The contributions of model studies for fundamental understanding of polymer mechanochemistry

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The exciting field of polymer mechanochemistry has made great empirical progress in discovering reactions in which a stretching force accelerates scission of strained bonds using single molecule force spectroscopy and ultrasonication experiments. Understanding why these reactions happen, i.e., the fundamental physical processes that govern coupling of macroscopic motion to chemical reactions, as well as discovering other patterns of mechanochemical reactivity require complementary techniques, which permit a much more detailed characterization of reaction mechanisms and the distribution of force in reacting molecules than are achievable in SMFS or ultrasonication. A molecular force probe allows the specific pattern of molecular strain that is responsible for localized reactions in stretched polymers to be reproduced accurately in non-polymeric substrates using molecular design rather than atomistically intractable collective motions of millions of atoms comprising macroscopic motion. In this review, we highlight the necessary features of a useful molecular force probe and describe their realization in stiff stilbene macrocycles. We describe how studying these macrocycles using classical tools of physical organic chemistry has allowed detailed characterizations of mechanochemical reactivity, explain some of the most unexpected insights enabled by these probes and speculate how they may guide the next stage of mechanochemistry.

Introduction

Polymer mechanochemistry studies the effect of force on the kinetic and thermodynamic stabilities of monomers within a stretched polymer. Whether a macromolecule is in solution, in a melt, a glass or a part of a network, the extreme aspect ratio resulting from a long chain of small units creates an axis along which tensile force can be easily generated.[1-3] As a result, polymer chains are predisposed to become (over)stretched, however they are used throughout their lifetimes. Knowledge of how this overstretching (or equivalently of how the applied tensile force) affects chemical stability is therefore crucial to understanding the molecular basis underlying the mechanical response of existing polymers and designing new advanced polymer materials.[4-8] The current conceptual framework is far from complete and leaves many questions with fundamental importance to be answered.[2,9,10]

The gaps in our current understanding of why and how mechanochemical reactions happen have not prohibited the discovery of 50+ reactions accelerated by force,[11-13] the success probably attributable to intuitions developed by organic chemists studying strained molecules.[14] A major risk of relying on existing trends to find new chemistry is evident by the dominance among both experimentally realized and computationally hypothesized mechanochemical reactions those that are accelerated by tensile (stretching) force. Discussions of the likelihood of other reaction patterns, including inhibition of molecular fragmentations by tensile force[15] or acceleration of such fragmentations by compressive force,[16] are far fewer in the mechanochemical literature. The situation persists even though such responses derive logically from the most-used model of mechanochemical kinetics,[17,18] have precedence in the related field of high-pressure chemistry[19], and attracted considerable interest among early practitioners of the field.[20]

As valuable as the idea of molecular strain has proven in guiding the empirical search for new mechanochemical reactions, it is far less useful in forming the basis of quantitative models of mechanochemical kinetics.[17] The concept of molecular strain energy, so central for quantitative

discussions of the reactivity of small strained molecules, is of little use in interpreting polymer mechanochemical reactions because strain energy is an extensive scalar property (i.e., it depends on molecular size and can have identical values for molecules strained along different axes). In contrast, changes in the activation barriers of monomer reactions in stretched polymer chains are largely independent of the chain size[4,21] and reflect the structural anisotropy of polymer chains. Instead, restoring force (the gradient of strain energy along a chosen axis) is used because it is intensive and vectoral.[18,22,23]

These distinct manifestations of molecular strain in small molecules and in a stretched polymer may at first suggest that an attempt to replicate localized reactivity responsible for polymer mechanochemistry in non-polymeric substrates is futile. Indeed, the feasibility of model studies of polymer mechanochemistry had been treated with skepticism for some time,[12] with particular emphasis on the likely difficulty of reproducing the tensile force, which is generated so easily along the thin narrow axis of a polymer backbone, in much less structurally anisotropic small strained molecules, which tend to exhibit compressive strain. Fortunately, this view proved to be unnecessary pessimistic.[24] In this review we highlight how model studies of polymer mechanochemistry reveal a much greater complexity and richness of polymer mechanochemistry than could be inferred from studies of stretched polymers and the potential it offers to turn polymer mechanochemistry into a rigorous quantitative field at the interface of chemistry, physics and engineering, with considerable technological impact.

Importance of model studies

The ideal technique of experimental polymer mechanochemistry would allow a predetermined force to be applied at a known rate and/or for a known time period to a sufficiently large ensemble of polymer chains to generate enough products for their chemical identity and homogeneity to be established convincingly, for example through detailed spectroscopic characterization. No such experimental methods exist currently: the two most common techniques are complementary and allow important details of force-dependent reactivity to be estimated when combined with detailed quantum-chemical calculations and conventional tools of physical organic chemistry.

Single Molecule Force Spectroscopy (SMFS) allows a single polymer chain to be stretched to a force of up to 2.5 nN, but the only observable is a force/extension curve, which contains only limited information about the chemical nature of the product. Reactions which break the chain or extend its contour length by at least a few nm are observable. Conversely, ultra-sonication of dilute polymer solutions, which transiently stretches a fraction of the dissolved chains enough for them to react, allows spectroscopic characterization of the products but knowledge of the stretching conditions which yield these products is minimal, e.g., how much, how fast and for how long a reacting chain is stretched and whether the full chain or only a part of it is stretched .[2] Although the rate at which the composition of the sonicated solution changes is easily quantifiable, it contains no information about microscopic reaction kinetics as it would for homogeneous thermally-activated reactions because the distribution of forces among dissolved polymer chains in a sonicated solution is unknown. In other words, the mechanochemical equivalent of the Boltzmann distribution, which underlies the transition state theory, does not exist. Quantitative molecular interpretations of sonication experiments therefore require multiple assumptions of unknown validity. Again only accelerated reactions are observable.

These limitations necessitate the development of complementary approaches to studying mechanochemical reactions that allow reliable spectroscopic characterization of the products, measurable microscopic reaction kinetics and detailed computational quantitation of force distributions responsible for the observed products and kinetics. So far, the only such approach known is based on reproducing the molecular strain experienced by a monomer of a stretched polymer in a suitably designed macrocycle, i.e., to model polymer mechanochemistry in non-

polymeric substrates by using molecular design, rather than micromanipulation techniques, to impose well-defined force on diverse reactive sites.

To have broad utility, such a model must be small enough to be amenable to routine DFT calculations and allow the monomer to be subjected to a range of forces at very high loading rates. For force-accelerated reactions, the larger the instantaneous force experienced by the reactant, the faster its survival probability decreases with time. As a result, increasing reactant strain must compete with the reactant converting to the product: the faster the force increases (i.e., the faster the loading rate), the greater the instantaneous force is achieved at which the reactant converts to the product. This condition applies both at the level of individual macrocycles and ensemble.

The only chemical implementation of the ideas articulated above reported to date is based on macrocycles of stiff stilbene, in which the monomer whose mechanochemistry is studied is incorporated into a molecular moiety ('linker') connecting the C6/C6' atoms (Figure 1). Isomerization of stiff stilbene from *Z*->*E* increases this C6-C6' separation stretching the monomer-containing linker. If the linker is short enough to prevent *E* stiff stilbene from adopting its preferred planar geometry with the maximum separation of the C6, C6' atoms, a tensile load on the monomer is generated in the *E* isomer. Varying the length of this linker yields a series of macrocycles, across which the force exerted on the monomer in the *E* isomers can be incremented by ~50 pN up to ~750 pN.

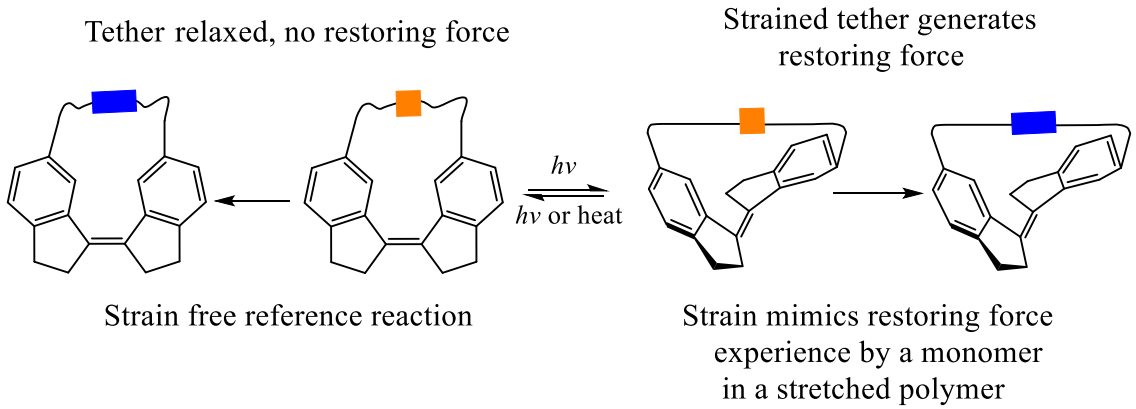


Figure 1- Stiff stilbene macrocycles allow external force to be applied to a monomer in a way that mimics that of a stretched polymer. The key to generating the restoring force is the tether length, which must be too short for stiff stilbene to adopt its minimum energy conformation in the *E* isomer. In addition to model studies of polymer mechanochemistry, stiff stilbene derivatives were proposed or prototyped for applications in photoactuating or photoresponsive materials,[25] thermal storage of solar energy,[26,27] molecular motors,[28] optical control of catalysis,[29,30] sensing[31] and self-assembly.[32,33]

In addition to the large difference in molecular dimensions of the two isomers of stiff stilbene, its advantages for applications as a molecular force probe include the high strain-free activation free energy of thermal isomerization and its fast and efficient photoisomerization, which allows strained molecules to be generated rapidly and in high enough concentrations for reaction monitoring. The alkyl rings of stiff stilbene prevent strain relief via rotation available to other stilbene and azo analogues, thereby maximizing the molecular strain achievable in a macrocycle.

Relative kinetics of three reactions determines if a specific mechanochemical transformation is suitable for quantitative study by molecular force probes: the formation of the strained macrocycles containing strained but unreacted monomer (imposing force) and relaxation of this macrocycle either by the reaction of this monomer (mechanochemistry) or by isomerization of strained *E* stiff stilbene to its *Z* congener (unproductive path).[34] The simplest case is when the mechanochemical reaction is considerably slower than the *Z*->*E* photoisomerization but considerably faster than the unproductive *E*->*Z* relaxation. Depending on the rate of the substrate reaction, the strained macrocycle containing the unreacted monomer may be isolable and fully characterizable

spectroscopically. At the other extreme of relative rate constants, the unproductive relaxation by thermal *E*->*Z* isomerization is faster than the kinetics of the mechanochemical reaction, and the latter can be quantified accurately only if a steady state concentration of the strained *E* macrocycle is maintained high enough by continuous photoisomerization of the *Z* macrocycle to allow the mechanochemical product to accumulate at a detectable rate. This strategy also requires that *E*/*Z* isomerizations not be accompanied by any side reactions,[34] as is discussed in greater detail below.

The quantum yield of *Z*->*E* photoisomerization decreases and thermal *E*->*Z* relaxation is accelerated as the strain of the *E* macrocycle, and therefore the magnitude of the tensile force exerted by *E* stiff stilbene on the monomer, increases.[25] Consequently, the kinetic of imposing a large force on the reactive site becomes increasingly unfavorable. The situation is not unique to molecular force probes: the largest force accessible in SMF experiments is often limited by detachment of the macromolecule from the tip or the surface.

Stiff stilbene macrocycles: synthesis and measurements.

Mechanochemical studies with molecular force probes require 4 steps: synthesizing *Z* macrocycles, photoisomerizing them to the *E* analogs, measuring the monomer kinetics in both *E* and *Z* macrocycles, and calculating the restoring force of the monomer in each macrocycle by DFT benchmarked against measured activation parameters.

The easy synthesis of stiff stilbene via McMurry coupling contributes to its attractiveness as a force probe because McMurry coupling is compatible with many functional groups.[35,36] To generate the *Z* isomer selectively over its more thermodynamically favorable *E* analogue an intramolecular coupling is required. The linker connecting the two indanones can contain the monomer or be sacrificially cleaved after coupling to yield *Z* stiff stilbene for subsequent macrocyclization with the desired monomer. C6 substituted indanones are most readily available synthetically and therefore have been used in all reported force probes so far.

The force is transduced from stiff stilbene to the monomer via the linker, making its size and composition an important design parameter: too short a linker would correspond to the *E* macrocycle too strained to access,[34,37] whereas too long a linker allows *E* stiff stilbene to adopt its strain free minimum energy conformation, imposing no force on the monomer. Computations suggest that linkers of between 7 and 13 atoms long, accommodating a monomer of up to 7 atoms, would allow a usefully incremental change in force across a set of synthetically accessible macrocycles of varied size. So far only monomers contributing up to 5 atoms to the length of the linker have been studied by this method. The conformational preference of the linker mean it is never a perfect force transducer but sp^3 atoms appear to be closest to an ideal linker, and sp^2 atoms less efficient at transducing the force from stilbene to the monomer.[24] The different efficiencies of each hybridized atom type can be exploited to reduce the increment by which force varies across a macrocyclic set by utilizing equal sized linkers with various combinations of sp^2 and sp^3 atoms.[24]

Three generic synthetic routes have been established to synthesize stiff stilbene macrocycles: intramolecular coupling of a pair of indanones connected by a monomer containing linker (‘build

around'), intramolecular linking of the two arms attached to a preformed *Z* stilbene ('join up'), and intermolecular cyclisation onto a *Z* stilbene diol ('plug in') (Figure 2).

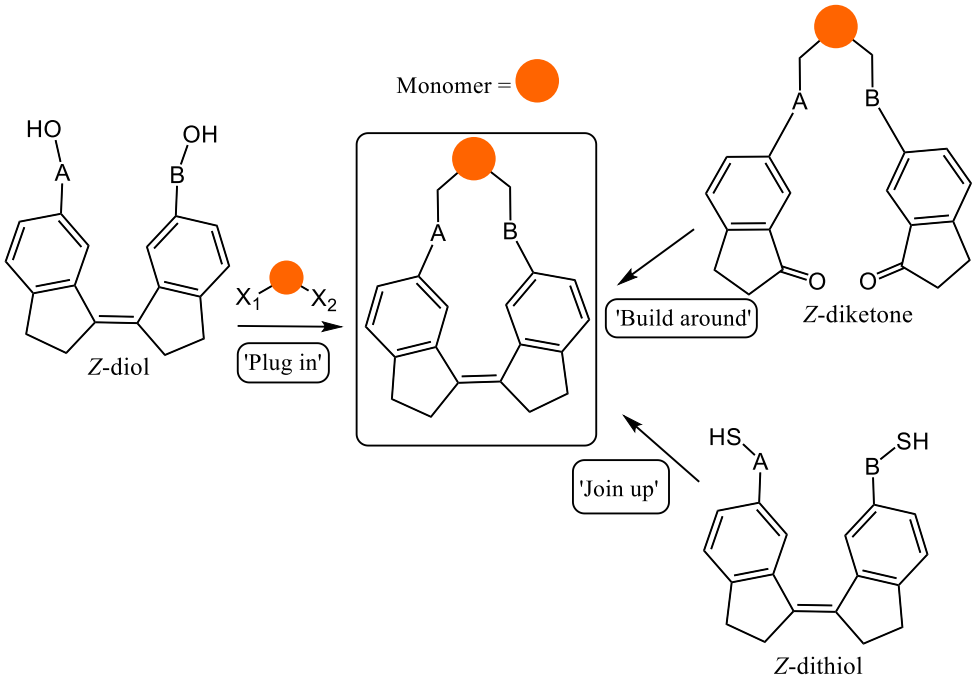
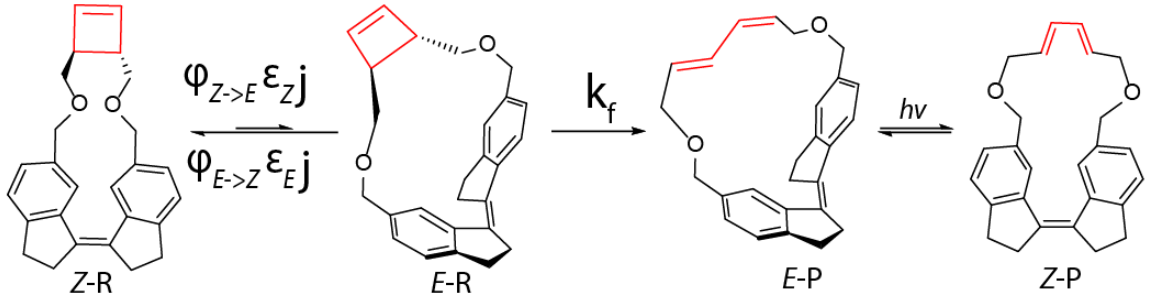


Figure 2. The three established routes of synthesizing monomer containing stiff stilbene macrocycles. The 'join up method' has so far exclusively been used to incorporate disulphides into the macrocycles, for the 'build around' and 'plug in' methods, many different monomers are suitable for each. A and B are various combinations of O, CH_2 and C=O moieties.

Once *Z* macrocycles are synthesized, their strained *E* analogs are best accessible by photoisomerization. Although stiff stilbene is not as strongly photochromic as azobenzene, the absorption spectrum of *Z* isomer is redshifted relative to that of *E* by 15 – 25 nm, depending on substituent, which is sufficient to yield photostationary states with high (>85%) *E* content for all but the most strained macrocycles. Whilst *E* isomers can usually be separated from their *Z* analogs if desired, the ratios of rate constants of the substrate reaction in the two isomeric macrocycles can often be measured more accurately on the mixtures.[15] In analysis of force-dependent kinetics ratios of rate constants, or equivalently, differences of the activation free energies, enthalpies or entropies, $\Delta\Delta G^{\ddagger}$, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, respectively, are more informative than absolute values because the latter are sensitive to the nature of the linkers in addition to the absolute applied force.

The most strained *E* macrocycles require additional steps to obtain mechanochemical kinetics because the reduced *Z*->*E* quantum yield and *E*->*Z* barrier to thermal isomerization prohibit generating spectroscopically detectable concentrations. An example is the macrocycle of *E* stiff stilbene and trans-disubstituted cyclobutene (red), *E*-R (Figure 3). When *Z*-R was irradiated at 365 nm, corresponding to the largest ratio of the extinction coefficients of the two isomeric stiff stilbenes to minimize *E*->*Z* photoisomerization, no new species were observed at <20 °C reaction temperature. At temperatures >35 °C only the isomeric macrocycles corresponding to ring-opening isomerization of cyclobutene, *Z*-P and *E*-P, were detected. Because ring-opening of cyclobutene in *Z*-R is negligibly slow at temperatures <85 °C in the dark, the appearance of the diene product during continuous irradiation at 35 °C suggest an undetectable intermediate, which was ascribed to *E*-R based on the same reaction in larger macrocycles, where *E*-R analogs are isolable.



equation 1 $$\frac{[Z\text{-R}]}{v_Z} = \frac{1}{\varphi_{Z\to E}\,\varepsilon_Z}\left(\frac{k_{E\to Z}}{k_f}+1\right)\frac{1}{j} + \frac{\varphi_{E\to Z}\,\varepsilon_Z}{\varphi_{Z\to E}\,\varepsilon_Z}\frac{1}{k_f}$$

Figure 3-A method to derive activation energies for reactions occurring within spectroscopically undetectable *E* macrocycles. In the equation 1, [*Z*-R] and v_z are instantaneous concentration of *Z*-R and instantaneous rate of its depletion, respectively, k_X is the rate constant of thermally-activated cyclobutene isomerization within the *E* macrocycle (X = f) or of relaxation of *E-R* to *Z*-R (X = *E*→*Z*, non-productive reaction), ε_X is the extinction coefficient of isomer X (*Z* or *E*) at the irradiation wavelength, j is incident photon flux density and $\varphi_{x\to y}$ is the quantum yield for the subscript photoisomerisation. Note that cyclobutene is transparent at the irradiation wavelength and is photochemically inert. Adopted from ref. [34] with permission.

Since *E*-R is undetectable, the activation parameters of cyclobutene isomerization under force imposed by stiff stilbene in *E*-R cannot be obtained simply by measuring how its concentration changes with reaction time. Instead, it required measurements of the rate of depletion of *Z*-R under continuous irradiation as a function of both the photon flux (which affects the kinetics of *Z*-R → *E*-R photoisomerization) and the reaction temperature (which affects the kinetics of cyclobutene isomerization and *E*-R → *Z*-R unproductive relaxation). Assuming steady-state concentration of *E*-R in this reaction, equation 1 (Figure 3) establishes the relationship between the instantaneous concentration of *Z*-R and its depletion rate, v_Z, the microscopic kinetics of the steps that produce or deplete *Z*-R ($k_{E\to Z}$, $k_{Z\to E}$, k_f) and the experimental parameters (temperature, T and photon flux density, j). As predicted by eq. 1, the [*Z*-R]/v_Z ratio was shown experimentally to increase linearly with inverse photon flux density over a 10-fold range of fluxes and 40 °C range of reaction temperatures. The activation parameters of cyclobutene isomerization in *E*-R were obtained from a linear regression of the log of the intercept of the [*Z*-R]/v_z vs. 1/j plot at 4 temperatures vs. 1/T, whereas those of thermal *E*->*Z* relaxation from a similar graph of the intercept of the [*Z*-R]/v_Z vs. 1/j graph. Further analysis yielded the quantum yields of *Z*->*E* and *E*->*Z* isomerization, which combined with measurements on less-strained macrocycles demonstrated approximately linear dependence of the quantum yields on the restoring force of the C6/C6' coordinate of stiff stilbene in *E* macrocycles.

When the kinetics of substrate reaction in *E* macrocycle are derived from measurements on a continuously irradiated sample, one might wonder if it is affected by the so-called "hot-ground-state" phenomenon. The latter refers to a product of a photochemical reaction traversing a subsequent activation barrier before fully thermalizing. When an electronically excited molecule relaxes to the ground state, it sheds most of the energy acquired when it absorbed a photon into the environment by means of intermolecular vibrational energy transfer (VER). When VER is slower than the rate at which the molecular geometry changes, a photochemical reaction may transiently produce a molecule whose vibrational temperature exceeds that of its surroundings. Such "hot" molecule may react further much faster than the identical but fully thermalized (i.e., equilibrated with the environment) analog. Such "hot-ground-state" effects are well known in gas-phase reactions,[38] but are extraordinarily rare in solution. Simple calculations based on the previously measured rates of VER in stiff stilbene and the RRKM (Rice–Ramsperger–Kassel–Marcus) kinetic

theory unequivocally rule out the contribution of "hot-ground-state" effects to accelerated reactions in *E* stiff stilbene macrocycles generated under continuous irradiation.[24,39]

An important, if little studied, question in polymer mechanochemistry is how applied force affects reaction mechanisms.[1] Such mechanistic analyses of experimental mechanochemical reactivity require the knowledge of force-dependent activation enthalpies and entropies, which are readily available from measurements with molecular force probes. Conversely, the technical challenge of temperature-dependent SMF measurements limit the available kinetic data to apparent rate constants, whereas sonication yields only bulk rate constants that have no known relationship with microscopic reaction probabilities and hence activation energy.[2]

To be broadly useful to polymer mechanochemistry, the activation parameters measured in stiff stilbene macrocycles must be expressed as a function of the force experienced by the reacting moiety in these macrocycles. This force is not directly derivable from a measured quantity but is calculated quantum-chemically. Unlike such calculations of stretched polymer, these can be benchmarked against measurable parameters such as activation energies. DFT calculations confirmed that stiff stilbene distorts the reactive site in the same way as in a stretched polymer. The conclusion is based on the similar distributions of restoring forces of the reactive site stretched by *E* stiff stilbene in the macrocycle and by a harmonic spring acting on the two terminal atoms of the reactive site.

Molecular force probes as tools to study polymer mechanochemistry

To date, model studies of polymer mechanochemistry have focused primarily on answering fundamental questions of mechanochemical reactivity that cannot yet be addressed by studying polymers themselves. As such they complement sonications of dilute polymer solutions that have been used primarily to demonstrate new force-accelerated dissociation reactions[2] and single-molecule force spectroscopy (SMFS) that has helped to quantify how molecular architecture of a stretched chain affects chain mechanochemistry and micromechanics across different length scales.[40-42] So far the model studies in mechanochemistry yielded three broad lessons. First, they allowed experimental validation of the foundational idea of contemporary mechanochemistry,[12] that force, when properly defined, is a suitable quantitative length-invariant measure of kinetically-significant molecular strain.[43] This postulate underlies all existing quantitative discussions of mechanochemical reactivity.[1,18] Second, they are responsible for the current, albeit still-evolving, understanding of the complex relationship between force, reaction mechanism and kinetics.[15,44-46] This contribution exploits the fact that reactions of a monomer stretched by stiff stilbene are far more amenable to detailed kinetic and mechanistic characterization than the same reactions induced by sonication or SMFS. Third, they demonstrated that the orientation of the scissile bond relative to the pulling axis has no correlation with how much the kinetics of bond scission is affected by applied force.[15] Such lack of correlation removes a major constraint on design of mechanoresponsive polymers. These lessons are briefly discussed below.

Experimental demonstration of force being length-invariant measure of kinetically significant strain

The concept of force (or more precisely, restoring molecular force) is central for quantitative discussions of polymer mechanochemistry because it is a size-independent quantifier of kinetically-relevant molecular strain. In other words, knowing the restoring force of a monomer in a stretched macromolecule is thought to enable accurate predictions of the monomer's kinetic and thermodynamic stabilities regardless of the length of the chain or the physical mechanism that maintains the chain in its unfavorable stretched geometry. Yet, no fundamental law of physics requires force to underlay such a quantitative relationship between molecular strain and changes in chemical reactivity. This fact necessitates experimental demonstration that force accurately

quantifies the portion of molecular strain that affects molecule's stability at any scale from <1 nm (monomer) to >10 μm (polymer chain) and potentially longer.

This demonstration was provided by studies of force-accelerated isomerization of cis-1,2-disubstituted dibromocyclopropanes (DBC) to allyl bromides using molecular force probes.[43] The rates of this isomerization were measured in a series of increasingly large stiff-stilbene macrocycles across which the restoring force of stretched DBC in the *E* isomer was calculated to increase from 0 to 400 pN. The force-dependent activation free energy, $\Delta G(f)$, derived from these measurements matched closely $\Delta G(f)$ calculated quantum chemically by applying tensile force directly to the C terminus of the DBC moiety.

This $\Delta G(f)$ was then used to predict the ensemble-average single-chain micromechanics of a polymer of DBC up to 1.5 nN, which was previously measured by SMFS.[47] This prediction relied on 2 key assumptions. First, each monomer was assumed to react independently of any other monomer in the chain (i.e., mechanochemical isomerization was non-cooperative). Second, at the range of applied forces where mechanochemical isomerization occurs at detectable rate (>1 nN), the force experienced by each monomer of a chain approximately equals the force applied at ends of a 1 μm-long chain, which is the only force estimated in SMFS. Both assumptions were validated by calculated $\Delta G(f)$ of conformational ensembles of homologous series of increasingly long oligomers of DBC and extrapolating the results to the size-independent limit taking advantage of previously derived theoretical[18] and computational[21] approaches. Interestingly, these calculations also suggested that at applied force <1 nN a polymer chain is a poor transmitter of applied force, i.e., the fraction of the applied force experienced by each monomer (mechanochemical coupling coefficient[12]) is <1. This finding means that molecular interpretation of mechanochemical features of force/extension curves that occur at <1 nN (e.g., isomerization of spiropyranes[48]) is even more challenging than that of reactions occurring at higher forces because the force experienced by the reacting monomers cannot be approximated reliably from knowledge of the applied force.

The excellent agreement between the measured and predicted force/extension curves for the polymer of DBC (Figure 4) confirms that force, when properly defined, accurately captures the effect of stretching a reactive site on the kinetic and thermodynamic stabilities of this site, regardless of what physical process causes the stretching (e.g., compressed *E* stiff stilbene in macrocycles, a compressed virtual spring in DFT calculations or the directional motion of a macroscopic object in SMFS), or the length-scale at which the force is applied (from <1 nm in direct calculations of $\Delta G(f)$ to 2 nm in macrocycles to 1 mm in SMFS). As indicated in the next section, molecular restoring force can only be defined with respect to an internal coordinate of the distorted molecule, so that the predictive capacity of the force formalism depends on proper selection of this coordinate. When this criterion is satisfied, force enables quantitative discussions of strain-induced chemistry over at least a 10^4 fold variation in length scales and 10^{11} – fold range of reaction half-life.

Without diminishing the validity of the preceding paragraph, the excellent agreement in Figure 4 may be somewhat fortuitous. At the time of this work, the magnitude of the variation of the applied force at which individual monomers react ("transition force"), which reflects the stochastic nature of SMFS, and its dependence on the length of the stretched segment were unknown and each measured force/extension curved was assumed to approximate the ensemble behavior, which was predicted from measured and computed $\Delta G(f)$. Later studies, in which the applied force corresponding to the mechanochemical isomerization of each individual monomer was measured for a range of polymer chains,[40] demonstrated unexpected large variation in the "transition force" for otherwise identical monomers. Extrapolating from these later findings, the measured force/extension curves in Figure 4 may deviate by up to 150 pN (yellow shaded region) from the ensemble-average curve of the same chain.

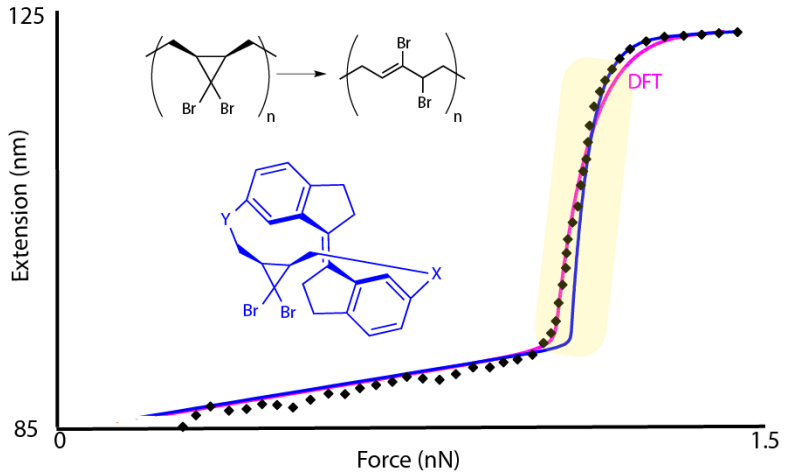


Figure 4-Restoring force dictates monomer reactivity regardless of how it was generated. The measured force extension curve of a dibromocyclopropane polymer (black dots), the predicted curve derived from extrapolation of the force/ΔG relation measured in stiff stilbene macrocycles(blue) and the predicted curved derived from ΔG(f) calculated by DFT (magenta). Yellow shading indicates estimated difference between ensemble and single-chain behavior. Adapted from [43] with permission.

Enumerating the complex relationship between force, rate and mechanism

Mechanochemical reactivity in polymers is often presented as accelerated dissociation of chemical bonds in response to tensile force, with a simple monotonic relationship between the magnitude of the force and the dissociation kinetics. This view is rationalized by invoking Eyring's ansatz[49] (the activation energy is proportional to the product of the applied force and the difference in the molecular length along the pulling axis (force vector) between the reactant and the transition state), which seemingly requires bond dissociations to be accelerated by tensile force as long as the scissile bond is longer in the transition state than in the reactant.[50] Implicit in this view is that such reactions are either elementary (i.e., a single activation barrier separates the reactant and the product) or that the applied force changes all activation barriers by the same amount. Although all mechanochemical reactions studied to date in sonicated solutions or by SMFS involve accelerated dissociation of at least one backbone bond (which sometimes may trigger further non-mechanochemical reactions), the apparent agreement reflects the limitations of the existing methods of inducing mechanochemical reactions in polymers, rather than some fundamental law of chemistry, or the prevalence of tensile-force accelerated bond dissociations among mechanochemical reactions.

Reported model studies, supported by detailed DFT-level calculations and occasional SMFS measurements,[40] illustrate the importance of competition, among distinct reaction mechanisms and/or individual steps of multi-step dissociation mechanisms, in determining mechanochemical reactivity. This competition reflects unique dependencies of individual activation barriers on applied force and suggests rich opportunities for exploiting it to study dynamics of overstretched polymer chains and to control the mechanochemical reaction networks and feedback loops that drive response of bulk polymeric materials to large mechanical loads. However, realizing this potential requires a systematic generalizable approach to analyzing and predicting the effect of force on reaction mechanisms.

Mechanochemical homolysis of a covalent bond, such as those responsible for fracture of overstretched polystyrene or polyacrylate macromolecules, *Z->E* isomerization of stiff stilbene, isomerization of trans-dialkyl cyclobutenes to butadienes[24,34] and of certain dihalocyclopropanes to allyl halides,[3] and S_N2 substitutions[50,51] appear to comprise the simplest cases of mechanochemical kinetics. Computational and experimental evidence suggest that at any force each reaction traverses a single activation barrier, whose height decreases monotonically with tensile force, uncomplicated by competing reaction paths.

The next level of complexity involves reactions that are elementary in the absence of (or at low) force but whose mechanism changes as the force increases. Examples include the force-accelerated dissociation of Diels-Alder adducts of anthracene and maleimide,[52] for which computations reveal the minimum-energy mechanism that switches from concerted at <0.2 nN to stepwise at higher force and isomerization of cis-3,4-disubstituted cyclobutenes to butadienes, where an open-shell singlet transition state becomes more stable than the closed-shell analog as force increases and is responsible for the domination of the "orbitally-forbidden" isomerization path at tensile force >1.5 nN as evidenced both by computation and by sonication experiments on cis-3,4-disubstituted cyclobutene containing chains (Figure 5).[45,53]

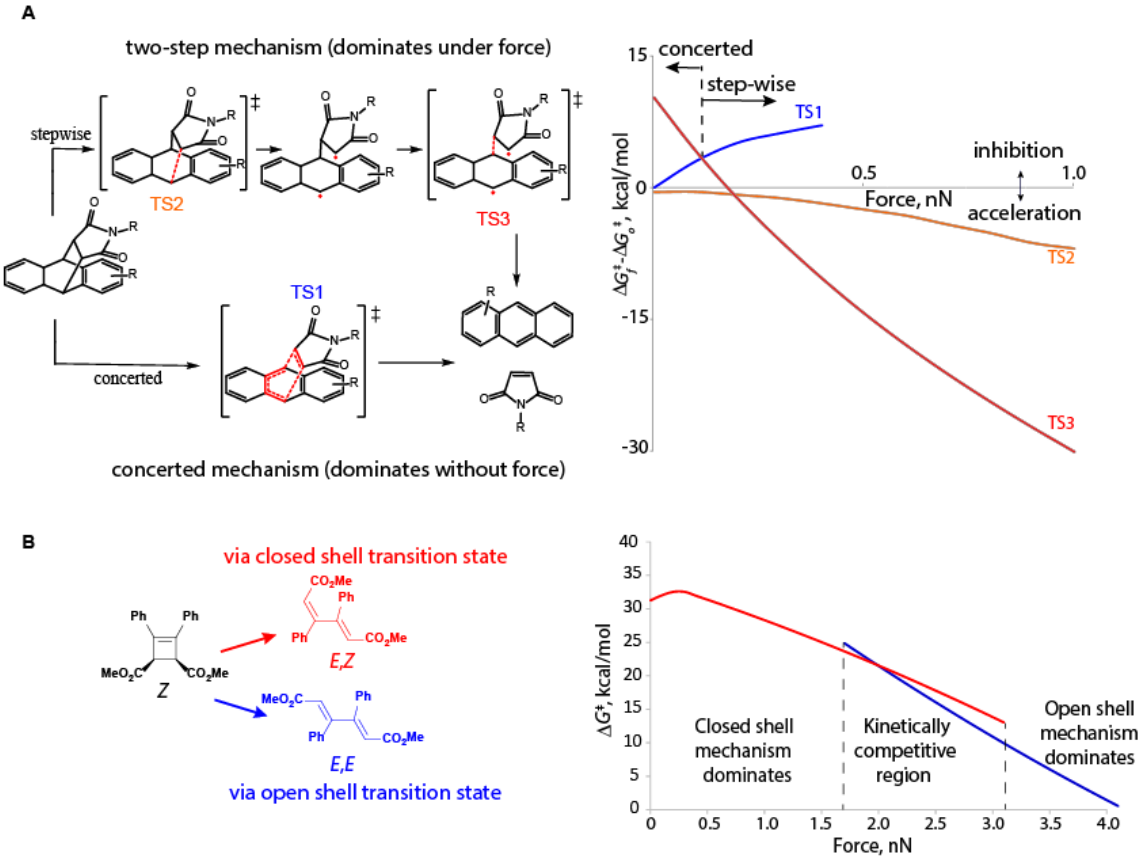


Figure 5- Tensile force changes the reaction mechanism of the dissociation of anthracene-maleimide adduct and of the isomerization of cis-3,4-substituted cyclobutenes. In anthracene-maleimide adducts the crossover occurs at low force (~200 pN), whereas in the isomerization the two mechanisms remain kinetically competitive over a ~1.5 nN range.[40,45,52] The open-shell mechanism (blue curve in b) does not exist at force <1.6 nN. Adopted from refs. [2] (a) and [45] (b).

Multi-step reactions manifest particularly diverse mechanochemical behavior: first, their mechanochemical kinetics spans the range from force-accelerated dissociations (e.g., those involving cyclobutane cores),[46,54,55] to insensitivity to applied force (e.g., hydrolysis of esters of carboxylic acids[56,57] or thiol/disulfide exchange[58]) to inhibition by tensile force (e.g., hydrolysis of siloxane ethers).[15] Second, their mechanisms are particularly sensitive to applied force, almost always yielding non-monotonic force/rate correlations. It is for these reaction types that model studies have been particularly productive as illustrated below on two examples: a force-dependent change in the rate-determining step of a two-step dissociation mechanism that is accelerated by force, and competition between force-destabilized and force-stabilized mechanisms that changes observed kinetics from force-inhibited to force-accelerated.

The first example describes the 2 step reduction of an organic disulphide by phosphine. In the absence of force the 2nd reaction step is rate-determining and the "inner" barrier is kinetically invisible.[44] This reaction was studied because it is one of the few for which the rate constant of a non-rate determining step can be determined experimentally by measuring the pH dependence of the reduction rate. The independent method of estimating the size of the strain-free inner barrier was used to validate force-dependent measurements as discussed below.

The study used a series of 6 stiff-stilbene/disulfide macrocycles synthesized by the 'join up' method (Figure 2). Each *E* disulfide macrocycle is strained and therefore destabilized relative to the *Z* analog (by $SE_{Reactant}$, Figure 6), as is the 1st transition state of the reduction (albeit by a smaller amount, $SE_{TS1}<SE_{Reactant}$), whereas the energies of the acyclic intermediate and the 2nd transition state are identical in the two isomers (Figure 6). In other words, disulfide reduction allows partial relief of ground-state molecular strain in TS1 and full relief in the intermediate by virtue of ring opening. As a result, as the macrocycle size decreases and the tensile force on the S-S moiety increases, the partially-strained *E* isomer of TS1 is progressively destabilized relative to strain-free TS2 even though both transition states are stabilized relative to the reactant (the fully strained *E* disulfide): blue vs. green vs. red curves, Figure 6. Since TS2 is the least stable transition state in the absence of force (or equivalently in the *Z* macrocycles), at some force the rate-determining transition state for reduction of macrocyclic *E* disulfide switches from TS2 to TS1. Consequently, although the reaction is faster in the *E* macrocycle than in its Z analog (i.e., it is accelerated by tensile force of any magnitude), the rate is much more sensitive to force at low forces, when the acceleration is driven by full relaxation of molecular strain of the *E* macrocycle in TS2, than at higher force, when only partial relaxation of strain in (now rate-determining) TS1 is possible. For the macrocycles in Figure 6, the rate-determining step changes when the restoring force of the disulfide moiety reaches 120 pN. Importantly, extrapolating this second region to 0 force gives an estimate of the energy of TS1 in the strain free reaction that agrees with the value obtained experimentally, verifying this simple model of a multi-barrier reaction and providing a method of estimating otherwise kinetically invisible energy barriers.

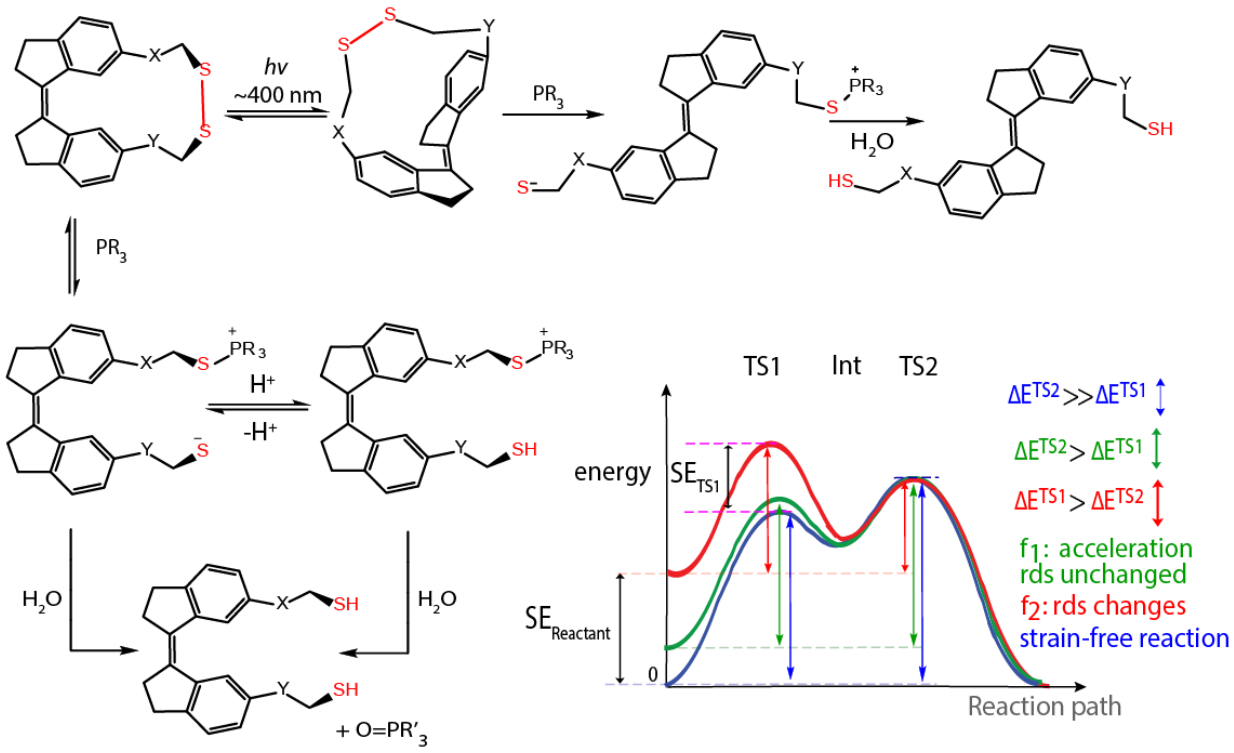


Figure 6- Tensile **force changes the rate determining step of this disulphide reduction.** In macrocycles 1-6 X and Y consist of various combinations of (CH_2) and O(CH_2). Energy is reference to TS2 since this is acyclic species is unaffected by force.[44]

Rather than being a rarity, changes in rate determine steps are likely the norm for multi–barrier reactions. Only when all other barriers are reduced at all forces by at least as much as the rate determining barrier would the nature of the rate-determining step remain force-independent. Such a requirement is unlikely to be met because the necessarily distinct geometries of sequential transition states ensure that force affects the geometry and the relative energy of each transition state uniquely.

The same process that is responsible for changing the rate-determining step often causes a change in the minimum-energy reaction mechanism with force. The best studied example is methanolysis of diphenyl siloxanes (Figure 7), whose complex mechanochemistry, in which its reactivity is inhibited at low force and accelerated at higher force, was verified using molecular force probes and computations.[15] Unlike SN2 substitutions at sp^3-C atoms, ligand exchange at Si can proceed by a variety of multi-step mechanisms, depending on the nucleophile, leaving group, spectator ligands and solvent.[59] Methanolysis of strain-free diphenyl siloxane occurs preferentially by axial entry of MeOH (TS1ax, path 1: right sequence in Figure 7) and departure of an equatorial EtOH (TS2ax). The alternative mechanism in which the nucleophile attacks in the equatorial plane of the forming trigonal bipyramid (TS1eq), followed by eventual departure of one of the axial ethoxides (path 2) is calculated to be 3 kcal/mol higher in energy. Yet the formation of the transition states of path 1 requires contraction of the ensemble-average separation of the two ethoxide ligands (illustrated in Figure 7 for the O…O distance by the magenta arrow), whereas in both transition states of path 2 the equivalent pairs of atoms of the two EtO ligands are further apart than in the reaction.

These structural differences become critically important when tensile force is applied at the terminal C atoms of the EtO ligands: path 1 is destabilized by this force because the formation of its transition states requires atoms to move against applied force, which raises the potential energy of the object that applied the force. Conversely, path 2 is stabilized by force, until it becomes dominant at ~200 pN. As a result, the rate of methanolysis reaches the minimum at ~200 pN, followed by acceleration

while remaining below its strain-free rate up to 500 pN, when the energy of TS1eq decreases below that of strain-free TS1ax. This reaction therefore mimics the force-dependent kinetics of certain protein complexes, whose dissociative stability increases when they are pulled apart with low force and decreases at higher force. Unlike these so-called biological catch bonds,[60] the molecular mechanism responsible for force-dependent inhibition of siloxane methanolysis has been enumerated in sufficient detail to generalize to any localized reaction, and to enable both the design of new molecules with pre-determined force/rate correlations and validation of the general models of mechanochemical kinetics.

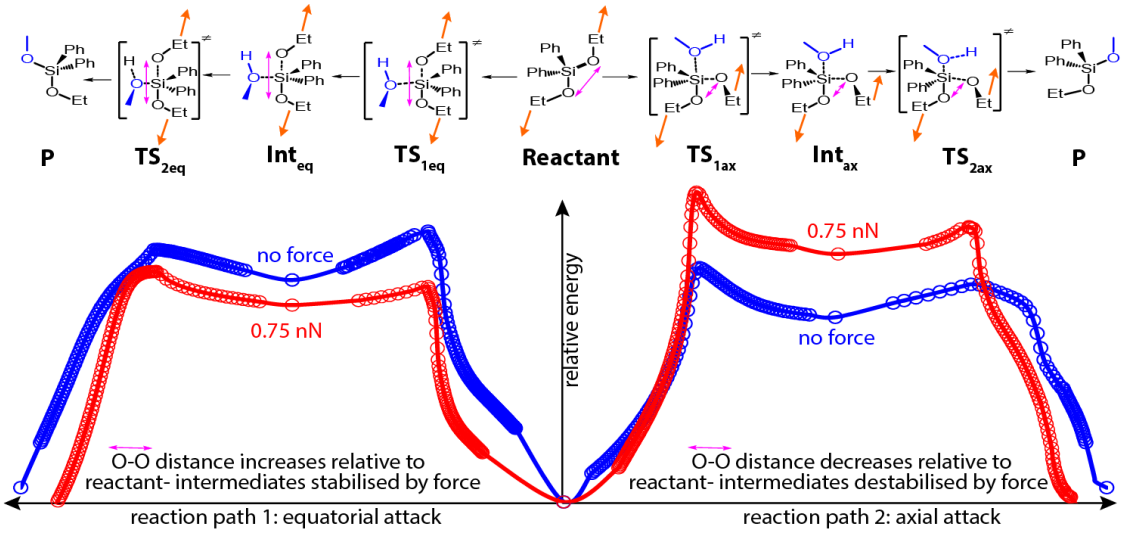


Figure 7-Tensile force destabilizes the lowest-energy mechanism of siloxane methanolysis but stabilizes the higher-energy mechanism. This mechanistic competition leads to non-monotonic dependence of the reaction rate on tensile force, which decreases with force up to ~200 pN. The complex mechanochemical kinetics can be rationalized and predicted with useful accuracy by considering changes in the (Et)O…O(Et) distance of the reacting siloxane from the reactant to the rate-determining transition state. Energy diagrams are reaction-path calculations at the B3LYP/6-311++G(d) level of DFT in methanol-parameterized SMD model of reaction solvent with the reaction coordinates normalized to enable comparisons. Adopted from ref. [15] with permission.

Force-accelerated dissociation of unloaded covalent bonds in preference over loaded bonds.

Although the assumption that tensile force always accelerates dissociation of covalent bonds "aligned" with the pulling axis is usually justified by pointing out that scissile bonds elongate monotonically as the reactant progresses towards the product, quantum-chemical calculations demonstrate that such monotonic elongation is far from universal.[56] Furthermore, in siloxane methanolysis the scissile Si-O bond increases monotonically but the reaction is still inhibited because of the formation of the rate-determining transition state requires the movement of multiple atoms against the applied force (i.e., the molecule contracts along the pulling axis despite one of its bond elongating). The force-dependent rate of phosphoester[15] nucleophilic displacement, measured using molecular force probes, illustrates the other fallacy that seems to underlie the current intuitive understanding of how reactant structure affects its stability under force: the orientation of the scissile bond relative to the pulling axis has little bearing on mechanochemical kinetics.

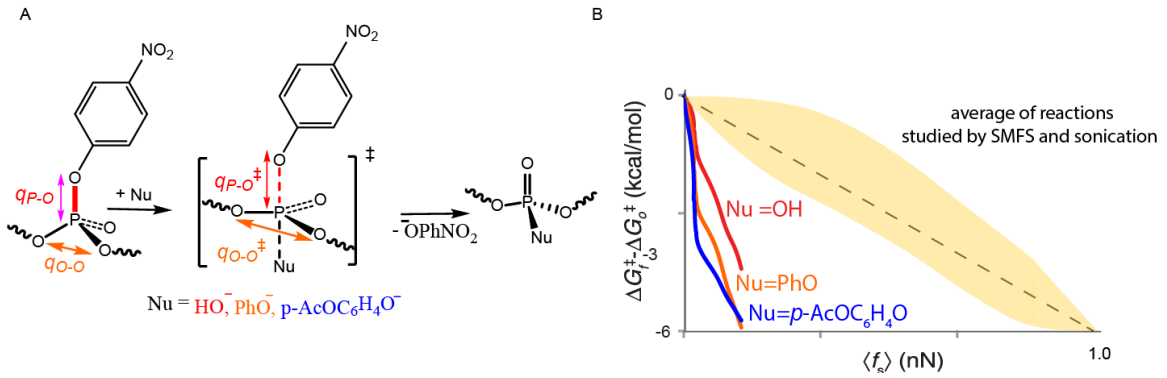


Figure 8- Force accelerated dissociation of an unloaded bond. A) The scissile bond length ($q_{P\text{-}O}$), increases between reactant and transition state but is uncoupled to the force applied. The accelerated kinetics observed is therefore due to the increased O-O bond distance ($q_{O\text{-}O}$) arising through bond angle changes. B) shows how the ratio of force experienced by the scissile bond (F_s) to activation energy of the rate determine step compares to reactions studied in polymers, which all fall into the yellow shaded region.[15]

Stretching a phosphoester increases the electrophilicity of P and makes the ester more reactive towards diverse nucleophiles (Figure 8). Yet of the three P-O bonds susceptible to nucleophilic displacement, only the bond that is orthogonal to the pulling axis is destabilized by the force (compare with the response of pyrophosphates[50]). This seemingly counterintuitive outcome reflects the fact that only displacement of the P-O bond orthogonal to the pulling axis allows the transition state to elongate along the force vector by virtue of placing the spectator ligands into the equatorial plane of the trigonal bipyramidal transition state (unlike methanolysis of siloxanes, nucleophilic displacement at P is an elementary reaction). Conversely, displacement of a P-O bond along the pulling axis would require a contraction of the molecule against the applied force (see the siloxane example).

Although the scissile P-O bond is not directly coupled to applied force, it is not entirely unloaded. Instead, its restoring force is ~1 – 5% of that of the other P-O bonds that are approximately colinear with the pulling axis because the distribution of load among molecular degrees of freedom is quite complex.[18] This allows a quantitative comparison of the sensitivity of the kinetics of phosphate solvolysis to that of all other mechanochemical reactions reported to date. Because all such reactions involve dissociation of one or more bond, the trends are most apparent when compared to the change in the activation free energy of each reaction as a function of the restoring force of the scissile bond, f_s. Despite the mechanistically diverse range of reactions studied in polymers, their mechanochemical kinetics is surprisingly similar: each is accelerated by (6 ± 3)–fold per 0.1 nN of f_s (Figure 8b; the reported examples, however, vary dramatically in how efficiently the applied force is transmitted to the scissile bond, with the corresponding coupling coefficients[18] ranging from ~1 to <0.1 even at force >1 nN). In contrast, phosphate solvolysis is accelerated >10^4-fold per 0.1 nN.

While these examples refute the usual assumption that tensile force invariably lowers dissociative stabilities of bonds aligned with the force vector, they and several other reactions also demonstrate that predicting the effect of force on the kinetics of nucleophilic displacement at a backbone atom of a stretched macromolecule is fairly simple.[51] Such reactions proceed through a trigonal bipyramidal transition state in which the two segments of the backbone on either side of the electrophilic atom either both occupy the equatorial plane or one is placed in the axial position, while the other is equatorial. The former elongates the contour length of the macromolecule and is therefore stabilized by tensile force. The latter usually contracts the contour length and is thus destabilized. Force-dependent nucleophilic backbone fracture will therefore be inhibited for any reaction that requires the leaving group to occupy the axial position of this bipyramidal transition state, a condition that is true for all known nucleophilic displacement reactions at 2nd and 3rd row elements.

Conversely, nucleophilic displacement of side-arms, which would place the macromolecular segments into the equatorial position, are accelerated.

Conclusion

Despite the more limited range of forces that molecular force probes can subject a monomer to (<0.75 nN) compared to those accessible by single-molecule force spectroscopy (<2.5 nN) or elongational flows of polymer solutions (unknown but probably up to 4 nN)[2], they have produced far more diverse patterns of mechanochemical kinetics than has been achieved with polymers. In addition to accelerated dissociation of covalent bonds along the pulling axis studied by SMFS and sonication, molecular force probes demonstrated that tensile force can accelerate dissociation of bonds orthogonal to the pulling axis, without straining them, and inhibit dissociation of bonds aligned with it.[15] Emerging evidence suggests that low-to-moderate force is equally likely to increase dissociative stability of a covalent bond as to decrease it and the dominance of the former response (e.g., shaded area in Figure 8b) reflects the bias of the existing experimental techniques and "intuition". Detailed mechanistic studies enabled by molecular force probes revealed the atomistic origin of this diversity of mechanochemical responses and yielded general, intuitive and theoretical validated models for usefully accurate predictions of force-dependent kinetic stabilities of structurally diverse reactants in the presence of nucleophiles.

This ease of mechanistic studies of mechanochemical reactions in molecular force probes also means that they remain the primary source of our current understanding of how force affects reaction mechanisms. Although the potential of force-dependence kinetics to reveal parts of strain-free reaction surfaces that are not amenable to characterization in the absence of force has long been recognized,[44,61] attempts to exploit the complex (but often predictable[15,40,45,62]) force-dependent changes in the relative heights of individual activation barriers of multi-step reactions either in design of new mechanoresponsive materials, or for fundamental studies of chain dynamics, have yet to be reported. Similarly, experimental and computational evidence suggests the importance of competing mechanisms, whose relative contributions change with force, in determining kinetic stabilities of diverse reactive moieties under force. Yet little evidence exists that such competition is considered (at least not explicitly) in the design of new reactions or in molecular interpretation of characterized reactions.

The modest size of molecular force probes allows the restoring force of each molecular coordinate (e.g., internuclear distances) of the strained reactive site to be quantified accurately by quantum-chemical computations, a level of detail that remains inaccessible for stretched polymers. This advantage was already exploited to validate experimentally the key postulate of mechanochemical kinetics (that force is a scale-invariant measure of molecular strain)[43] and offers the potential to advance considerably our understanding of the effect of molecular strain on chemical reactivity.[9] Another largely unexploited[16,63] opportunity offered by molecular force probes is to study separately individual steps of complex mechanochemical reaction networks and feedback loops that likely underlie many practical manifestations of polymer mechanochemistry (e.g., in amorphous materials and melts[2]). Finally, molecular force probes offer a means of connecting polymer mechanochemistry with small-molecular mechanochemistry[1] in which usually bond-forming reactions are induced by grinding or milling powder mixtures.[64]

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