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Reaction dynamics in the formidable gap*

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Abstract: One of the least understood and least exploited aspects of nanoscience is dynamic coupling between directional translation at mesoscales (lengths above ~50 nm) and changes in local chemical bonding (lengths below ~1 nm). A major cause is the traditional dominance of two distinct and seemingly incompatible models for describing dynamics at the two scales: continuum mechanics based on the balance of forces, i.e., mechanical equilibrium (lengths above ~50 nm) and activated escape from an energy well, i.e., chemical equilibrium (below ~1 nm). These models yield meaningful results within their respective dimensional limits but leave processes in between in the gray area of conceptual ambiguity and technical intractability. Such processes underlie phenomena as diverse as catastrophic failure of strained materials, operation of motor polymers, behavior of polymer flows, and mechanosensing.

Chemomechanics integrates the two conventional dynamic models into a single internally consistent, scale-independent framework that is essential for a quantitative understanding and the efficient exploitation of dynamic coupling across the "formidable gap" at ~1–50 nm. Chemomechanics holds promise (1) to facilitate significantly the design of new stress-responsive and actuating polymers, including those optimized specifically for the propulsion of autonomous nanomechanical devices and for use in micro- and nanoscale stress sensors; and (2) to yield general predictive molecular relationships between chemical composition, structure, and mechanical properties of polymers both at the single-chain and bulk levels. Theoretical and experimental studies of dynamic coupling across the formidable gap have traditionally been carried out within soft-matter physics. As far as I am aware, my group was the first to approach the problem from a chemist's perspective. Below, I summarize the state-of-the-art of chemical understanding of processes in the formidable gap from both theoretical and experimental perspectives.

Keywords: long-range interactions; macrocycles; mechanochemistry; molecular strain; polymers; reaction dynamics.

INTRODUCTION: REACTIONS IN STRETCHED POLYMERS

The vast majority of reactions studied and used by chemists proceed by highly synchronous rearrangements of atoms confined to a tiny volume of space, rarely larger than 1 nm^3, while negligibly perturbing the random motion beyond these limits [1,2]. Qualitatively, a sequence of a few unique configurations of a small number (<100) of atoms [3] in internal mechanical equilibrium is sufficient to model the dynamics of such reactions. A single number, the reaction coordinate, describes the structural difference between each of these configurations and the transition state (the highest-energy configuration) and quantifies the reaction progress. The randomly fluctuating environment surrounding these small

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nuclear assemblies is represented as a continuum, whose bulk properties (temperature, pressure, viscosity, or dielectric constant) determine how much (or little) it affects the structures and relative energies of the reacting molecule(s). The simplicity of this model tremendously facilitates conceptual and technical [3,4] understanding of chemical reactivity.

Yet some of the most important phenomena in biology [5–9] and, increasingly, technology [10–17] deviate drastically from this pattern. There, the concerted atomic rearrangements in very simple molecules bring about, or are brought about by, directional dynamics at length scales up to 1 mm. Such multiscale dynamic coupling enables motility [5], active intracellular transport [18,19], cell divisions [20], and possibly mechanosensing [21], thus allowing our very existence. Macroscopic stresses that drive polymer flows in solution [22–25], in solids [15], or at interfaces [26] accelerate simple reactions within the polymers by up to 10^{15}-fold, leading to their fragmentation and, ultimately, material failures [16]. Propulsion of autonomous nanomechanical devices may only be achieved by coupling them dynamically to the correlated atomic motion of chemical reactions [5,27,28]. Chemically or photochemically driven actuating polymers (i.e., "artificial muscles") are thought to be required to reproduce animal-like mobility in macroscopic robots [29].

The minimal ground and transition states in such processes consist of quadrillions of atoms [9] as they include both the macromolecule and the sufficient volume of its surroundings to yield internal mechanical equilibrium, making an atomistic definition of these states, and hence the classical reaction-coordinate path formalism untenable. Because the existing theories of chemical kinetics do not offer a systematic strategy to partition ground and transition states in these phenomena into a small part amenable to quantum-chemical atomistic descriptions and the rest that can be treated as a continuum, new kinetic models are required.

One promising strategy relies on the concept of force to integrate the continuum-mechanics models of conformational behavior of polymers with the conventional chemical kinetic formalism. In fairly simple systems, such as steady elongational flows of dilute polymer solutions or single polymer chains bridging a pair of retracting microscopic force probes, the effect of experimental control parameters on observed (or inferred) macromolecular conformation dynamics can often be described successfully with continuum models based on a single degree of freedom, sometimes called "mechanical" coordinate, τ [9,22]. For long flexible polymers, τ can be approximated as the difference between the separation of the termini of a polymer and its strain-free contour length [30]. More generally, τ is a generalized numerical description of a large-scale (10s to 100s of nm) macromolecular conformation [9]. A single degree of freedom, τ, suffices to model conformational dynamics of an inert macromolecule stretched by interaction with its environment.

However, overstretching a polymer (i.e., extending its end-to-end distance above the strain-free contour length) often dramatically increases the reactivity of its constituent monomers [15,24]. Even such a localized chemical reaction can substantially perturb the conformational dynamics of the polymer and its interaction with its environment [22]. Likewise, large-scale conformational behavior of motor or allosteric proteins is often controlled by binding or catalytic transformation of small-molecule substrates, such as ATP [7]. In these situations, a single "mechanical" degree of freedom is insufficient to describe the dynamics [9].

A localized reaction in a polymer can be modeled as a rare but rapid (ps) change in local chemical bonding of a tiny portion of the polymer (reactive moiety) during which the large-scale macromolecular configuration (and hence the mechanical coordinate) is assumed to remain static, followed by a slow (μs–ms) relaxation of the rest of the molecule (and its surroundings) to a new equilibrium geometry [9]. In other words, a conventional picture of a chemical reaction as a synchronous evolution of molecular geometry from the minimum-energy reactant through the minimum-energy transition state to the product, characterized by a single rate constant (Fig. 1A), is replaced in a macromolecule by a collection of rate constants describing localized reaction kinetics in polymers of different conformations, τ, $k(\tau)$, Fig. 1B (white arrows). The distribution of macromolecular conformations can be esti-

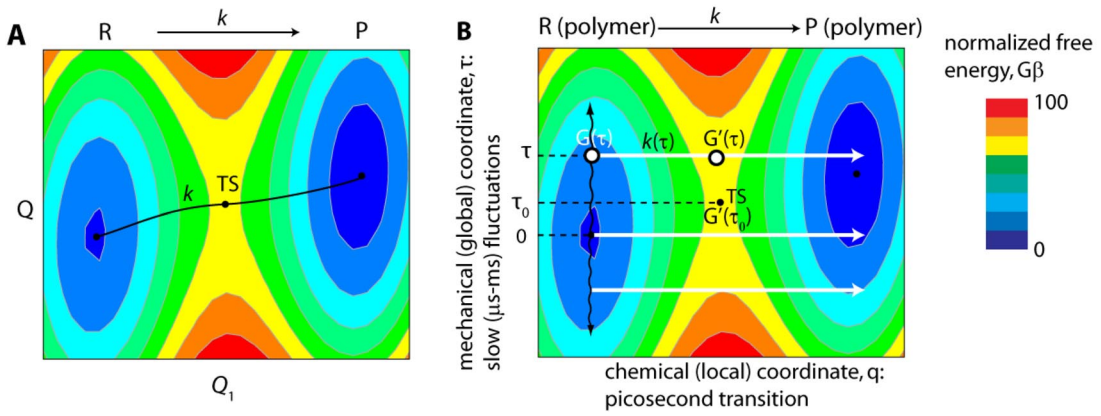

Fig. 1 Comparison of reduced-dimensionality reaction energy surfaces of a small reactant (A) and of a polymer (B). The color scale corresponds to free energy in units of thermal energy, β^{-1}.

mated using simpler models [22] than those required to describe changes in covalent chemical bonding, making the dynamics problem more tractable.

If the chemical reaction is irreversible, the steady-state dynamics of a macromolecule stretched to an ensemble-average restoring force F_τ is characterized by rate constant $k(F_\tau)$, eq. 1, where $P(\tau, F_\tau)$ is the probability density function describing the distribution of macromolecular conformations in an ensemble with the average restoring force F_τ, $k(\tau)$ is the rate constant of the chemical reaction in the macromolecular conformer corresponding to τ, and β is the inverse thermal energy. The simplest distribution of macromolecular configurations, important in dilute polymer solutions and in single-molecule force experiments, is Boltzmann [31] with the equilibrium geometry characterized by the mechanical coordinate $\tau_{eq.} = F_\tau \lambda_\tau$ (eq. 2), where λ_τ is the stretching compliance of the polymer along τ, and λ_c is the compliance of the object that stretches the polymer, e.g., the microscopic force probe or the flowing solvent. The canonical transition-state-theory expression [2] for $k(\tau)$ is given by eq. 3, where $G^{\ddagger}(\tau)$ is the free-energy difference of the transition and ground states of the localized reaction in the macromolecular conformation τ.

$$k\left(F_\tau\right) \propto \int_{-\infty}^{\infty} P\left(\tau, F_\tau\right) k\left(\tau\right) d\tau \tag{1}$$

$$P\left(\tau, F_\tau\right) = \sqrt{\frac{\pi}{\left(\lambda_\tau^{-1} + \lambda_c^{-1}\right)}} e^{-\left(\lambda_\tau^{-1}+\lambda_c^{-1}\right)\left(\tau - F_\tau \lambda_\tau\right)^2 \beta/2} \tag{2}$$

$$k\left(\tau\right) \propto e^{-\Delta G^{\ddagger}(\tau)\beta} \tag{3}$$

Two special cases of eq. 1 are often used in discussions of biophysics of motor proteins [5,8,9] (Fig. 2): in the so-called Brownian ratchet model $k(\tau)$ is set to 0 in all macromolecular conformations except that of the strain-free product ($\tau = \tau_p$). The other extreme, the power stroke model sets $k(\tau)$ to 0 for all τ except 0, the macromolecular conformation of the strain-free reactant. Qualitatively, in the Brownian ratchet model the reaction proceeds by a slow thermal excitation to a high-energy macromolecular conformer, τ_p, which is then "trapped" by the "instantaneous" chemical transition. A power stroke corresponds to the chemical reaction occurring in the minimum-energy macromolecular conformation, which generates a strained conformation of the product, following by its slow conformational relaxation to the energy minimum, τ_p. These models are popular in biophysics because they require

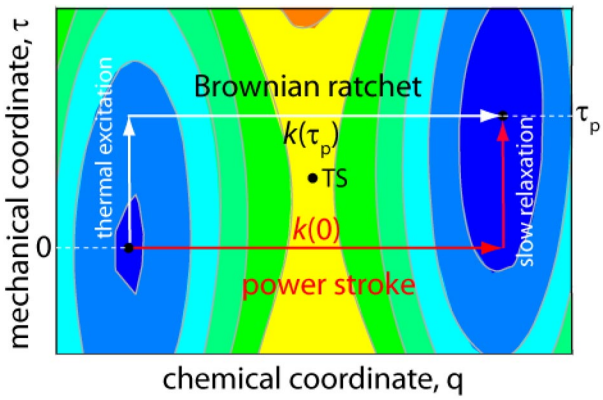

Fig. 2 Two limiting cases of the chemomechanical model: Brownian ratchet in which the localized reaction is assumed to occur only in the macromolecular conformation corresponding to the strain-free product (τ_p) and power stroke in which the localized reaction is assumed to proceed only in the strain-free reactant conformation. In the Brownian ratchet model, the localized reaction "traps" the unstable macromolecular conformation, in mechanical analogy to the Feynman ratchet [9]. In the power stroke model, the large-scale structural changes resemble that of a macroscopic motor, in which the free energy of a chemical reaction is used to create a strained state, followed by its relaxation to the equilibrium geometry, τ_p. This relaxation can, in theory, be used to perform work on an external object.

minimal chemical information, with the values of $k(\tau_p)$ or $k(0)$ usually selected to reproduce the observed or postulated macromolecular conformational dynamics, rather than the underlying chemistry. However, these models have been criticized [31] for misrepresenting the fundamental aspects of coupling between mechanical (global) and chemical (local) dynamics.

Chemically meaningful evaluation of eq. 1 requires the explicit functional form of the free energy reaction surface for the relevant macromolecular conformations, $G(\tau)$. Empirical steered molecular dynamics calculations of $G(\tau)$ for unfolding of biopolymers during which weak noncovalent interactions rearrange are now almost routine [32]. In contrast, calculations of $G(\tau)$ for reactions of direct interest to chemists and material scientists, i.e., involving covalent-bond rearrangements, remain largely untenable. At present, quantum-chemical molecular dynamics simulations have been carried out only for the simplest reactions (such as unimolecular electrocyclic isomerization of cyclobutene) in the smallest molecular fragments and at very high restoring forces, F_τ [33–35]. As this situation is unlikely to improve significantly anytime soon due to the prohibitive scaling of quantum-mechanical methods with molecular size, general and quantitative strategies to estimate $k(F_\tau)$ from the measured and calculated properties of isolated reactive moieties are required.

Chemomechanics provides one such strategy. The chemomechanical formalism is predicated on the existence of an internal coordinate of isolated, strain-free minimal reactant (reactive moiety) that can serve as the chemical coordinate, q (a local degree of freedom that quantifies progress of the reaction, i.e., changes in local chemical bonding), such that its difference between the ground and transition states of a reaction are proportional to changes in the mechanical variable, τ, between the same stationary points, i.e., the mechanical coordinate can be expressed as a linear function of the chemical coordinate. Since such a chemical coordinate q describes the geometry of the minimal reactant, it is readily available experimentally (for minima) or computationally (for transition states). The problem then is reduced to finding the proportionality constant, $\alpha_{\tau q}$, to quantify coupling between the mechanical and chemical coordinates (chemomechanical coupling), i.e., how sensitive the overall geometry of the macromolecular reactant is to changes in local chemical bonding, as approximated by q. Because of this approximation, q is not unique. In other words, suitable q will depend on the nature of the mechanical coordinate, the level of approximation one seeks, and the generality of the solution. Correspondingly, the same reac-

tion may be characterized by different chemomechanical coupling coefficients, depending on one's choice of q. As I describe below, force-dependent kinetics of all reactions of the same mechanism can be described by the same type of chemical coordinate in overstretched flexible polymers.

Ideally, one would like to define the chemical coordinate so that the corresponding $\alpha_{\tau q}$ depends only on the reactive moiety and is largely invariant to the size and the chemical composition of the rest of the macromolecular reactant, in which case $G(\tau)$ can be approximated using the known parameters of the minimal reactant. In the simplest case, quadratically expanding the free energy of the polymer around its strain-free transition and ground states [i.e., $G'(\tau'_{\mathrm{o}})$ and $G(0) \equiv 0$, respectively, Fig. 1B] yields eqs. 4–5, where $\Delta G^{\ddagger}_{\mathrm{o}} = G'(\tau'_{\mathrm{o}})$ is the energy of the strain-free transition state relative to strain-free ground state, i.e., the activation free energy of the reaction in the strain-free macromolecular conformer corresponding to $\tau = 0$, λ_τ is the stretching compliance of this conformer and $\Delta\lambda_q$ is the difference in the compliance of chemical (local) coordinate q of the isolated strain-free reactive moiety in the transition and ground states. These values are assumed to be independent of the macromolecular strain because of the large difference in stiffness of a long flexible polymer and small localized moiety. Consequently, the different kinetics of a localized reaction in a stretched and strain-free polymer reflects solely the changes in the distribution of macromolecular conformations, $P(\tau, F_\tau)$, as its equilibrium geometry shifts from $\tau_{\mathrm{eq.}} = 0$ in the absence of strain to $\tau_{\mathrm{eq.}} = F_\tau \lambda_\tau$ at restoring force F_τ.

$$G'(\tau) = \Delta G^{\ddagger}_{\mathrm{o}} + \frac{\partial^2 G'(\tau'_{\mathrm{o}})}{\partial \tau^2}\frac{(\tau - \tau'_{\mathrm{o}})^2}{2} + \cdots = \Delta G^{\ddagger}_{\mathrm{o}} + \frac{(\tau - \alpha_{\tau q}\Delta q_{\mathrm{o}})^2}{2(\lambda_\tau + \Delta\lambda_q)} + \cdots \tag{4}$$

$$G(\tau) = \frac{\partial^2 G(0)}{\partial \tau^2}\frac{\tau^2}{2} + \cdots = \frac{\tau^2}{2\lambda_\tau} + \cdots \tag{5}$$

Truncating the expansions at the 2nd-order term and combining eqs. 1–5 yields eq. 6 for changes in the rate constant of a localized reaction resulting from stretching a macromolecule to restoring force F_τ (k_{o} is the rate constant in strain-free polymer). If $\lambda_\tau + \Delta\lambda_q > 0$ (i.e., the mechanical coordinate is not the full reaction coordinate) eq. 6 reduces to eq. 7. The second equality of eq. 7 shows that the change in the reaction barrier due to stretching a macromolecular reactant equals the difference in the strain energy of the ground and transition states (1st and 2nd terms, respectively). In other words, although eq. 6 is based on the assumption that the constrained degree of freedom (τ) of the reactant varies slowly (μs–ms), provided that this degree of freedom remains in thermal equilibrium with the environment (i.e., its distribution is Boltzmann, eq. 2), the strain-induced change in the activation barrier is the same as for a reaction that follows the minimum-energy path. In other words, eq. 7 establishes the equivalency of the strain-induced barrier changes in macromolecular and non-macromolecular reactants, confirming a qualitative argument made over 50 years ago [1]. The equivalency allows the chemomechanical formalism to be validated and refined using tractable nonpolymeric reactants before progressing to the experimentally and computationally more demanding studies of reactions in stretched polymers [36–42].

$$\frac{k(F_\tau)}{k_{\mathrm{o}}} = \frac{\int_{-\infty}^{\infty} e^{-((\lambda_\tau^{-1}+\lambda_c^{-1})(\tau-\lambda_\tau F_\tau)^2 + (\lambda_\tau+\Delta\lambda_q)^{-1}(\tau-\alpha_{\tau q}\Delta q_{\mathrm{o}})^2 - \lambda_\tau^{-1}\tau^2)^{\beta/2}}\, d\tau}{\int_{-\infty}^{\infty} e^{-((\lambda_\tau^{-1}+\lambda_c^{-1})\tau^2 + (\lambda_\tau+\Delta\lambda_q)^{-1}(\tau-\alpha_{\tau q}\Delta q_{\mathrm{o}})^2 - \lambda_\tau^{-1}\tau^2)^{\beta/2}}\, d\tau} \tag{6}$$

$$\beta^{-1}\ln\frac{k(F_\tau)}{k_{\mathrm{o}}} = \frac{\lambda}{\lambda + \Delta\lambda_q}\left(F_\tau\alpha_{\tau q}\Delta q_{\mathrm{o}} + \frac{F_\tau^2}{2}\Delta\lambda_q\right) = \frac{F_\tau^2}{2}\lambda - \frac{F_\tau^2}{2}\frac{\lambda}{\lambda + \Delta\lambda_q}\left(\lambda - \frac{\alpha_{\tau q}\Delta q_{\mathrm{o}}}{F_\tau}\right) \tag{7}$$

CHEMOMECHANICS IS VALID FOR STRAINED REACTANTS OF ANY SIZE

The effect of molecular strain on chemical reactivity has traditionally been discussed within the formalism of linear free-energy relationships (LFERs), by postulating that a fraction of the ground-state strain energy contributes to the standard free energy of reaction [1]. Although no methods exist to estimate this fraction other than from quantum-chemical calculations (which obviates the need for the strain-energy approximation in the first place), for many different reactants this fraction was found empirically to be 0.1–0.7 [43], allowing semi-quantitative estimates of strain-induced changes in the activation energy in related reactions.

Any approach based on ground-state strain energy is not applicable to reactions in stretched polymers and other anisotropically strained media because strain energy increases with the size of the ground state whereas the strain-induced barrier lowering does not. Consequently, the same reaction may have vastly different proportionality constants between the ground-state strain energy (which can be estimated from experimental parameters) and its free energy of activation (or standard free energy) depending on the size of the nonreactive parts of the macromolecule.

The formalism underlying eqs. 6–7 provides an alternative means of relating the ground-state strain to the change of the activation barrier by exploiting the intensive property of restoring force and using a chemomechanical coupling coefficient to relate macroscopic and molecular properties of the system. The chemomechanical coupling coefficient quantifies how sensitive the global geometry of the reacting macromolecule (as measured by the mechanical coordinate) is to the structural difference of the reactive moiety in its ground and transition states. For example, computations and experiments (partly discussed below) suggest that simple fragmentation of stretched long flexible polymers is characterized by the chemomechanical coefficients between 2 and –2 when the scissile bond is selected as the chemical coordinate. In other words, the ensemble-average end-to-end distance of an overstretched macromolecule undergoing a single-barrier, single-bond fragmentation may increase or contract by up to twice the elongation of the scissile bond in its transition state depending on the nature of the reactive moiety, regardless of the overall length the of polymer.

Most covalent bonds between 2nd and 3rd row elements elongate by <1.5 Å in the transition states of their dissociation [44]. It seems plausible that a dissociating bond between a transition metal and a ligating 2nd or 3rd row atom would elongate by <2.5 Å in its transition state, but relatively little structural data is available for such transition states. Consequently, at room temperature, a macromolecule in mechanical equilibrium with 1 nN of external tensile force may fragment up to ~15 orders of magnitude faster than the same unstretched molecule, in reasonable agreement with estimates of rate enhancements [15] (the often negative compliance of a scissile bond in the transition state makes the contribution of the $\Delta\lambda_q$ term in eq. 7 inhibitory). Correspondingly larger accelerations may be expected if fragmentation can proceed by the dissociation of metal–ligand bonds [45]. In either case, the restoring force of the scissile bond may be substantially less than the mechanical force. However, stretching a macromolecule can also inhibit its fragmentation, at least until a competing fragmentation mechanism becomes kinetically accessible.

In contrast to long flexible polymers, the chemomechanical coupling coefficient of motor proteins may exceed 10^3 for catalytic hydrolysis of ATP [9]. Undoubtedly, this hydrolysis proceeds by a complex sequence of elementary steps, and its detailed analysis requires a generalized formulation of the chemomechanical formalism for pre-equilibrium kinetics, which remains to be developed. A major challenge in designing stress-responsive polymers is to understand, and ultimately reproduce, the large-scale structures that allow significant magnification of sub-Å structural changes resulting from highly localized chemical reactions, such as dissociation of a single P–O bond by ATPase.

The chemomechanical formalism has the potential to yield usefully accurate extrapolations of the known kinetics and mechanisms of reactions in conventional non-macromolecular reactants to polymers stretched by interaction with the environment. The availability of such extrapolations should significantly facilitate the design of monomers for stress-responsive polymers, including self-healing, self-

assessing, and actuating materials and is essential for developing truly atomistic models of polymeric materials under external loads. The realization of this potential requires experimental and theoretical validation of the two key postulates of the chemomechanical formalism:

- The chemomechanical coupling coefficient, $\alpha_{\tau q}$, is sufficiently invariant to the size and chemical composition of the polymer beyond the reactive moiety to allow usefully accurate estimates of strain-induced changes in the activation barrier of the same reaction in diverse macromolecular reactants.
- The relationships between the mechanical coordinate and kinetics of localized reactions follow simple intuitive rules valid for all reactions following the same mechanism regardless of the structure or chemical composition of the reactive moiety.

Studies of reactions in stretched macromolecules presently lack the accuracy and scope needed to validate the chemomechanical formalism [32,46]. Consequently, the 1st postulate is directly amenable to computational testing only. The second assertion has been tested fairly extensively using properly designed non-macromolecular rings. The strategies and results of such tests are described below.

Figure 3 illustrates the computational validation of the 1st postulate for electrocyclic isomerization of *trans*-3,4-disubstituted cyclobutene to the corresponding butadiene derivative. We calculated the ground and transition states of this reaction in a series of cyclobutenes in which the separation of the terminal methyl groups of the side arms was constrained by a harmonic potential (spring in Fig. 3A) to

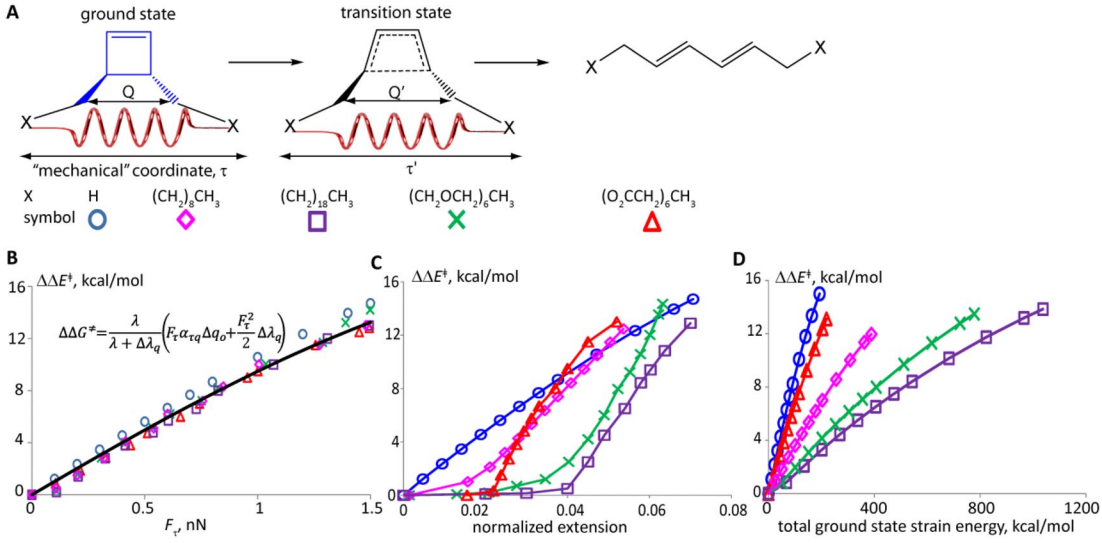

Fig. 3 Computational validation of the key postulate of the chemomechanical formalism: the chemomechanical coupling constant, $\alpha_{\tau q}$, is invariant to the size or the chemical composition of the reacting polymer beyond the minimum reactive moiety for electrocyclic isomerization of *trans*-cyclobutene (A). B: Calculated (B3LYP/6-31G* in the gas phase) change in the electronic energies of activation for five reactants of varying size and composition as a function of the mechanical force, F_τ, along the constrained $CH_3 \cdots CH_3$ distance of the reactant (points). The activation energies of the corresponding strain-free all-anti conformers were used as the reference. The black line is the prediction according to eq. 7 (reproduced in the inset) using the nonbonding distance Q (A) as the chemical coordinate; $\Delta q_o = Q'-Q$ and $\Delta\lambda_q = \lambda_{Q'}-\lambda_Q$ were calculated in strain-free *trans*-3,4-dimethylcyclobutene at B3LYP/6-311++G(3df,2pd) level of the DFT. The chemomechanical coefficient, $\alpha_{\tau q}$ of 0.91 was used. C: correlation between calculated change in the activation energy and the normalized extension of the reactant. D: correlation between the calculated change in the activation energy and the total ground-state strain energy of the reactant. In C and D, solid lines are for guiding eyes only.

mimic a reactive moiety in a stretched polymer. In this computational model, the methyl-methyl separation is the "mechanical" coordinate. By systematically increasing the equilibrium distance of the constraining potential and keeping its force constant far below that of the molecule, we calculated the electronic energy of activation of this reaction as a function of the restoring force of the "mechanical" coordinate. The relationship between the mechanical force, F_τ, and the change in the activation energy is essentially independent of the nature or the length of the side chains (Fig. 3B). These explicitly calculated barriers are predicted with excellent accuracy by eq. 7, using the $CH_3\cdots CH_3$ distance in the *minimal* reactant, *trans*-3,4-dimethylcyclobutene, as the chemical coordinate, Q. Whereas explicit calculation of the barrier in the longest *trans*-3,4-cyclobutene derivative required ~500 cpu-hours at a modest B3LYP/6-31G* level of the density functional theory, eq. 7 yields the same answer using the values of Δq_o and λ_q calculated in *trans*-3,4-dimethylcyclobutene at a much higher level of theory (B3LYP/6-311++G(3df,2pd)) and with less than 1 % of the computational resources.

Whereas the correlation between strain-induced barrier lowering and the restoring force of the $CH_3\cdots CH_3$ degree of freedom is invariant to the length or the chemical composition of the "polymer" beyond the minimal reactive moiety, this is not the case for either strain itself or ground-state strain energy (Figs. 3C,D). Consequently, restoring force is the only measure of structural distortion of a long flexible polymer that is related to changes in its reactivity.

AN INTUITIVE MODEL OF FORCE-DEPENDENT KINETICS OF NUCLEOPHILIC REACTIONS

We obtained similar results for a number of other reactions, ranging from *cis*/*trans* isomerizations of olefinic bonds to bimolecular nucleophilic displacements at 2nd and 3rd row elements, such as S, P, and Si. These calculations revealed that the relationship between the mechanical force and the strain-induced changes in the activation barrier becomes intuitive when the chemical coordinate is defined using simple rules identical for all reactions of the same mechanism. Figure 4 illustrates these rules for a major reaction class, single-step nucleophilic displacements.

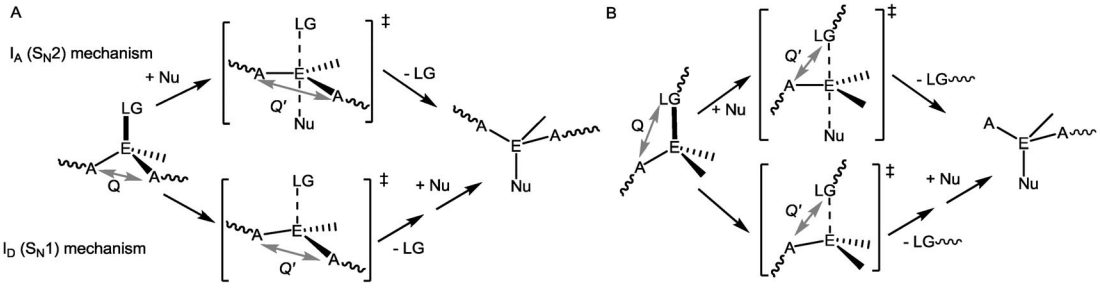

Fig. 4 Intuitive model of force-dependent kinetics of single-barrier nucleophilic displacement at a tetrahedral atom (E) for the two limiting reaction mechanisms. The scissile bond is highlighted in bold; LG is the leaving group; A are the spectator atoms bound to E; wiggly lines signify polymer chains; Nu is nucleophile. In A the scissile bond is orthogonal to the polymer backbone, and in B it is a part of the backbone. Q is the nonbonding separation of the two atoms connecting E to the rest of the polymer; $\Delta q_o = Q'–Q$.

Such reactions are typically thought to proceed by one of the two limiting mechanisms: the associative interchange, I_A (or S_N2) and the dissociative interchange, I_D (or S_N1) [47]. The I_A (S_N2) reactions proceed though a trigonal-bipyramidal transition state, whereas the rate-determining step of the I_D (S_N1) mechanism is the formation of a 3-coordinate intermediate through a trigonal pyramidal transition state (Fig. 4B). The formation of either transition state is accompanied by the elongation of both

the scissile bond and the nonbonding separation between the spectator ligands (A); as well as a contraction of bond angles between the scissile and all other bonds at the electrophilic site, E, as the spectator ligands migrate to the equatorial plane of trigonal pyramid.

For either mechanism, intuitive, qualitatively accurate predictions of the kinetics of bond dissociation as a function of the mechanical force are obtained by defining the chemical coordinate, Q, as the separation of the two atoms that connect the electrophilic center (E) to the rest of the stretched polymer. Because such a chemical coordinate is nearly collinear with the polymer contour length, the change in the latter between the ground and transition states of a nucleophilic displacement at a single backbone atom would be proportional to Δq_o (Fig. 4). Experiments and calculations confirm such proportionality, suggesting that aliphatic C and ether O atoms behave effectively as omnidirectional joints (see below).

If the scissile bond is orthogonal to the polymer backbone (Fig. 4A) and hence to the mechanical force vector, the formation of the transition state is necessarily accompanied by the elongation of both the chemical coordinate and the polymer contour length, corresponding to a positive value of the product, $\alpha_{\tau q}\Delta q_o$ (eq. 7) and consequently, the rate-accelerating contribution of the linear term in eq. 7. Alternatively, if the scissile bond is a part of the polymer backbone (Fig. 4B), i.e., the mechanical force and the scissile bond are approximately collinear, the elongation of the scissile bond and the contraction of the bond angles make the opposing contributions to Δq_o. A long E–A bond and a "tight" transition state would result in small or even negative Δq_o, whereas a short E–A bond and "loose" transition state would maximize Δq_o. A possible example of the former would be basic hydrolysis of a siloxane [47], while an example of the latter would be hydrolysis of a primary alkyl sulfonate [39].

The above argument suggests an overstretched polymer containing an electrophilic site is intrinsically more reactive toward release of a side chain connected to that site than a strain-free polymer, whereas its nucleophilically assisted backbone fragmentation may be accelerated, decelerated, or unaffected by overstretching the polymer.

Because changes in all internal coordinates of a minimal reactant along the reaction path are correlated, in theory, any such coordinate that is sufficiently different between the corresponding strain-free minimal ground and transition states can serve as the chemical coordinate in eqs. 6–7. However, the chemomechanical coupling constants of most such coordinates cannot be predicted from simple models. For example, the obligatory elongation of the scissile bond in the transition state may be accompanied by a contraction of the contour length and end-to-end separation of the reacting polymer because of the changes in other *local* degrees of freedom (such as contraction of bond angles to the scissile bond) during the reaction. Because such changes are not captured by the scissile bond elongation but affect the end-to-end separation, the relationship between the chemical and mechanical coordinate becomes more complex and unique for each reaction even if they follow the same mechanism.

The scissile bond may be a convenient chemical coordinate for comparisons of force-dependent bond-dissociation kinetics proceeding by different reaction mechanisms or for reactive centers whose connection to the rest of the polymer cannot be approximated as omnidirectional joints. An example would be flexurally rigid molecular fragments, such as alkynes, which could act as levers to magnify the changes in a local degree of freedom (Fig. 5).

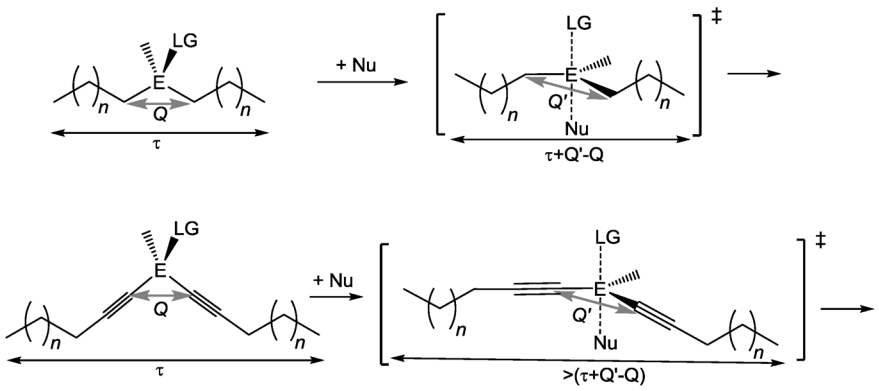

Fig. 5 Chemomechanical coupling between the chemical coordinate, Q, and the mechanical coordinate, τ, approaches ~1 only in the limit of the electrophilic atom E connected to the rest of the polymeric reactant by omnidirectional joints. Methylene, CH_2, and ether, O, linkers behave as effectively omnidirectional joints [36,38–40]. In contrast, if rigid fragments are bound between the reactive site and the rest of the macromolecule, they can act as levers to magnify the changes in the chemical coordinate between the ground and transition states, resulting in larger changes in the mechanical coordinate relative to the chemical coordinate.

EXPERIMENTAL VALIDATION OF THE CHEMOMECHANICAL MODEL

To validate these conclusions experimentally, we have developed [36–42] an alternative to conventional force spectroscopy. In the latter, a reactive moiety is incorporated in a long flexible polymer, which is controllably stretched using micromanipulation techniques [47] or with far less control by sonicating its dilute solution [15]. Our approach relies on a series of increasingly strained macrocycles of the *E* isomer of stiff stilbene (Fig. 6) whose C6,C6' axis is constrained by a molecular strap (X, Y) containing the reactive moiety (blue sphere). The strained *E* macrocycle is readily available by photoisomerization of the strain-free *Z* analog at ~400 nm. This *Z* macrocycle serves both as a convenient precursor to the strained *E* isomer and as a strain-free reference reactant electronically very similar to the strained *E* analog. Varying the length and conformational flexibility of the inert parts of the strap provides a simple way to vary the strain of the reactive moiety in small increments (<50 pN) over a substantial range (>600 pN).

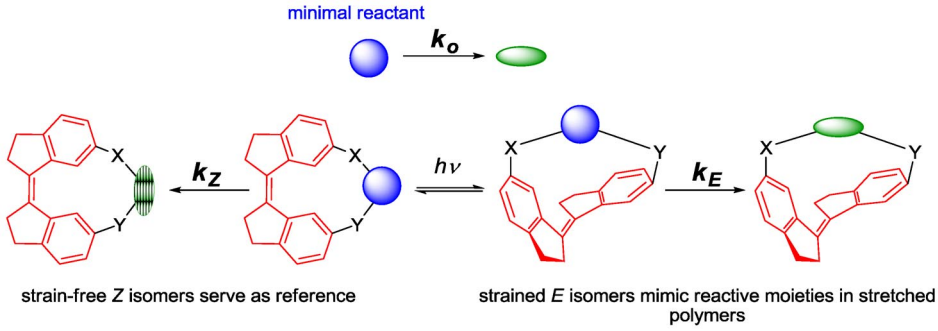

Fig. 6 General scheme of a strategy to measure force-dependent kinetics of a localized reaction (blue sphere converting to green oval) using strained macrocycles of *E* stiff stilbene (red) without the complications of manipulating polymers.

The chemical inertness of stiff stilbene makes it compatible with diverse chemical reactions, allowing the effect of strain on reaction kinetics to be studied broadly within the same general molecular architecture. The high aspect ratio of stiff stilbene (its strain-free *E* isomer is planar and the *Z* isomer is nearly planar) effectively limits the steric interaction between the reactive moiety and stiff stilbene, mimicking the highly anisotropic tensile strains of reactive moieties in stretched polymers. Finally, the large free energy of activation of thermal $E \rightleftarrows Z$ isomerization of free stiff stilbene (~43 kcal/mol) minimizes its thermal relaxation in even highly strained *E* macrocycles. Hence, stiff stilbene is the molecular-scale functional analog of microscopic force probes used in single-molecule force spectroscopy (Fig. 7), and we call it a molecular force probe.

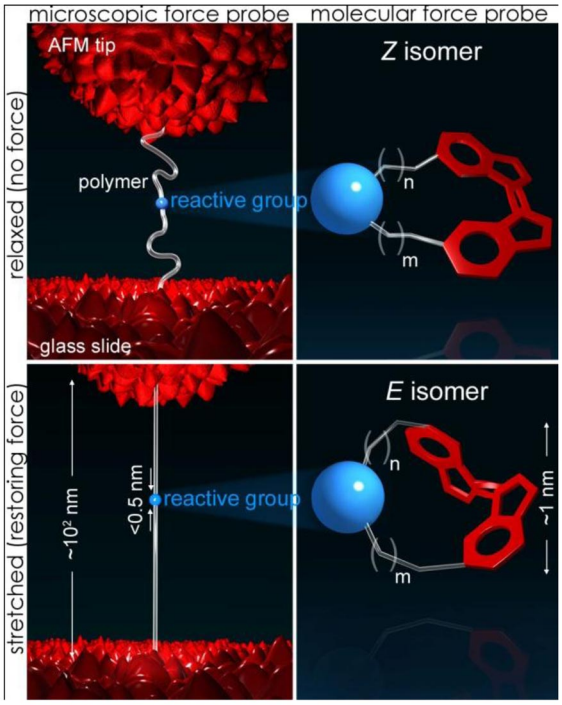

Fig. 7 Left: Measurements of force-dependent kinetics of localized reactions by conventional single-molecular force spectroscopy require the incorporation of the reactive moiety (blue sphere) into a long flexible polymer, attaching this polymer to a pair of microscopic force probes (here, the tip of an atomic force microscope and a glass slide) and stretching it by separating the probes. The size of the reactive moiety is typically less than the surface roughness of the probes or the magnitude of their thermal fluctuations, which significantly limits the accuracy of the measurements and the scope of reactions amenable to such studies. Right: a reactive moiety incorporated in a 5–10 atom-long inert strap constraining the *E* isomer of stiff stilbene (red) experiences approximately the same pattern of strain as in stretched polymer. The modest size of the reactant facilitates the design, implementation, and molecular interpretation of the measured rates. The strain of the reactive moiety is controlled by the length and conformational flexibility of the strap so that a series of ~10–12 macrocycles of 15–20 endocyclic atoms can reproduce the range of the restoring forces accessible in a typical single-molecule force experiment. The strained *E* isomers are obtained by photoisomerization of strain-free *Z* analogs, which are synthesized using conventional chemistry. Adapted from ref. [44] with permission.

Stiff stilbene allows the kinetics of diverse chemical reactions to be measured as a function of the restoring force of any molecular degree of freedom of the reactive moiety following this experimental design:

- A series of strain-free *Z* macrocycles containing between 15 and 22 endocyclic atoms are synthesized using standard methods, such as stereoselective intramolecular McMurry coupling of a pair of indanones linked by a strap containing the reactive moiety [40].
- Irradiation of dilute solutions of *Z* macrocycles at ~400 nm generates photostationary mixtures containing 3–70 % of the strained *E* isomer. The smaller (and hence the more strained) the *E* macrocycle is, the lower its fraction in the photostationary state due to the lower quantum yield of $Z \rightarrow E$ photoisomerization. This strain-dependent quantum yield is the primary factor limiting the maximum strain (and restoring force) accessible with this method.
- Although individual isomers are readily available by chromatographic separation of the photostationary mixture, such separation is rarely necessary or even desired. Instead, the kinetics of the substrate reaction is measured in both isomers simultaneously in competition experiments using the photostationary mixture. When the difference in the relative reactivities of the two isomers is too large that only one isomer reacts under given experimental conditions, the more inert analog serves as a convenient internal standard. The modest size of the reactants greatly simplifies, and increases the accuracy of, measurements of the activation parameters using the whole range of experimental techniques of chemical kinetics. We typically monitor reaction progress by UV–vis spectroscopy or high-performance liquid chromatography (HPLC), because of the ease of automation and the small amount of material required.

The interpretation of the experimental results within the force formalism relies on quantum chemical calculations of the structures of the ground and transition states and the corresponding restoring forces, which cannot be measured directly. A good agreement between the calculated and measured activation parameters (i.e., free energies and enthalpies of activation, $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$, respectively) supports the validity of such calculations.

The best evidence that the measured differences in the free energies of activation of a substrate reaction in the two isomers of individual macrocycles, $\Delta\Delta G^{\ddagger}$, reflect primarily the externally imposed strain of the reactive moiety (i.e., the macrocycles reproduce the mechanism of the kinetic perturbation in overstretched polymers) comes from the observation that eq. 8 is valid for all macrocycles measured so far. In eq. 8, $<\tau_Z>$, $<\tau_E>$ and $<\tau'_Z>$, $<\tau'_E>$ are the ensemble-average strains of an internal coordinate of stiff stilbene in the ground and transition states, respectively, of the *Z* and *E* isomers of the same macrocycle (Fig. 8); $<\lambda_Z>$ and $<\lambda_E>$ are the compliances of this coordinate in the macrocycle; and λ_Z and λ_E are the compliances of the same coordinate in the *Z* and *E* isomers of isolated, strain-free stiff stilbene. Internal coordinates of stiff stilbene for which eq. 8 is universally valid are the C_{Ar}–C=C–C_{Ar} dihedral and the C6,C6' separation (black arrows, Fig. 8), among others.

$$\Delta G_Z^{\ddagger} - \Delta G_E^{\ddagger} = \Delta\Delta G = \frac{\langle \lambda_Z \rangle}{2\lambda_Z^2}\left(\langle \tau'_Z \rangle^2 - \langle \tau_Z \rangle^2 \right) - \frac{\langle \lambda_E \rangle}{2\lambda_E^2}\left(\langle \tau'_E \rangle^2 - \langle \tau_E \rangle^2 \right) \quad (8)$$

The universal validity of eq. 8 for reactions as mechanistically diverse as electrocyclic isomerization and nucleophilic displacements suggest that factors known to control reactivity of small strained molecules such as differential solvation, steric hindrance, or substituent effects [1,43,48] cannot account for the observed $\Delta\Delta G^{\ddagger}$ values either within a single macrocyclic pair or across the series. In other words, several molecular coordinates of stiff stilbene mimic the mechanical coordinate of an overstretched polymer in its effect on reaction kinetics.

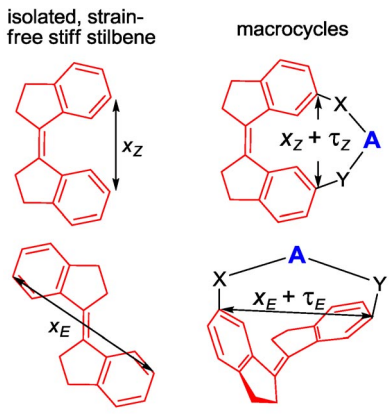

Fig. 8 An example of an internal coordinate of stiff stilbene (C6,C6') for which eq. 8 is valid regardless of the nature of X, Y, and A and the definition of strain of this coordinate in a single conformer, τ_E or τ_Z.

Because accurate structures of both ground and transition states of diverse reactions in stiff stilbene macrocycles are readily available, the restoring force of any molecular degree of freedom at any stationary point can be calculated directly. Consequently, analysis of measured $\Delta\Delta G^{\ddagger}$ is most informative as a function of the restoring force of the chemical coordinate, Q. The corresponding correlations, $\Delta\Delta G^{\ddagger}$ vs. F_q, can be extrapolated to any overstretched polymer whose chemomechanical coupling constant is known from quantum-chemical calculations or potentially experiment. In this case, eq. 7 reduces to an approximate eq. 9, where $\langle F_{qZ}\rangle$ and $\langle F_{qE}\rangle$ are Boltzmann-average restoring forces of coordinate Q in the ground-state conformers of the Z and E isomers of a macrocycle, Δq_o and $\Delta\lambda_q$ are the difference in coordinate Q and in its compliance, respectively, between the transition and the ground states of the minimal strain-free reactant.

$$\Delta\Delta G \approx \left(\left\langle F_{qZ}\right\rangle - \left\langle F_{qE}\right\rangle\right)\Delta q_o + \frac{\Delta\lambda_q}{2}\left(\left\langle F_{qZ}\right\rangle^2 - \left\langle F_{qE}\right\rangle^2\right) \tag{9}$$

Several algorithms exist to estimate the restoring force of the chemical coordinate, depending on its intrinsic compliance and the thermal accessibility of multiple conformers of the minimal reactant with different values of the chemical coordinate. For example, the restoring force of a very stiff (e.g., a covalent bond) or a very compliant (e.g., associated with multiple distinct conformers) chemical coordinate is calculated most accurately by eq. 10, where τ is the strain of one of the internal coordinates of stiff stilbene that approximates a "mechanical" coordinate (e.g., C6,C6' axis or the dihedral angle), and $\lambda_{\tau q}$ is the off-diagonal element of the molecular compliance matrix of the macrocycle corresponding to harmonic coupling between coordinates τ and q (see next paragraph). In contrast, strains and restoring forces of modestly stiff coordinates, such as the separation of the CH_3 groups of *trans*-3,4-dimethylcyclobutene [36,37], of the CH_2 groups of EtSSEt [38], or of the $CH_3\cdots O$ pair of ethyl mesylate, $CH_3CH_2OSO_2CH_3$ [39], are easily calculated directly as the difference of their values in the minimal strain-free reactant and the corresponding macrocycle and as the ratio of this strain and the compliance of coordinate Q in strain-free minimal reactant, respectively.

$$F_q = \frac{\lambda_{\tau q}}{\lambda_q \lambda_\tau}\tau \tag{10}$$

It is important to emphasize the difference between $\lambda_{\tau q}$ and $\alpha_{\tau q}$. The former establishes the new minimum-energy value of molecular coordinate q when some other internal degree of freedom of the

molecule (in our case, τ) is distorted either by thermal fluctuations or by an external constraint. For example, if harmonic vibrations of *trans*-3,4-dimethylcyclobutene result in elongation of the methyl–methyl distance by τ, the methyne–methyne bond elongates by $\tau\lambda_{\tau q}/\lambda_{\tau}$~0.003$\tau$. In contrast, $\alpha_{\tau q}$ relates changes in τ and q only along the minimum-energy reaction path. For example, the elongation of the methyl–methyl and scissile (HC–CH) bonds between the ground and transition states of strain-free *trans*-3,4-dimethylcyclobutene is 0.76 and 0.41, giving $\alpha_{\tau q}$ ~ 1.9.

Figure 9 shows representative examples of the agreement between the measured (points) and calculated (lines) values of differences of rate constants of three reactions using "intuitive" chemical coordinates (shown by black arrows). In these three reactions, the restoring force of the chemical coordinate is approximately equal to the restoring force of the mechanical coordinate if these minimal reactants are incorporated in the polymer through their methyl groups. Consequently, measured $\Delta\Delta G^{\ddagger}$ vs. F_q correlation is likely to be equivalent for these reactions in overstretched polymers.

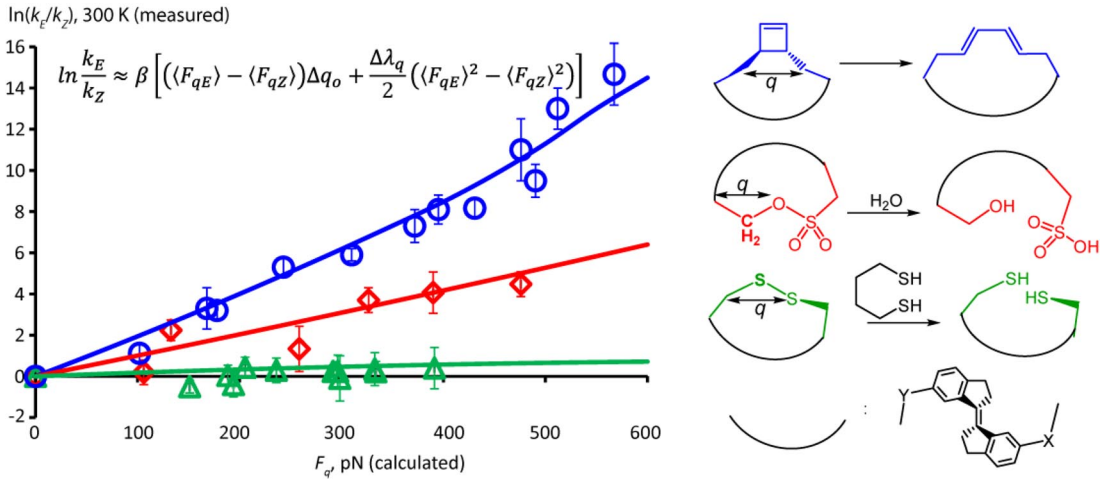

Fig. 9 Measured (points) and calculated (lines) rate-force correlations of three reactions (right). The rate constants are plotted against the restoring force of the chemical coordinate, q (shown on structures by arrows). Data from refs. [36–40].

For these intuitive chemical coordinates, the chemomechanical coupling coefficients are ~1. Other *strained* internal coordinates of the reactive moieties could have been used as well but they would have different chemomechanical coupling coefficients and would not be as universal. For example, $\alpha_{\tau q}$ ~ 2 if q is the scissile C–C bond in cyclobutene isomerization and $\alpha_{\tau q}$ ~ 0.52 if q is the scissile or C–O bond in hydrolysis of the primary sulfonates. In contrast, the elongation of the scissile S–S bond during thiol/disulfide exchange does not couple to other internuclear distances of the disulfide, corresponding to $\alpha_{\tau q}$ ~ 0.

CONCLUSIONS

The reactivity of small strained molecules has been studied for over a century now [1,43,49,50]. Because of the diverse molecular structures of such molecules, their strain is quantified not by geometrical descriptors but by so-called ground-state strain energy. Although the definition of the latter is conceptually ambiguous, it allows a semi-quantitative relationship between molecular strain and reactivity using the formalism of LFERs. Such relationships are adequate to guide the design of new reactants whose molecular strain is used to control (usually accelerate) desired reactions [49].

A qualitative connection between the often enhanced reactivity of small strained molecules and of stretched polymers was recognized long ago [1]. A quantitative relationship, however, proved to be elusive. Unlike small strained molecules, stretched polymers remain strained only as long as they interact with their surroundings, such as rapidly flowing solvent or a retracting force probe. While their strain energies could be defined, they do not correlate with changes in reaction rates [51]. The fundamental reason is that such strain energies neglect changes in strain of the surroundings that is also a part of the ground and transition states of the reaction.

From a chemist's view, the strain-energy/LFER construct is a special case of the chemomechanical formalism for spatially confined strain. A conceptual relationship between these two seemingly disparate ideas is often obscured by the lack of molecular interpretation of the "mechanical" force used in chemomechanical models when they are formulated as extensions of continuum mechanics [9]. To adapt them to problems of interest to a chemist, it is important to define clearly mechanical force, as a Newtonian descriptor of mesoscale dynamics, and restoring force, which we use as a quantifier of strain of any molecular degree of freedom. Molecular restoring force is intrinsically related to the molecular compliance matrix [52], as its invariance to the set of internal coordinates in which it is defined or the completeness of such coordinate systems allows (1) strain of one part of the molecule to be related to that of another part and (2) strains of the same moiety in different environments to be compared without conceptual ambiguity.

This brief review described a model that relates a macroscopic property (mechanical force) to the molecular one (reaction rate) using the concept of chemomechanical coupling coefficients. Compare the chemomechanical model described here to the established kinetic theories: in the transition-state theory the bulk property is temperature and the coupling parameter is activation free energy; in the Kramers theory, the bulk property is viscosity and in the Marcus theory of outer-sphere electron transfer, the bulk property (dielectric constant) couples to kinetics through ion charge [2].

Available results of quantum-chemical calculations suggest that the chemomechanical coupling constant is determined primarily by the structure of the reactive moiety and the reaction mechanism and is largely insensitive to the size or the chemical composition of the macromolecular reactant beyond the reactive moiety. Consequently, the knowledge of the rate constant of the minimal strain-free reactant as a function of its restoring force should suffice to predict accurately the rate of its reactions in an overstretched polymer. This conclusion remains to be validated experimentally.

A relationship between global mechanical force and local restoring force is of limited practical value in the absence of methods to measure the kinetics of localized reactions as a function of their restoring forces. While considerable world-wide effort has been devoted to quantum-chemical calculations of such relationships [33–35], we have developed an experimental method to measure them [36–42].

Having measured the force-dependent kinetics of representative reactions of the major mechanistic classes (nucleophilic ligand displacement, electrocyclic fragmentation, and isomerization of the C=C bond), we determined that force-dependent kinetics of all reactions of the same mechanism correlates well with the restoring force of the same type of internal degree of freedom. For example, in all ligand displacement reactions we studied, this degree of freedom is the internuclear distance between a pair of atoms connecting the electrophilic atom to the rest of the strained (macro)molecule. This observation can be understood within a simple geometrical model of nucleophilic displacement reactions (Fig. 4).

Our work shows that the concept of restoring force is useful in correlating molecular strain and reactivity of non-macromolecular reactants. Unlike classical LFER-based rate–strain relationships, rate–force correlations are independent of the total size of the reactant and potentially allow accurate predictions of rates of localized reactions in stretched polymers or rationalization of such rates in molecular terms. I speculate that the most immediate impact of integrating the chemomechanical formalism in molecular design and synthesis will manifest in accelerating the following:

- the development of a quantitative molecular understanding of the operation of photoactuating polymers at the single-chain level and ultimately defining (a) the thermodynamic, kinetic, and structural properties of an ideal photoactuating monomer and (b) the fundamental limits of energy conversion efficiency, power output, and work per monomer of macromolecular photoactuation;
- the molecular understanding of the behavior of polymers in flows, starting with simple elongational flows of dilute polymer solutions and ultimately progressing toward concentrated polymer solutions and solids by enabling the design and calibration of mechanochromes—bistable chromophores (or fluorophores) with different absorption (or emission) profiles of the two isomers and simple force-dependent kinetics of isomerization; and
- the design of small and oligomeric molecules for photothermal energy storage and conversion by exploiting the ability to quantify the directional nature of molecular strain, which should allow one to design strained reactants to maximize both the standard energy of the reaction and its activation energy instead of the inverse relationship postulated by the LFERs.

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