were limited to sonicated solutions. An intermolecular cascade was used to tune the emission wavelength of a mechanoluminescent reaction.[125]

Each cascade discussed above includes a single (initiating) mechanochemical step. Two complementary cascades comprised solely of mechanochemical steps are known,[59,103] both exploiting dissociation of a cyclobutane core to control the transmission of mechanical load to the 2nd component. These two cascades illustrate how adjusting the relative mechanochemical stabilities of distinct reactive sites within a macrocyclic monomer yields unexpectedly complex (and potentially more useful) load-dependent polymer behavior that is observed in chains of containing a single reactive site,[104,145] or two reactive sites connected in series.[59,155]

Multimodal mechanophores. The vast majority of the mechanochemical reactions discussed above generate a single productive response, e.g., change optical properties of the material (mechanochromism) or initiate a reaction cascade. A few reactive groups have been reported that combine mechanochromism with either high thermal reactivity, enabling crosslinking[156,157] or polymerizations,[116] or photoreactivity, making the remodelled material optically healable.[104,174] The former is illustrated by spirothiopyran (**R7**, Figure 4) and bisimidazole (**R1**), whose product adds rapidly to activated C=C bonds (Figure 6) or initiates radical polymerizations, respectively. The latter are exemplified by cinnamate[59,104] and anthracene[174] dimers. The anthracene/maleimide adduct (**R8**, Figure 4), whose dual response originates from the distinct properties of the individual products[157] illustrates a complementary approach.

POWDER MECHANOCHEMISTRY

Contemporary powder mechanochemistry is far less amenable to conceptual systematization than polymer mechanochemistry. The reason is a combination of its much greater empirical diversity (in substrate classes, reactions, and experimental techniques) and the range of physical processes that may affect reaction kinetics and mechanisms, the paucity of experimentally and/or computationally tractable implementations of powder mechanochemistry similar to polymer mechanochemistry by single-molecule force spectroscopy and the lack of a general interpretational framework for processes in milled solids.

Chemical compositions of diverse polymers, small organic, metal-organic and inorganic compounds and extended solids have been demonstrated to change upon ball milling or grinding of their powders. Reported transformations of non-macromolecular substrates are dominated by association of two or more molecules into larger assemblies, including polymerizations. Evidence that covalent powder mechanochemistry yields products or proceeds by sequences of elementary reactions distinct from those of the solution reactions of the same reactants is surprisingly limited. Notable exceptions is mechanochemical synthesis of solvolytically labile molecules (Figure 7) which are inaccessible by solution chemistry,[193-197] and potentially of some radical couplings.[198]
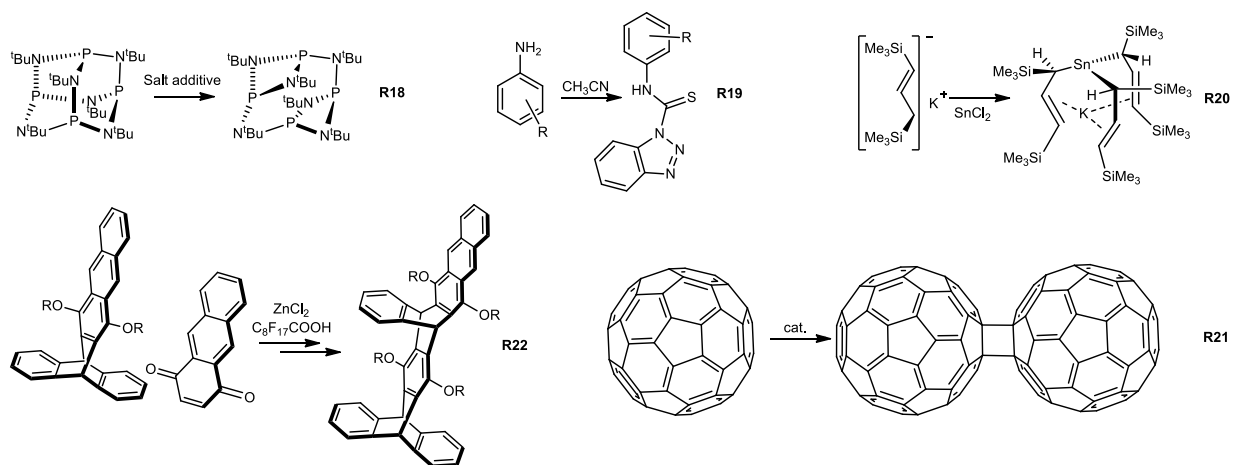
Figure 7. **Reactions reported to proceed in milled solids but not in solution**.

Similarly, most reported differences between reactions of milled polymers and of sonicated polymer solutions are attributable to the high concentration of chains and their slow diffusion in solids. Reactions in both scenarios are dominated by chain fracture, usually to macroradicals.[84] In solution, these macroradicals convert to stable chains by reactions with the solvent or small-molecule radicals derived from solvent sonolysis.[16] In milled polymers, such macroradicals are considerably more persistent[84,116,118] thanks to inhibited recombination of macroradical pairs and the absence of a solvent. Conversely, the high concentration of chains supports macroradical/chain reactions that require minimal diffusion, including H-atom abstraction from adjacent chains and addition to sp^2 C atoms of unsaturated polymers, yielding polymer grafting.[184]

Processes in milled powders are at least as impervious to quantitative molecular interpretation as those of sonicated polymer solutions. In both cases, the experimentally measured sample-average compositions do not reflect the microscopic reaction conditions because, unlike purely thermal reactions, the miniscule fraction of reacting molecules in sonicated solutions or in milled powders is not in thermal (Boltzmann) equilibrium with the rest of the sample. The well-known difficulties of spectroscopic detection of reactive intermediates in solution chemistry are greatly compounded by the technical difficulty of monitoring the compositions of milled solids. Unlike sonicated solutions, which are easy to sample frequently for ex-situ NMR, IR and SEC analysis and amenable to in-situ monitoring by optical spectroscopy, sampling of milled solids is impractical and in-situ monitoring is limited to X-ray powder diffraction and vibrational spectroscopy.[62,199] Slow diffusion precludes trapping of reactive intermediates or creating kinetic competition experiments. Interpretation of the results is further complicated by the potential importance of phase transitions[200,201] and interfacial processes, changes in the surface area, slow mass and heat transfers,[202] transient redox reactions,[203] and the poorly understood effects of milling parameters,[70,204] including the additives, and the material of the reaction vessel and milling balls. There is little agreement[1,2] on whether covalent reactions in milled samples occur preferentially at liquid/solid interfaces, among components of melts,[200] or in transiently compressed solid solutions.[3]

A model of reactions kinetics for powder mechanochemistry, parallel to the force-dependent model of polymer mechanochemistry does not exit. The common macroscopic empirical approaches to rationalizing observed bulk mechanochemical kinetics in ball milling assume that the reactions are driven by the energy transferred from moving balls to the milled medium during collisions of milling balls, including with the reactor walls.[205] A macroscopic implementation of this approach, called the

16

energy-dose model,[206] assumes that the sample-average kinetics is an empirical function of only macroscopic energy flux, which can be estimated with useful accuracy from processing conditions. Conceptually, it resembles Zhukov's model of kinetics in loaded polymeric materials,[83] which considered the sample-average reaction rate to depend exponentially on material stress as the only kinetic variable. The microscopic approach[207] attempts to account for details of collisions, including collisions between individual particles of the milled solid, and corresponding changes in their shape and contact areas, and the generation of local hot spots. The latter effect appears to be most amenable to mathematical modeling and comprises the earliest model of powder mechanochemistry,[86] but whether the available empirical evidence supports[202] or refutes a significant role of such local heating in mechanochemical reactions is vigorously debated.[205] We were unable to find examples of any kinetic model having been applied to reactions in milled organic solids.

MODEL STUDIES OF MECHANOCHEMISTRY

The intractable complexity of coupling of collective motion of billions of atoms to the concerted motion of a few atoms comprising a chemical reaction and the existing experimental and computational limitations mean that fundamental molecular understanding of mechanochemistry requires model studies. Our ability to reproduce the distortions of a monomer of a stretched polymer outside macromolecules and control the magnitude of the strain by molecular design rather than macroscopic motion has been a major contributor to the much more sophisticated understanding of the molecular basis of polymer mechanochemistry than mechanochemistry of small molecules by allowing detailed experimental and computational characterization of reactions, including those inhibited or unaffected by tensile load that cannot yet be studied in polymers.

So far, the only means of reproducing the distribution of molecular strain of a monomer of a stretched polymer is to incorporate this monomer in macrocycles of E stiff stilbene (Figure 8a), with the resulting restoring force of the monomer being controlled by the macrocycle size.[99,101,102,208-212] The three most important findings of such model studies are experimental validations of the key assumption of the force-based model of polymer mechanochemistry[102] and of a simple model of how force affects multibarrier reactions,[212] and demonstrations of patterns of mechanochemical reactivity experimentally inaccessible in stretched polymers.[101]

The only molecular model of mechanochemistry in existence assumes that molecular restoring force fully captures the effect of distorting a molecule on its kinetic and thermodynamic stability, irrespective of the molecular size, chemical composition or topology, or the physical mechanism responsible for the distortion.[97,210] This assumption was validated for axial stretching by demonstrating that the activation free energies, $\Delta G^{\ddagger}$, of isomerization of cis-dialkyldibromocyclopropanes (DBC, Figure 8b) derived from SMFS and measured across a series of increasingly-strained E macrocycles follow the same $\Delta G^{\ddagger}(f)$ curve calculated using a short DBC-containing molecular segment coupled to a harmonic spring (the generic model of polymer mechanochemistry discussed above). The experimental data covers 10^{11} range of molecular half-lives and 5000 range of constrained internuclear distances, establishing force as a useful measure of kinetically significant molecular strain across these scales. In addition to confirming the force-based model of mechanochemical reactivity, this finding demonstrated that micromechanics of a mechanochemically active chain can be predicted with useful accuracy from experimentally-validated calculations of $\Delta G^{\ddagger}(f)$ in a single isolated strained monomer.
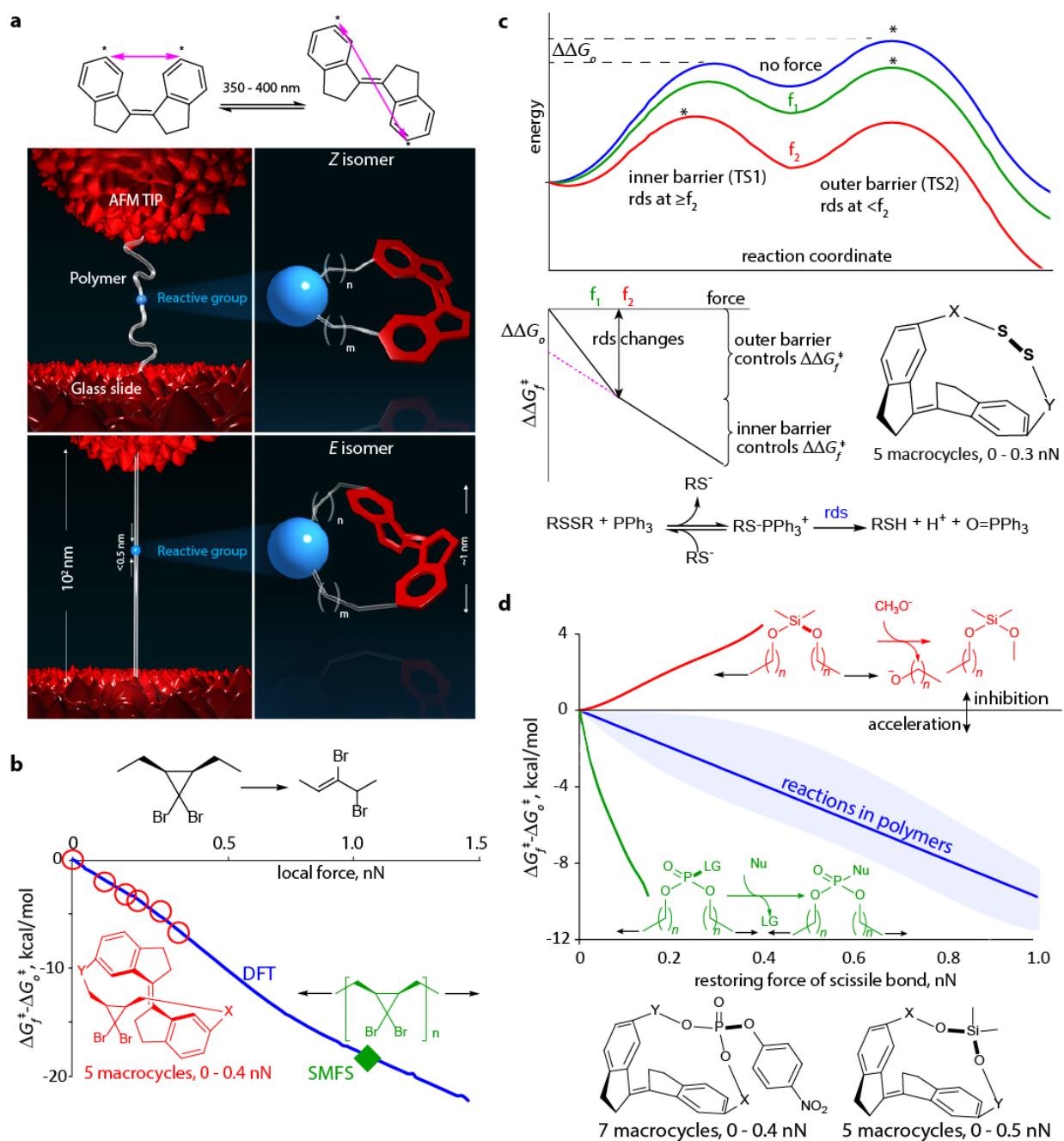
Figure 8 **Summary of model studies of polymer mechanochemistry**. (a) The difference in the C6/C6' distance of the Z and E isomers of stiff stilbene (top) enables its use as a molecular force-probe to reproduce single-molecule force spectroscopy for individual monomers (bottom cartoon, adopted from [209]). (b) Mechanochemical kinetics of isomerization of dibromocyclopropane (DBC) is identical in its polymer stretched by AFM (green diamond), in a series of increasingly strained macrocycles (red circles) and calculated quantum-chemically for a single DBC moiety coupled to a virtual spring (blue line). The restoring forces of DBC in the polymer and the macrocycles were derived from DFT-level calculations benchmarked against experimental force/extension curve or $\Delta G^{\ddagger}$, respectively. Data plotted is from [102]. (c) A mechanochemical reaction over a two-barrier energy landscape may experience a force-dependent change in the rate-determining step (marked by *) and hence manifest biphasic force/rate

correlation. This prediction was validated in disulfide reduction by phosphines using a series of increasingly strained macrocycles. Adopted from [212]. (d) Whereas reactions in polymers manifest very similar mechanochemical kinetics (blue area), macrocycles enable studies of much more diverse patterns of reactivity (red and green). Data plotted is from [101].

While a single energy barrier separates DBC from its product (elementary isomerization), computations and model studies suggest that most mechanochemical reactions traverse multiple reaction barriers.[212] This prevalence requires a simple, general and intuitive model of estimating how force affects which barrier is rate-determining. The only reported model assumes that in molecular fragmentations the reactant elongates monotonically as it progresses along the reaction path, making barriers later in the reaction mechanism (outer) more sensitive to force than earlier (inner) ones. Consequently, reactions whose strain-free rates are limited by an outer barrier would manifest two or more distinct kinetic regimes under force, as new inner barriers become rate-determining with increasing force (Figure 8c). This prediction was validated in a two-step reduction of disulfides with phosphines, whose kinetics is limited by the second step (hydrolysis of a phosphonium intermediate) at force <120 pN and the first step (nucleophilic displacement at S) at higher force. A competing reaction mechanism was ruled out as the origin of the two kinetic regimes (as suggested for some SMFS experiments) by demonstrating that the height of the strain-free inner barrier extrapolated from the $\Delta G^{\ddagger}(f)$ correlation over $120 - 260$ pN matched that measured directly on the strain-free reaction. Inner barriers that do not affect reaction kinetics are challenging to characterize experimentally, which this study achieved by exploiting the reversibility of any elementary step preceding the rate-determining barrier. Similarly-detailed analyses of reactions in SMFS remain beyond our current capabilities.

Despite their structural and mechanistic diversity, all reactions demonstrated in stretched polymers for which force-dependent mechanisms and $\Delta G^{\ddagger}(f)$ were reported manifest similar mechanochemical behavior, accelerating 5.3±0.7-fold per 0.1 nN of force experienced by their scissile bonds, $\langle f_s \rangle$ (blue area, Figure 8d).[101] Model studies confirmed that this uniformity is not a fundamental feature of polymer mechanochemistry by providing experimental counterexamples of bond dissociations that are either inhibited by tensile force or whose acceleration is up to 300-fold more sensitive to $\langle f_s \rangle$ than any other mechanochemical reaction reported to date.[101] Tensile load inhibits siloxanes solvolysis (red, Figure 8d), despite fragmenting the molecule along the pulling axis, but accelerates dissociation of the P-O bond in phosphotriesters that is orthogonal to the pulling axis (green). Both force/rate correlations were predicted computationally using the spring model discussed above and validated using series of increasingly strained E stiff stilbene macrocycles.

The detailed mechanistic data explained why the obligatory elongations of scissile bonds during molecular fragmentations does not ensure their accelerated fracture by stretching force. Both the inhibiting contraction of siloxane and accelerating elongation of phosphate along the pulling axis in their respective RDSs are driven by contraction or expansion of bond angles around Si or P, respectively, which offsets the scissile Si-O bond elongation and to which the scissile P-O bond contributes nothing because it remains orthogonal to the pulling axis throughout the reaction. The latter ensures that the negligible restoring force of the scissile P-O bond in phosphotriesters (<2% of the applied force) makes the reaction hypersensitive to the scissile bond strain. Conversely, in the only other example of mechanochemically accelerated dissociation of a non-backbone bond (**R16**, Figure 4), a higher fraction of the applied force distributes to the scissile C-C bond and its elongation contributes meaningfully to the transition-state geometry, yielding unexceptional 3-fold acceleration per 0.1 nN of $\langle f_s \rangle$.

This analysis also revealed that the approximate solutions of eq. 1 are very sensitive to the choice of the local coordinate defining $\langle \Delta q \rangle$ and for force-inhibited reaction identifying higher-energy reaction paths

that are accelerated by force are essential for accurate predictions of mechanochemical kinetics over a useful range of forces.

Mechanochemical siloxane solvolysis remains the only synthetic analogs of biological catch bonds[61,213] and proves that complex molecular interactions responsible for catch bonds are not prerequisites of inhibition of molecular fragmentations by tensile load. The preference of phosphates to dissociate the P-O bond orthogonal to the stretching axis suggests an alternative approach to mechanochemically triggered release of small molecules or oligomers to those offered by the cascades in Figure 6.

We are not aware of any systematic effort to develop tractable experimental models of mechanochemistry of non-polymeric molecules. Simple unimolecular reactions were induced in small organic molecules by action of an AFM tip.[53,54] A study of nanoindentation of a molecular crystal indicate a potential route of connecting single-molecule studies with powder mechanochemistry.[89] Certain reactions in crystalline solids under hydrostatic pressure[55,214] suggest how non-polymeric molecules can be designed to undergo highly anisotropic molecular distortions in response to isotropic load, thus making these reactions amenable to quantitative molecular analysis based on the idea of molecular restoring force. Finally, examples of AFM studies of synthetic molecular motors[45,47,215] (or "optomechanical" analogs[216]) suggest a potential approach to productive model studies of actuating materials.

SUMMARY

Mechanochemistry refers to a highly diverse collection of phenomena in which the rate of a chemical reaction is directly affected by velocity and direction of collective motion of billions of atoms. When molecular environment inhibits translations and rotations of individual molecules, such collective or mechanical motion can distort (strain) some of these molecules, destabilizing them kinetically and/or thermodynamically.[1,13,56] A mechanochemical reaction is a means of relieving this molecular strain when other forms of molecular relaxation (i.e., translation or rotation) are excluded.

The highly anisotropic geometry of macromolecules makes them particularly good at translating mechanical motion into distortions of bond distances, angles and torsions of their backbones. Molecular strain has long been known to accelerate diverse small-molecule reactions,[82] although the molecular distortions responsible for known polymer mechanochemistry are unusual and have, until recently, proven difficult to reproduce through molecular design. Transient generation of molecular strain may[8] or may not[217] be essential for the operation of all biological motor proteins, but examples of biological mechanotransduction that rely on distortions of protein structures to modulate their reactivity are well established.[7,19,20,218,219] Although polymers facilitate coupling of mechanical motion and molecular strain, they are not necessary. With enough effort, a single small organic molecule can be strained with an AFM tip, inducing it to react.[52-54] Despite the rarity of such experiments and the simplicity of the observed reactions, they suggest that transient molecular strain is responsible for the few examples[193-197] of unusual reactivity in milled organic solids.

Whereas bio- and polymer mechanochemistry benefited from shared methodological and conceptual advances, polymer and powder mechanochemistry continue to develop as separate fields with little exchange of ideas. The well-controlled fairly tractable single-molecule force experiments, indispensable in bio– and polymer mechanochemistry, remain peripheral to powder mechanochemistry. Consequently, despite our at-best qualitative understanding of mechanochemistry of bulk samples, quantitatively accurate predictions of single-chain mechanochemistry, possible for a decade,[104] underpin the usefully robust interpretational framework of contemporary polymer mechanochemistry.

Conversely, the practical impact of powder mechanochemistry far exceeds that of its polymer analog. We suggest that model studies which reproduce mechanochemical reactivity without the intractable complexity of macroscopic motion may bridge polymer and powder mechanochemistry, benefiting both.

Authors declare no competing interests.

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