

Polymer Mechanochemistry: A New Frontier for Physical Organic Chemistry

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Polymer mechanochemistry aims at understanding and exploiting the unique chemistry that is possible when stretching macromolecular chains beyond their strain-free contour lengths. This happens when chains are subject to a mechanical load, in bulk, in solution, at interfaces or as single molecules in air. Simple polymers such as polystyrene or polymethacrylate fragment via homolysis of a backbone C-C bond, and much contemporary effort in polymer mechanochemistry has focused on creating polymers which undergo more complex and interesting reactions, with such productive mechanochemical responses including mechanochromism and load strengthening. Comparatively less progress has been achieved in creating an internally coherent, theoretically sound interpretational framework to organize, systematize and generalize the existing manifestations of polymer mechanochemistry and to guide the design of new mechanochemical systems. The experimental, computational and conceptual tools of physical organic chemistry appear particularly well suited to achieve this goal, benefiting both fields.

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1. Introduction

Mechanochemistry refers to a wide range of phenomena in which the kinetic stability of a molecule is affected by macroscopic motion, without changes in local temperature or pressure. Macroscopic motion that stretches macromolecular chains can dramatically accelerate reactions of their monomers, for example reducing the half-life of a covalent bond from many times greater than the age of the universe itself to the microsecond timescale at room temperature¹.

The high anisotropy of macromolecules means that stretching them strains their constituent monomers in ways not possible in small molecules, both in terms of the magnitude of structural distortions, and its patterns. Stretching a chain of polyethylene until its half-life towards fragmentation (by homolysis of one of its backbone C-C bonds) reduces to ~15 years at 300 K (corresponding to ΔG^\ddagger of 30 kcal/mol) increases its strain energy by 5 kcal/(mol CH₂). Both the kinetic stability and the strain energy “density” of such a stretched chain are comparable to those of hexamethyldewar benzene and hexamethylprismanes (whose strain energies relative to hexamethylbenzene are ~60 and ~120 kcal/mol, respectively, and ΔH^\ddagger for isomerization to hexamethylbenzene are 32 and 34 kcal/mol.² The importance of these strained isomers of benzene to our current understanding of chemical reactivity is well acknowledged.³ Unlike the modest number and limited structural diversity of highly strained molecules prepared to date, a variety of small reactive moieties can be (and have been) decorated with a pair of polymer chains. Stretching such polymers is a nearly universal strategy of straining the embedded reactive site as much as or more than any small molecule synthesized to date. And in contrast to the heroic synthetic effort required to obtain prismane⁴, a polymer chain can be stretched simply by subjecting its solution to ultrasound. Likewise, these polymer chains can be attached to different positions of a small reactive moiety. Stretching such macromolecular “connection” isomers strains the reactive site along different molecular axes^{5,6}, introducing an idea of anisotropy in discussion of reaction kinetics.

In other words, polymer mechanochemistry provides a unique means of studying the effect of extreme molecular strain on chemical reactivity. Extrapolating from the impact that studies of strained small molecules have had on our understanding of chemical reactivity, careful mechanistic investigations of mechanochemical reactions in the best traditions of physical organic chemistry will greatly broaden the range of reactions sensitive to molecular strain and mechanistic paths for relaxation of this strain, and likely reveal new patterns of strain-induced reactivity and identify new potentially generalizable strategies of controlling this reactivity by manipulating molecular structure. The new models required to describe quantitatively the effect of molecular strain on chemical

reactivity in polymer mechanochemistry will likely benefit any field where intractably many molecular degrees of freedom affect chemical reactivity, from more accurate descriptions of solvation effects⁷ to chemical kinetics in cells⁸. More speculatively, polymer mechanochemistry may have utility in small-molecule synthesis by enabling reactions without resorting to high temperatures or pressures.⁹ The need for polymer handles and the modest selectivity of mechanochemical reactions observed to date make this proposition somewhat less certain¹. Mechanochemistry has traditionally been used to modify properties of polymeric materials (e.g., mastication), and more elaborate modifications by mechanochemical post-polymerization modification may be practical.¹⁰

Mechanochemical phenomena are multiscale processes, i.e., they result from a complex sequence of events generated by correlated motions on the length scales from $\sim 1 \mu\text{m}$ to $< 1 \text{ nm}$, and the timescale from $\sim 1 \text{ ms}$ to a few picoseconds.^{11,12} In contrast, the vast majority of conventional chemical reactions involve correlated atomic motion only within a $\sim 1 \text{ nm}^3$ volume that is complete within a few ps to 100 ns.¹³ Consequently, mechanochemistry allows the conceptual and technical tools of chemistry to be applied to problems that far exceeds the conventional bounds of chemistry, where “quantum meets classical and molecular meets bulk material”.¹⁴

An equally compelling reason to study polymer mechanochemistry is its technological importance.^{1,15,16} Polymers are both critical to the everyday functioning of our society and subject to mechanical loads throughout their lifecycles.¹⁷ Increasing amounts of empirical evidence suggest that mechanochemical responses of existing polymeric materials are important, if poorly understood determinants of their application niches. Exploiting mechanochemistry to design materials with desired molecular responses to mechanical loads is likely to lead not only to considerable improvement in existing processes and devices, but also to yield fundamentally new technological solutions. For example, mechanochromic materials that change local optical properties in response to either instantaneous or cumulative loads hold potential to signal regions of a material which are most likely to fail¹⁸⁻²², a property that would be useful at every stage of material development and use.

Materials which respond to localized loads that exceed a pre-defined threshold by forming new load-bearing bonds, thus increasing the density of bond over which the load distributes, could prevent catastrophic failure of materials.²³⁻²⁶ Combining these two productive responses to mechanical loads in a single material may offer even more exciting opportunities.^{27,28}

Mechanical stress plays a key factor in many physiological processes, which offer diverse examples of (mostly) non-covalent polymer mechanochemistry. The ~ 1 Å elongation of the pyrophosphate P-O bond during catalytic hydrolysis of adenosine triphosphate (ATP) is transduced and amplified by kinesin and dynein motor proteins to transport objects orders of magnitudes larger than themselves as they move along microtubule tracks.²⁹ The unusually high toughness of structural protein titin, which is responsible for passive elasticity of muscle, results from reversible dissociations of thousands of H bonds when the protein is stretched.³⁰ The phenomenology of biological mechanotransduction and the interpretational framework used to discuss its molecular basis is sufficiently distinct from those of polymer mechanochemistry to make its inclusion in the current review untenable. Fortunately, a number of thoughtful treatments of the topic have recently appeared in the literature.³¹

Advances in polymer mechanochemistry are reviewed regularly, with particular emphasis on phenomenology. Key reviews published by the end of 2016 are listed in ref. ¹ and organized by review type. We are aware of reviews that have appeared since, both phenomenological: ^{28,32}. The objective of this review is to raise the awareness of the field of polymer mechanochemistry among physical organic chemists and to illustrate rich research opportunities that await anyone interested in applying the formalism of physical organic chemists to problems in contemporary polymer mechanochemistry. We are motivated by a conviction that for polymer mechanochemistry to fulfil its fundamental and technological potential, the recent explosion of empirical observations has to be matched by equally impressive advances in conceptual foundation for interpreting and generalizing experimental (and computational) finding and for enabling prediction. As a result, we focus on the aspects of polymer mechanochemistry that are rarely reviewed, especially quantitative models currently used to discuss

mechanochemical kinetics and the most common experimental methods to study mechanochemical phenomena, with particular emphasis on their limitations and outstanding unresolved questions of interpretation. Empirical observations are described only in so far as they illustrate these broader points.

2. A quantitative model of mechanochemical kinetics

The simplest example of coupling of chemical kinetics to macroscopic motion, and thus the simplest example of a mechanochemical system, is two macroscopic beads bridged by a single macromolecule moving away from each other at a constant velocity. This scenario is approximated in single-molecule force (SMF) experiments, in which a polymer chain is attached at one end to an atomic force microscopy (AFM) tip, and at the other to a modified surface which is then retracted from the tip (see section 3.1. Single-molecule force spectroscopy). If the separation of the beads is below a critical value (which depends on the chain contour length and chemical composition), the motion of the beads is suitably described by Newtonian mechanics and balance of forces (e.g. using the Langevin equation to account for thermal fluctuations). In this regime the macromolecular bridge behaves simply as a collection of mechanical elements with a conceptually simple (if mathematically complex) relationship between extension (end-to-end distance) and the restoring force. As in a macroscopic spring, the two parameters increase simultaneously, requiring ever-increasing force applied to the beads to maintain the constant retraction velocity.

Once the bead separation exceeds the critical value (typically larger than the contour length of the free macromolecule), the evolution of the system no longer follows Newtonian mechanics. In this overstretched geometry, the macrochain is chemically unstable on the timescale of the experiment, i.e. its composition, and hence the contour length, changes faster than the position of the beads. The system no longer behaves as a classical object, but rather as a quantum-mechanical one. In this regime, a quantitative description of the evolution of the system requires a quantitative relationship between changes in the relative position of the beads (or equivalently, the end-to-end separation of

the macromolecule) and the probabilities of the monomers making up the overstretched macromolecule undergoing chemical reaction. Such a relationship is not available within conventional chemical kinetics but must be derived by integrating the formalism of activated escape from an energy well with the variables of classical mechanics.

In theory, quantum mechanics offers a detailed description of the evolution of the system regardless of how much the macromolecular bridge is stretched. In practice, the total size of the dynamic system and hence the total number of parameters needed to describe its evolution quantum-mechanically make such an approach untenable and unlikely to yield generalizable insights. If the reactions induced by stretching the chain are highly localized, as is true for the vast majority of mechanochemistry of synthetic polymers, only a small fragment of the system described above around the reactive site where the chemical bonding changes needs to be treated quantum-mechanically. It should be possible, just as it is in many other chemical problems, to coarse-grain the remaining degrees of freedom of the system, both molecular (i.e. the rest of the polymer) and macroscopic (translating beads), i.e. to represent their effect on the kinetic and thermodynamic stability of the reactive site by a small number of parameters. This is true even if the macromolecule has multiple equivalent reactive sites (e.g. scission of an overstretched polyethylene chain, in which every backbone C-C bond has approximately equal probability to homolyze) as long as they behave independently, i.e. don't manifest cooperativity.

The simplest implementation of this approach is a short segment of the macromolecular chain, containing the reactive moiety, attached at its terminal atoms to a compressed harmonic spring. We will postpone until later in the review discussion of important but subtle questions of how large the segment needs to be, how thermal and ensemble effects could be treated, and what the parameters of the spring should be (see section 2.3 Complicating factors: ensemble effects, the minimum length of the macromolecular segment, multibarrier reactions and competing mechanisms.). This molecule/harmonic spring construct has at least three stationary states, i.e. configurations of atoms

in which each atom experiences zero net force and the restoring force of the stretched molecular fragment is identical in magnitude and opposite in direction to the restoring force F of the compressed spring (i.e., internal mechanical equilibrium). Just as in a free molecule, these states will correspond to two energy minima (reactant and product) and the saddle point separating them (transition state). Knowing the energy of the transition state relative to the reactant, ΔU^\ddagger , allows the rate at which the molecule will change its composition (or equivalently, the probability that it will change its composition over a fixed timeframe) to be estimated using the standard transition state theory (TST) for any spring. Because the energy of a harmonic spring is a simple function of its elongation and force constant, it is productive to analyze the total energy of each state of the molecule/spring construct as a sum of the energies of the molecular component and the spring, Eqs. 1 and 2, where l_{TS} and l_R is some quantifier of the length of the compressed spring at the transition state and reactant, respectively.

$$\Delta U^\ddagger = \underbrace{U_{mol}^{TS} - U_{mol}^R}_{\text{quantum mechanics}} + \underbrace{U_{spring}^{TS} - U_{spring}^R}_{\text{classical mechanics}} \quad (1)$$

$$U_{spring}^{TS} - U_{spring}^R = \frac{k(l_{TS} - l_0)^2}{2} - \frac{k(l_R - l_0)^2}{2} = \frac{k}{2} \underbrace{(l_{TS} + l_R - 2l_0)}_{\approx F} (l_{TS} - l_R) \quad (2)$$

If the spring is much softer than the molecular fragment (i.e. $l_0 \gg l_{TS} \sim l_R$), the restoring force of the spring, F , will be largely insensitive to the internuclear distance across which it is coupled, allowing the parameters of the spring (k and l_0) to be subsumed into force F acting on the molecular fragment (Eq. 3). Eq. 3 can be viewed as a master equation of mechanochemical kinetics, which explains why mechanochemistry is discussed in terms of force and which underlies most quantitative discussions of mechanochemical reactivity.

$$\Delta U^\ddagger(F) = U_{mol}^{TS}(F) - U_{mol}^R(F) - F(l_{TS}(F) - l_R(F)) \quad (3)$$

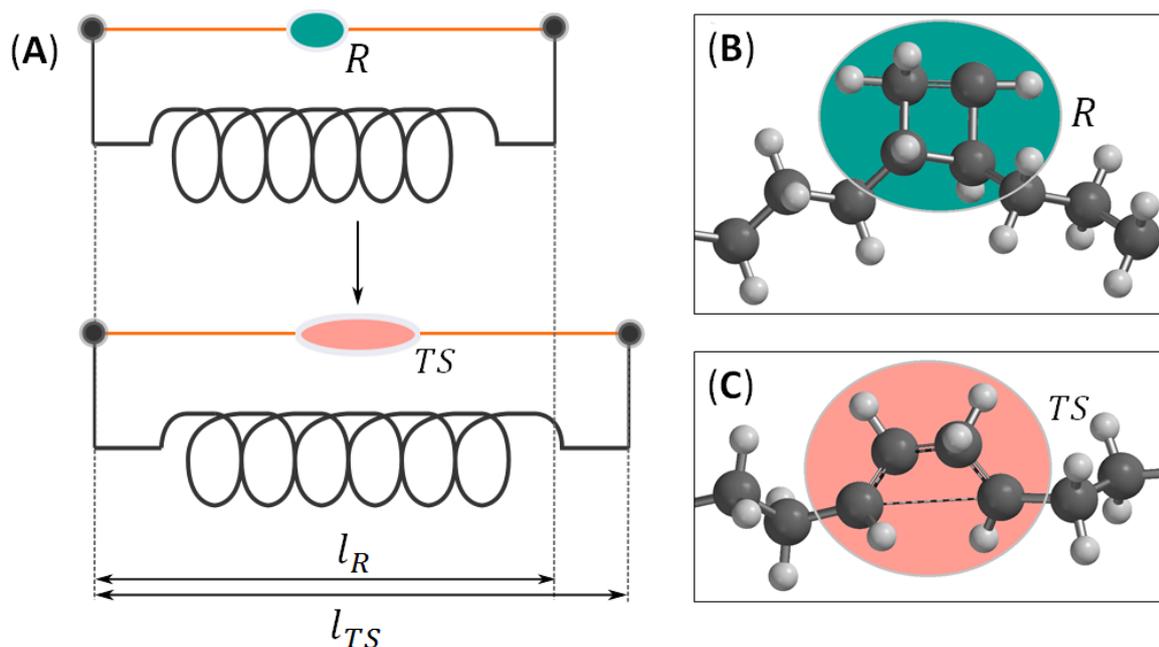


Fig. 1: (A) A reactive site (green sphere) in a polymer fragment stretched by an attached compressed harmonic spring reacts through a transition state (pink oval) which is longer along the constrained axis than the reactant state. The composition of the molecular fragment outside of the reactive moiety (grey) is unchanged. The resulting lengthening of the compressed spring reduces its strain energy, thus lowering the reaction barrier. (B-C) An example of such reactive site is cyclobutene, whose transition state for electrocyclic ring-opening is $\sim 2 \text{ \AA}$ longer than the reactant. C atoms are represented by dark gray spheres and H atoms by lighter gray spheres.

Eq. 3 is valid as long as the assumptions of the TST are applicable. If force changes so fast that the strained molecule is no longer in thermal equilibrium with its environment, as may be the case in some steered molecular dynamics simulations³³, Eq. 3 will fail, but such ultrahigh loading rates may not be experimentally accessible, making such failure of no practical significance.

Practical applications of Eq. 3 require the knowledge of U , $l_R(F)$ and $l_{TS}(F)$. For most (but not all) localized chemical reactions, these parameters are available with a varying degree of accuracy from quantum-chemical calculations.¹ An important exception is mechanochemiluminescence of 1,2-dioxetanes,^{21,26} whose complex non-adiabatic dissociation mechanism^{34,35} is not yet amenable to

usefully accurate quantum-chemical calculations of force-dependent barriers. Much empirical discussion of mechanochemical reactivity, however, remains based on various approximations of Eq. 3, and the plethora of the reported equations of mechanochemical kinetics, from the original Eyring-Bell ansatz to the more-recent two-dimensional and complete harmonic models, are simplifications of Eq. 3. Most often these approximate models are applied to measured (usually by single-molecule force spectroscopy) force-dependent reaction kinetics to estimate a structural parameter of the transition state ($l_{TS}(0) - l_R(0)$). This parameter is also used as an empirical quantifier of how sensitive the reaction rate is to stretching of the molecule.

2.1 Approximate solutions of the master equation of mechanochemical kinetics

2.1.1 Zeroth-order approximation: the Eyring-Bell (EB) model

The simplest approach to evaluating Eq. 3 is to assume that stretching the molecule has no effect on either its intrinsic reactivity (i.e. $U_{TS}(F) - U_R(F) = U_{TS}(0) - U_R(0)$) or the structural differences between the reactant and the transition states ($l_{TS}(F) - l_R(F) = l_{TS}(0) - l_R(0)$). These assumptions reduce Eq. 3 to

$$\Delta U^\ddagger(F) \approx \Delta U^\ddagger(0) - F(l_{TS}(0) - l_R(0)), \quad (4)$$

or the more commonly shown expression for the force-dependent rate constant, $k(F)$, Eq. 5, or the corresponding survival probability (i.e., the probability that the molecule will not have reacted by reaction time t), $S(t, F)$. In the literature, the $l_{TS}(0) - l_R(0)$ term is often written as Δx^\ddagger . k_B is the Boltzmann constant; $k(0)$ and $S_0(t)$ are the parameters in strain-free molecule.

$$k(F) = k(0)e^{\frac{F(l_{TS}(0) - l_R(0))}{k_B T}} \quad (5)$$

$$S(t, F) = [S_0(t)]e^{-\frac{F(l_{TS}(0) - l_R(0))}{k_B T}} \quad (6)$$

If the force is time-dependent, the 0th-order approximation of Eq. 3 can only be expressed in general as survival probability (Eq. 7).

$$S(t, F) = e^{-k(0)} \int_0^t e^{\frac{F(\tau)(l_{TS}(0) - l_R(0))}{k_B T}} d\tau \quad (7)$$

The 0th-order approximation of mechanochemical kinetics is often traced to the work of Eyring, who considered the flow of polymer chains³⁶, and to a later paper by Bell, in the context of cell adhesion.³⁷ An important but mostly overlooked difference between the 0th-order models in use today and those considered by Eyring or Bell is that the latter simply postulated that barrier height depends linearly on applied force without any attempt to define the proportionality constant (apart from the obvious statement that it must have a dimension of length), much less ascribe it to specific changes in molecular geometry. At present, probably the most commonly abused application of the 0th-order approximation, which is often referred to as Bell or Eyring-Bell (EB) equation, is to determine the elongation of a scissile bond in the transition state of a reaction from single-molecule force experiments. These attempts often use a version of the 0th-order approximation which includes time-dependent force, first considered by Evans³⁸, who derived Eq. 7 from the Kramers formulation of chemical kinetics.^{39,40}

Eqs. 4-7 predict that a reaction whose transition state is longer than the reactant along the constrained axis ($l_{TS}(0) - l_R(0) > 0$), is accelerated by tensile force ($F > 0$ by convention). This acceleration results solely from the decrease in the strain energy of the compressed spring, enabled by the localized elongation of the reactive site. Since the spring represents molecular degrees of freedom of the stretched macrochain removed from the reactive site, the 0th-order approximation of mechanochemical kinetics postulates that tensile force accelerates a chemical reaction when the formation of the transition state allows partial relief of molecular strain in the non-reactive degrees of freedom. To achieve this partial strain relief, the reactive site should elongate in the transition state. The EB model remains by far the most commonly used model of mechanochemical kinetics due to its conceptual and technical simplicity, despite substantial evidence of its shortcomings.⁴¹⁻⁴³

It is sometimes suggested that Eq. 4 can be improved by replacing the $F(l_{TS}(0) - l_R(0))$ with a path integral along the reaction coordinate. This is wrong, however, because the transition state theory

requires the activation energy to be a state function, i.e., a function whose value only depends on the initial and final state and not on the path connecting the two.

2.1.2. First-order approximation: tilted potential energy surface and cusp model

The assumption that stretching a molecule doesn't change its intrinsic reactivity clearly contradicts a large body of literature attesting to the strong effects of molecular strain on chemical kinetics in non-polymeric substrates (where the relaxation of the molecular degrees of freedom outside the reactive site contribute minimally to the changes in reaction barriers, i.e., the $F(l_{TS} - l_R)$ term of Eq. 3 is irrelevant). The 1st-order approximations of Eq. 3 all assume (either implicitly or explicitly) that the constrained distance is a normal mode of the reactant and either a normal mode of the product (sometimes referred to as "cusp model", Fig. 2(B)) or the reactive mode of the transition state (in which case the model is called "tilted potential energy surface"⁴⁴ or "extended Bell"). Other formulations of the tilted potential energy surface (TPES) or cusp model appear in the literature, but they all reduce to the assumption above. Only under the assumption of the constrained distance being a normal mode or the reactive mode can the force-dependence of the energy of each stationary state and of the constrained distance be expressed as a function of the same single parameter of that state, k_i ($i = R, TS$ or P , Eqs. 8-9), whose physical meaning is the force constant of the constrained distance. Note that while k_R and $k_P > 0$, $k_{TS} < 0$. What happens with the equations (and the model) when this aphysical assumption is relaxed is discussed below.

$$U_i(F) = U_i(0) + \frac{F^2}{2k_i} \quad (8)$$

$$l_i(F) = l_i(0) + \frac{F^2}{k_i} \quad (9)$$

Substituting $U_i(F)$ and $l_i(F)$ of master Eq. 3 by Eqs. 8-9 yields Eq. 10 for the TPES model, which deviates from the 0th-order (EB) model (Eq. 4) by the presence of the quadratic term $-\frac{F^2}{2} \left(\frac{1}{k_{TS}} - \frac{1}{k_R} \right)$.

Because the TPES is internally consistent only if $k_{TS} < 0$, this quadratic term must be positive and

increase the reaction barrier relative to the 0th-order (EB) estimate. The outcome is a manifestation of the Hammond effect, which postulates that a barrier-lowering perturbation makes the reactant and the transition state more “alike”, both structurally ($[l_{TS}(0) - l_R(0)] > [l_{TS}(F) - l_R(F)]$) and energetically ($[U_{mol}^{TS}(0) - U_{mol}^R(0)] > [U_{mol}^{TS}(F) - U_{mol}^R(F)]$).⁴⁵ While the latter lowers $\Delta U(F)$, the former decreases the strain energy of the coupled spring that is released in the transition state, because it decreases how much the compressed spring relaxes. The quadratic dependence means that difference between the 0th- and 1st-order approximations increases with force. The TPES is illustrated in Fig. 2(A).

$$\Delta U^\ddagger(F) \approx \underbrace{\Delta U^\ddagger(0) - F(l_{TS}(0) - l_R(0))}_{EB \text{ (0}^{th} \text{ order) model}} - \frac{F^2}{2} \left(\frac{1}{k_{TS}} - \frac{1}{k_R} \right) \quad (10)$$

The TPES operates only if the constrained distance is the reactive mode in the vicinity of the transition state, otherwise, Eqs. 8-9 ($i = TS$) are invalid (see next section). In practice, no multiatomic molecule has ever been reported that satisfies this criterion, and the TPES has been used to discuss force-dependent barriers of reactions in which both k_R and k_{TS} are positive. Such use is sometimes rationalized by claiming that F is a “component” of applied force acting along the strain-free reaction coordinate. However, such a distinction is meaningless because Eqs 8-9 are simultaneously valid only if the constrained distance is a normal (reactive) mode; otherwise, force will increase the molecular energy faster than proportionally to the elongation of the constrained distance. Whether the internal inconsistency between the underlying assumption of the model and the numeric parameters used in it is the main reason for the aphysical kinetics predicted by Eq. 10, even when the more obvious errors are avoided, is unknown.

In the cusp model, the activation barrier height is determined by the intersection of the energy wells corresponding to the reactant and the product (Fig. 2(B)). In contrast to the TPES, the length of the constrained distance at the intersection, l_{int} , is independent of the stretching force, allowing the master equation to be reduced to the approximate form of Eq. 11.

$$\Delta U^\ddagger(F) \approx \Delta U^\ddagger(0) - F(l_{int}(0) - l_R(0)) + \frac{F^2}{2k_R} \quad (11)$$

Note that the only difference between Eqs. 10 and 11 is the absence of the $F^2/2k_{TS}$ term, which is expected since in the cusp model the intersection is equivalent to an infinitely stiff transition state ($k_{TS} = \infty$). Given the similarity between Eqs. 10-11, especially at low forces, it is somewhat surprising that in the few cases where the same experimental data were fitted to these equations, fairly large differences in $l_{TS}(0) - l_R(0)$ were obtained.⁴⁶ The reason that the cusp model predicts a higher activation barrier than the EB model is the same as in the TPES: a Hammond-effect shift of the reactant geometry towards the intersection that decreases the energy the constraining spring releases as the molecular geometry changes from the (shifted) reactant to the (stationary) transition state.

While the cusp model avoids the aphysical assumption of the constrained distance being the reactive mode in the vicinity of the transition state, it is only applicable for non-scissile mechanochemical reactions, i.e., reactions in which the macromolecule doesn't fragment. Otherwise, the assumption of infinitely compliant constraining spring (to achieve the constant stretching force irrespectively of the structural differences between the reactant and the transition state or intersection) would correspond to the infinite reaction energy and an infinite elongation of the constrained internuclear distance in the product.

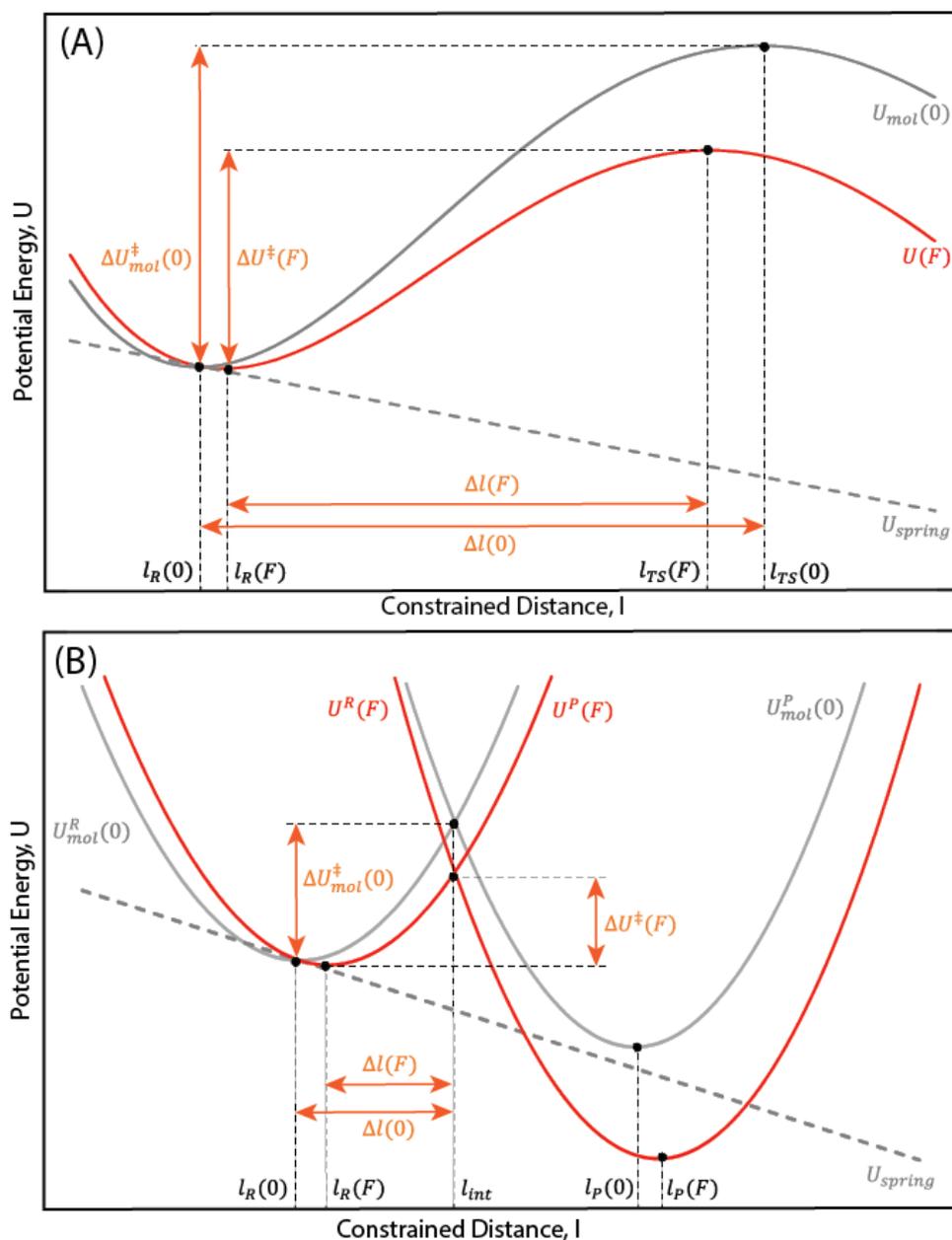


Fig. 2: Illustration of (A) the tilted potential energy surface, and (B) the cusp model for the 1st-order approximation of the effect of external force on chemical reactivity.

The cusp model is equivalent to the Marcus theory of electron transfer.^{47,48} While the Marcus-like treatment of nucleophilic displacement reactions was previously shown to be a productive strategy in rationalizing structure/reactivity relationships in the gas phase,⁴⁹ it is not obviously conceptually acceptable to treat an arbitrary reaction in a stretched polymer as a non-adiabatic process. Practically, other assumptions of the model, particularly the validity of Eqs. 8-9, may introduce considerably

greater errors in the derived parameters than the assumption of non-adiabaticity or an infinitely rigid transition state.

2.1.3. Second-order and complete harmonic approximations

The obviously aphysical assumption of the 1st-order models (so-called tilted potential energy surface, extended Bell or cusp models) prompted some attempt to analyze force-dependent reaction kinetics in terms of two-dimensional reaction surfaces, with one coordinate being the constrained internuclear distance l , and the other a collective coordinate that represents the remaining $3N-7$ nuclear degrees of freedom, q .⁵⁰ This approach again follows the well-established precedent of physical organic chemistry (e.g. the “Bema-hapothle” model⁵¹) and suffers from the same limitations, as discussed elsewhere.¹² Within this model, the expressions for the molecular energy of state i (R or TS) is given by Eq. 12, where k and k' are harmonic force constants of the constrained distance l and the collective coordinate q , and k'' is the coupling constant (equivalent to the “interaction parameter” of Bema-hapothle). The coupling constant k'' is a direct consequence of the constrained distance not being a normal mode of the molecule and hence l and q not being orthogonal. Otherwise, $k'' = 0$ and Eq. 12 reduces to Eq. 10 (1st-order models). Note that unlike k_{TS} of the 1st-order model, the 2nd-order model makes no assumption of which of the three force constants of the TS are negative, and the coupling constant k_R'' can be either negative or positive.

$$U_i(F) = U_i(0) + \frac{F^2}{2 \left(k_i - \frac{k_i''^2}{k_i'} \right)} \quad (12)$$

The consequence of non-zero coupling between the two coordinates of the 2nd-order approximation is that constraining a single internuclear distance of a molecule to a non-equilibrium value can cause other internuclear distances to elongate or contract, even if those distances are orthogonal to the constrained distance in the 3D Cartesian (physical) space (Fig. 3). Likewise, whereas the 1st-order models predict that tensile force acting on the transition state always lowers its energy ($U_{TS}(F) < U_{TS}(0)$), force can lower or raise the energy of the transition state, depending on the relative

magnitudes of 3 harmonic constants, k_{TS} , k'_{TS} and k''_{TS} . In that respect, the 2nd-order model is a considerable improvement over the 1st-order models, because every quantum-chemical calculation reported to date revealed that force destabilizes transition states even when $\Delta U(F) < \Delta U(0)$ due to partial relaxation of the coupled spring.

The corresponding approximation of the master equation is given by Eq. 13, which, as expected, reduces to Eq. 11 if l is assumed to be a normal/reactive mode (i.e., $k''_R = k''_{TS} = 0$)

$$\Delta U^\ddagger(F) \approx \underbrace{\Delta U^\ddagger(0) - F(l_{TS}(0) - l_R(0))}_{EB \text{ (0}^{th} \text{ order) model}} - \frac{F^2}{2} \left(\frac{1}{k_{TS} - \frac{k''_{TS}}{k'_{TS}}} - \frac{1}{k_R - \frac{k''_R}{k'_R}} \right) \quad (13)$$

The main difference between the 2nd-order and 1st-order models is that the former accommodates anti-Hammond effects, and $\Delta U(F)$ estimated by eq. 13 can be larger or smaller than $\Delta U(F)$ estimated by the EB model (an internally consistent 1st-order approximation of $\Delta U(F)$ always exceeds the EB estimate of $\Delta U(F)$, although the reported applications of eq. 11 are not internally consistent). In other words, the 2nd-order correction to the activation energy will in general be non-zero even if the constrained coordinate l is orthogonal to the reaction path in the vicinity of R, TS or both (Fig. 3). The practical significance of this additional flexibility of eq. 13 is not clear, because at present there doesn't appear to be any theoretically valid method of estimating k' and k'' , e.g., by quantum-chemical calculations, precluding predictions of $\Delta U(F)$ from strain-free molecular parameters using eq. 13. Conversely, any coefficients derived from fitting experimental data to eq. 13 would lack a clear molecular interpretation.

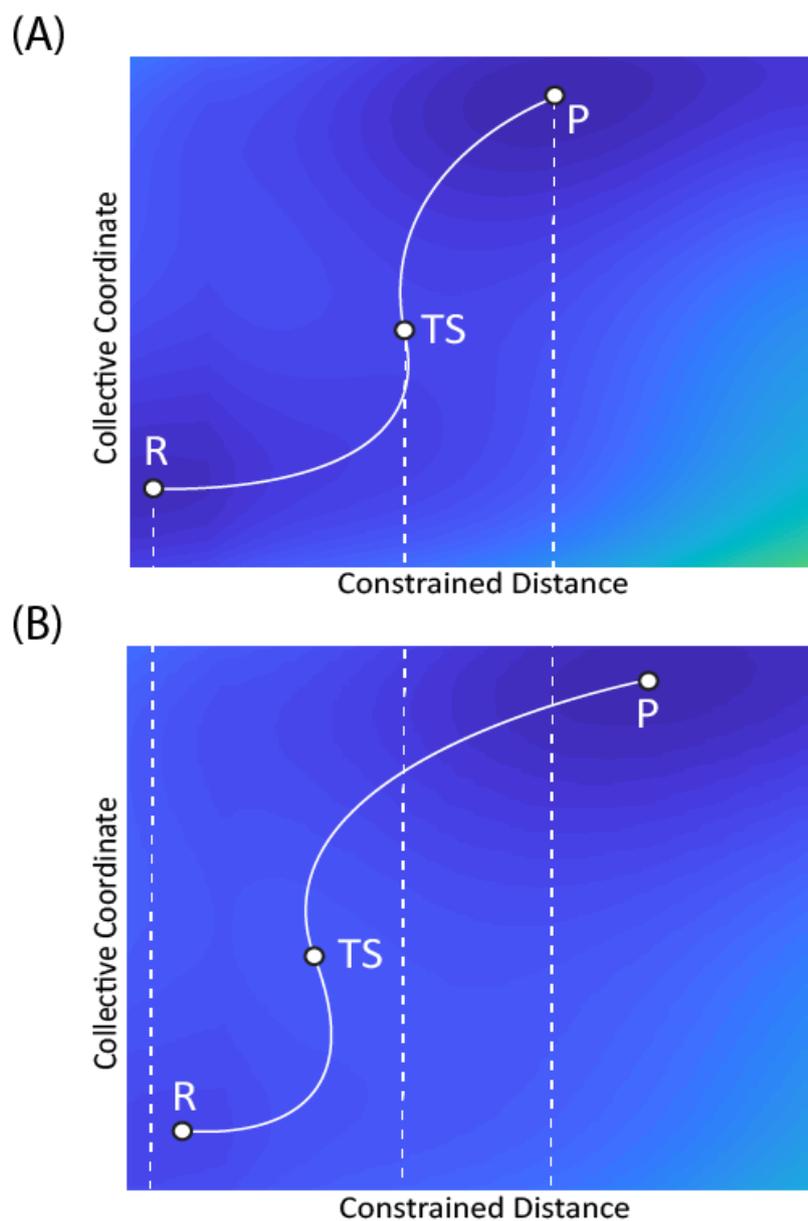


Fig. 3: A two-dimensional potential energy surface for a reaction occurring in reactive moiety within a macromolecule (A) in the absence of force, and (B) in the presence of a compressed spring, which qualitatively changes the position of the reactant, transition state, and product, and the minimum-energy reaction pathway (all highlighted). Note that the reactant and transition state do not necessarily become closer along the constrained distance upon stretching the macromolecule. Warmer and colder colors correspond to higher and lower energies, respectively.

It is conceptually trivial to extend the 2nd-order approximation to a non-redundant set of $3N-6$ internal coordinates in the harmonic approximation.^{43,52} If the first coordinate of the set is the constrained

distance, this full harmonic approximation of master Eq. 3 is given by Eq. 14, where $C_i(1,1)$ is the compliance of the constrained coordinate in state i . The compliance is obtained by inverting the full Hessian matrix (a matrix of the 2nd-order derivatives of energy with respect to the 3N-6 internal coordinates) of the strain-free geometry. Most quantum-chemical methods produce this Hessian in an analytical frequency calculation, but the large size of a Hessian of even a moderately sized substrate makes accurate calculations of its inverse technically challenging. In our own work^{41,42,53-61} we found that molecular compliances of molecules containing up to 100 atoms can be calculated with useful accuracy on geometries converged to RMS force of $<10^{-6}$ atomic units, using high accuracy integration grids and Cholesky-decomposition method for matrix inversion.

$$\Delta U^\ddagger(F) \approx \underbrace{\Delta U^\ddagger(0) - F(l_{TS}(0) - l_R(0))}_{EB \text{ (0}^{th} \text{ order) model}} - \frac{F^2}{2} (C_{TS}(1,1) - C_R(1,1)) \quad (14)$$

Partial compliance matrices of only a few reactant/transition state pairs have been reported. In all cases, $C_{TS}(1,1) > 0$ but no generalizable relationships between C_{TS} and C_R has emerged, so that the harmonic-approximation estimate of $\Delta U(F)$ can be smaller or larger than the EB estimate. In other words, the constrained distance in some transition states is softer than in the reactant ($C_{TS} > C_R$), while in other the reverse is true. The advantage of Eq. 14 is that all elements have rigorously defined molecular interpretation and are available from quantum-chemical calculations. The approach underlying Eq. 14 also allows the restoring force of any molecular degree of freedom (e.g., an internuclear distance) in addition to that of the explicitly constrained distance to be calculated as a function of F , which is of practical and conceptual importance. In general, Eq. 14 allows much more accurate predictions of force-dependent barriers by replacing the constrained distance l and the applied force F with a properly selected internuclear distance and its restoring force (see the next section).

2.2. Accuracy of the conventional approximations and systematic strategies of improving them.

The very few reported analyses of the accuracy of various approximation of Eq. 3 were performed by comparing the force-dependent activation free energies estimated by Eqs. 4, 10, 11, 13 or 14 to $\Delta U(F)$ values calculated quantum-chemically.^{41,43,60} Most of these analyses didn't consider the question of how faithfully $\Delta U(F)$ values from quantum-chemical calculations reproduced physical reality, which is a complex and largely unresolved problem in polymer mechanochemistry, as discussed elsewhere.¹ Invariably, the 0th-order approximation of Eq. 3 produced the largest errors and the "complete" harmonic approximation (Eq. 14) performed the best, with the accuracy decreasing at larger forces. The main cause of the (often substantial) errors is anharmonicity of the constrained distance, which is equally problematic for unimolecular and bimolecular reactions. Anharmonicity increases with the size of the molecular moiety (i.e., the macromolecular segment that is treated atomistically instead of being modelled as a compressed harmonic spring) and cannot be eliminated simply by making the molecular fragment smaller (which makes the constrained coordinate stiffer and generally more harmonic), as it introduces its own artifacts^{1,42,60}. The so-called Taylor expansion and local coordinate approaches considerably improve the estimates of $\Delta U(F)$ at minimal incremental computational cost. The Taylor expansion approach recognizes that all approximate solutions of Eq. 3 (i.e., Eqs. 4, 10, 11, 13 or 14) are Taylor expansions of $\Delta U(F)$ with respect to F truncated as the 1st or 2nd term. It was therefore suggested⁶² that as long as the approximations of eq. 3 are used to empirically quantify the reaction "sensitivity" to stretching force from experimental measurements (e.g., single-molecule force experiments) a more productive approach may be to fit the experimental data to a Taylor expansion of $\Delta U(F)$ truncated at the highest order compatible with the quality and quantity of the experimental data. In this approach, the fitting parameters would be analogous to nucleophilic constants of physical organic chemistry that could be usefully compared across different reactions, polymer architectures and/or loading conditions. The measured force-dependent kinetics reported to date appears to lack

the accuracy and/or dynamic range needed to estimate the Taylor coefficients of 2nd- or higher order with useful accuracy, but such an analysis may be more productive than attempting to ascribe any deviation of the measured correlations from those predicted by EB to changes in the underlying reaction mechanisms (which are difficult if not impossible to extract from single-molecule force experiments alone). The lack of molecular interpretation of the Taylor expansion coefficients beyond the 2nd-order means that at present the Taylor expansion approach does not allow estimates of $\Delta U(F)$ to be improved systematically from computed parameters of strain-free reactants and transition states.

The local coordinate approximation appears to be the most general and promising approach to dealing with anharmonicity of the constrained distance.^{41,42,53-56,58,59,61} Stretching a molecule by constraining one of its non-bonding distances to a non-equilibrium value distorts other molecular coordinates (distances, bond angles and torsions) and the magnitude of this distortion is captured by the restoring force of each coordinate. The molecular compliance matrix C (e.g, Eq. 14) allows the restoring force of any internal coordinate to be expressed as a function of the stretching force F . Each reactive site studied to date appears to have at least one internuclear distance (a) that is considerably more harmonic (i.e., its restoring force is approximately proportional to its absolute strain) than the constrained distance and (b) whose restoring force, F , is a much better predictor of the activation energy of the stretched reactant than the applied force F using eq. 13. Furthermore, for reactions of the same mechanistic type (e.g., S_N2 displacements), force-dependent activation barriers of multiple structurally distinct reactants is predicted accurately using the same internal coordinate, the separation of the two atoms that connect the electrophilic atom to the polymer.^{41,42,54,56,57,59-61}

The local-coordinate approximation improves the accuracy of predicting the reaction kinetics in a stretched macromolecule in the harmonic approximation (i.e., using eq. 14)^{41,42,60}. It also simplifies such predictions technically by allow them to be separated into two simpler problems: estimating the activation barrier as a function of the restoring force of a local coordinate in a minimal reactant and

estimating the relationship between the applied force and this local restoring force. A rigorous definition of the minimum reactant doesn't exist and appears to depend on the reaction: dimethylcyclobutene⁴¹, dimethyldibromocyclopropane⁵⁸ and tetramethylpyrophosphate⁵⁷ were all demonstrated to yield local force/activation energy correlations that accurately extrapolate to larger homologues, including polymers. The use of the minimal reactant increases the maximum level of theory at which the strain-free geometries and energies can be practically calculated and decreases the number of conformers that need to be optimized for correct calculations of free energies (see next section). The relationship is independent of the polymer in which the reaction occurs and hence applicable to polymers with different backbones by combining it with the dependence of the local restoring force on the applied force.

This latter parameter, sometimes called the chemomechanical coupling coefficient, defines the capacity of the polymer backbone to transmit the applied force to these sites or redistribute it away from them. The chemomechanical coupling coefficient of a few simple backbones (e.g., polyesters, acrylates and simple aliphatic hydrocarbons designed to model polystyrene) were reported.⁴¹ Importantly, the calculated values appear to be rather insensitive to the model chemistry, with even semi-empirical methods (e.g., PM6) giving acceptable results, and similar in the reactant and the transition state. The latter comparison, performed at the DFT level, seems to suggest that the coupling coefficient is determined primarily by the micromechanics of the polymer backbone, which is insensitive to the bonding pattern of the reactive site, rather than by vibrational coupling between the degrees of freedom of the two fragments. The chemomechanical coupling coefficient depends on the length of shorter polymer segments but reaches length-independent value for a few repeat units. By explicitly defining the two independent determinants of reaction kinetics in stretched polymers (the intrinsic mechanochemical reactivity of the localized sites and the chemomechanical coupling coefficient), the local-coordinate approximation enables practical calculations of single-chain micromechanics of mechanochemically labile polymers,^{25,58,63} simplifies identification of broad

structure/activity correlations⁶² and facilitates the design of polymers with pre-determined mechanochemical profiles by enabling independent control over the chemistry and the critical force above which the chemistry is observed.^{64,65}

The observation that the local restoring force enables accurate predictions of localized reaction kinetics in stretched polymers⁵⁸ establishes a conceptual connection between molecular strain and chemical reactivity irrespective of the size of the reactant, or how the strain is imposed on the reactive site: by incorporating it into a strained non-polymeric molecule, or by stretching a macrochain containing the site in its backbone. The only condition is that the imposed strain is anisotropic. In macromolecules this anisotropy is imposed by the very large aspect ratios of the polymers; in small molecules, only specific molecular architectures are expected to achieve comparable degree of anisotropy⁶² (which can be estimated with the help of the compliance matrix).

2.3 Complicating factors: ensemble effects, the minimum length of the macromolecular segment, multibarrier reactions and competing mechanisms.

Up to this point the discussion of the quantitative model of mechanochemical kinetics (i.e., Eq. 3) has omitted any consideration of how the model predictions are affected by the length of the atomistically-treated polymer segment, or the fact that the reactant and transition states of molecules of interest in polymer mechanochemistry are conformational ensembles, i.e., comprised of multiple conformers in rapid equilibrium. Quantum-chemical calculations, performed on homologous series of diverse reactants, including cyclobutenes, cyclopropanes, phosphotriesters and siloxanes, suggest that both effects are significant, particularly at forces <2 nN.^{12,42,56,57,59,60} For bimolecular reactions, such as hydrolysis of pyrophosphate esters, approximating each state by its lowest energy conformer systematically overestimates calculated $\Delta U(F)$ by up to 3 kcal/mol by neglecting so-called conformational entropy effects.⁵⁷ In these reactions, the higher coordination number of the electrophilic atom in the transition state relative to the reactant means that the transition state is comprised of significantly fewer thermally accessible conformers (i.e., conformers within ~ 1.5

kcal/mol of the conformational minimum) than the reactant. Equivalently, the reactant state is enriched in conformers with particularly short end-to-end separations (across which force is applied). These additional reactant conformers are particularly strongly destabilized by tensile force, reducing the total number of thermally accessible conformers in the reactant state and increasing the free energy of this state relative to that of the minimum energy conformer of the reactant state faster with tensile force than the free energy of the transition state relative to that of its minimum-energy conformer. In other words, the existence of a conformational ensemble leads to greater destabilization of the reactant state by force, and hence, a larger decrease in the activation free energy, that would be predicted by considering only 1 conformer for each state.

In extreme cases, ignoring the fact that rates are governed by relative energies of states rather than individual conformers leads to qualitatively incorrect predictions. For example, neutral methanolysis of siloxanes is calculated to proceed by two competing two-step mechanisms, one of which is accelerated by force, and the other inhibited. Considering only the minimum energy conformers predicts the two mechanisms to be approximately isoenergetic, whereas the force-inhibited path has a lower strain-free activation free energy when complete conformational ensembles are used. The difference is larger for larger homologues and no size-independent limit of force-dependent activation energy for this reaction was identified.⁴²

Eq. 3 and its complete-harmonic approximation (Eq. 14) was extended to free energies using the statistical mechanics formalism.⁵² Note that while the approximation of the infinitely compliant spring underlying Eq. 3 is simply a convenience and potential energy of activation can be calculated for coupled spring of any compliance (irrespective of whether the result is physically relevant¹), a closed-form expression of activation free energies could only be obtained if the coupled spring was infinitely compliant.

The application of Eq. 3, regardless of how the terms are estimated (i.e., from explicit quantum-chemical calculations at multiple forces or by extrapolating strain-free parameters) to unimolecular

(single-barrier) reactions is conceptually straightforward. Estimates of force-dependent kinetics of multibarrier reactions require more care because relative energies of individual stationary states (i.e., intermediate and transition states) in general manifest different dependencies on force, often leading to changes in the rate determining step.^{25,42,61,63} Additionally, it is not uncommon for force to stabilize intermediates below the reactant, in which case the intermediate may accumulate and the overall reaction rate may be determined by the rate of decay of this intermediate rather than the reactant.²⁵ In such cases, the dependence of the reaction rate on force can change significantly as the force increases. Failure to account for such changes, for example, by equating the total activation energy to the extrapolated energy of the rate-determining transition state in strain-free molecule can lead to qualitatively incorrect predictions.¹

The role of competing reaction paths in determining mechanochemical reactivity was ignored until recently.^{25,42,63,66} It's very likely that for most if not all mechanochemical reactions studied to date multiple reaction mechanisms are kinetically competitive over a range of applied forces. This is particularly true if the minimum-energy path in strain-free reactant is inhibited by force. Known examples include isomerizations of cis-dimethylcyclobutene and its derivative,⁴⁶ and of trans-dimethyldihalocyclopropanes⁶⁷ and retro-Diels-Alder reactions of certain adducts of anthracene.^{1,6} In all cases, the minimum-energy concerted reaction mechanisms in strain-free reactants are strongly destabilized by force whereas the higher-energy diradical alternative is stabilized by force. Neglecting the existence of such competing paths may lead to qualitatively incorrect predictions of mechanochemical reactivity, as illustrated recently.^{1,6} In the absence of robust automated procedures for finding all reaction paths that a molecule can follow, including those that may seem kinetically inconsequential in strain-free reactants much depends on one's breadth of empirical knowledge of chemical reactivity.

3. Experimental techniques of polymer mechanochemistry

Macromolecules are easy to stretch, but hard to maintain at a well-defined accurately known strain (or equivalently, restoring force). Twisting, stretching or compressing a macroscopic sample of a polymer stretches some fraction of polymer segments. This method, while simple, allows no control over the magnitude of the distortion of individual chains or how long the fragments are maintained in the stretched state. At the other extreme is single-molecule force spectroscopy, which allows segments of individual isolated macromolecular chains to be stretched up to their fragmentation at rates from <10 nm/s to >10 μ m/s or maintained at approximately constant strain or restoring force for up to a few seconds. The cost of this control is the technical complexity, with only a handful of groups worldwide able to perform single-molecule force experiments relevant to polymer mechanochemistry. In between these two extremes are several techniques of vastly different technical difficulty for stretching macromolecules, with varying degree of control over the imposed strain. Many of these techniques rely on coupling between a macromolecular solute and hydrodynamic flows to stretch chains.

3.1. Single-molecule force spectroscopy

A macrochain or its segment can be stretched and maintained in a stretched conformation only if it couples to its surroundings at a minimum of two atoms. To a useful approximation, this conceptually simplest mechanism of chain stretching is realized in single-molecule force spectroscopy (SMFS). In theory, in an SMF experiment a polymer chain is anchored to a functionalized surface at one end, and to a micro-cantilever tip on the other (in practice, parts of the chain are often absorbed at one or both surfaces, an effect which is discussed in greater detail later in this section. The surface is then retracted from the tip, extending the end-to-end separation beyond its equilibrium value, thus stretching the chain. The restoring force of this stretched chain deflects the cantilever, with this deflection measured and converted to the force using a number of empirical equations.⁶⁸ Note that SMF experiments do not measure the restoring force, as is often mistakenly assumed.

SMF experiments are performed in one of two modes: constant velocity (dynamic force spectroscopy) and constant force (or “force-clamp”). In the former, the two surfaces anchoring the macromolecular bridge are retracted at a constant velocity and the data is recorded as a force/extension curve. In the latter, the chain is rapidly stretched to a desired restoring force and then maintained at this force by moving the surface: the extension is recorded as a function of the time the chain is maintained at a fixed force.

In dynamic force spectroscopy, the strain of the chain increases continuously until the half-life of one or more of its monomers decreases to the ms timescale, at which point a localized reaction happens. If the reaction either breaks the chain or increases its strain-free contour length by at least ~ 1 nm, a mechanical instability, in which the extension increases while the force decreases, becomes resolved from the usual thermal fluctuations. This mechanical instability is a direct consequence of the vastly different timescales required for local rearrangement of chemical bonding that constitutes a reaction and reestablishment of mechanical equilibrium between a stretched macrochain and AFM tip.⁵² The abrupt rearrangement of local bonding occurs on the 10-100 ps timescale, followed by a redistribution of macromolecular conformers on the ~ 1 μ s timescale (corresponding to the longest relaxation time of a macrochain with contour length on the order of 1 μ m) to accommodate the new local geometry. On these timescales the AFM tip is stationary (e.g., its thermal fluctuations occur on < 1 kHz scale) and therefore out of mechanical equilibrium with the suddenly elongated chain. This longer chain allows partial relaxation of the bent AFM tip, which is recorded as a decrease in the applied stretching force. The larger the difference in the contour length of the polymer before and after the reaction, the larger this force drop is. If a stretched macromolecule is made of multiple mechanochemically reactive non-scissile sites, multiple mechanical instabilities are resolved, producing a “sawtooth” pattern. If an individual reaction increases the polymer contour length by < 1 nm, multiple sites will produce a plateau on the force/extension curve where the extension increases at approximately constant force, instead of the sawtooth pattern. Continued stretching of the chain eventually results in the failure of the macromolecular bridge by any number of plausible reactions.

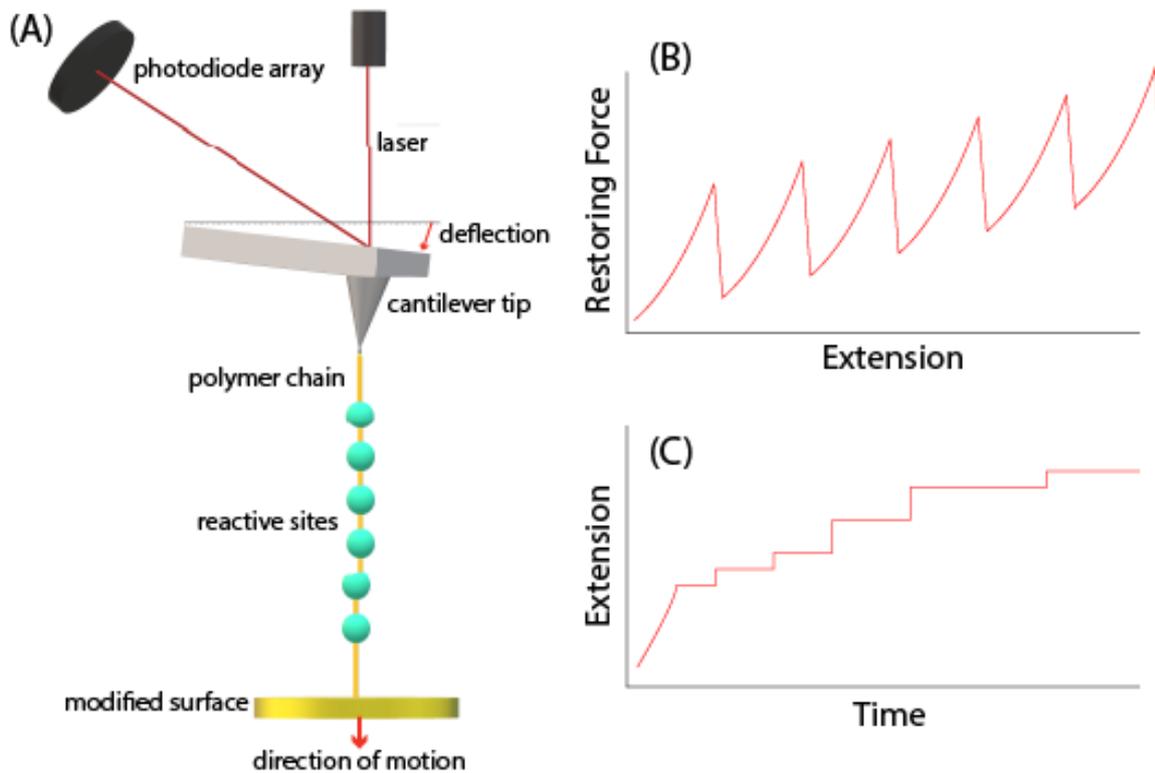


Fig. 4: Simplified illustration of AFM-based single-molecule force experiment. A polymer chain is attached at its termini to a cantilever tip, and a reactive surface, and the latter surface is retracted. In dynamic force spectroscopy, the retraction typically occurs at a constant velocity, gradually stretching the polymer and deflecting the cantilever, which is measured by the change in the position of the reflected laser beam at the detector. In the force-clamp mode, quick retraction to achieve a desired cantilever deflection is followed by restricted movement necessary to maintain this deflection. The data from the two variants is reported either as the force/extension (B) or extension/time (C) curves. When stretching destabilizes one or more monomer of the macromolecular bridge enough for it to react a mechanical instability results, producing either a sawtooth pattern (B) or an abrupt elongation of the polymer contour length due (C). Thermal fluctuations of the tip and the macromolecule result in small, random fluctuations of the extension are not shown in B-C. The drawing in A is not to scale, with the AFM tip being many an order of magnitude larger than the macromolecule.

The force-clamp mode of SMFS relies on a feedback mechanism, whereby the position of the glass slide relative to the AFM tip is varied at below-kHz frequency to maintain the constant deflection of

the AFM tip (and hence an approximately constant stretching force acting on the polymer). The data is recorded as extension vs. time. The extension of a chemically-inert macromolecule would fluctuate randomly within an Å-scale range, determined by the stiffness of the cantilever and the temperature. A reaction occurring within the stretched macromolecule that increases its contour length results in an abrupt increase in the recorded elongation. Multiple reactions will produce a “staircase” extension profile, equivalent to the sawtooth pattern observed in force-ramp SMFS. While performing SMF experiments in the force-clamp mode may seem appealing to avoid the complications of time-dependent rate constants (e.g., Eq. 7), technical limitations, including the narrow range of accessible forces, poorer resolution of extension and thermal drift restrict the application of the force-clamp mode in polymer mechanochemistry. A recently published study comparing the results obtained by the two methods suggested that they yield approximately equivalent information.⁶⁹

Molecular interpretation of SMF experiments, either qualitative (which reaction occurred, and by what mechanism) or quantitative (at what rate the reaction proceeds, and how it depends on force), is far more challenging than is generally acknowledged by the practitioners of the field and could definitely benefit from a closer cooperation with physical organic chemists than has been the case thus far. SMF experiments remain the only experimental technique of estimating mechanochemical kinetics of diverse reactions, and are therefore critical for advancing our understanding of chemical reactivity in highly stretched macromolecules, for improving and validating new experimental and computational methods of quantifying macromolecular reactivity, and for developing applications of mechanochemical phenomena. Improvements in the quality of data that is available from SMF experiments are likely to have a disproportionate impact on the development of polymer mechanochemistry as a bona fide discipline. However, such improvements require broad awareness of and an agreement on the primary determinants of the reliability of molecular interpretations of SMF experiments. It is with this objective that we articulate below our understanding of these determinants.

At present, SMF experiments do not allow spectroscopic characterization of the reaction products. Signatures of mechanical instability, whether resolved (sawtooth) or not (plateaus) in dynamic SMFS, or abrupt increases in the chain extension in force-clamp SMFS are the only indicators that a reaction has occurred in these experiments. Reactions that don't increase the polymer contour length are thus invisible to SMFS. The nature and localization of scissile reactions that fragment the macromolecular bridge can rarely be identified reliably, and such reactions should be viewed as largely unsuitable for SMF studies (an important exception is SMFS of polymers containing a single labile backbone bond, e.g., ref. ⁷⁰). In the other extreme, resolving contour length elongations resulting from reactions of individual non-scissile reactive sites will most likely yield credible identification of the underlying chemistry if the observed distribution of individual chain elongations matches that obtained by high-quality quantum-chemical calculations of the assumed reaction using a fragment of the stretched macromolecule. So far only one reported study,²⁵ mechanochemical dissociation of cinnamate dimers, has achieved such resolution, but the molecular design used to ensure the sufficiently large increase in the contour length upon dissociation of individual dimers is general enough to be applied to many other reactions.

Significantly more numerous are examples of SMF experiments on polymers containing multiple equivalent non-scissile reactive sites where reactions of individual sites cannot be resolved in the force/extension curves, because each increases the contour length only by a few Å.³² Such small increments produce a plateau in force/extension curves without a sawtooth pattern and the only reliable approach reported to date of verifying the nature of the reaction is to compare the full experimental force/extension curve, including the regions before and after the plateau, to the curve extrapolated from quantum-chemical calculations of the candidate reaction(s).^{58,63} The need to model the portions of the force/extension curve where no reaction happens (either because the reactive sites are too stable kinetically at low force or because all reactive sites have already reacted at high force) is to estimate the number of the reactive sites independently of how much each elongates (conversely, the length of the plateau is a product of these two unknowns). Short of such modelling,

no reliable means exist of estimating the number of reactive sites per strain-free contour length of the macromolecule with useful accuracy from the force/extension curve. Such estimates are technically more challenging and probably less accurate for copolymers, because multiple ratios of monomers can yield very similar force/extension profiles. Although this ratio can be constrained somewhat by the monomer ratio determined spectroscopically for a bulk sample, the single-molecule nature of SMF experiments means that the composition of the measured macrochain will almost certainly deviate from that measured in a bulk sample. The outstanding question is the probability of such deviation as a function of its magnitude. An illustrative, but not conclusive example is provided by force/extension curves of copolymers of isomeric cinnamate dimers,²⁵ where the composition of each stretched chain was estimated both from the number of mechanical instabilities, and the micromechanics of the chain prior to the reaction. Although the two methods appear to yield the ratios in a reasonably good agreement, the chain-to-chain variation of the composition was considerable, illustrating the caution warranted when using quantities measured on bulk samples to characterize individual chains.

The technical difficulty of modelling force/extension curves from quantum-chemical calculations means that molecular interpretation of most SMF experiments relevant to polymer mechanochemistry relies on mostly qualitative arguments, and therefore might be best viewed as tentative.

Quantitative interpretations of SMF experiments typically aim at estimating how “sensitive” the reaction rate is to force (usually by fitting the experimental observations to the Bell-Evans equation, despite the long-articulated concerns that such fits do not yield a unique set of parameters⁷¹) or, more infrequently, estimating the strain-free reaction rates (activation energies) of reactions that are too slow to be measurable (e.g., dissociation of various covalent bonds). Such fitted or extrapolated values were used to validate the nature of the reaction responsible for the observed chain micromechanics, or even to speculate about the structure of the transition state or the reaction mechanism.

Quantitative interpretation of SMF experiments is even more challenging than qualitative interpretation and is plagued by two largely unresolved and rarely acknowledged problems: the lack of reliable means of extracting ensemble-average parameters (e.g., activation free energies, geometrical changes) from intrinsically stochastic limited-statistics measurements on single molecules, and the difficulty of controlling the pulling geometry at the atomic level.

Every known model of mechanochemical kinetics relies on activation energy, which is an ensemble quantity, i.e., it is only meaningful for a sufficiently large collection of particles (e.g., reacting molecules) to average out thermal fluctuations of observed quantities (e.g., rate constants or survival probabilities). In contrast, the behavior of polymer chains in single-molecule experiments is governed by single-molecule statistics. To appreciate the difference, consider a hypothetical macromolecule containing 10^{12} equivalent non-scissile reactive sites (a molecule with so many reactive sites is not synthetically accessible). We'll stretch this molecule very rapidly to restoring force F and monitor by whatever means available (e.g., increase of the chain contour length) the change in its composition due to the mechanochemical reaction as we maintain the chain at this restoring force (i.e., perform a force-clamp experiment). This data can be converted to the reaction rate constant at force F , $k(F)$. If we repeat the experiment with an identical macromolecule, we may expect the two rate constants to be within ~15% of each other if we are competent experimentalists, the variance being a reflection of experimental error.

In practice, the vast majority of SMF experiments reported to date were performed on macromolecules containing fewer than 100 equivalent reactive sites for synthetic polymers and as few as 8 sites for proteins, whose monodispersity (i.e., all chains have exactly the same length and the number of the reactive sites) eliminates one important source of experimental variability. Repeating the above experiment with a macromolecule containing only 8 reactive sites will have only ~7% chance of exactly half of these sites having reacted within the same time ($\ln(2)/k(F)$) that exactly half of the sites in the hypothetical large analogue do. Repeating this experiment 20 times increases the chance

that the inferred average rate constant is between half and twice the ensemble-average value (i.e., in the $(0.5-2)k(F)$ range) to only <50% even if all other sources of variability are eliminated, which is impossible. The fairly slow convergence of rate constants (and parameters derived from them, such as the “length” of the transition state) to the ensemble-average values means that quantitative interpretation of SFM results based on reactions of fewer than $\sim 10^3$ sites is probably unreliable until more powerful mathematical methods of extrapolating limited statistics to the thermodynamic limit have been devised.

Because many reaction rates increase exponentially with force, the rate constants derived from dynamic measurements may, in theory, converge to the ensemble limit faster²⁵ with the number of reactive sites than for the force-clamp experiment. In practice, this advantage of dynamic SMFS is diminished, and may even be eliminated by the dependence of the critical force in such experiments on the polymer contour length and its compliance. The dynamic force spectroscopy controls chain extension (tip retraction) rate, whereas reaction kinetics is controlled by the restoring force, and longer macromolecules thus require more time to reach the same restoring force as shorter chains. Consequently, the longer chains experience smaller effective loading rate and hence the survival probabilities of individual reactive sites decrease slower with time than in shorter chains (Eq. 7). Longer chains also have more equivalent reactive sites, and the probability of one site reacting increases as a power of the number of the equivalent sites. Because of the high dispersity (index >1.5) of synthetic polymers used to date in the reported SMF experiments and limited control over the interactions between the chain and the surfaces (see next paragraph), the length of chain segments that are stretched in such experiments varied by up to 5-fold among repeats. The net result is that the force at which the chain micromechanics is detectably affected by mechanochemical reactivity in repeat SMF experiments varied by hundreds of pN. These effects are not considered by any model of mechanochemical kinetics, but are amenable to numerical simulations using data obtained by quantum-chemical calculations.²⁵

Technical idiosyncrasies of SMFS may also introduce systematic errors that have so far appeared to be impossible to quantify, much less to eliminate. Although SMF experiments are often depicted with the stretched chain being aligned with the direction of motion of the positional scanner and hence with the axis of the cantilever deflection (z direction), this alignment is highly improbable. Far more likely are geometries in which the backbone of the stretched chain forms an angle to the direction of the motion. Likewise, it's highly unlikely that the chain is connected at the apex of the cantilever tip, instead of somewhere on its side. Both factors (illustrated in Fig. 5) result in the chains in SMF experiments very likely being stretched to the larger restoring force that the one derived from the deflection of the cantilever because cantilevers are much easier to bend vertically than laterally and the lateral component of the restoring force is thus not measured and may be currently unmeasurable. Since it appears impossible with the current configuration of SMF experiments for a chain to bind in a way that the cantilever deflection force exceeds the chain restoring force, repeat measurements cannot compensate for off-axis stretching, and the reported forces are probably systematically underestimated by a factor that can neither be estimated nor eliminated in repeat measurements.

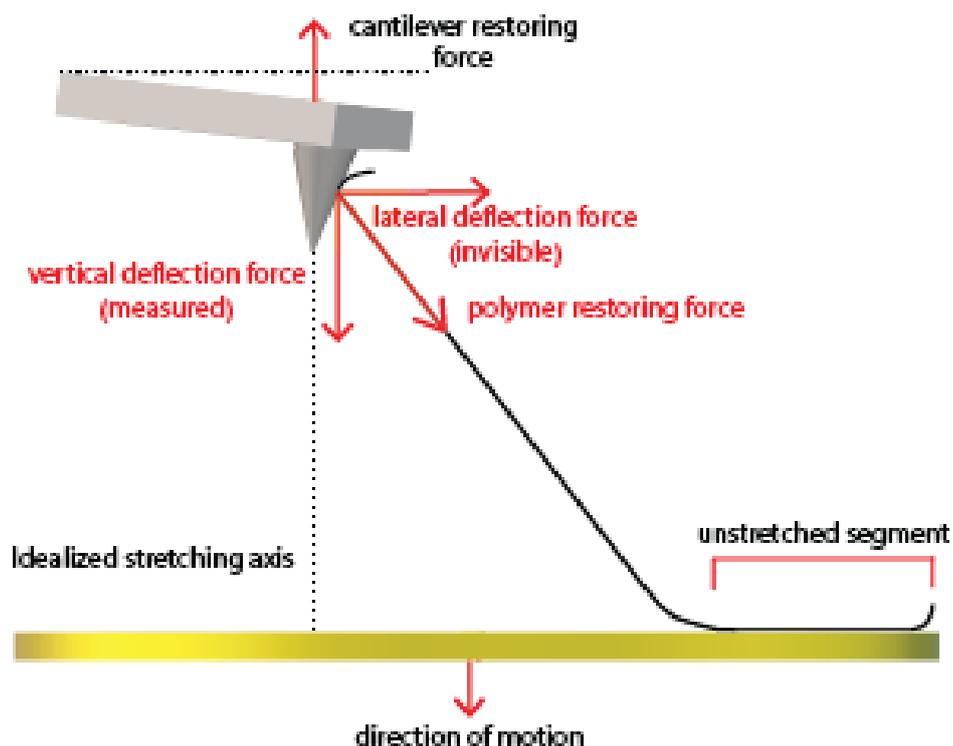


Fig. 5: Illustration of a major mechanism whereby SMF experiments underestimate the restoring force of the stretched macromolecule: the chain being misaligned with the direction of motion of the surfaces (illustrated by the broken line) and the chain binding to the tip off apex. The restoring force of such a chain can be separated into vertical and lateral components, only the former being measured due to the high stiffness of the cantilevers in the horizontal plane.

Reactions that are reversible on the time scale of an SMF experiments allow the same transition to be observed multiple times within the same macromolecule by performing repeated cycles of retraction/return. Such cycling would allow statistical averaging of the measured kinetics without variability of stretching multiple macrochains or the need for multiple equivalent reactive sites. It would also allow experimental testing of the Jarzynski equality⁷² on reactants whose ensemble-average reactivity can be readily quantified or computed quantum-chemically. Unfortunately, so far, no reaction of interest to polymer mechanochemists has been identified that is reversible on the timescale of an SMF experiment. Isomerization of spiropyran to merocyanine should be reversible

based on the estimated strain-free kinetics⁷³ but stretching of macromolecules containing two different spiropyran derivatives yielded irreversible isomerization for unknown reasons.⁷⁴

Optical and magnetic tweezers, in which a macromolecule is bound to one or two microbeads whose position(s) are manipulated by intense focused electromagnetic fields have been utilized to stretch biopolymers and quantify forces generated by various motor proteins.⁷⁵ These techniques generate forces <100 pN (vs. up to ~5 nN by AFM), which is insufficient to accelerate reactions involving covalent bond rearrangement to the second timescale. Consequently, optical and magnetic tweezers have not been used in polymer mechanochemistry.

3.2. Flow fields

A number of experimental techniques exist that rely on hydrodynamic coupling between a polymer solute and solvent in a flow to stretch the macromolecules. It is practically impossible to generate a fluid flow with flow rate that is uniform in space. A velocity gradient perpendicular to the flow direction (which is realized in a fluid flowing past a surface, whereby the solvent flow increases from zero immediately at the interface (stagnation layer) to a maximum far away from the surface) creates shear. A velocity gradient along the direction of flow produces elongation. The strength of the flow is quantified by a strain rate, $\dot{\epsilon}$, or shear rate, $\dot{\gamma}$, which reflects flow velocity gradient along or perpendicular to the flow direction, respectively, per unit length. In practical flows both components are present, although certain portions of flows may approximate pure shear or pure elongational flows. Quasi-steady-state elongational flows are produced by the filament-stretching device⁷⁶ (uniaxial flow), cross-slot and four-roll mill devices⁷⁷ (planar flows). Transient elongational flows are generated in abrupt-contraction devices and by ultrasonication^{9,15} (see section 3.2.2. Sonication). In all these geometries turbulent flows are also present, and their contribution to the observed mechanochemistry is rarely known⁷⁸. Although the rapid and chaotic changes in flow velocity of turbulent flows largely preclude elucidation of the microscopic conditions responsible for mechanochemistry, they are studied in large part due to the industrial importance of using

macromolecules for drag reduction, as polymer degradation severely reduces the efficiency of this process with time.¹

Two key parameters determine the fate of a macromolecular chain in a dilute solution under flow: the Deborah or Weissenberg number, and accumulated (or Hencky) strain.⁷⁹ The former is a product of the strain or shear rate and the longest relaxation time of the polymer, τ_1 . In flows with rates below approximately half $1/\tau_1$ the polymer solute remains in its coiled geometry, only marginally affected by the flow. The longest relaxation time increases linearly with the solvent viscosity and as a power of 1.5 of the polymer contour length. Synthetically accessible polymers in common organic solvents have relaxation times in the 100 ns – 10 μ s range (e.g., τ_1 of 1 MDa and 100 kDa polystyrene in THF at 300 K are 7 μ s and 0.2 μ s, respectively). Quasi-steady-state elongational flows with strain rates on the order of 10^4 s⁻¹ have never been demonstrated experimentally, making such flow geometries of limited value for studying mechanochemistry of synthetic polymers (synthetic polymers can be stretched when dissolved in special high-viscosity solvents, e.g., Boger fluids, which introduce their own complications⁷⁹ and have not been used in polymer mechanochemistry). In contrast, DNA polymers with relaxation times in the seconds range are readily available and such chains can be stretched easily even in disposable PDMS-made cross-slot devices⁸⁰.

In theory, a macromolecule in elongational flow with a strain rate exceeding $0.5/\tau_1$ would undergo abrupt coil-stretch transition, whereby the end-to-end distance of the chain increases close to its contour length (in elongational flows) or to a substantial fraction of it (in shear flows). In practice, the coil-stretch transition is quite slow and requires a substantial residence time in the flow, which is quantified by the Hencky strain. For a flow with time-independent strain or shear rate, Hencky strain is a product of this rate and the residence time. For Hencky strain below a certain threshold value, which depends on the Deborah number, stretching is highly transient, and the observed macromolecular conformations vary greatly from one molecule to another.⁷⁹ It seems safe to speculate that polymers of interest in contemporary polymer mechanochemistry cannot be fully stretched in

any experimentally realizable flows, and any discussion of the molecular origin of the observed reactivity of such solutes should acknowledge that bulk response arises from a broad (and currently unknown) distribution of conformers (Fig. 6).

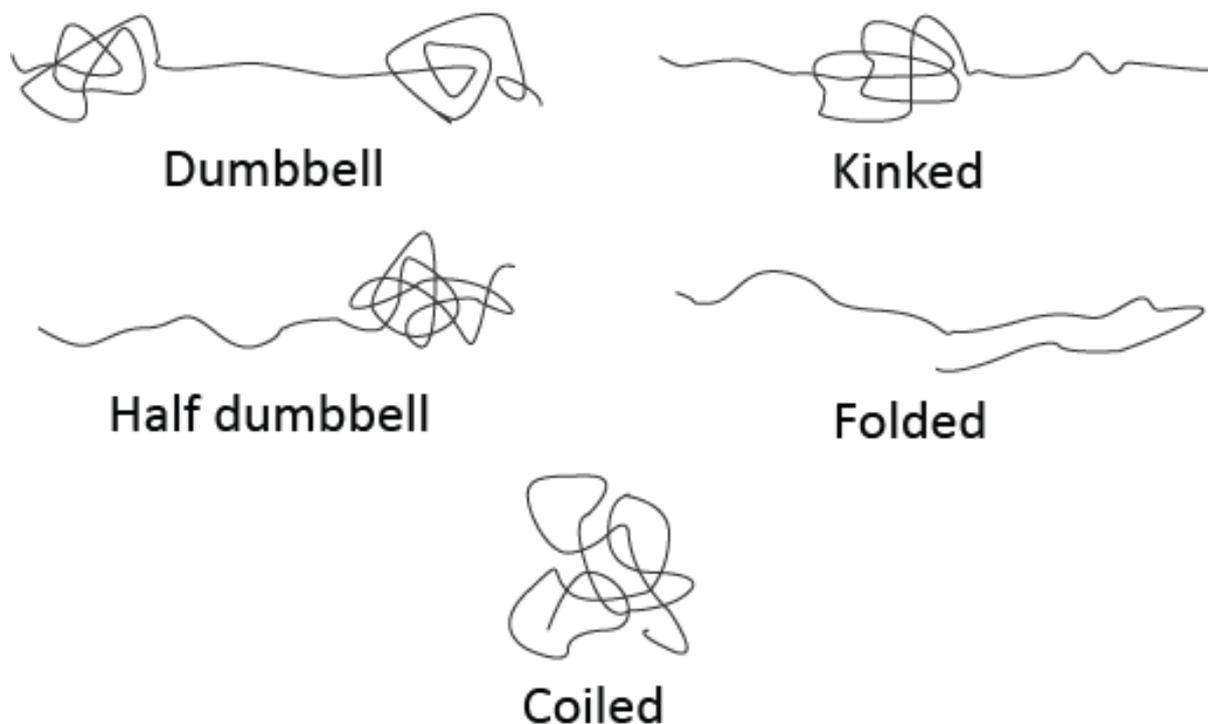


Fig. 6: Cartoon representation of the types of DNA conformers thought to occur in quasi-steady-state-elongational flows at Hencky strain corresponding to undetectable amount of coiled chains. Based on data from ⁸⁰ and ⁸¹)

3.2.1 Quasi-steady-state elongational flows

Quasi-steady-state elongational flows are characterized by an existence of a central stagnation point with zero net fluid velocity. Such flows are typically induced in either a cross-slot device (Fig. 7) ⁸² or four-roll mill.⁷⁷ The solvent strain rate is controlled either by the pressure difference between inlet and outlet channels in the cross-slot device, or by the speed of the rollers. A dissolved macromolecule is occasionally trapped at the stagnation point, where (at least in theory) it can be kept for hours with an adequate feedback mechanism. In practice, the achievable residence time depends on the desired strain rate, and decreases very rapidly at the strain rates relevant in polymer mechanochemistry

because of the difficulty in maintaining the required flow stability rather than mechanochemical fragmentation.

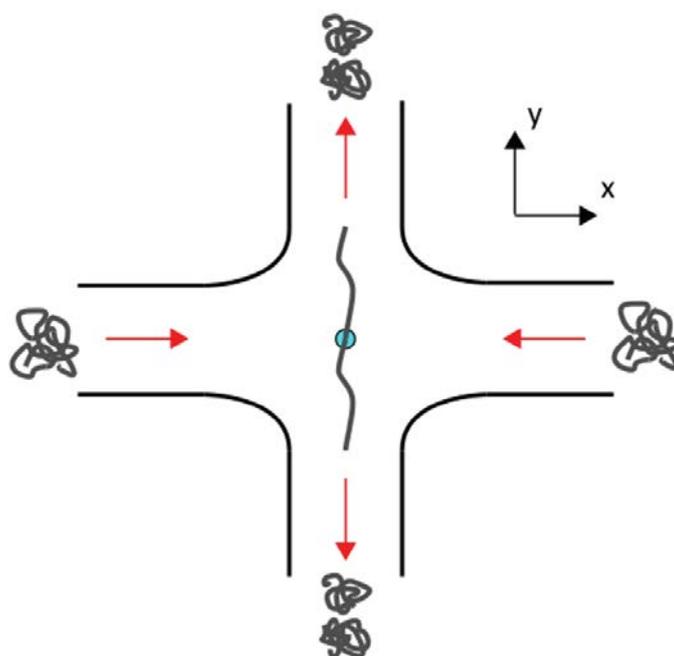


Fig. 7: Illustration of the cross-slot device used to study polymer extension and degradation in QSSF. Two opposing channels along the $\pm x$ directions pump solvent containing a single macromolecule into the device, and two opposing channels along the $\pm y$ directions suck out the solution. The strain rate experienced by the trapped macromolecule is controlled by changing the velocity of the pumped solution. The central stagnation point is marked with a pale blue circle. In this region, net fluid velocity along either axis is zero.

Indeed, no convincing evidence of mechanochemistry in polymers stretched in quasi-steady-state elongational flow has ever been reported. Simulations suggest that early observations of polymer fragmentation in such flows appear to result from chain fragmentation in turbulent flows at the edges of the cross-slot device.⁷⁸ The primary contribution of QSS elongational flow to the current discussions of polymer mechanochemistry is a force distribution along a chain trapped at the stagnation point, which is often erroneously assumed to represent force distribution along a chain stretched in any flow field¹. This force distribution is derived from the simplest possible implementation of the classical

bead-spring model,⁷⁹ which represents a polymer chain as a series of spherical beads connected by harmonic springs. The implementation neglects the hydrodynamic interactions, which account for the distortion of the flow field by the beads; the excluded volume interactions, which account for repulsive or attractive bead-bead interactions not mediated by the springs, and thermal fluctuations, which ensure that a chain geometry is more complex than that of a rigid rod. These assumptions result in a quadratic dependence of the force experienced by a bead (or equivalently the restoring force of a spring attached to it) on its position relative to the center of mass of the chain, independently of the parameters of the model (radius of the beads, friction coefficient, and spring force constants). The same dependence is obtained if the chain is assumed to be a rigid slender rod in a 1D solvent flow.

This “rigid-rod” model is almost certainly irrelevant to any experimentally observed mechanochemistry in flows, simply because the underlying assumptions are too unrealistic. While the importance of hydrodynamic or excluded-volume interactions may not be obvious, the assumption of the chain being in internal mechanical equilibrium (i.e., behaving as a slender rigid rod) seemingly requires Hencky strains that are unachievable with any experimentally demonstrated flows and polymer contour length relevant for contemporary studies in polymer mechanochemistry. The application of this rigid-rod model for sonication is sometimes justified by arguing that a parabolic force distribution along the chain is required to explain the “mid-chain” scission of polymer chains in flows. The latter refers to a common observation that the molar mass distribution (MMD) of the product of chain fragmentation in flows has the maximum at the chain mass approximately half that of the original polymer. This “mid-chain” scission, however, is consistent with an arbitrarily large number of force distributions along the chain,¹ and the argument unfortunately conflates a macroscopic observation (MMD averaged over fragmentation of many molecules comprising the bulk sample) with the microscopic conditions (the distribution of fragmentation probability along an average fragmenting chain) responsible for it. Imagine that contrary to the rigid-rod model described above, only a small segment of each fragmenting chain is stretched (i.e., fragmenting chains resemble those in Fig. 6 instead of rigid rods) but that any portion of the chain has a non-zero probability to be

stretched. The symmetry argument alone suggested that this probability will be higher for segments closer to the chain center of mass than those farther away. The ensemble-average outcome of this scenario is the prevalence of chains with half of the original mass even if every backbone bond of the stretched segment of individual fragmenting chains has the same restoring force and the same fragmentation probability.

3.2.2. Sonication

Sonicating a dilute solution of a polymer is by far the most popular technique of polymer mechanochemistry. It's as easy to perform technically as it is difficult to understand at the microscopic or molecular levels, or indeed quantify reliably.

In sonication, transient elongational flows needed to stretch a macromolecular solute are generated by the collapse of cavitation bubbles. Passing sound waves of frequencies in kHz ranges through a liquid creates acoustic cavitation, which is the nucleation, growth, and subsequent collapse of cavities within solution (bubbles). The acoustic field of the ultrasound waves dilates and contracts the bubbles, eventually causing them to collapse violently. Such a collapse of an isolated cavitation bubble creates a spherically symmetrical transient elongational flow field with fluid elements closer to the bubble edge having higher velocity than those farther away, as illustrated in Fig. 8.¹⁵

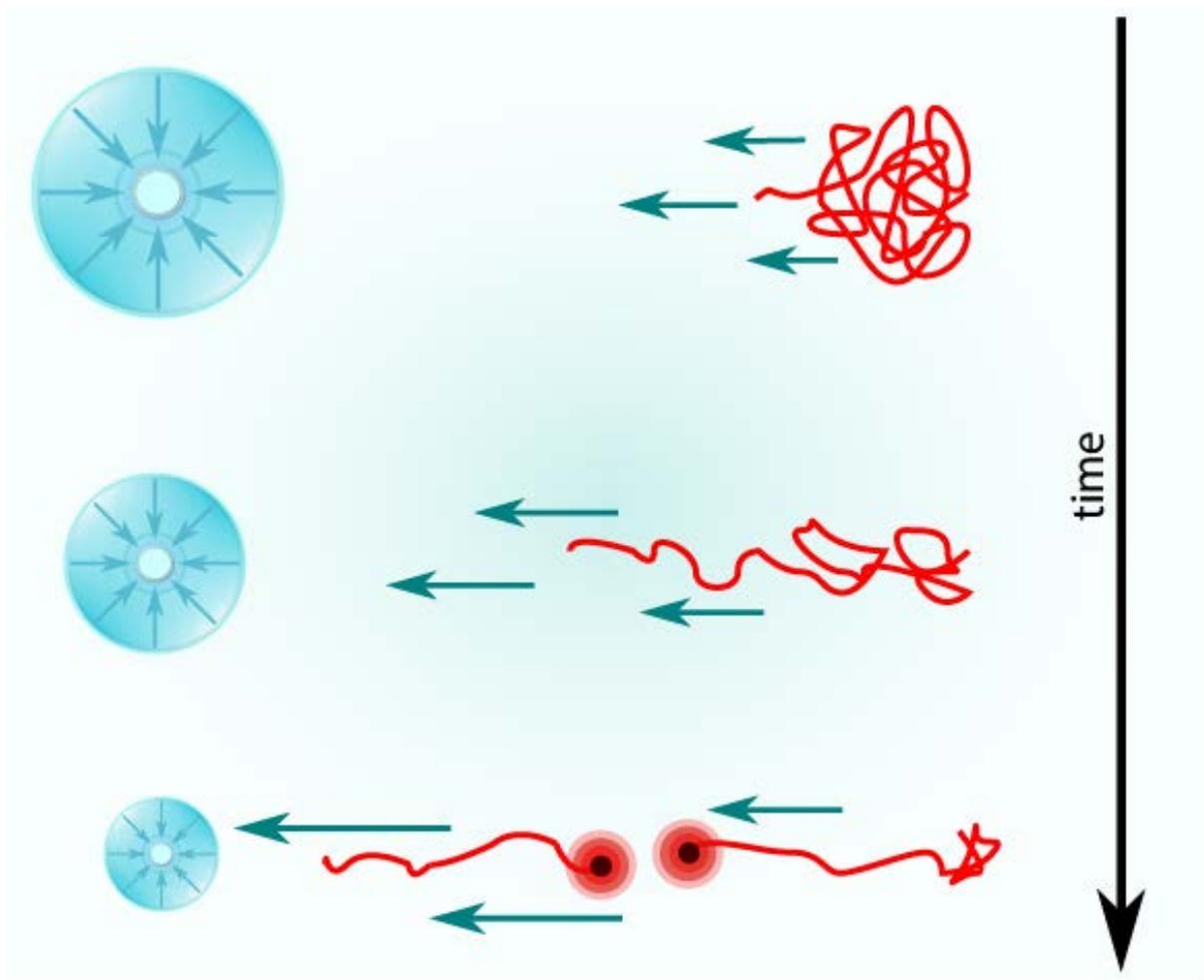


Fig. 8: The mechanism by which ultrasonic degradation of a polymer chain occurs during sonication. At the moment of bubble collapse (top), the polymer chain is coiled in solution and its instantaneous shape is roughly spherical. As the cavity rapidly decreases in size, the surrounding solvent molecules are drawn towards it, and the segments of the polymer chain closest to the bubble are stretched. At the latter stages of bubble collapse (bottom), the solvent strain rate is sufficient for the chain to fragment. Arrows show the direction of solvent motion at each point, with the magnitude of its velocity represented by its size.

Sonication of commercial polymers, such as polystyrene or polyacrylates, results in their fragmentation as evidenced by a gradual decrease in the average molar mass of the solute as sonication progresses. Chain fragmentation first produces highly reactive macroradicals, which are probably quenched by a reaction with the solvent or (more likely) sonolytically generated small-

molecule radicals, i.e., species produced inside the collapsing bubbles from solvent vapor or dissolved gasses, but not the polymer solute which cannot enter the bubbles. Recombination of macroradicals is likely to be negligible because no evidence of a reaction between a macroradical and a polymer chain has ever been reported (e.g., sonication of a polymer containing sp^2 C atoms could be expected to create a product with higher molar mass than the original reactant due to high reactivity of macroradicals towards addition to sp^2 C atoms). The very limited chemistry possible on stretching simple polymers such as polystyrene makes sonication of their solutions of limited interest in polymer mechanochemistry (a topic of some interest is the scaling of a bulk rate of mechanochemical fragmentation of a polymer on its molar mass, which is reviewed in ¹). Instead, contemporary focus has been on sonicating solutions of polymers comprised of one or multiple reactive sites embedded in inert polymer backbones. In most cases these reactive sites are dissociatively more labile than the rest of the polymer backbone bonds, in theory resulting in the stretched polymer fragmenting preferentially at the reactive site (site-selective fragmentation) instead of elsewhere along the backbone (non-selective fragmentation). In practice, both selective and non-selective fragmentations are detectable during sonication. Examples of scissile reactive sites are Diels-Alder adducts and cinnamate dimers. Two types of non-scissile reactive sites studied to date are dihalocyclopropanes and spiropyrans.

Sonication of solutions of such polymers yields some of the same products that are thought to be generated in single-molecule stretching of isolated macrochains or in bulk polymer samples under macroscopic loads. Sonication of polymers containing multiple equivalent reactive sites allows accurate spectroscopic identifications of the products of sonication,³² something that is not possible in single-molecule force experiments and is rarely done for solid loaded polymer samples. UV-vis and/or fluorescence spectroscopy is particularly valuable in confirming site-selective fragmentation if the studied reaction is mechanochromic, i.e., it yields a product with optical properties distinct from the reactant. In contrast, a reduction in the average molar mass of the sonicated sample can be caused

by both selective and non-selective fragmentation and hence cannot be used to distinguish between these two paths (for a recently demonstrated example see ref. ⁶).

Consequently, sonicating a polymer solution is an easy and qualitatively reliable way of testing if the kinetic stability of a particular reactive site is affected by stretching it, if the products of sonication are amenable to spectroscopic characterization. In other words, sonication is useful to confirm force-acceleration of both scissile and non-scissile mechanochromic reactions (i.e., regardless of whether they result in chain fragmentation or not), and of non-scissile reactions that occur at multiple equivalent reactive sites per chain. In contrast, acceleration of non-mechanochromic scissile reactions to an extent greater than that of the “inert” backbone bonds cannot generally be established reliably by sonication. Sonication of chains containing multiple scissile reactive sites yields fragmented chains with most reactive sites intact, because once the chain fragments by the dissociation of a single site, the probability of it getting stretched enough to accelerate the dissociation of another site on the experimental timescale becomes negligible. As a result, NMR spectra of such sonicated polymers are dominated by the intact reactive sites, precluding the quantitation of the reaction extent. Several workarounds are known, but none allows the extent of the reaction to be estimated, i.e., it is impossible to establish if the mechanosensitive reaction is accelerated by force to any greater degree than dissociation of the “inert” bonds of the backbone, which always happens in sonication.

Every reactive site that has ever been incorporated in an “inert” polymer backbone in context of polymer mechanochemistry is, in the absence of force, more labile, often by many orders of magnitude, than the dissociation of the backbone bonds. Of particular interest are thus examples where the macromolecules manifest no preference for reaction at such reactive site over fragmentation at the adjacent backbone bonds, because such cases are rare and challenge the “intuition” of how the kinetics of molecular fragmentation responds to tensile load. Several reactions appear to be insensitive to tensile load when the respective polymers are sonicated but are accelerated, albeit to a small degree, in bulk loaded materials. The difference probably reflects the

highly transient nature of chain stretching in sonication, which dictates that only reactions over barriers <10 kcal/mol ($t_{1/2} \sim 1 \mu\text{s}$) are observed. The longer relaxation times of chains in solids probably mean that a stretched polymer segment may remain in its non-equilibrium geometry for longer than a few microseconds, allowing reactions over barriers in excess of 10 kcal/mol to be observed.

Sonication has been shown to initiate reaction cascades, whereby a primary stable product of mechanochemical reaction reacts with another component of the sonicated solution. Such experiments are valuable in supporting the existence of similar cascades in bulk materials under load, where they have been exploited to yield mechanochromic and load-strengthening responses.

Practically nothing is known about the microscopic conditions responsible for polymer mechanochemistry in sonicated solutions. Our current understanding of the dynamics of isolated cavitation bubbles is quite sophisticated, but no attempt to establish the feasibility of mechanochemical reactions in a flow field generated by an isolated collapsing bubble has ever been reported. Instead, polymer solutions are sonicated using macroscopic immersion acoustic horns that produce indeterminate number of cavitation bubbles, hundreds or thousands of which may entrain to form bubble clouds whose dynamics is not understood. Under these conditions the observed chemistry may not even result from the collapse of individual bubbles, but rather from shock waves created by a synchronized collapse of bubble clouds. A simple hand-waving argument suggests that the conditions experienced by mechanochemically reacting chains in sonicated solutions are quite extreme. The low limit of the maximum fluid strain rate that is generated during sonication is based on the observation that even chains as short as ~ 20 kDa polystyrene fragment during sonication, which requires that they reside, at least transiently, in flow fields with straining rates of $>0.5/\tau_1 \sim 3 \cdot 10^6 \text{ s}^{-1}$. At the most utilized sonication frequency of 20 kHz, a bubble must collapse within $<25 \mu\text{s}$ (the duration of a single compression cycle) with the fluid strain rates $>10^6 \text{ s}^{-1}$ generated only at the final stages of collapse. This means that a chain segment can go from a strain-free geometry to being stretched to several nanoNewtons of force in $<1 \mu\text{s}$, a loading rate that is $\sim 10^5$ times greater than can be generated

in single-molecule force experiments. A polystyrene chain has ~50% survival probability against fragmentation within 1 μ s at 5 nN, which gives a very approximate upper limit of the extent of strain a chain experience during sonication. An average chain may be stretched multiple times before fragmenting.

Few attempts to estimate the microscopic conditions responsible for mechanochemistry in sonicated solutions have been reported. To date, the most useful insights have come from analysis of the fraction of mechanochemically reacted chains that have undergone site selective chemistry vs. non-selective fragmentation. While this effort remains in very early stages, quantifying the microscopic conditions in sonicated solution is likely the most important factor of in realising the full potential of sonication to understand chemical reactivity at extreme strains and loading rates.

Although most reports of sonication of polymer solutions contain some characterization of the rate at which the bulk composition of the sonicated solution changes with sonication time, both technical and fundamental limitations ensure that such data is far less valuable in gaining the molecular insights than kinetic studies in physical organic chemistry generally are.

The fundamental reason is that macroscopic rate constants of a sonicated solution are a complex and unknown convolution of multiple microscopic probabilities. In conventional kinetic studies, a rate constant reflects the microscopic probability of a molecule to react because every reacting molecule scales the same energy barrier and the probability of doing so is determined by the Boltzmann distribution of the reactant molecules. In contrast, at any moment in a sonicated solution, different macromolecules have to traverse vastly different activation barriers to undergo the same reaction, based on how much each is stretched by the flow field, how fast this field changes in time, the history of the molecule in this field and the probability that the molecule will remain in the field among other contributions.

The practical difficulties are related to the finite dispersity of polymer samples, i.e., they are comprised of chains of (sometimes vastly) different lengths, and hence propensity to undergo mechanochemistry

in flows. A consequence of this dispersity is the need to discuss the composition of a polymer sample in terms of its molar mass distribution (MMD), rather than a small number of components. Sonication of a polymer solution fragments polymer chains, changing the MMD of the solute. In theory these time-lapsed MMDs can be used to estimate the distribution of fragmentation probabilities along the polymer chain, which can allow various assumptions about the microscopic conditions responsible for the observed bulk changes to be assessed. In practice, such analyses are technically complex. As a result, most reports in the literature reduce each MMD to a single distribution moment (e.g., number-average or mass-average molar mass) and then fit a set of these moments to one of a plethora of empirical rate laws proposed in the literature to describe the time evolution of the molar mass of a sonicated polymer. This procedure discards important details about reaction kinetics. Worse still, the resulting fitting parameters from most such models (including the most commonly used one now) are neither mechanistically significant, nor allow comparisons across different experiments, because the underlying models were derived either from an internally inconsistent set of assumptions or for conditions too dissimilar to those for which they are applied. An example of the former is to simultaneously postulate that the probability of a backbone to break decreases linearly with the number of backbone bonds, and that chains with fewer than a minimum number of backbone bonds do not break. An example of the latter is to fit the rate of molar mass decrease of the polymer claimed to break only at a single site to a model that postulate that each backbone bond has the same fragmentation probability.

Any reaction induced by stretching a polymer chain for a 1 μ s or less is likely to follow pseudo-first order kinetics. This in theory would eliminate the need for empirical models of MMD evolution and would allow the kinetics to be described by the ensemble-averaged first-order rate constant of the depletion of the total mass fraction of the chains comprising the original reactant. In practice, most sonication experiments have been conducted with polymers of such large dispersity that the MMDs of the reactant and the product cannot be quantify individually, as they overlap. Many reported sonication experiments were conducted on samples in which the average molar mass of the largest

10% of the chains was 10-fold or greater than the average molar mass of the smallest 10% of the chains. MMDs measured on such samples manifest clear evidence of preferential depletion of the higher-mass component, which produces fragments of mass indistinguishable from that of a fraction of the reactant, further complicating molecular interpretation of the kinetics of changes in the bulk composition of the sonicated sample.

All these problems can be overcome by using very low-dispersity polymers ($PDI < 1.005$), high-resolution size-exclusion chromatography, and cleverly designed reactive sites that allow one to differentiate whether multiple products of sonication result from intra- vs. interchain kinetic completion. Such experiments, however, remain to be reported.

3.4. Mechanochemical reactivity without macroscopic motion

Mechanochemical reactions are manifestations of molecular strain induced by macroscopic motion, such as macroscopic flow of a fluid, translation of an AFM tip or distortions of the macroscopic dimensions of a bulk polymer sample. Atomistic studies of such processes are particularly challenging. Two broad approaches suggest that the effect of anisotropic molecular strain on chemical reactivity can be studied productively without the complexities of macroscopic motion: one relies on small-molecule macrocycles and the other on overcrowded polymers that spontaneously stretch at certain interfaces. The latter was reviewed in detail recently⁸³; the other is briefly analyzed below. Because molecular strain, unlike its engineering counterpart, is a qualitative concept, no rigorous definition of what makes molecular distortion anisotropic is possible. We find functional definition to be informative: a molecular fragment is axially strained if its geometry deviates from that of the same molecular fragment in a stretched macromolecular segment by less than a threshold RMS value. Such comparisons require the two structures to be optimized quantum-chemically and are thus only as reliable as the chosen model chemistry.

One approach reported by our group in 2009^{53,55} is to dispense with macromolecules altogether, and attempt to reproduce the distortion that a reactive site in the backbone of a stretched macromolecule experiences in a strained macrocycle (Fig. 9). Evidence accumulated since then clearly demonstrates that the approach doesn't simply succeed in reproducing in a small molecule the reactivity observed by stretching polymers containing the same reactive sites,⁵⁸ but also offers insights into mechanochemical reactivity not attainable by any other experimental technique.^{42,61}

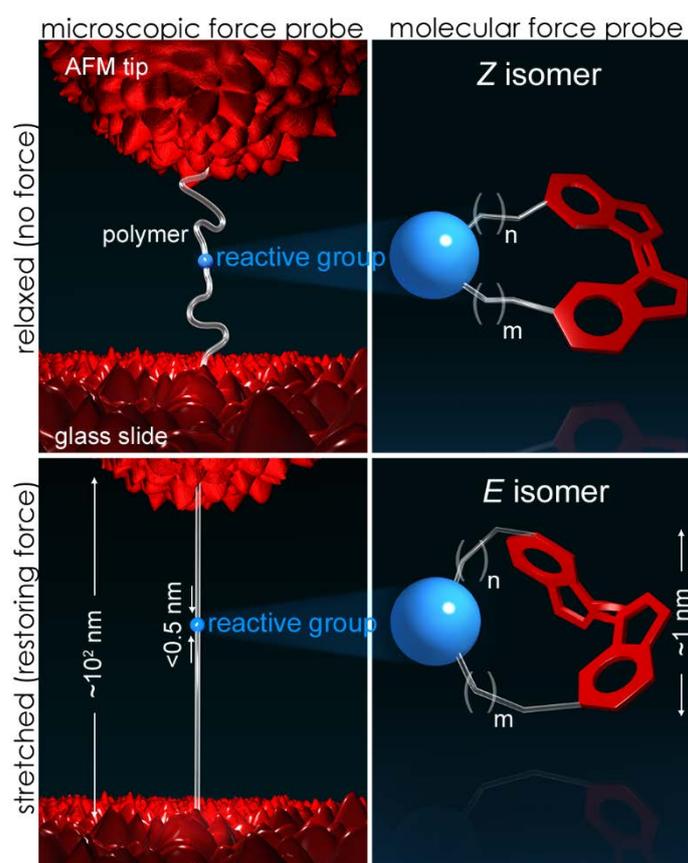


Fig. 9. Schematic comparison of an SMF experiment on a polymer chain containing a reactive site (blue) with an experimental model using stiff stilbene (right panels). Reproduced with permission from ref. ⁵⁵.

The approach uses *E* stiff stilbene to impose an approximately axial tensile strain on a reactive site connected to the C6, C6' carbon atoms of stiff stilbene by short inert linkers. The magnitude of the imposed strain is controlled by the length and the conformational flexibility of these linkers, producing a series of increasingly strained macrocycles in which the reactive site geometry approximates that in

macromolecules stretched to between 100 pN and 800 pN, in increments as small as 50 pN. The Z isomers of these macrocycles are strain free regardless of the linkers, and are valuable both as efficient synthetic precursors of the strained isomers, and as strain-free references. Comparing the kinetics of the reactive site reaction in the two isomers of the same macrocycle allows the effect of the anisotropic strain to be isolated from any other influences, including the linkers and the solvent. In other words, stiff stilbene acts as a molecular force probe, in analogy to the microscopic force probes of single-molecule force spectroscopy (SMFS) (Fig. 9).

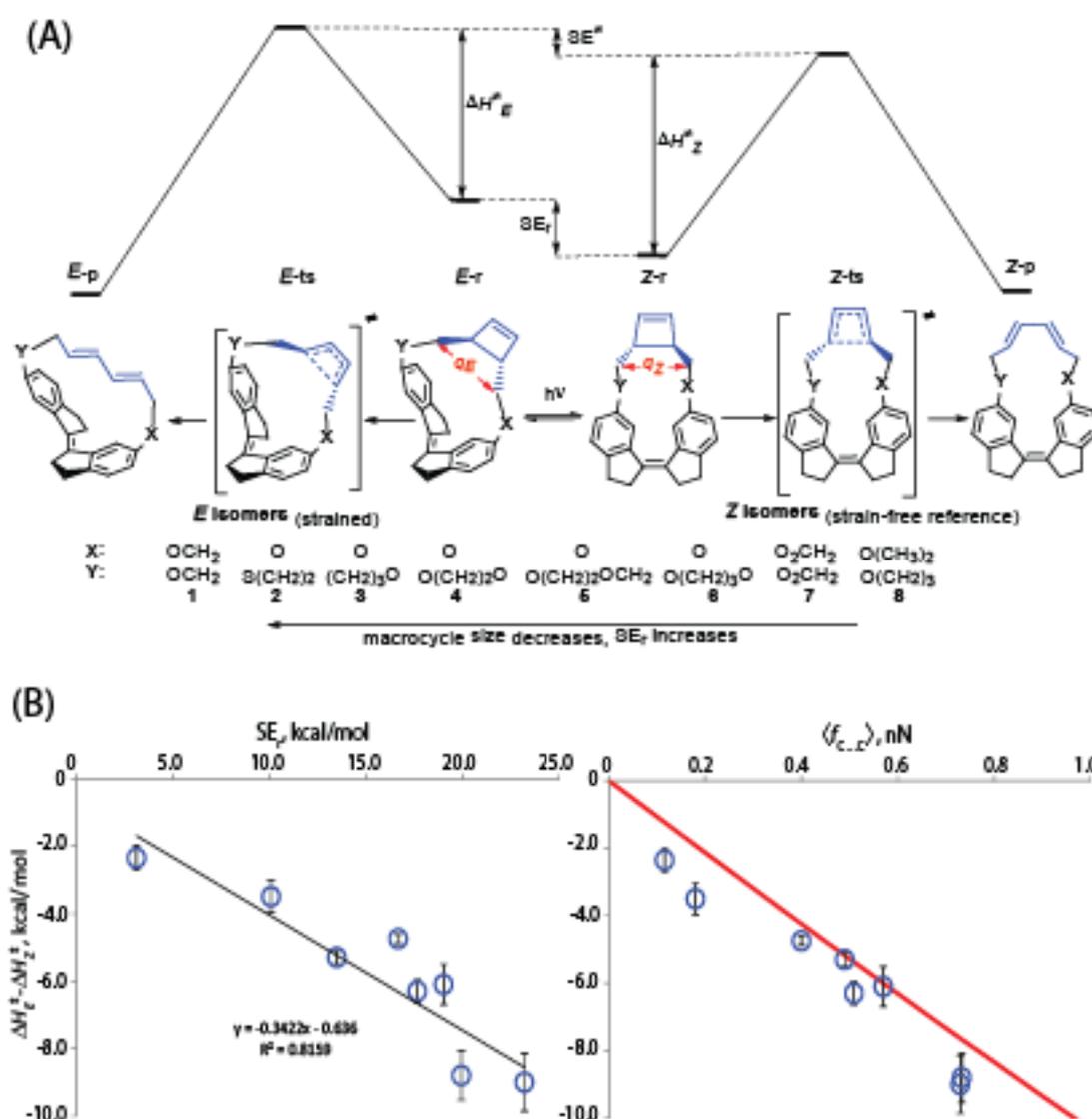


Fig. 10. Illustration of the use of stiff stilbene to measure intrinsic mechanochemical kinetics of a classical electrocyclic reaction, isomerization of *trans*-3,4-dialkylcyclobutene to a diene (blue) using a

series of stiff-stilbene macrocycles (A). The measured activation enthalpy is comparable across the series for *Z* macrocycles but decreases with decreasing macrocycle size for *E* analogues. The measured difference in activation enthalpies between the strain-free *Z*-isomer and strained *E* analogue of the same macrocycle, $\Delta H^\ddagger_E - \Delta H^\ddagger_Z$, correlates well both with the calculated strain energy difference of the two isomers (B) and the restoring force of the non-bonding exocyclic C...C distance of the reactive moiety (defined by red arrows in (A)), (C). The red line in (C) is the activation enthalpy of the same reactive moiety in a stretched polymer segment with the same restoring force of the local coordinate as in an *E* macrocycle. Reproduced with permission from ⁸⁴.

The ability to study quantitatively the effect of anisotropic strain on localized chemical reactivity in small molecules instead of stretched macromolecules offers practical and conceptual advantages. First, small-molecule reactivity, including reaction kinetics, selectivity and mechanisms, is amenable to detailed characterization by the full complement of experimental and theoretical tools of modern chemistry. Second, unlike SMF experiments, molecular force probes are studied in ensembles, obviating the need to estimate ensemble properties from single-molecule statistics. Third, unlike polymer mechanochemistry in flow fields, all reacting molecules are subject to the same uniform conditions, and macroscopic reaction rates reflect the microscopic reaction probabilities. Fourth, molecular force probes are suitable to quantify mechanochemical kinetics that is beyond the scope of other techniques, including reactions that are strongly inhibited by force or even just too weakly accelerated by force to compete with chain detachment in SMF or chain fragmentation in flow fields. Finally, because the whole macrocycles are amenable to full atomistic description at a quantum-mechanical level, molecular force probes allow the key assumption of mechanochemical kinetics, that the effect of many molecular degrees of freedom on localized kinetics is captured quantitatively by a single parameter with the meaning of molecular restoring force, to be evaluated with unprecedented detail.

For the observed reactivity trends in series of stiff stilbene macrocycles to advance our understanding of polymer mechanochemistry, they must be expressed as a function of the restoring force of a local coordinate of the reactive site (which then can be related to the single-chain force as described in 2.2. Accuracy of the conventional approximations and systematic strategies of improving them.). The physical meaning of this force is the same in the macrocycles and in stretched polymer chains: a quantifier of kinetically-significant molecular strain energy of a portion of the molecule. At stationary states, whose relative energies determine the reactivity, the molecules are in internal mechanical equilibrium with zero force on every atom. In other words, no Hamiltonian exists whose eigenvalue is a restoring force to a molecular coordinate of a macrocycle, and estimates must rely on one of several existing models¹. A similar reliance on a model underlies the single-chain stretching forces reported in SMF experiments, where the restoring force of the stretched macromolecule is neither controlled nor measured directly, but rather estimated from the deflection of the cantilever. Contrary to common belief, these estimates are subject to both systematic and random errors, including the lack of molecular-level details or control over the chain/surface interaction (see 3.1. Single-molecule force spectroscopy) and the limits of the simple models used to relate the measured deflection to the force (e.g., the beam equation) to capture such dependence accurately, particularly at high forces. In other techniques of polymer mechanochemistry, including flow fields and bulk materials under loads, the magnitude of the distortion of the chain responsible for the observed reactivity cannot be estimated at all.

The two main contributions of molecular force probes to our understanding of polymer mechanochemistry are the validation of the local assumption of mechanochemical kinetics (see 2.2. Accuracy of the conventional approximations and systematic strategies of improving them.) and experimental demonstration of the diverse range of responses of molecular fragmentation kinetics to axial tensile strain. In addition to the conventional notion that stretching a molecule accelerates its fragmentation along the stretching axis (which follows the Bema-hapothle or free-energy relationship postulate) molecular force probes provided examples of reactive sites that are kinetically stabilized

against fragmentation along the stretching axis or that are kinetically destabilized towards fragmentation orthogonal to the pulling axis. Neither pattern is consistent with the free-energy postulate (either linear or quadratic), because either corresponds to an aphysical value of the normalized reaction coordinate for the position of the rate-determining transition state, α . A perturbation (e.g., stretching) that both inhibits a reaction and lowers its standard free energy requires $\alpha < 0$ and one that accelerates a reaction without affecting its standard free energy (or enthalpy) requires $\alpha > 0$ (by definition, $\alpha = 0$ for the reactant and $\alpha = 1$ for the transition state). In contrast, the local-coordinate approximation of mechanochemical kinetics (see 2.2. Accuracy of the conventional approximations and systematic strategies of improving them.) both adequately rationalizes all demonstrated types of responses of the kinetics of molecular fragmentation to tensile strain and supports design of new reactive sites that are likely to follow each of these patterns.

In addition to serving as molecular force probes, the capacity of stiff stilbene to impose anisotropic molecular strain was exploited in self-assembly,⁸⁵ molecular motors⁸⁶ and catalysis control⁸⁷. Proposed or speculated applications of stiff stilbene include thermal storage of solar energy² and molecular photoactuation.⁸⁸ Unfortunately, a recent claim that at least highly strained *E* macrocycles may cause non-statistical reaction dynamics of the attached reactive sites is highly unlikely to be correct.⁸⁴ In the vast majority of chemical reactions, the reactant(s) remain in thermal equilibrium with its environment, and to a very good approximation, the reaction probability is proportional to the fraction of molecules with energies in excess of the rate determining activation barrier.¹³ In non-statistical reaction dynamics,⁸⁹ which occurs in some gas-phase reactions and potentially in conformational rearrangements of some proteins in solution, the reactant is not in thermal equilibrium with its environment and the vibrational temperature of an average reactant molecule exceeds the temperature of its thermal bath. This excess energy generally results from a photon absorption (as stiff stilbene does at ~375 nm), or a preceding exergonic reaction. In solution such molecules dissipate this energy by vibrational energy relaxation (VER) at the sub-ps timescale.⁸⁴ In

theory, a highly vibrationally excited (“hot”) molecule can traverse a sufficiently small activation barrier before it thermalizes, in which case the observed rate will far exceed the one predicted by the transition state theory. In practice, no molecule larger than ~10 atoms in solution has ever been shown to manifest non-statistical reaction dynamics.

The two main disadvantages of the molecular force probes relative to their microscopic analogues in SMFS for studying mechanochemical reactivity are the meaningfully smaller maximum force that they can impose on the reactive site, and the maximum size of the reactive site that can be stretched by stiff stilbene. The former is determined by the kinetics of thermal *E*->*Z* relaxation and the synthetic difficulty of obtaining highly strained *E* macrocycles. The same mechanism that lowers the kinetic stability of many (but not all) reactive sites incorporated in *E* macrocycles also lowers the kinetic stability of the *E* stiff stilbene itself. The activation free energy of *E*->*Z* isomerization is lowered from ~42 kcal/mol in strain free stiff stilbene to ~16 kcal/mol at ~750 pN,⁵³ which makes such highly strained *E* macrocycles isolable only at impractically low temperatures. Likewise, such highly strained macrocycles are synthetically hard to access. The simplest means of generating *E* macrocycles is by irradiation of strain-free *Z* analogues at ~375 nm, which photoisomerizes stiff stilbene with a quantum yield that decreases almost linearly with the strain energy of the resulting *E* macrocycle. Because stiff stilbene is only weakly photochromic, the photostationary states of smaller macrocycles contain only a small fraction of the *E* isomers, which complicates their isolation and characterization.

4. Brief analysis of empirical research in mechanochemistry

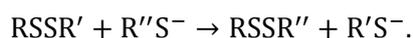
Acceleration of ~20 distinct reactions in stretched polymers has been demonstrated so far, mostly by sonication. These are summarized in ref. ¹. Dissociation of ladderenes to oligoacetylene (which is related to the well-known mechanochemical [2+2] cycloreversion^{25,63,90}) is probably the most noteworthy new mechanochemical reaction reported¹⁰ since. At least 6 such reactions have been demonstrated to occur both in sonicated solutions and in mechanically loading (usually axial compression or grinding) bulk samples, confirming that sonication mimics at least qualitatively the

behaviour of polymer chains in loading scenarios that are technologically more relevant but technically more challenging to study than sonication. Isomerization of dihalocyclopropanes, benzocyclobutene and spiropyran, and [2+2] cycloreversions have been studied by SMFS, in sonicated solutions and in bulk materials.

By the exacting standards of modern physical organic chemistry, our understanding of these reactions is poor. About half of all known mechanochemical reactions were demonstrated only once, using a single mode of loading (e.g., sonication or axial loading of bulk samples) and the assumption of mechanochemical activation, while plausible, lacks credible support from quantum-chemical calculations. Kinetics or even selectivities of many reactions remain to be quantified. Reaction mechanisms remain largely hypothetical even for the most extensively studied examples. The situation in large part attests to the fact that contemporary polymer mechanochemistry is very much an emerging field still in the exploratory stages and far more effort is devoted to learning what's possible instead of why it is possible.

4.1. Much ado about dissociation of the disulfide bond

The kinetic stability of the disulfide bond towards either homolysis or nucleophilically-assisted heterolysis (S_N2 displacement) has been a subject of a surprising number of reported studies, both experimental and computational. Homolytic S-S bond scission may be important in determining the behaviour of vulcanized rubbers under load, whereas thiol/disulfide exchange is a reaction that has been studied extensively by physical organic chemists, is used widely as dynamic cross-links in polymeric materials and is of significant biochemical importance.



Thiol/disulfide exchange (reaction above) is an elementary (single-step) reaction that proceeds through a classical S_N2 pseudo-trigonal bipyramidal transition state. Fernandez et al reported⁹¹ that stretching a titin containing engineered disulfide bonds in neutral aqueous solution of dithiothreitol accelerated disulfide bond reduction ~2-fold per 100 pN of applied force, a relatively small

acceleration by standards of polymer mechanochemistry. Further SMF experiments by the same group using different small-molecule reductants produced broadly similar results.⁹² Interestingly, the deduced force-rate correlation extrapolated to zero force yielded the strain-free rate constant ($\sim 6.5 \text{ M}^{-1}\text{s}^{-1}$) that is similar to those reported for the DTT reduction of disulphide bonds in several folded proteins, where the disulphide bonds reside in a fairly hydrophobic local environment and are thought to be relatively inaccessible to the solvent and hence the polar reductant solute (e.g., a-chymotrypsinogen A, $k = 9 \text{ M}^{-1}\text{s}^{-1}$)⁹³. In contrast, this extrapolated strain-free rate constant is 10-200 times smaller than those for the reduction of small-molecule organic disulphides and ~ 10 times smaller than those in proteins with solvent-accessible disulphide bonds (e.g., trypsinogen at $>50 \text{ M}^{-1}\text{s}^{-1}$) under comparable conditions.⁹⁴

This trend of the rate constants suggest that the acceleration of thiol/disulphide exchange observed upon stretching titin more likely reflects force-induced conformational changes in the protein environment that the intrinsic sensitivity of the disulphide moiety to tensile strain, which is independent of its surroundings. In these SMF experiments, titin was partially unfolded by subjecting it to stretching force of 130 pN for 1 s, but this “pre-stretching” doesn’t eliminate the possibility that protein residues continue to dominate kinetically significant force-dependent variations in conformational compositions of the reactant and/or transition states at larger forces. Likewise, the conformational complexity of a polypeptide makes its chemomechanical coupling coefficient (i.e., the fraction of the applied force that is transmitted to the reactive site) far more sensitive to force than a simple hydrocarbon. The documented importance of force-dependent conformational changes in other $\text{S}_{\text{N}}2$ reactions involving even very short polymer fragments (e.g., neutral methanolysis of Pr vs. Me derivatives of dialkyldiphenylsiloxane, R_2SiPh_2 ,⁴² or basic hydrolysis of ethyl vs. methyl derivatives of tetraalkylpyrophosphate, $(\text{RO})_2\text{P}(=\text{O})(\text{O})(\text{RO})_2\text{P}(=\text{O})$ ⁵⁷) at forces up to 1 nN renders the idea that a protein serves simply as an innocent transmitter of applied force fantastical.

Experimental estimates of intrinsic force/rate correlation of simple alkyl disulphide using molecular force probes and quantum-chemical calculations of force-dependent activation free energies of this reaction agree that the kinetics is insensitive to force below 500 pN.⁵⁴ The result was rationalized by observing negligible elongation of the disulphide moiety in the transition state along the pulling axis. In contrast, the same methodology revealed that reduction of the disulphide moiety by phosphines in water is accelerated by force⁶¹, albeit weakly and by a complex mechanism, a conclusion that qualitatively agrees with SMF experiments.⁹²

Several reported molecular-dynamics simulations of mechanochemistry of thiol/disulphide exchange using the BLYP functional produced contradictory conclusions.⁹⁵⁻⁹⁹ The considerable technical challenge of accurately reproducing experimental kinetics in MD simulations is illustrated by the fact that the most sophisticated to-date MD simulation of an S_N2 reaction of disulphide overestimated the measured activation free energy by 1.5 fold or 10 kcal/mol (vs. an error of 1 kcal/mol for static calculations⁵⁴). Although these calculations generally aim at reproducing trends rather than absolute values, this large error suggests that the available computational methodology is not yet capable of correctly capturing the stereoelectronic factors that determine the activation barriers of S_N2 reactions at S^{100,101} and the role of explicitly-modelled water.¹⁰² It is probably not justified at present to think that this error remains constant in magnitude as the moiety is distorted and hence is factored out in the predicted trend. Importantly, several of these studies reported that accelerated thiol/disulphide exchange was associated with a very unusual conformer of the disulphide moiety with the C-S-S-C torsion of 180° (vs. the equilibrium value of ~90°). At higher levels of theory, the structure with the 180° torsion remains a transition state for rotation around the S-S bond up to at least 2 nN, suggesting that lower forces do not accelerate thiol/disulphide exchange in small organic disulfides, in agreement with the molecular-probe results.

The totality of the available data seems to suggest that at forces <0.5 nN the kinetics of thiol/disulphide exchange is far more sensitive to force when the S-S bond resides in the backbone of

polymers with complex ternary and quaternary structures (e.g., polypeptides or bottlebrush polymers⁸³) than in a simple organic disulphide. The origin of this difference remains to be established.

In contrast to the controversy surrounding mechanochemical kinetics of nucleophile-assisted S-S bond dissociation, force definitely accelerates homolysis of the S-S bond, including in bottlebrush polymers at interfaces⁸³ and in sonicated solutions,¹⁰³ although in the latter case the contribution of S-S bond homolysis mediated by sonolytically generated radicals¹⁰⁴ to the observed chemistry remains to be quantified.

4.2. Emerging trends in contemporary empirical studies

The bimolecular nature of S_N2 reactions complicates both accurate quantitation of mechanochemical kinetics and its molecular interpretation. Unimolecular reactions are free of these complications and offer advantages both for fundamental studies of the effect of anisotropic strain on chemical reactivity and its exploitation. The two most extensively studied reactions are isomerizations of dihalocyclopropanes and spiropyrans (Fig. 11). Isomerization of multiple dihalocyclopropane moieties in a single chain increases its length considerably¹⁰⁵ and generates allylhalides that are susceptible to nucleophilic displacement. As a result, blends of poly(dichlorocyclopropanes) and polymers with carboxylic groups in side chains undergo self-strengthening in shear.²⁴ Mechanochemical isomerization of dihalocyclopropane has been studied extensively as an example of force-induced violation of the orbital conservation rules.⁴⁶ Spiropyrans are currently the most popular mechanochromic moiety for use in polymer, in part owing to the very low loads needed to induce color,⁷⁴ which results from thermodynamically or kinetically controlled isomerization of colorless spiropyran to colored merocyanine (other approaches to realizing mechanochromism in polymer materials are reviewed in ^{22,26}). Spiropyran isomerization is one of the few reactions where anisotropy of mechanochemical activation was studied, albeit qualitatively.

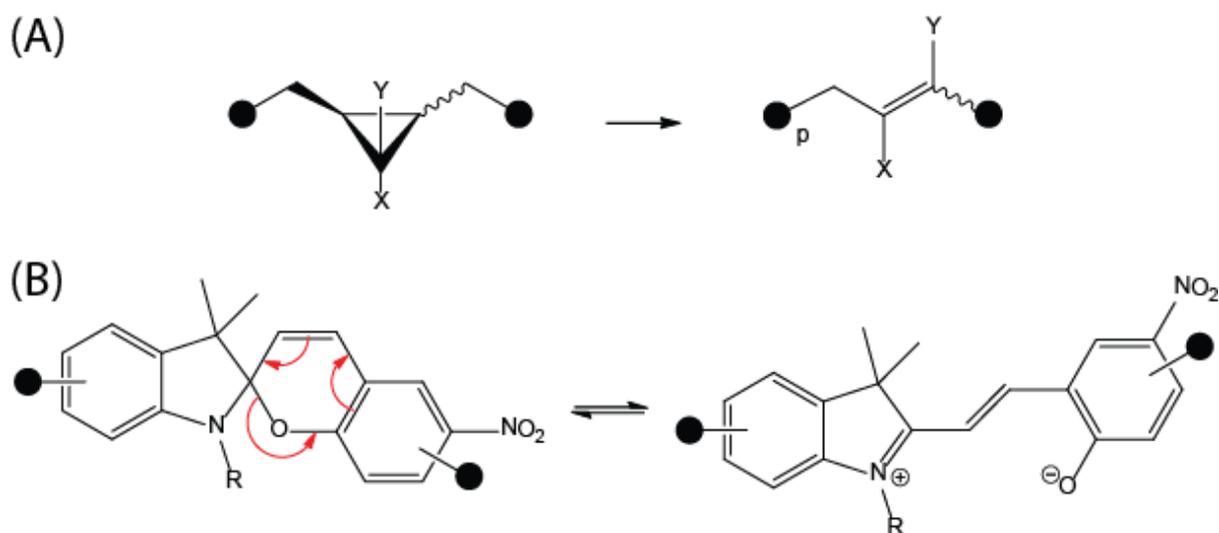


Fig. 11. The two most commonly studied mechanochemical reactions: isomerization of dihalocyclopropanes (A), where $X = Y = \text{Cl}$ or Br or $X = \text{F}$, $Y = \text{Cl}$; and of spiropyrans (B). Black spheres signify point of attachment to macromolecules.

Design of mechanochemical reaction cascades has emerged as one of the more frequently pursued goals in contemporary polymer mechanochemistry. In such cascades, the product a mechanochemical reaction is a reactant, initiator^{28,106-110} or catalyst^{24,27,111,112} of subsequent non-mechanochemical reaction(s), Fig. 12. An alternative to a mechanochemical cascade⁶³ is reaction gating whereby a reactive site blocks transmission of applied force to another site until the first one reacts. In the only demonstration to date, the gate was a cyclobutane derivative and the protected site was dichlorocyclopropane (Fig. 13). Thermal dissociation of strain-free cyclobutanes to two olefins is negligibly slow, but is accelerated by tensile loading, as is isomerization of dihalocyclopropanes. Cyclobutane, however, withstands much higher tensile load than dichlorocyclopropane, so that the threshold force at which the latter isomerizes is determined by the mechanochemical kinetics of the gating reaction instead of the substrate (i.e., dichlorocyclopropane). Another conceptually interesting and promising direction has been integration of multiple productive responses to anisotropic strain in a single reactive moiety, resulting in so-called multi-modal “mechanophores”.^{25,27}

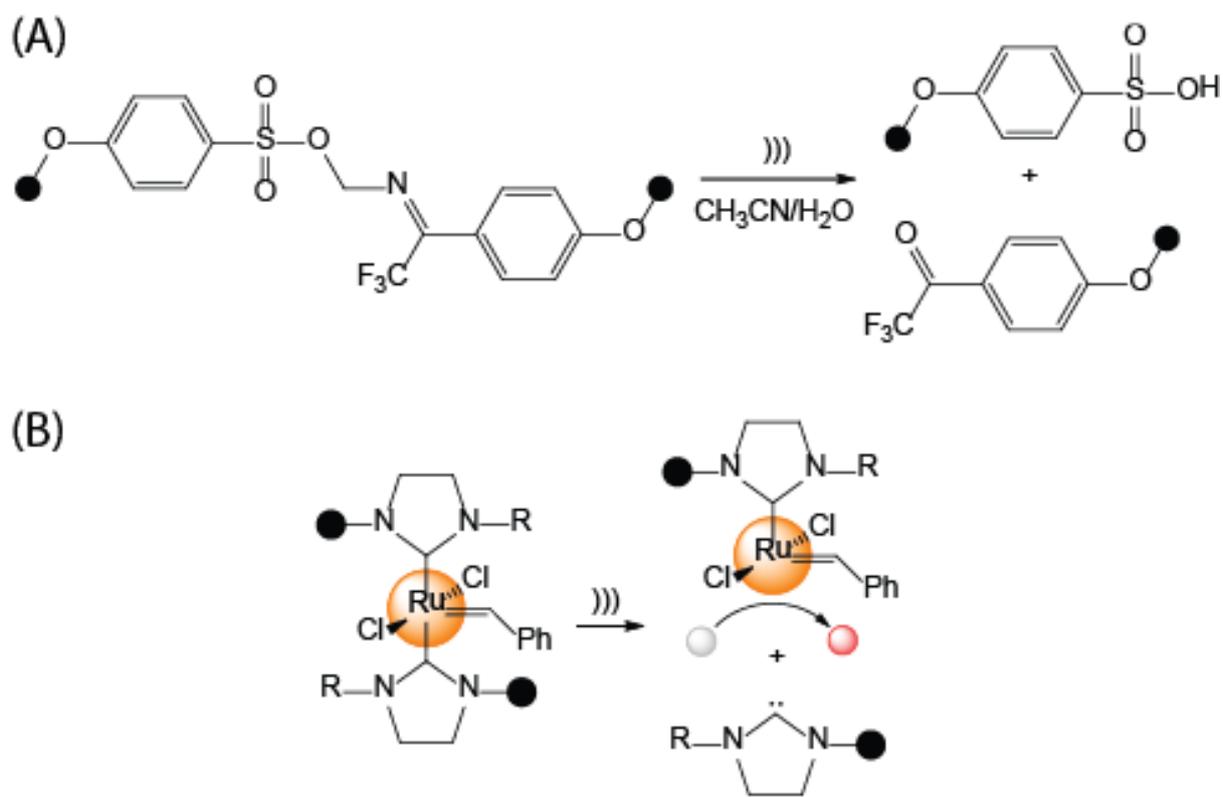


Fig. 12. Two examples of mechanochemical reaction cascades: the generation of a mechanoacid, in analogy to photoacids used in photolithography¹¹² and of a catalyst (for ring-closing metathesis).¹⁰⁷

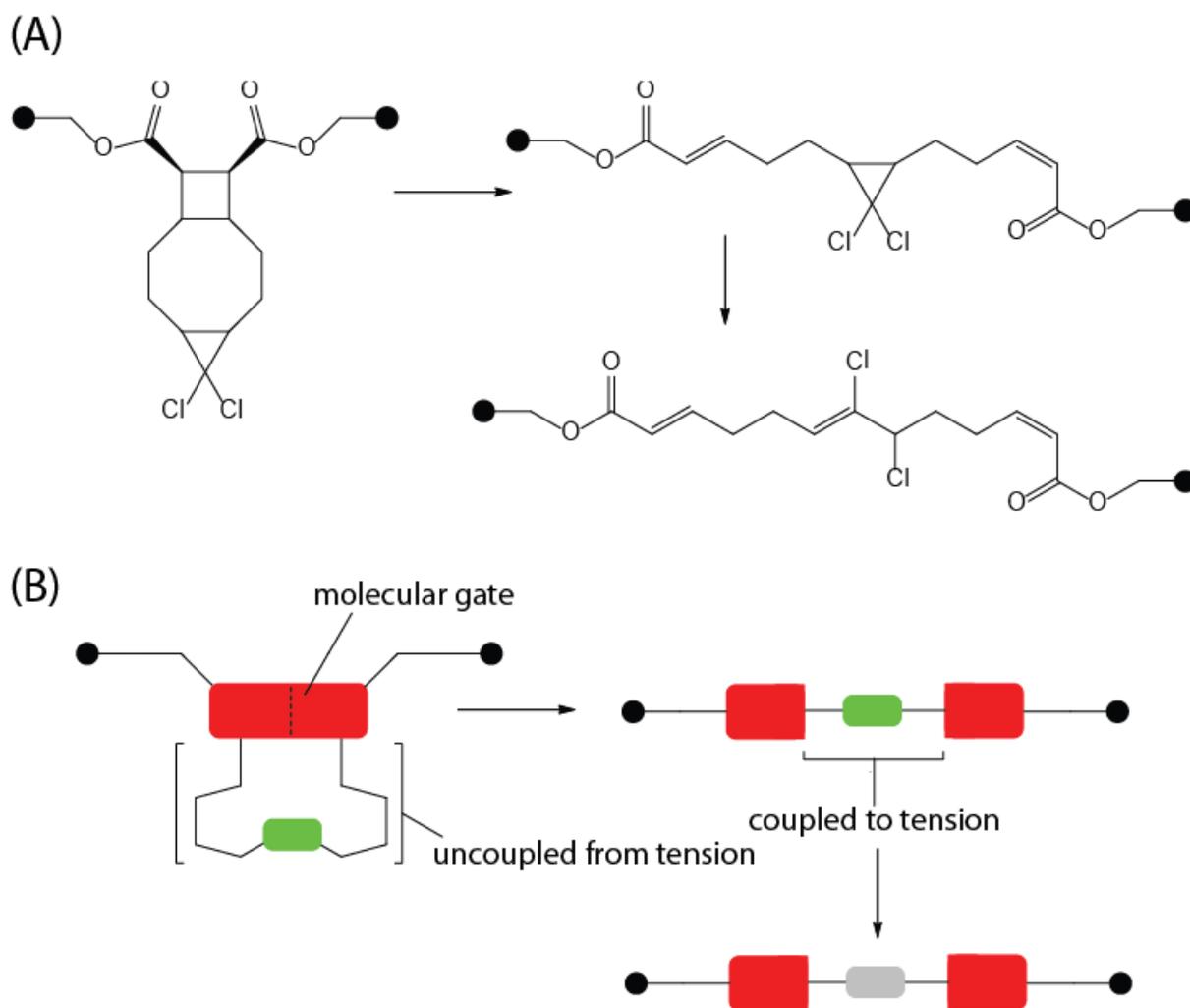


Fig. 13. An example of single-molecule cascade or mechanochemical reaction gating. (A) The reactive site undergoes two sequential transformations: mechanochemical dissociation of the gate, which allows applied force to be transmitted to the 2nd reactive site (dichlorocyclopropane), which isomerizes as soon as the gate is opened. This sequence ensure (B) A cartoon representation of the principle of mechanochemical gating .

5. Summary

Polymer mechanochemistry is an emerging discipline at the interface of chemistry, physics and engineering, which aims at understanding and exploiting unique reactivity that becomes accessible when a polymer chain is overstretched.¹ Polymer chains become overstretched in a variety of technologically important processes, and the reactivity of such overstretched chains often determines

bulk response of the material to mechanical load, including catastrophic material failure and more gradual, but no less detrimental, material aging. In laboratory, micromanipulation techniques and flow fields allow individual macromolecular chains to be stretched with some degree of control over the magnitude and the duration of the imposed strain, and the rate at which it is imposed.

Chemical consequences of stretching polymer chains are typically discussed in terms of the effect of force on reactivity. The reason is that macromolecular chains are most often stretched when a macroscopic (or microscopic) object moves directionally, be it the movement of arms that stretches a rubber band, a retraction of an AFM tip that stretches a single macromolecule connecting it to another surface, or the rapid flow of a polymer solution through narrow channels. Force is a variable that allows, at least in theory, to describe quantitatively both macroscopic motion and the effect of this motion on reaction dynamics.^{11,52} For example, force allows us to extrapolate the kinetic stability of a stretched chain of an arbitrary length from the reactivity of a single monomer, either calculated or observed in properly designed macrocycles.^{25,58,63}

The outcome of overstretching a simple polymer such as polystyrene or polyacrylate is rather boring, as the chain simply fragments by homolysis of a backbone bond (although the resulting macroradicals may manifest rich chemistry).¹ Modern synthetic methods allow diverse reactive moieties to be decorated with two or more macromolecular chains so that when the resulting polymer is stretched, large and anisotropic strain is imposed on the reactive site. Likewise, multiple reactive sites can be connected in series by mechanochemically “inert” linkers.³² Stretching such polymers yields diverse chemistry, from site-selective fragmentation, to chemomechanoluminescence²¹ and stabilization of structures that are transition states in strain-free reactive sites¹¹³. Evidence suggests that some reactions proceed by mechanisms that are kinetically negligible or through intermediates or transition states that do not exist in the absence of strain^{42,46}. Attaching polymer chains to different pairs of atoms of the same reactive moiety enables one to study anisotropy of strain/reactivity relationship.⁶

Mechanochemical reactions have been used to control other reactions, either by producing well-defined reactive species,^{26,27,111} or redistributing imposed strain.⁶³

Although it may seem intuitive that stretching a molecule would accelerate its fragmentation along the stretching axis, the kinetic response of reactive sites to such anisotropic straining is far richer than that. Both computations and experiment indicate that stretching a molecule along one axis either inhibits its fragmentation along this axis, or accelerates its fragmentation along an orthogonal axis.⁴² Such responses lack functional analogies in the macroscopic world and don't seem to follow the free-energy relationships of physical organic chemistry⁵¹ but are amenable to quantitative predictions within the formalism of local restoring force.

This proliferation of empirical mechanochemical data offers physical organic chemists a great opportunity to influence the evolution of the field by helping to discover the mechanisms of mechanochemical reactions, which remain little studied, and show how to exploit this knowledge to guide the design of new mechanochemical reactions. Likewise, while we can calculate force-dependent activation barriers of many reactions, we don't know how accurate the results are in general: for certain reactions quantum-chemical calculations reproduce experimental measurements quantitatively;^{25,58,63} for others they are even qualitatively incorrect. We need to learn how to extract better quality quantitative molecular data from experimental techniques of polymer mechanochemistry, particularly sonication, and expand the range of molecular architectures that reproduce the highly anisotropic strains imposed on small reactive sites in stretched polymers without the complexity of coupled macroscopic motion.

Studying overstretched polymer chains offers an opportunity to greatly expand our understanding of chemical reactivity, particularly of highly strained molecular geometries not accessible synthetically, and to create new materials with unique modes of response to mechanical loads.²³ Physical organic chemistry has much to offer to realize this opportunity.

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