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Experimentally realized mechanochemistry distinct from force-accelerated scission of loaded bonds

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Abstract: Stretching polymer chains accelerates dissociation of a variety of internal covalent bonds, to an extent that correlates well with the force experienced by the scissile bond. Recent theory has also predicted scenarios in which applied force accelerates dissociation of unloaded bonds and kinetically strengthens strained bonds. We report here unambiguous experimental validation of this hypothesis: detailed kinetic measurements demonstrate that stretching phosphotriesters accelerates dissociation of the unloaded P-O bond orthogonal to the pulling axis whereas stretching organosiloxanes inhibits dissociation of the aligned loaded Si-O bonds. Qualitatively, the outcome is determined by phosphoester elongation but siloxane contraction along the pulling axis in the respective rate-determining transition states. Quantitatively, the results agree with a simple mechanochemical kinetics model.

Main Text: The chemical responses of polymers to mechanical loads play an important role in polymer applications and the prospective design of new stress-responsive and energy transducing materials.⁽¹⁻⁴⁾ Thus far, only one type of covalent mechanochemical response has been demonstrated experimentally: accelerated dissociation of loaded (i.e., strained by applied force) bonds. Density functional theory (DFT) calculations indicate that the activation free energies, ΔG^\ddagger , of mechanistically diverse organic reactions reported to date ⁽⁵⁻¹³⁾ decrease approximately proportionally to the restoring force of the scissile bond, $\langle f_s \rangle$, with the slope averaged over 0-1.5 nN ranging from 0.18 Å to 1.1 Å (average 0.7 ± 0.2 Å, corresponding to (6 ± 3) -fold acceleration per 0.1 nN of $\langle f_s \rangle$ at 300K: Fig. S1, Table S1). Yet theory⁽¹⁴⁻¹⁶⁾ and computations⁽¹⁷⁻²¹⁾ suggest that stretching force can inhibit rather than accelerate dissociation of strained covalent bonds and accelerate dissociation of unloaded over loaded bonds. Experimental evidence for such unconventional mechanochemistry has been elusive. Contradictory, often irreproducible reports from the 1970s and 80s of load-inhibited reactions in bulk polymers are now considered erroneous.^(22, 23) A more recent claim⁽²⁴⁾ contradicts quantum-chemical computations (Fig. S2) and awaits validation. Dissociation of certain biological adducts is weakly inhibited by force < 0.1 nN⁽²⁵⁾ but the small magnitude and the complex underlying molecular mechanisms limit the impact of such examples on polymer mechanochemistry.

The lack of experimental validation of such unconventional mechanochemistry bears out the considerable challenges of designing synthetically accessible molecules that can be strained along the necessary molecular axis, induced to react at suitable rates, and monitored to quantify these rates reliably. Here we show that force accelerates dissociation of the unloaded P-O bond

of phosphotriesters (Fig. 1, reactions 1a-c) and accelerates or inhibits dissociation of loaded Si-O bonds of organosiloxanes, depending on force magnitude and solution acidity (reactions 2a-b).

Figure 1. Reactions shown here to have unconventional mechanochemistry. The grey double-headed arrows specify the internal molecular coordinate, O...O, whose restoring force is useful for rationalization and prediction of the mechanochemical kinetics; *p*-AcOC₆H₄O⁻ is *p*-acetylphenoxide.

We first demonstrate that mechanochemistry of reactions 1 and 2 deviates from the conventional pattern of accelerated dissociation of a loaded bond by quantum-chemical calculations at B3LYP/6-311+G(d) with SMD as the reaction-solvent model. Although the performance of B3LYP in calculating reaction barriers is mixed, in our benchmarking of 9 functionals B3LYP reproduced all available experimental activation free energies, ΔG^\ddagger , for reactions 1 and 2 with the smallest mean error (0.7 kcal/mol, Tables S3-4). Because solvation affects nucleophilic-displacement mechanisms and kinetics, we calculated ΔG^\ddagger for multiple microsolvation patterns (Figs. S6-8 and Table S2). We obtained the best agreement between experimental and calculated ΔG^\ddagger with singly-microsolvated nucleophiles ([HO...H...OH]⁻ and [H₃CO...H...OC₃H]⁻) for reactions 1a-c and 2a, and with two molecules of methanol as an H⁺-transfer bridge from the nucleophile (CH₃OH) to the leaving alkoxide for reaction 2b. Our calculations reproduced the accepted mechanisms of reactions 1a-c (single-barrier associative-interchange, Fig. S3) and 2a (two-barrier associative, Fig. S4)(26). Methanolysis of siloxanes (reaction 2b), whose mechanism was not reported, was calculated to proceed by two competing associative paths, with the nucleophile entering adjacent to the leaving group(26), Fig. S5. To establish that the computed results reflect mechanochemistry of phosphate- and siloxane-containing macromolecules, we calculated complete conformational ensembles of 3 increasingly large homologues of each molecule (*n*=0-2, fig. 1) as recommended previously(27).

To understand how force affects the reaction kinetics and mechanisms we repeated these calculations with stretching force of up to 2 nN applied between the terminal C atoms of the alkoxy substituents, using the method validated theoretically(16) and experimentally(13, 28) and reviewed(18, 29). These calculations indicate that while the mechanism of reactions 1a-c is insensitive to force (Fig. S3), force causes mechanistic cross-over in reactions 2a-b (Fig. S9) by destabilizing the strain-free minimum-energy paths and stabilizing the higher-energy alternatives. As a result, these alternative mechanisms become dominant at 1.5 nN (reaction 2a) or 0.5 nN (reaction 2b), yielding complex non-monotonic dependence of the activation energies on force, ΔG_f^\ddagger (Figs. 2, S10). For each reaction, the 2 largest homologues manifested comparable ΔG_f^\ddagger (Fig. S10), suggesting that they are representative of arbitrarily large analogs, including polymers.(27)

Figure 2 illustrates how ΔG_f^\ddagger correlates with the restoring forces of the scissile bond, $\langle f_s \rangle$, and of the O...O non-bonding distance (grey arrows in Fig. 1), $\langle f_{O...O} \rangle$. These restoring forces quantify a fraction of molecular strain (imposed either externally by stretching a macrochain, or internally in strained macrocycles described below) distributed over different parts of the molecule.(12, 15, 18, 27, 29, 30) Of several proposed(31, 32) force-based schemes to quantify strain and its distribution we used one based on molecular compliance(16, 33) because it is theoretically sound, depends only on atoms defining the coordinate, which allows comparisons across structurally distinct reactants, and unlike the alternatives,(34) is experimentally validated.(28)

Figure 2. Force-dependent changes in the activation free energies, $\Delta G_f^\ddagger - \Delta G_o^\ddagger$. The energy difference is plotted as a function of the restoring force of the (A) scissile P-O or Si-O bond, $\langle f_s \rangle$ or (B) of the O...O coordinate (defined by the arrows in figs. 1 and 3), $\langle f_{O...O} \rangle$. ΔG_o^\ddagger is the strain-free activation free energy. Circles are the experimental data,

with $\Delta G_f^\ddagger - \Delta G_o^\ddagger = \Delta G_E^\ddagger - \Delta G_Z^\ddagger$ for each E/Z pair of the macrocycles (see below). The error bars define the 68% confidence intervals calculated according to eqs. S22-S25. See Data S1 and Tables S5-6, S14 for the plotted data; $\langle \rangle$ signifies ensemble-averaging. The lines are averages of the 2 largest homologues.

The $\Delta G_f^\ddagger - \Delta G_o^\ddagger$ vs. $\langle f_s \rangle$ correlation (Fig. 2A) illustrates the extent to which the mechanochemical kinetics of reactions 1a-c and 2a-b deviates from the previously-established pattern (dashed line): whereas the previously-reported reactions are accelerated (6 ± 3) -fold per 0.1 nN of $\langle f_s \rangle$ (Fig. S1), P-O bond scission in reactions 1a-c is accelerated $>10^4$ -fold. Conversely, scission of the loaded Si-O bond in reaction 2a is inhibited ~ 2 fold per 0.1 nN. The non-monotonic ΔG_f^\ddagger of reaction 2b results from a competition between a reaction mechanism that is destabilized ~ 150 -fold per 0.1 nN and the alternative that is stabilized by very typical 4-fold (fig. S8). Our calculations suggest that such competition is common for Si-O bond dissociations in neutral or acidic medium (Figs. S14-S16), explaining the reported(35) accelerated failure of siloxane bridges at ≥ 0.8 nN in acid. Although any force accelerates nucleophile-free Si-O bond heterolysis, its barrier is too high to be relevant (Fig. S17).

The $\Delta G_f^\ddagger - \Delta G_o^\ddagger$ vs. $\langle f_{O\dots O} \rangle$ correlation (Fig. 2B) allows the computed force-dependent kinetics to be validated experimentally using series of increasingly strained macrocyclic phosphoesters and siloxanes (Fig. 3), in which *E*-1,1'-biindanylidene (*E* stiff stilbene) exerts a well-defined stretching force on the reactive moiety with magnitude controlled by the macrocyclic size. We previously demonstrated(28) that ΔG_f^\ddagger derived from such macrocycles predict quantitatively mechanochemical kinetics in polymers in single-molecule force spectroscopy (SMFS). We used macrocycles because reactions 1a-c and 2a-b cannot be studied by SMFS, which is limited to reactions that increase the macrochain contour length by several nm or break it and are either accelerated or only very weakly-inhibited by force.

We synthesized strain-free *Z* isomers of macrocycles **1** through **19** in 4 to 6 steps and 5 to 17% overall yields (Fig. S18). Irradiating solutions of *Z* macrocycles yielded strained *E* analogs in up to 80% yield (Fig. S19 and Tables S7-8). All compounds were fully characterized by NMR, HRMS and UV-vis (Tables S7-8,10). We measured the kinetics of reactions 1a-c in H₂O:CH₃OH (2:1 molar ratio) by monitoring the absorbance of generated *p*-nitrophenolate (Table S11, Figs. S20-22). Reactions 2a-b were measured in CH₃OH and monitored by HPLC (Table S12-13, Fig. S23). We performed all kinetic measurements in the dark to avoid photoisomerizing stiff stilbene and under pseudo-first order conditions in the nucleophile. The reactions were first-order in the macrocycle and in the nucleophile, consistent with the literature (the order of reaction 2b in nucleophile could not be determined because it was the solvent). The reaction products were confirmed by NMR, HPLC and HRMS (Tables S15-S16).

Figure 3. Macrocycles used to measure mechanochemical kinetics of reactions 1-2. The scissile bonds are in bold. Macrocycles **2**, **3**, **6**, **7** exist as diastereomers due to point chirality of P and axial chirality of stiff stilbene (Tables S7-8) and the kinetics was measured on diastereomeric mixtures. In **Z15** and **E19** the two non-equivalent Si-O bonds dissociated in parallel (Fig. S23 and Tables S10, 12-13). The grey arrows define the O...O distance whose restoring force is used to compare the computed and measured mechanochemical kinetics (fig. 2B).

All *E* macrocyclic phosphates (reactions 1a-c) reacted faster than their *Z* analogs, with competition experiments yielding rate constant ratios, k_E/k_Z , of 2 to 12, 4 to 210 and 4 to 50 for OH⁻, PhO⁻ and *p*-acetylphenoxide, respectively, at 25 °C (Tables S11-14). Methanolysis of *Z* siloxane macrocycles proceeded in two steps (Fig. 3B, Tables S12-13), with statistical ratios of the sequential rate constants in symmetrical *Z* macrocycles, $k_1^Z/k_2^Z \sim 2$. Conversely, we observed no intermediates in methanolysis of **E8** to **E12** and **E15** to **E16**, consistent with slower dissociation of the first (strained) Si-O bond--which breaks the macrocycle to relax the distorted *E* stiff stilbene and the siloxane moiety (Fig. 3B)-- than the second (strain-free) Si-O bond, i.e.,

$k_2^E > k_1^E$. The conclusion that *E* stiff stilbene inhibits the first Si-O bond dissociation primarily by straining it is also consistent with the identical dissociation rates of the 2nd (strain-free) Si-O bond in *E* and *Z* siloxanes ($k_2^E/k_2^Z \sim 0.9$). Conversely, the ratios of the rate constants for methanolysis of strained (*E*) and strain-free (*Z*) Si-O bonds (k_1^E/k_1^Z) were 0.01 to 0.1 in reaction 2a and 0.03 to 1.9 in reaction 2b. Rate constants measured at 3 or 5 temperatures over 25 to 60 °C (6 to 25 °C for *E1*) yielded activation entropies between -17 and -53 eu (average -28 ± 7 eu; Tables S5-7), consistent with the calculated associative mechanisms.(26)

To enable comparisons between the measured kinetics of reactions 1a-c and 2a-b in macrocycles **1** through **19** and the computational models of stretched polymers (Fig. 2B), we quantified excess molecular strain responsible for the difference in the reactivity of the *E* and *Z* isomers of each macrocycle ($\Delta G_{E}^{\ddagger} - \Delta G_{Z}^{\ddagger}$, Table S14) as the ensemble-averaged restoring force of the O...O distance (arrows in Fig. 3), $\langle f_{O...O} \rangle$ (eq. S1). We chose the O...O distance because it is one of the two coordinates common for all macrocycles and because the negligible restoring force of the other common coordinate (scissile bond) in *E1* through *E7* precludes its use for comparisons among the macrocycles. We suggest that $\langle f_{O...O} \rangle$ correctly reflect the stereoelectronic factors responsible for the variation of the kinetics of reactions 1a-c and 2a-b across the macrocycles because $\langle f_{O...O} \rangle$ were derived from the same calculations that accurately reproduced measured ΔG^{\ddagger} (Table S8: mean error of 1.8 kcal/mol).

Qualitatively, mechanochemistry of reactions 1a-c and 2a-b is consistent with the conventional understanding of how force affects reaction rates: transition states that are longer along the pulling axis than the corresponding reactants are stabilized by stretching force and vice versa(36). While in the transition states of reactions 1a-c both the scissile P-O bond and the

molecule elongate along the pulling axis (Fig. 4A), in reactions 2a-b the molecule contracts in the rate-determining transition states, despite the simultaneous elongation of the scissile Si-O bond. The structural origin of this difference is the preference of the leaving group in nucleophilic displacements for an axial position of the trigonal-bipyramidal transition state. In phosphates, force acts across the termini of the spectator alkoxy moieties. The movement of these moieties in the equatorial plane of the trigonal-bipyramidal transition state requires the O-P-O angle to increase, and the molecule elongates monotonically as it progresses along the reaction path (dashed arrows, Fig. 4A) irrespectively of what happens to the scissile bond length. In contrast, the departure of an equivalent alkoxide group in siloxanes is energetically preferable from an axial position, so that the formation of the rate-determining transition state requires a contraction of the analogous O-Si-O angle, which shortens the terminal C-C separation to a greater extent that the elongating scissile Si-O bond increases it. As a result, a siloxane first contracts along the pulling axis, which destabilizes the molecule when tensile force is acting on it, before elongating and eventually breaking.

Figure 4. Structural rationalization and model predictions of the results. (A) An overlay of the strain-free minimum-energy conformers of the reactant (magenta) and the rate-determining transition state (blue) for reactions 1a and 2a, omitting H atoms and phenyls. The dashed arrows define the pulling axes. (B). Comparison of $\Delta G_f^\ddagger - \Delta G_o^\ddagger$ from DFT calculations (black) and extrapolations of strain-free kinetics using three internuclear distances: scissile bond (green), O-O (red, solid arrows in (A)) and ${}_{\text{Me}}\text{C}\cdots\text{C}_{\text{Me}}$ (magenta, dashed arrows in (A)). Blue dotted lines are extrapolated $G_f^\ddagger - G_o^\ddagger$ for the two competing paths of reaction 2b using the O-O distance and the resulting difference in the reaction activation energy $\Delta G_f^\ddagger - \Delta G_o^\ddagger$ is red. For the other coordinates, only $\Delta G_f^\ddagger - \Delta G_o^\ddagger$ is shown.

A major challenge in polymer mechanochemistry is to develop practical means of estimating kinetic stabilities of monomers under mechanical load. The simplest approach is to approximate $\Delta G_f^\ddagger - \Delta G_o^\ddagger$ by the product of applied force, f , and the difference of a single internuclear distance

between the strain-free rate-determining transition and reactant states, Δq° . The accuracy of such estimates depends strongly on the choice of this internuclear distance as illustrated in fig. 4b, where quantum-chemically calculated $\Delta G_f^\ddagger - \Delta G_o^\ddagger$ of reactions 2a-b (black) are compared with the estimates based on the elongation/contraction of two coordinates routinely used to rationalize mechanochemical reactivity (defined by the C atoms of the terminal methyl groups, $\langle \Delta q_{C...C}^\circ \rangle$ and by the scissile bond, $\langle \Delta q_s^\circ \rangle$), and of the O...O separation, $\langle \Delta q_{O...O}^\circ \rangle$ (all illustrated in Fig. 4A).

The scissile bond performs poorly (even predicting acceleration instead of inhibition of reaction 2a, green line) because it is too local, i.e., it fails to account for structural changes elsewhere in the molecule required for bond breaking.(37, 38) The strain-free separation of M_eC atoms across which force is applied vastly overestimates the force effect (either inhibition or acceleration) because $\langle \Delta q_{C...C} \rangle$ varies so much with force that its strain-free value poorly reflects structural differences of force-coupled states responsible for changes in reaction kinetics (Fig. S11).

Contrary to previous speculations(11, 14-19, 24, 27, 29, 39, 40), assuming that the coordinate is harmonically force-dependent only worsens the extrapolations (Fig. S12). The O...O distance outperforms the conventional coordinates, as it does in other nucleophilic displacements studied(6, 11, 12, 17, 37), reproducing the exact results within a factor of 2 (red line). It is also the only coordinate that correctly predicts force-dependent mechanistic crossover in reaction 2b and the resulting non-monotonic $\Delta G_f^\ddagger - \Delta G_o^\ddagger$ correlation, thus illustrating that the minimum of the $f\Delta q^\circ$ products for individual reaction paths well approximates net $\Delta G_f^\ddagger - \Delta G_o^\ddagger$ of a reaction with competing mechanisms (dotted lines, Fig. 4B and Fig. S13). Such competition is likely common in force-inhibited reactions, and properly quantifying the contributions of individual paths to the reaction activation energy is necessary to obtain realistic predictions of force-coupled reactivity.

The O···O separation in reactions 1-2 exemplifies a previously suggested(6, 11, 12, 14-17, 37) universal coordinate for estimating force-dependent activation energies of nucleophilic displacements. This coordinate is defined by the two atoms that connect the electrophilic atom (i.e., P in reactions 1a-c and Si in reactions 2a-b) to the molecular moieties that transmit the external load to the reactive site, which are backbones in polymers and the linkers connecting the phosphate or siloxane sites to *E* stiff stilbene in macrocycles **1** through **19**. The computational and experimental data on reactions 1a-c and 2a-b confirm that this universal coordinate performs well across the whole range of mechanochemical responses, i.e., accelerated and inhibited dissociation of loaded bonds and accelerated dissociation of unloaded bonds. The universal coordinate renders predictable the mechanochemical kinetics of reactions not studied previously by allowing force-depending kinetics to be estimated from strain-free geometries and obviating the need for demanding computations of strained geometries.

Our work confirms the existence of two mechanochemical phenomena distinct from force-accelerated scission of a loaded bond: accelerated dissociation of an unloaded bond, which is not perturbed by the applied force; and inhibited dissociation of a loaded (and weakened) bond. Quantum-chemical calculations suggest that the force-dependent kinetics measured in non-polymeric models quantitatively reflect the reactions in polymers, where analogous measurements are not yet possible.

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Supplementary Materials:

Materials and Methods

Figures S1 to S23

Tables S1 to S17

Equations S1 to S25

NMR spectra

References (41-62)

Data S1