

Experimental quantitation of molecular conditions responsible for flow-induced polymer mechanochemistry

Robert T. O'Neill,¹ Roman Boulatov^{1*}

¹Department of Chemistry, University of Liverpool, Liverpool, L69 7ZD; boulatov@liverpool.ac.uk

Abstract Fragmentation of macromolecular solutes in rapid flows is of considerable fundamental and practical significance. The sequence of molecular events preceding chain fracture is poorly understood, because such events cannot be visualized directly but must be inferred from changes in the bulk composition of the flowing solution. Here we describe how analysis of same-chain competition between fracture of a polystyrene chain and isomerization of a chromophore embedded in its backbone yields detailed characterization of the distribution of molecular geometries of mechanochemically reacting chains in sonicated solutions. In our experiments the overstretched (mechanically-loaded) chain segment grew and drifted along the backbone on the same timescale as, and in competition with, the mechanochemical reactions. Consequently, only <30% of the backbone of a fragmenting chain is overstretched, with both the maximum force and the maximum reaction probabilities located away from the chain center. We argue that quantifying intrachain competition is likely to be mechanistically informative for any flow fast enough to fracture polymer chains.

In stationary solutions polymer chains exist as coils whose end-to-end distances are many times shorter than their contour lengths.¹ When a polymer solution flows rapidly near a surface^{2,3} or is sonicated,⁴⁻⁶ the average geometries of some chains elongate. Flows destabilize conformers with short end-to-end distances, producing a partially uncoiled chain in which a contiguous segment of the backbone adopts the longest strain-free conformation (green structures in Fig. 1a).^{7,8} A sufficiently fast flow can stretch a portion of this conformer beyond its strain-free length, primarily by distorting backbone bond angles ('overstretching', magenta structures in Fig. 1a). The resulting tensile force on the constituent bonds (and monomers) causes mechanochemical reactions that are non-existent or negligibly slow in strain-free chains, such as chain fracture.^{5,9}

In the laboratory, optimizing flow parameters to suppress chain fracture enabled detailed studies of chain uncoiling, albeit to less-than-full extension.⁸ Because this comparatively slow uncoiling greatly changes the macromolecular shape, it is directly visualizable under optimal conditions and amenable to coarse-grained simulations. The much faster overstretching affects chain dimensions little and requires quantum-chemical treatment. Consequently, uncoiling dynamics, particularly in steady flows, is much better understood⁷ than the molecular events and geometries of overstretched chains responsible for flow-induced mechanochemistry.¹⁰

Macroscopic kinetics of mechanochemical reactions and its dependence on variables such as chain length or solution viscosity have been studied extensively in diverse flows.¹¹⁻¹³ These dependences, however, are difficult to interpret molecularly.¹⁴ Experimentally, flow-induced chain fracture may reflect primarily unwanted and uncontrollable aspects of practically achievable flow fields, such as turbulence near walls of flow cells, shock waves in sonicated solutions or flow instabilities that limit the residence time of a chain at stagnation points.¹⁵⁻¹⁷ Conceptually, bulk mechanochemical kinetics reflects a complex convolution of the probabilities of dissolved chains to become (partially) overstretched and of these chains to react before the local fluid strain rate decreases below a threshold needed to maintain the required strained molecular geometry. Existing experimental designs do not allow the constituent probabilities, and the attendant molecular conditions, to be estimated. As a result, little consensus exists on even the key molecular events that precede any mechanochemical reaction in a macromolecular solute.

Unlike the macroscopic kinetics, changes in the solution composition from competition between two or more mechanochemical reactions within the same chain (Fig. 1d) reflect only molecular reaction probabilities. The latter can be calculated as a function of the force on the reacting moieties by established quantum-chemical methods.¹⁸⁻²⁰ Consequently, this force and the underlying molecular conditions experienced by the reacting chains become directly quantifiable from experiment. Implementation of this approach has been precluded by the difficulty of designing polymers that enable unambiguous differentiation between products of intra- and intermolecular competition. For example, in sonicated solutions, polymers of dihalocyclopropanes^{21,22} and macrocyclic

cyclobutanes^{23,24} both fracture and isomerize but because neither polymer allows the fraction of isomerized monomers in the fractured and intact chains to be quantified, how often, if ever, the two reactions occur in the same chain remains unknown. The operational simplicity and accuracy of quantifying mass-resolved compositions of a mechanochemically reacting polymer solution by UV-vis absorption spectroscopy⁵ favors the use of a bistable mechanochromic moiety whose isomers interconvert negligibly slow without force and endow the three products of the isomerization/fracture competition (Fig. 1d) of any chain mass with distinct absorption spectra.

Here we describe measurements and analysis of such competition which suggests that in a dilute sonicated solution the overstretched segment grows, drifts towards chain center and reacts all on comparable timescales and that the observed mechanochemistry reflects complex averaging of distinct microscopic reaction probabilities of chains partitioning among very different local environments. We characterized these conditions as the chain-size-dependent distributions of the lengths of the overstretched segments, their positions along the backbones, the time the chains remain overstretched, and the maximum forces they experience during this time. Contrary to a common belief, at any time only <30% of a chain is sufficiently strained to react mechanochemically, with the maximum force located away from the chain center. Our choice of sonication for the first demonstration of our approach is motivated both by the particularly limited understanding of molecular conditions in sonication solutions and by their importance in contemporary experimental polymer mechanochemistry.

Results

Polymer design

We studied 9 polystyrenes (PS) with the average strain-free contour lengths, L , from 60 to 530 nm, containing a single *Z*-stiff stilbene^{25,26} (*Z*-SS) moiety per chain either at its center (**1c-4c**) or at $\sim 0.2L$, $\sim 0.3L$ or $\sim 0.35L$ from the center (**1o-5o**), Fig. 2. We synthesized these polymers by reacting dibromo-terminated *Z*-SS with either excess CO₂H-terminated low-dispersity PS to yield **1c-4c** or with an equimolar mixture of two polystyrenes of different sizes to yield, after size-exclusion chromatography (SEC), **1o-5o**. The distinct absorption spectra of PS, *Z*-SS and *E*-SS allow accurate quantitation of both the average number of SS moieties per chain and the fraction of these moieties that are *Z*, χ_Z , of a polymer sample by deconvoluting its spectrum (Extended Data Figure 1). In **1c-5o**, these values were 0.96 – 1.06 and 0.83 – 0.9, respectively (Table S1).

Synthesizing **1c-5o** by coupling pairs of macromolecules enabled both precise control and accurate quantitation of the distributions of SS locations along the backbones of **1c-5o** (Fig. 2b and Supplementary Fig. 10a-b). We calculated these distributions by assuming that **1c-5o** were formed by statistical combinations of pairs of the precursor chains, whose molar mass distributions (MMD) we measured independently. The good agreement between the measured and simulated MMDs (Fig. 2c and Supplementary Fig. 10c) validates the remarkably-narrow calculated SS distributions, with 72-85% of chains in each sample containing SS within $0.05L$ of the sample-average value.

Sonication experiments

We sonicated **1c-5o** as THF solutions of 1 mg/mL concentration under standard protocol,²³ and quantified their compositions by SEC. We determined the fraction of the *Z* and *E* isomers of stiff stilbene for each mass fraction by deconvoluting its absorption spectrum at 300 – 400 nm into those of the two isomers (Extended data Fig. 1). The total amount of SS in sonicated solutions remained constant, confirming that sonication did not destroy SS.

Sonication changed the unimodal MMD of the intact polymer (black line in Fig. 3a) to a bimodal distribution with the maximum of the newly formed component at $\sim M_p/2$, indicating chain fracture. Simultaneously, the high and largely mass-independent fraction of *Z*-SS, χ_Z , of the intact sample gradually decreased and became strongly mass-dependent (Fig. 3b and Supplementary Fig. 11). The

monotonic reduction of χ_z of chains with mass $>0.8M_p$ reflects isomerization of Z-SS without chain fracture (orange arrows); whereas the presence of Z-SS in chain fragments ($\chi_z > 0$ of chains with mass $<0.7M_p$) means that some Z-SS survive chain fracture without isomerizing (black arrows in the scheme in Fig. 3b). Fracture-coupled Z-SS isomerizations (magenta arrows) are responsible for consistently lower χ_z values at $(0.35-0.7)M_p$ (product chains) than χ_z at $>0.8M_p$ (reactant chains) at any sonication time. The same applies to χ_z of chains at $(0.4-0.6)M_p$ vs. $(0.15-0.3)M_p$. The SS-free products of chain fragmentation do not affect the accuracy of χ_z because such fragments are transparent at >300 nm used to quantify χ_z .

The depletion of chains with masses $>0.8M_p$ manifested unimolecular kinetics (Supplementary Fig. 14). The corresponding bulk rate constants, k_f , increased as a power of the chain mass (Fig. 3c) with k_f of smaller chains being more sensitive to mass, m , than larger chains, e.g., $k_f \propto m^{3.2 \pm 0.1}$ for 22 kDa vs. $k_f \propto m^{2.0 \pm 0.1}$ for 280 kDa. The kinetics is independent of the location of SS along the backbone and identical to chains without SS (Supplementary Fig. 16). Z \rightarrow E isomerization in intact chains also followed unimolecular kinetics and the corresponding rate constants, k_i , scale as a power of k_f (Fig. 3d). The k_i/k_f ratio estimates mechanochemical selectivity,^{21,27} i.e., the capacity to achieve desired (usually site-selective) chemistry without (usually deleterious) non-selective chain fracture. This selectivity decreases both with the chain size and the fractional displacement of SS from chain center. For example, 1.7 ± 0.2 chains of **1c** of 22 kDa isomerize without fragmentation for each fractured chain, but only 0.28 ± 0.02 chains of **4c** (280 kDa) do. Displacing SS from the chain center by $0.3L$ reduces this number ~ 5 -fold in a 53 kDa chain (**2o**) and ~ 7 -fold in a 160 kDa chain (**4o**). These factors don't scale with the number of backbone bonds per SS, suggesting a complex dependence of local conditions on chain mass. Sonication of polymers containing Z-SS at a chain terminus yielded no detectable amount of E-SS (Supplementary Fig. 15).

Force-dependent activation free energies from DFT

To enable molecular interpretation of the experimental data, we used a previously reported and experimentally validated method^{24,28,29} to calculate the free energies of activation, ΔG^\ddagger , of two reactions - homolysis of the central C-C bond in $H(CH_2CHPh)_4CH_3$ (a polystyrene model) and isomerization of Z-(6,6-bismethoxy stiff stilbene) - as a function of stretching force applied across the terminal $_{Me}C \cdots C_{Me}$ distances (Fig. 4). E-SS is thermodynamically more stable than Z-SS at any force and under standard conditions Z \rightarrow E isomerization is negligibly slow up to ~ 0.5 nN. Above 2 nN isomerization ΔG^\ddagger becomes nearly force-independent because the greater compliance of the Z isomer than the TS along the pulling axis makes the two geometries increasingly similar as force increases (Fig. 4b). At 5.8 nN homolysis of the $_{Ar}C-C(sp^2)$ bond of the cyclopentane ring of SS becomes faster than C=C bond isomerization. This homolysis does not fracture the chain but would probably irreversibly bleach SS,³⁰ which we didn't observe. Both calculations and experiments³¹ suggest that at practically relevant forces only the $RH_2C-CH(Ph)R$ bond contributes to fracture of **1c-5o** (Extended Data Fig. 2).

Molecular models of flow-induced mechanochemistry

Molecular models of mechanochemistry aim to relate the conditions experienced by individual reacting chains to the observed compositions of product mixtures.²⁷ In flow-induced mechanochemistry, these product mixtures reflect contributions of individual monomers that depend on their location along the reacting backbones.^{5,33} For example, product MMDs reflect the fractions of chain scissions occurring by dissociation of each backbone bond i.e., the distribution of relative fragmentation probabilities along the chain (e.g., eqs. 7-9 in Methods and eqs. S3, S4, S6-S7 in the SI). Mass-dependent χ_z reflect both the probabilities of Z-SS at each backbone location to isomerize and of chain fracture to yield an SS-containing fragment of the corresponding mass, i.e., they also depend on the distribution of isomerization probabilities in each fragmenting chain.

Consequently, χ_z are much more sensitive to how forces acting on a reacting chain vary both in time and along the backbone, than MMDs.

We assumed that all reaction-probability distributions (and corresponding force distributions) depend on chain length but not on the presence or location of SS, which accounts for <0.4% of monomers comprising the chain, and that reacting chains of each length populate multiple microenvironments, each producing its own distributions of reaction probabilities along backbones. The observed mechanochemistry reflects averaging of such single-chain distributions proportionally to each microenvironment's contribution.

The "Modeling" section of the Methods describes our overall approach to parameterizing each model to match measured MMDs and χ_z as closely as the model allowed. The eponymous SI section describes how we transformed these parameters to the corresponding force and reaction probability distributions, MMDs and χ_z using a reported method;³¹ and our analysis of the results. Below we summarize the key findings: how the assumption of instantaneous mechanochemical reactions of the literature models makes them inconsistent with our measurements, a model free of this assumption, and the reacting-chain geometries and timescales it reveals. Fig. 5 illustrates the performance of each model qualitatively, by comparing MMD and χ_z at a single sonication time (40 min) for a single sample (**3c**) with the respective model predictions; and quantitatively using proxies of the dispersity of the product MMDs and the extent of fracture-coupled isomerization of Z-SS, averaged over all sonication times for the whole series of **1c-5o**. Extended Data figure 3 compares measured MMDs and χ_z for **4o** with those predicted by each model across the full range of reaction extents.

The reported models

The simplest, most-used model (Fig. 1a, left) limits mechanochemistry to fully overstretched chains,^{21,34} whose backbone bonds experience force that decreases quadratically with the fractional distance from the chain center, where it is highest (f_{\max}), to 0 at the termini. We find that the corresponding distribution of relative fragmentation probabilities is largely independent of the chain size (up to 3000 monomers or ~310 kDa for PS), f_{\max} (up to 6 nN) or how f_{\max} changes with time (independent of, proportional to, or exponentially increasing with, time: Supplementary Fig. 18). Applied to **1c-5o** it yields considerably more uniform product MMDs than observed, as illustrated by the predicted product peaks (yellow line in Fig. 5a) being much narrower and chains of $(0.5 \pm 0.05)M_p$ mass being nearly twice as abundant as observed (Fig. 5c). Both deviations reflect a model that badly underestimates the relative susceptibility of off-center backbone bonds to mechanochemical scission in a sonicated chain, i.e., the parabolic decrease of the force from the chain center being too steep. It similarly yields isomerization probabilities too sensitive to the distance from the center of a fracturing chain (Supplementary Fig. 18), overestimating the extent of isomerization of centrally located Z-SS (**1c-4c**) and underestimating it for off-center Z-SS (**1o-5o**).

Several reported models allow fracture of partially uncoiled chains (Fig. 1a, right), with the overstretched segment fixed either at the chain center^{35,36} or at locations distributed along the chain.^{17,37} In the latter scenario fracturing chains of each size comprise an ensemble of geometries, each with a different segment of the backbone overstretched. Shortening these segments makes the resulting ensemble distributions of reactions probabilities less sensitive to how the force varies within each segment and more sensitive to how the segments distribute along the chain (Supplementary Fig. 22). This allows the fraction of chains fracturing by scission of a particular backbone bond to be determined by the probability of this bond falling within the overstretched segment, not by its force relative to that of the central bond. Consequently, the measured MMDs can be reproduced with suitably-distributed short ($\leq 0.05L$) segments, but χ_z cannot, because as the segments shorten, ensemble distributions of fragmentation and isomerization probabilities in fracturing chains become increasingly similar. In contrast, the observed isomerization propensity of

Z-SS is much less sensitive to its proximity to the chain center than dissociation susceptibility of a backbone C-C bond: chain-centered Z-SS are only ~5-7 times more likely to isomerize than Z-SS at $(0.5 \pm 0.3)L$ in chains of the same length, whereas the analogous ratio for scission of backbone C-C bonds is $>10^3$. Accordingly, the “overstretched-segment” model cannot be parameterized to reproduce accurately the measured MMDs and χ_z simultaneously.

Dynamic model consistent with the experiments

Our measurements suggest the distributions of fragmentation and isomerization probabilities along the chain are more dissimilar than the assumption of instantaneous mechanochemical reactions allows. The alternative is for the length and the position of the overstretched segment, and hence the distribution of force along the backbone, to change on the timescale of mechanochemical reactions. To test this hypothesis quantitatively in the absence of any reported characterizations of chain dynamics in solvent flows generated by imploding cavitation bubbles, we used eqs. 1-3 as tractable physically plausible approximation of this dynamics. Eqs. 1-3 relate the fraction of the backbone that is overstretched (λ_{os}) or between the center of the overstretched segment and the closest chain terminus (δ); and the highest force on a backbone bond, f_{max} , to time, t , since the emergence of an overstretched segment. Although λ_{os} , δ and f_{max} in individual chains probably fluctuate with t , the capacity of non-stochastic eqs. 1-3 to reproduce the measurements suggests that mechanochemical effects of such fluctuations are yet unobservable.

$$\lambda_{os} = 1 - e^{-k_s t} \quad eq. 1$$

$$\delta = 0.5 - 0.5e^{-(k_s + k_d)t} \quad eq. 2$$

$$f_{max} = (\alpha + \beta t)\lambda_{os}^2 \quad eq. 3$$

Eq. 1 is the simplest functional expression of the assumption that since the overstretched segment cannot exceed the whole backbone ($\lambda_{os} = 1$), its elongation must decelerates as its length increases, with k_s representing some averaging of (time-dependent) growth kinetics during mechanochemical reaction(s). Eq. 2 combines a previous suggestion^{37,38} that an overstretched segment originates at a chain terminus (similarly to the reported^{7,8,39} preferential uncoiling of linear chains from a terminus) with the plausible existence of two independent dynamic drivers of δ towards 0.5 (chain center). One is the overstretched-segment elongation (geometrically, δ must not exceed $\lambda_{os}/2 \leq 0.5$); the other is drift of this segment toward chain center with effective rate constant k_d . Finally, eq. 3 generalizes a common conjecture that f_{max} of an overstretched backbone scales with the fluid strain rate, $\dot{\epsilon}$, and the squared chain length, to time-dependent $\dot{\epsilon}$ of imploding cavitation bubbles.³² It avoids any assumptions about functional form of $\dot{\epsilon}(t)$ by representing the $f_{max} \cdot \lambda_{os}^2$ coupling coefficient as a two-term Taylor expansion of loading-time independent (α) and linearly-ramping (β) contributions.

We used eqs. 1-3 first to find reaction-probability distributions that reproduce accurately measured MMDs and χ_z (Fig. 6a-b) and then to relate these distributions to the geometries (λ_{os} , δ , f_{max}) of the reacting chains and reaction timescales. We find that the measured MMDs reflect the instantaneous length and location of the overstretched segment at chain fracture, which has observable probability only at $f_{max} > 5.2$ nN (Figs. 6c-d). Conversely, Z-SS isomerization probabilities (Fig. 6b) represent the evolution of the overstretched segment over the time, $\Delta t_{stretch}$, its f_{max} exceeds 2.5 nN. At $f_{max} < 2.5$ nN, isomerization of Z-SS is undetectably slow on the timescale of bubble implosions, making it impossible to estimate how accurately eqs. 1-3, or its parameters, describe chain behavior prior to its f_{max} reaching 2.5 nN.

During $\Delta t_{stretch}$ the average overstretched segment elongates by ~0.1L, its f_{max} increases by >3.0 nN and its location shifts from <0.3L to ~0.4L (Extended Data Fig. 4), with segment growth and drift each contributing approximately equally to this shift. As a result, ~10% of the backbone closest to the

terminus remains mechanochemically inert even when overstretching starts at that terminus. The drift more than doubles the fraction of the backbone where Z-SS isomerization is observable compared to λ_{os} at fracture and displaces it toward the chain terminus. The resulting decoupling of the two reaction-probability distributions is impossible in static models, explaining why the latter don't reproduce the measured MMDs and χ_z simultaneously even when using more fitting parameters.

The quantitative relationship between the reaction-probability distributions of the observed MMDs and χ_z , and the structural descriptors of the fragmenting chains (λ_{os} and δ , Figs. 6c-d) from eqs. 1-3 is qualitatively intuitive. For example, the much smaller force required to isomerize Z-SS on the sub- μ s timescale (>2.5 nN) than to break a C-C bond (>5.2 nN) causes almost every Z-SS moiety contained within the overstretched segment at chain fracture to isomerize. Yet, in **1c-4c**, where $>70\%$ of SS moieties are localized within the central 5% of the backbone, $\sim 40\%$ of Z-SS moieties survive chain fracture. These must remain outside the overstretched segment when the chain fractures (Fig. 1c), which requires this segment to be either very short, located off-center or both.

Conversely, the available experimental data are insufficient to relate the parameters of eqs. 1-3 (Extended Data Fig. 5) to characteristics of the mechanochemistry-inducing fluid flows, such as strain rates, $\dot{\epsilon}$. The narrow almost chain-length-invariant distributions of k_s and k_d (eqs. 1-2) potentially suggest that, unlike chain uncoiling, the evolution of λ_{os} and δ over $\Delta t_{stretch}$ requires few large-scale conformational transitions, which increase k_s with chain length.¹ The less-than-linear scaling of the coefficients of $f_{max}\lambda_{os}^2$ coupling (α and β , eq. 3) with chain length means that longer chains require more contiguous overstretched monomers to achieve the same f_{max} as shorter chains, i.e., they experience weaker hydrodynamic drag per monomer. This may mean that minimum $\dot{\epsilon}$ to initiate overstretching decreases with chain contour length, similarly to the well-established trend for chain uncoiling⁷ (Fig. 1a), despite the different relaxation mechanisms of enthalpic vs. entropic strain.^{40,41} The time-dependent coupling coefficient, β , increases sensitivity of f_{max} to λ_{os}^2 during $\Delta t_{stretch}$, allowing the chain loading rate ($\partial f_{max}/\partial t$) to increase with t despite decelerating elongation of the overstretched segment underlying eq. 1.

Our parameterization of eqs. 1-3 may not be unique, i.e., other distributions of k_s , k_d , α and β may reproduce measured MMDs and mass-dependent χ_z equally well. Similarly, tractable physically plausible relationships between λ_{os} , δ , f_{max} and t distinct from eqs. 1-3 may also approximate the competition between overstretching and mechanochemistry revealed by our measurements. Assessing these possibilities requires applying the reported method to other pairs of competing reactions, including site-selective chain fractures.

Discussion

The picture of a reacting chain in a sonicated solution afforded by the above analysis allows evaluation of several hitherto-untestable beliefs that inform the design and interpretation of experiments in contemporary solution polymer mechanochemistry.

First, we could reproduce measured mass-resolved χ_z only by allowing the reaction-probability distributions in individual fragmenting chains to be asymmetric with off-center maxima (Fig. 6a-b), which challenges the belief that chains in rapid flows react primarily or exclusively at chain center ("mid-chain selectivity"⁴²⁻⁴⁶). The equal probability of a dissolved chain to start uncoiling, and subsequently overstretching, at either terminus increases its apparent propensity to react at its center compared to individual overstretched chains, without changing the overall conclusions (Extended Data Fig. 6). For example, under the standard sonication conditions studied here, only 13-20%, depending on chain size, of polystyrene chain fractures involve scission of its central 5% of backbone bonds. "Multimechanophore" polymers,^{13,23,24,47-50} whose more labile backbone bonds are distributed uniformly or randomly along the chain, are calculated to follow a similar pattern.

Conversely, the distribution of fracture probabilities of a backbone containing a single labile bond may approach the distribution of the locations of this bond, although we are unaware of any relevant examples. Polystyrene containing a single anthracene/maleimide adduct, which is a popular scissile mechanophore,^{44,51,52} distributed as SS in **1c-4c** (Fig. 2b) is calculated to lie between these two limits, with dissociation of this adduct responsible, depending on chain size, for 68-98% of chain fractures, of which 57-74% occur within the central 5% of the backbone.

Second, asymmetric reaction-probability distributions in Fig. 6a-b reflect overstretched segments that grow and drift toward the chain center on a timescale of the mechanochemical reactions, causing such reactions to occur under rapidly and often non-monotonically varying force. Variations in locations of reactive sites among individual chains in a sonicated solution further broadens the range of loading regimes driving their reactions. For reactions proceeding by mechanisms that change with force,^{23,24,28,45,49,52} this heterogeneity of microenvironments may dominate the observable product distributions, possibly invalidating mechanistic analyses of such mixtures that assume uniform time-invariant force. Likewise, the greater number of monomers experiencing sufficient forces to undergo a detectable non-scissile mechanochemical reaction prior to chain fracture, relative to those comprising the overstretched segment at chain fracture, would explain the otherwise puzzlingly high yields of productive mechanochemistry per chain fracture of certain multi-mechanophore polymers,^{23,53} particularly far off-center⁵⁴.

Third, our simulations suggest that bulk mechanochemical selectivities (k_i/k_f ratios, Fig. 3d and Supplementary Fig. 28d) are primarily determined by the fraction of overstretched chains that fail to fracture after their f_{\max} exceeds the fracture threshold (5.2 nN in our experiments), probably because these chains become sufficiently overstretched only within 1-2 μ s of the complete bubble implosion when the flow disappears.^{28,32} This fraction varies from 57% for the smallest (250 monomers) to 24% the largest chain (2000) modeled chains. The lower survival probability of longer overstretched chains, despite their shorter time under force (1.4 \pm 0.3 vs. 0.8 \pm 0.2 μ s for chains of 250 and 2000 monomers) reflects the increasing number of loaded backbone bonds with chain size, which lowers the overall kinetic stability of the chain at constant f_{\max} . Yet, the average chain of 2000 monomers is only \sim 1.5 times more likely to fracture after reaching f_{\max} =2.5 nN than that of 250 monomers vs. the 260-fold difference of their bulk fragmentation rate constants (Fig. 3c). This suggests a yet-to-be-identified physical, not chemical, process occurring before each chain reaches f_{\max} =2.5 nN limits bulk mechanochemical kinetics. Consequently, a common practice of estimating molecular conditions experienced by individual reacting chains from bulk mechanochemical kinetics is likely invalid, as speculated previously.^{4,14,33}

Multiple types of solvents flows fracture diverse macromolecular solutes, in what is commonly accepted^{4,5,7,9,27,34,51,55} to reflect isothermal destabilization of strained bonds of an overstretched backbone. Site-specific mechanochemical reactions compete with chain fracture, both in sonicated solutions^{27,44,54} and other flows,⁵⁶ because homolysis of C-C bonds requires larger forces to proceed at detectable rate than almost any other known mechanochemical reaction, with multiple monomers of a fracturing chain experiencing such forces. Selecting site-specific non-scissile mechanochemical reactions (Fig. 1d) to compete with fracture of backbones of different compositions under diverse flow-specific conditions plausibly makes our method applicable to multiple manifestations of solution mechanochemistry. The computationally-demanding modeling used in this work reflects the complexity of molecular conditions responsible for mechanochemistry in sonicated solutions, but alternative coarse-graining approaches may simplify quantitative analysis of measured intrachain selectivities, albeit by reducing the accessible level of detail.

In conclusion, we demonstrated on an example of a sonicated solution that analysis of same-chain competition between mechanochemical fracture of a polymer chain and isomerization of a chromophore embedded in its backbone allows detailed characterization of the molecular events enabling flow-induced mechanochemistry. Under the studied conditions the length of the chain

segment strained enough to manifest mechanochemistry, its location along the chain and its forces all change on the same timescale and in competition with the decreasing chain survival probability. This competition displaces the location of the highest mechanochemical reactivity away from chain center, makes bulk mechanochemical selectivity rather than bulk fragmentation rates the indicator of the molecular conditions experienced by individual reacting chains, and yields appreciable chain fracture at forces spanning a ~ 0.8 nN range. We suggest that by lowering the lengthscale at which the chain behavior in rapid flows can be probed experimentally from ~ 1 μm of the optical methods to ~ 10 nm, our approach offers important opportunities for fundamental studies and practical exploitations of polymer rheology^{57,58} and mechanochemistry.^{59,60}

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Author contributions

RO performed all experiments and contributed to data analysis and writing. RB designed the study, developed the model and wrote the paper.

Competing interests

The authors declare no competing interests.

Fig. 1. Molecular models of flow-induced mechanochemistry and the experimental approach to testing them. (a) The limiting conformations of macromolecular solutes: a random coil; a fully uncoiled chain whose end-to-end distance equals its contour length and an overstretched chain whose backbone is stretched beyond its contour length. (b) Flow-induced chain fracture has been thought to start with an instantaneous uncoiling of either the full backbone (left) or its portion, at critical fluid flow rate, $\dot{\epsilon}_c$, followed by overstretching of the resulting longest backbone conformer and finally an instantaneously chain fractures once the force at the center of the overstretched segment, f_{max} , reaches a critical value, f_c . (c) Our work suggests a complex competition with the overstretched portion of the backbone growing and drifting towards chain center on the same timescale as mechanochemical reactions but the contribution of strain-free uncoiling (green structures in a-b) remains unknown. (d) Intrachain competition between a site-specific non-scissile mechanochromic reaction and chain fracture allows these models to be tested. We illustrate the method on a series of polymers of different lengths containing the mechanochromic moiety at several, precisely known backbone locations. In a sonicated solution, the measured variation in the fraction of chains that simultaneously isomerize and fragment (expressed as stoichiometric coefficient $\omega_{n,m}$) with the length of the chain ($n+m$) and the location of the isomerizable moiety in it ($n-m$) is consistent only with the dynamic model (c).

Fig. 2. The studied polymers. (a) synthesis, chemical structures and summary of key sample-average parameters: L is the strain-free contour length; \mathcal{D} is dispersity index; $\langle \rangle$ signifies number averaging and MFD_{SS} is mean fractional displacement of SS from the closest chain terminus; deviation of MFD_{SS} of **1c-4c** from 0.5 directly reflects the dispersity of the precursor polymers. See Supplementary Fig. 1 for further details. (b) The fraction of chains of **1c**, **1o**, **2o** and **5o** that contain stiff stilbene at the

specified fractional distance from a terminus. Calculated distributions in **2c-4c**, **3o** and **4o** are very similar to those of **1c**, **1o** and **2o**, respectively and are shown in Supplementary Fig. 9 together with the corresponding cumulative distributions. (c) measured and calculated MMDs of **2o** and the measured MMDs of the corresponding precursors. See Supplementary Fig. 10 for all other polymers. The discrete distributions in (b-c) have the bin size of 0.01L (b) and 100 Da (c). The plotted data is tabulated in the supplementary data file, suppdata.mat

Fig. 3 Summary of sonication experiments. (a) MMDs and (b) the fraction of Z-SS containing chains among all SS-containing chains of the same mass, χ_Z , as a function of the chain mass, of a sonicated solution of **3o**. Reactions responsible for monotonic decrease of χ_Z with chain mass are shown schematically; fragmentations of E-SS containing chains are omitted for clarity. (c-d) Log-log plots of (c) the measured unimolecular rate constants for fragmentation of **1c-5o**, k_f , as a function of the chain mass, and (d) unimolecular rate constants for isomerization of intact chains, k_i , as a function of corresponding k_f . Only a fraction of the measured rate constants is plotted for clarity. The solid lines are quadratic least-squares fits of (c) $\log(k_f)$ vs. $\log(\text{mass})$ and (d) $\log(k_i)$ vs. $\log(k_f)$ for **1c-4c** only (upper curve); lower curves in (d) are from vertically shifting the upper curve to best match the measured values for **1o**, **3o** and **5o** (middle curve), or **2o** and **4o** (lower curve). For each sample, χ_Z values are reliably quantifiable over a shorter range of chain masses than the mass fractions so that the data in (b) covers a shorter range of chain masses than in (a) and the data in (d) covers a shorter range of k_f than in (c). The rate constants are averages of 4 measurements, except for **1c** and **1o**, for which only 2 measurements were performed due to the very long sonication times required to achieve acceptable reaction extents. The legend in (a) also applies to (b); and the legend in (c) also applies to (d). See Supplementary Figs. 11-12 for MMDs, χ_Z , and SECs of **1c-5o**. The relative standard errors of k_f , k_i , chain masses and χ_Z , are 0.7%-4.7%, 2%-10%, 0.7%-3% and 1%-14%, respectively (Supplementary Figs. 9 and 13). The plotted data is tabulated in the supplementary data file, suppdata.mat

Fig. 4. Summary of the DFT calculations. (a) the activation free energies, ΔG^\ddagger , of fragmentation and isomerization as a function of extrinsic tensile force. The dashed line indicates ΔG^\ddagger corresponding to half-life, $\tau_{1/2}$, of 1 μs , the approximate timescale of cavitation bubble collapse in a liquid irradiated with 20 kHz ultrasound.^{5,32} Fracture ΔG^\ddagger of a chain with n bonds all under the same force is reduced, relative to that of the single bond, by $RT\log_e(n)$, where R and T are the gas constant and absolute temperature, respectively. The transition state for C-C bond homolysis cannot be located at <0.5 nN, which is common. (b) overlays of the geometries of Z-(6,6-bismethoxy stiff stilbene) (red) and the isomerization TS (blue) without force and coupled to 3.5 nN: note the much larger difference of the $\text{MeC}\cdots\text{C}_{\text{Me}}$ distance between the Z isomer and its TS at 0 nN compared to 3.5 nN ($\langle \rangle$ signify Boltzmann-averaging over 3 conformers comprising each strain-free state; at 3.5 nN each state contains a single conformer). This difference is usually the primary determinant of the ΔG^\ddagger vs. f slope.^{27,28} Tensile force distorts Z stiff stilbenes mostly by bending each indanone moiety, accompanied by only modest increase in the $\text{ArC-C=C-C}_{\text{Ar}}$ torsion of the isomerizing C=C bond to 39° at 3.5 nN from 11° at 0 nN. The black arrows represent applied force vectors. All calculations were at uBMK/6-31+G(d) in vacuum. The plotted data is tabulated in the supplementary data file, suppdata.mat

Fig. 5. Illustrative comparisons of experiments with predictions of the molecular models. (a-b) measured and calculated MMDs (a) and χ_Z (b) of **3c** at the same remaining mass fraction of the reactant chains, ζ_r . (experimentally reached at 40 min of sonication). (c) Ratios of the simulated mass fractions of chains with masses 0.45 M_p -0.55 M_p , to the measured ones, $\frac{\zeta_{\text{prod}}^{\text{sim}}}{\zeta_{\text{prod}}^{\text{exp}}}$, at the same ζ_r , averaged over all experimentally characterized values of ζ_r for **1c-5o** (M_p is the mass of the most abundant reactant chain in the original sample). Ratios >1 correspond to the simulation yielding too uniform fragmentation products (underestimating $\mathfrak{D}_{\text{prod}}$). (d) Differences between simulated and measured χ_Z of chains with masses of 0.45 M_p -0.55 M_p at the same ζ_r , averaged over all

experimentally characterized values of ζ_r for **1c-5o**. Negative differences correspond to simulations underestimating the extent of fracture-coupled isomerization. For each model, the simulated MMDs and χ_z reflect the combination of model parameters yielding the lowest total scaled norm of residuals (eq. 14, Methods) across the full set of experimental MMDs and χ_z . The horizontal dotted lines in (c-d) correspond to perfect matches between the measured and simulated values. See Supplementary Fig. 20-21, 23-24 and 26-27 for all simulated MMDs and χ_z , and the corresponding residuals. The plotted data is tabulated in the supplementary data file, `suppdata.mat`

Fig. 6. Summary of molecular conditions yielding the observed mechanochemistry. (a-b) the variation in the probabilities of (a) C-C bond homolysis and (b) Z-SS isomerization in individual fracturing chains of the same length with the fractional distance from the closest chain terminus, averaged over all microenvironments contributing to measured MMDs and χ_z . While the selectivity of chain fracture requires the full probability distribution in (a), each (x,y) pair in (b) describes a chain with unique location of Z-SS: for example a 250-monomer chain with Z-SS at the center (x=0.5) fragments to an E-SS chain 69% of the time (y=0.69), with Z-SS surviving 31% of chain fractures. (c) the time the chain is loaded to $f_{\max} \geq 2.5$ nN, $\Delta t_{\text{stretch}}$, and f_{\max} at chain fracture; (d) the fractional length of the overstretched segment λ_{os} , and the fractional distance from the closest terminus to the monomer experiencing f_{\max} , δ , at chain fracture. In (c-d) circles describe the values in the average fragmenting chain and bars define the narrowest range responsible for 80% of chain fractures; because distributions of λ_{os} and δ in bulk samples are non-symmetrical (Extended data Fig. 4) their averages are not in the middle of the ranges. The bin size of distributions in (a-b) is 0.002. The plotted data is tabulated in the supplementary data file, `suppdata.mat`

Methods

Experimental protocols

General procedure for synthesis of polystyrenes 1c-5o:

In a glove box, a solution of bis(3-bromopropyl)-2,2'-((2,2',3,3'-tetrahydro-[1,1'-biindenylidene]-6,6'-diyl)bis(oxy))(Z)-diacetate (1 eq.), K_2CO_3 (10 equiv.), and either monocarboxy-terminated polystyrene, PSCO_2H , of single nominal mass (2.1 equiv.) or of two different masses (1 equiv. each) in anhydrous DMF (1.5 – 2 mL) was stirred for 1 – 5 days depending on the polymers (larger polymers require longer reaction times). The reaction progress was monitored by size-exclusion chromatography (SEC); once a sufficient conversion was reached the mixture was removed from the glovebox and poured into a 1:1 mix of $\text{H}_2\text{O}/\text{EtOAc}$ (20 mL) at ~ 40 °C which was separated and the aqueous phase washed with ~ 40 °C EtOAc (2 x 10 mL). The combined organic phase was washed with H_2O (5 x 10 mL) and dried with MgSO_4 . The volume was reduced to ~ 8 mL and the solution was mass-fractionated by preparative gel-permeation chromatography (GPC) in 1 mL batches. Each 1 mL GPC fraction was analysed by SEC, fractions of similar mass distributions were combined and analysed again by SEC to yield MMDs used in simulations and in calculations of SS distributions (Supplementary Figs. 8, 10), as well as to confirm the expected SS/chain ratio of one and predominantly Z configuration of SS (Supplementary Table 1).

Determination of the extinction coefficients

The extinction coefficients of Z-SS, $\varepsilon_z(\lambda)$, and PSCO_2H at 240 – 400 nm were determined from absorbances of samples of known concentrations in fresh unstabilized THF (Extended Data Figure 1). The extinction coefficients of E-SS, $\varepsilon_e(\lambda)$, were derived by non-linear least-squares fitting to eq. 4 of a sequence of time-lapsed spectra of a 4.8×10^{-5} M solution of Z-SS in anhydrous THF irradiated with a 365 nm diode (FWHM = 7 nm), where $A(\lambda, t)$ is the measured absorbance of the solution at wavelength λ and irradiation time t , $A(\lambda, 0)$ is the absorbance of the starting solution at the same wavelength; and k_1 , k_2 (the rate constants of photochemical Z \rightarrow E and E \rightarrow Z isomerization at the used photon flux) and $\varepsilon_e(\lambda)$ were the fitting parameters. The absorption spectra of PSCO_2H at ambient

pressure and at the pressure of the Acquity PDA detector were indistinguishable, whereas those of Z and E SS were bathochromically shifted by 1.7 and 2.3 nm, respectively, without detectable change in the shape or $\varepsilon(\lambda)$.

$$\frac{A(\lambda, t)}{A(\lambda, 0)} = \frac{(\varepsilon_E(\lambda) - \varepsilon_Z(\lambda))(1 - e^{-(k_1+k_2)t})k_1}{k_1 + k_2} + \varepsilon_Z(\lambda) \quad (\text{eq. 4})$$

Sonication experiments

All sonications were performed on THF solutions of polymers at 1 mg/mL concentration with a two-horn sonicator, which allowed sonication of two samples of the same polymer simultaneously, in cylindrical 3-arm cells that formed gas-tight seals with horn collars. Each cell contained 5 mL of the solution, a PTFE-coated thermocouple for continuous temperature monitoring threaded through one side-arm, and N₂ inlet/outlet tubings threaded through another. 50 μ L aliquots of the sonicated solution were periodically withdrawn through the 3rd arm for SEC analysis (see Supplementary Fig. 11 for all PDA and RI detector outputs of SECs of sonicated solutions). Experiments were performed at total absorbed acoustic power of 14.6 \pm 0.5 W, as measured separately, delivered at 20% amplitude in the pulse mode (1 s on/1 s off). A recirculating chiller maintained the temperature of the sonicated solutions at 6 \pm 2 $^{\circ}$ C.

Processing of measured data.

Calculations of mass distributions (MMDs)

At the sampling rate of 10 s⁻¹ Acquity SEC captures multi-wavelength absorbance and Δ RI of each 10 μ L volume of the eluant. Because chain mass depends exponentially on retention time, t_{ret} , the mass range of chains in each such aliquot varies with its t_{ret} . Conversion of the measured detector output to MMD requires partitioning this output into bins of equal chain mass (rebinning), to avoid the artifacts inherent to the non-linearity of $t_{\text{ret}} \rightarrow$ mass transform, in 3 steps:

1. Backfill the gap between each measured pair of t_{ret} for 9 intermediate t_{ret} by pairwise linear interpolation.
2. Convert the expanded set of t_{ret} values (now incremented in 10 ms) to chain mass using the calibration curve. While the resulting chain masses remain non-uniformly spaced, the maximum increment is <2 Da.
3. Convert the result from step 2 to cumulative distribution and discretize it into 100 Da-wide bins (interpolating between two adjacent values if necessary), followed by normalizing the total output to 1 to obtain mass fractions.

Prior to conversion to MMDs, a linear baseline correction was applied to the detector output, contributions of Z-SS and E-SS to PDA output at 262 nm were subtracted and intensities of <0.1% (PDA) or <0.4% (RI) of the respective maxima were zeroed. Each MMD used in this work is an average of the MMDs derived from the PDA and RI outputs of the same sample (Supplementary Figs. S11-S12). The mean relative standard errors on chain masses are plotted in Supplementary Fig. 9a.

Calculations of mass-resolved χ_z

First, we used the above procedure to convert the PDA output at 300 – 400 nm to absorption spectra of each 1 kDa-wide fraction of chains. Second, the spectrum of each fraction with maximum absorbance >0.2 μ A was fitted to a sum of the spectra of Z-SS and E-SS by non-linear least-squares (Extended Data Fig. 1). Fitting errors on χ_z were calculated from Jacobian, J , returned by the lsqnonlin function of Matlab according to eqs. 5-6, where iJ is inverse J , $chol$ is Cholesky decomposition, I is the identity matrix of the same size as $J' \times J$, D is the measured spectrum that was fitted and n is the number of datapoints in it. The error of each reported χ_z was obtained as the square root of the sum of squares of the relative standard errors of individual repeats times reported χ_z (Supplementary Figs. 12-13).

$$ij = \text{chol}(J' \times J) \backslash (\text{chol}(J' \times J)' \backslash I) \quad (\text{eq. 5})$$

$$\sigma(\chi_Z) = \frac{1.96}{n} \sqrt{(D - J \times ij \times J' \times D)' \times (D - J \times ij \times J' \times D) \times \text{diag}(ij)} \quad (\text{eq. 6})$$

DFT calculations

All calculations were performed with the Gaussian 16 suite of software at the (u)BMK/6-31+G(d) level of DFT in vacuum. This model chemistry was previously demonstrated to reproduce accurately the measured activation free energies of *Z/E* isomerization of strain-free and strained stiff stilbenes.³⁰

The Berny algorithm was applied to locate stationary points. Tight convergence criteria and ultrafine integration grids were used in optimisations and frequency calculations. All force-coupled stationary geometries were optimized as previously described.^{28,40,61,62} Force dependent electronic energies, constrained distances and thermodynamic corrections (see below) were obtained by interpolation of the results of relaxed potential energy scans of either the $_{\text{Me}}\text{C}\cdots\text{C}_{\text{Me}}$ distance of stiff stilbene or $_{\text{Me}}\text{C}\cdots\text{C}_{\text{Me}}$ distance of the model of PS, $\text{H}[\text{CH}_2\text{CH}(\text{Ph})]_4\text{CH}_3$ of both the reactant (*Z*-SS and PS model) and the SS isomerization transition state at <4.5 nN. The SS isomerization TSs at force 4.5 – 6 nN were optimized using a compressed very soft virtual spring between $_{\text{Me}}\text{C}$ atoms (implemented with the *iop*(1/164) overlay procedure of Gaussian). The transition state for homolysis of the C-C bond in $\text{H}[\text{CH}_2\text{CH}(\text{Ph})]_4\text{CH}_3$ does not exist in the absence of force; the force-coupled transition states were obtained by first optimizing $\text{H}[\text{CH}_2\text{CH}(\text{Ph})]_4\text{CH}_3$ reactant coupled to a very soft virtual spring exerting the force of 5 nN, followed by the scan of the scissile C-C distance in this construct, stability test, frequency calculation of the highest-energy scan point, Berny reoptimization and another frequency calculations. TSs of C-C homolysis at all other forces were optimized by using the converged TS coupled to 5 nN and adjusting the equilibrium distance of the spring to exert a new force. The converged wavefunctions of all open shell structures were stable as confirmed by the stability test. The nature (minimum vs. saddle point) of all converged strain-free and select force-coupled geometries was confirmed by analytical frequency calculations.

Thermodynamic corrections (*TCs*) to electronic energies of individual converged geometries were calculated statistical-mechanically in the pseudo-harmonic oscillator/rigid rotor/ideal gas approximations, as $3RT + ZPE + U_{\text{vib}} - TS$, where *ZPE* is the zero-point energy, U_{vib} is the vibrational component of the internal energy and *S* is the total entropy. Vibrational frequencies below 500 cm^{-1} were replaced with 500 cm^{-1} as previously recommended,⁶³ to avoid the artifactually high contribution of such low-frequency modes to the vibrational entropy. The use of analytical frequencies calculated on converged force-coupled geometries in this study is theoretically sound because the calculation is performed on the molecule plus its infinitely-compliant constraint (rather than just the molecule), which is a stationary point with all internal forces at 0.^{20,64}

The C-C bond of the styrene repeat unit accounts for 99.5 – 99.97% of the backbone bonds in the polymers used in our study. The remaining backbone bonds contribute negligibly to chain fracture because (a) their calculated activation free energies were either higher or comparable to those of the primary backbone bond at all practically relevant forces (Extended Data Fig. 2) and (b) they are present in too small a fraction to effectively compete with the primary bond type.

Modelling

Overall approach and background concepts

The observed changes in the MMDs and χ_Z of sonicated solutions of **1c-5o** reflect the apparent bulk stoichiometry of the mechanochemical reactions of *Z*-SS, *E*-SS and SS-free polymer chains (eqs. 7-9, a>b). In eqs. 7-9, $\eta_{a,b}$ reflects mechanochemical selectivity; $\omega_{a,b}$ is the fraction of fragmented chains that simultaneously isomerized (magenta arrow in Fig. 3b) and γ_i is the fraction of fragmented chains from dissociation of the i^{th} backbone bond (or i^{th} monomer, depending on assumptions). Eqs. 7-9

accommodate the experimental observation that $\eta_{a,b}$ and $\omega_{a,b}$ depend on both chain size (as expressed by the degree of polymerization, $DP = a+b$) and the location of Z-SS in the chain (e.g., Fig. 3b), whereas fragmentation stoichiometry depends only on the chain DP, but not on the location of SS, its isomeric state or its presence (e.g., Supplementary Fig. 15), i.e., each γ_i is the same in eqs. 7-9.

$$\begin{aligned} PS_a Z_{SS} PS_b \rightarrow & \eta_{a,b} PS_a E_{SS} PS_b + (1 \\ & - \eta_{a,b}) \left[(1 - \omega_{a,b}) \left(\sum_{i=1}^a \gamma_i PS_{a-i} Z_{SS} PS_b + \sum_{i=1}^b \gamma_i PS_a Z_{SS} PS_{b-i} \right) \right. \\ & \left. + \omega_{a,b} \left(\sum_{i=1}^a \gamma_i PS_{a-i} E_{SS} PS_b + \sum_{i=1}^b \gamma_i PS_a E_{SS} PS_{b-i} \right) + 2 \sum_{i=1}^b \gamma_i PS_i + \sum_{i=b+1}^a \gamma_i PS_i \right] \quad (\text{eq. 7}) \end{aligned}$$

$$PS_a E_{SS} PS_b \rightarrow \sum_{i=1}^a \gamma_i PS_{a-i} E_{SS} PS_b + \sum_{i=1}^b \gamma_i PS_a E_{SS} PS_{b-i} + 2 \sum_{i=1}^b \gamma_i PS_i + \sum_{i=b+1}^a \gamma_i PS_i \quad (\text{eq. 8})$$

$$PS_{a+b} \rightarrow \sum_{i=1}^{a+b-1} \gamma_i PS_{a+b-i} \quad (\text{eq. 9})$$

The knowledge of these stoichiometric coefficients for all chains of equal or smaller DP than the largest chain present initially suffices to predict the composition of a remodeling bulk sample at an arbitrary extent of remodeling. In our work, we assumed that reacting chains of identical DP experience a distribution of conditions, and treated the sets of stoichiometric coefficients defining the mechanochemistry of chains of each DP as the DP-specific condition-averaged distributions along the backbone (Extended Data Fig. 4) of

- relative fragmentation probabilities, $\langle P_{frag} \rangle$, containing all γ_i ($i=1:DP$),
- fragmentation-coupled isomerization probabilities, $\langle P_{fciso} \rangle$, containing $\omega_{a,b}$ for all a,b combinations consistent with chain $DP=a+b$.
- ratio of fractions of overstretched Z-SS chains that isomerize without fracturing and of chains that fracture, $\langle \rho \rangle$, similarly containing all $\eta_{a,b} = (1 + \langle \rho(a, a+b) \rangle)^{-1}$.

The objective of modeling is to relate these apparent stoichiometric coefficients to the distribution of molecular conditions experienced by individual reacting chains using model-dependent parameters:

1. Overstretched chain: f_{max} , or constant linear or exponential loading rate ($\partial f_{max}/\partial t$ or $\partial \ln(f_{max})/\partial t$).
2. Overstretched segment: 2-4 parameters defining the distribution of overstretched segments and for each segment, the number of monomers, distance between segment and chain centers, and f_{max} .
3. Dynamic model: k_s , k_d , α and β explained in the main text.

Every model also has the parameter specifying how long the chain experiences the conditions, $t_{stretch}$. In all cases, the force on each monomer becomes 0 at $t_{stretch}$ or at chain fracture. All parameters were assumed to be independent of the presence of SS in the chain, or the reaction extent (and hence composition of the solution and the sonication time).

A model is consistent with experiment if combinations of model parameters and the fractions of reacting chains described by each combination exist that reproduce measured MMDs and χ_z for all studied chain sizes, SS distributions and remodeling extents. Converting a parameter set to MMDs and χ_z followed a similar workflow protocol for all models, with steps 1-3 applied to chains of each DP of interest:

1. calculate single-chain force profile, F , i.e., the restoring force of each monomer of a chain subject to conditions defined by a given combination of model parameters; if the force on

any monomer changes during stretching, calculate all force profiles up to t_{stretch} in suitable increments Δt .

2. convert force profile(s) from 1 to single-condition reaction probability distributions P_{frag} , P_{fciso} and ρ . These are collections of the stoichiometric coefficients of mechanochemical reactions (eqs. 7-9) in a single reacting chain and apply only to a specific set of molecular conditions (microenvironment).
3. generate condition-averaged single-DP $\langle P_{\text{frag}} \rangle$, $\langle P_{\text{fciso}} \rangle$ and $\langle \rho \rangle$ as weighted sum of multiple single-condition P_{frag} , P_{fciso} and ρ by defining the relative probabilities of each combination of the underlying model parameters to occur in a sonicated sample.
4. convert $\langle P_{\text{frag}} \rangle$, $\langle P_{\text{fciso}} \rangle$ and $\langle \rho \rangle$ covering a suitable range of chain DPs to MMDs and χ_z for each studied polymer **1c-5o** using the corresponding derived microscopic initial composition and measured bulk mass-dependent rate constants k_f (Fig. 3). This is the most resource-demanding step, particularly for chains with DP >1000 (~105 kDa for PS).

For models that assume stationary overstretched segments, F , P_{frag} , P_{fciso} and ρ need to be calculated only for segments of unique lengths; single-DP $\langle P_{\text{frag}} \rangle$, $\langle P_{\text{fciso}} \rangle$ and $\langle \rho \rangle$ are constructed from such segmental P_{frag} , P_{fciso} and ρ by using the distributions of overstretched segments in chains (e.g., eq. S11). Functional forms of F , P_{frag} , P_{fciso} and ρ for time-invariant force are given by eqs. S3-S5 and for time-dependent force by eqs. S6-S8.

Generation of model-derived MMDs and mass-resolved χ_z .

Measured MMDs and mass-resolved χ_z are determined by (a) the stoichiometries of mechanochemical reactions (eq. 7-9) of overstretched chains of every DP present in solution, averaged over the range of microscopic conditions present in the experiment and (b) the relative probabilities of a chain of each DP to become mechanochemically active. The former is reflected by $\langle P_{\text{frag}} \rangle$, $\langle P_{\text{fciso}} \rangle$ and $\langle \rho \rangle$ for each DP. In this work we calculated model-derived $\langle P_{\text{frag}} \rangle$, $\langle P_{\text{fciso}} \rangle$ and $\langle \rho \rangle$ for DP = 100, 250, 500, 750, 1250, 2000 and 3000. The latter is not available from existing molecular models but is captured by measured mass-scaling of bulk fragmentation rates, k_f (Fig. 3a). To simulate the evolution of MMDs and χ_z predicted by specific model for a given initial polymer composition we

1. interpolated model-derived $\langle P_{\text{frag}} \rangle$, $\langle P_{\text{fciso}} \rangle$ and $\langle \rho \rangle$ to every DP between 101 and DP_{max} ($DP_{\text{max}} \leq 3000$ is the largest chain in the initial sample) in 1 monomer increments;
2. calculated k_f for each DP between 100 and DP_{max} in 1-monomer increments using the polynomial from least-squares fitting of measured k_f vs. chain mass (black line Fig. 3a);
3. assumed that chains with $DP < 100$ react at the same DP-independent rate to the same DP-independent mixture of products as chains of 100 monomers (our samples didn't have any chains with $DP > 3000$ and measured MMDs had negligible contributions from chains with $DP < 100$)

Model-predicted changes in MMDs only are derivable from $\langle P_{\text{frag}} \rangle$ by eq. 10,

$$\begin{bmatrix} C_{i+1} \\ C_{i+1} \end{bmatrix} = \begin{bmatrix} 2P_{\text{frag}} \times (C_i \circ K)\Delta t \\ 0 \end{bmatrix} - \begin{bmatrix} 0 \\ C_i \circ (1 - K\Delta t) \end{bmatrix} \quad (\text{eq. 10})$$

Where

- C_i is an $(DP_{\text{max}}-1) \times 1$ vector of the number of chains with DP from 2 to DP_{max} , at simulation time i ; c_i is the number of chains of $DP=1$;
- K is an $(DP_{\text{max}}-1) \times 1$ vector of DP-dependent bulk fragmentation rate constants, such that $K(j)$ is the fragmentation rate constant for chain of $DP = j+1$;
- Δt is the timestep of the simulation (such that $K(DP_{\text{max}})\Delta t < 0.002$, although larger timesteps can be used to reduce the computation time at the expense of accuracy of compositions);
- P_{frag} is an $(m-1) \times (m-1)$ upper triangular matrix of $\langle P_{\text{frag}} \rangle$ of chains with DP from 2 to DP_{max} that satisfies conditions of eq. 11 ($j = \text{chain DP}$). The factor of 2 preceding P_{frag} reflects the fact that

each chain fracture produces two chains, i.e., the number of chains in a sonicated solution grows with sonication time (the mass balance is preserved because smaller chains have fewer monomers, i.e., $(1:DP_{\max})C_i = \text{constant}$ for any i)

$$P(i, j) = \begin{cases} 0 & \text{if } i > j \\ \langle P_{\text{frag}}(i, j) \rangle & \text{if } i \leq j \end{cases} \quad (\text{eq. 11})$$

and \circ is the element-wise (Hadamard) multiplication.

Simulating MMDs and χ_z simultaneously is much more demanding than simulating MMDs alone, and for **1c-5o** requires keeping track of concentrations (or absolute amounts for fixed-volume simulations as we did) of between $\sim 20,000$ (**1c**) and ~ 1 million (**4c**) components, i.e., chains of each DP that are either SS-free or containing either Z-SS or E-SS at all possible locations along the backbone. Because every mechanochemical fragmentation yields multiple products (eqs. 7-9) and almost every component is generated by multiple reactions, modeling the bulk composition of the solution requires numerical propagation of a system of coupled linear differential equations.

For this work we simplified a previously reported code for microkinetic modeling of bulk mechanochemical reactions (the adapted Matlab code is provided in the Code section of the SI with the usage notes and explanations; examples of input/output pairs are available at ⁶⁵). The depletion of macromolecular component, X, ($DP_X > 1$) during simulation step i , $\Delta_r C_{i+1}^X$ follows eq. 12 for X containing Z-SS at i^{th} monomer and eq. 13 for X being an E-SS or SS-free macromolecule. In eqs. 12-13, $k_f(DP_X)$ is the bulk fragmentation rate constant for DP_X and $\langle \rho(i_{ZSS}, DP_X) \rangle$ is the ratio of overstretched chains of X that isomerize without fracture to those that fracture, averaged over all microscopic conditions encountered in the sample (eqs. S5, S8):

$$\Delta_r C_{i+1}^X = -C_i^X k_f(DP_X)(1 + \langle \rho(i_{ZSS}, DP_X) \rangle) \Delta t \quad (\text{eq. 12})$$

$$\Delta_r C_{i+1}^X = -C_i^X k_f(DP_X) \Delta t \quad (\text{eq. 13})$$

The number of chains produced by depletion of each component X is then derived from $\Delta_r C_{i+1}^X$ and the reaction stoichiometry of X (eq. 7-9) contained in DP-specific $\langle P_{\text{frag}} \rangle$, $\langle P_{\text{fciso}} \rangle$ and $\langle \rho \rangle$.

Parameterization of the models

Each model was parameterized by finding combinations of model parameters and their relative weights that maximize the agreement between simulated and measured MMDs and χ_z across the full range of studied initial compositions. This agreement was quantified as the total scaled norm of residuals, obtained by summing eq. 14 over all 9 polymers **1c-5o**. In eq. 14 mf is mass-fraction, t_j is sonication time at which the composition of the sample was determined, n is the total number of sonication times with quantified solution composition, $DP_{\min}(t_j)$ and $DP_{\max}(t_j)$ are the DP of the shortest and longest chains with measured mass fractions at each t_j ; $DP'_{\min}(t_j)$ and $DP'_{\max}(t_j)$ are the same limits for χ_z^{exp} ; χ_z^{sim} are rebinned to match the 1 kDa increment of χ_z^{exp} . The 0.05 scaling factor accounts for the average value of χ_z^{exp} being ~ 200 -times larger than mf_{exp} and 10 times fewer χ_z^{exp} values at each t_j because χ_z^{exp} is quantified every 1 kDa and mf_{exp} every 100 Da.

$$\frac{1}{n} \sum_{j=1}^n \left(\frac{1}{DP_{\max}(t_j) - DP_{\min}(t_j)} \sum_{i=DP_{\min}(t_j)}^{DP_{\max}(t_j)} (mf_{\text{exp}}(i, t_j) - mf_{\text{sim}}(i, t_j))^2 + \frac{0.05}{DP'_{\max}(t_j) - DP'_{\min}(t_j)} \sum_{i=DP'_{\min}(t_j)}^{DP'_{\max}(t_j)} (\chi_z^{\text{exp}}(i, t_j) - \chi_z^{\text{sim}}(i, t_j))^2 \right) \quad (\text{eq. 14})$$

Alternative data-consistent forms of eqs. 1-3.

Eqs. 1-3 can only be parameterized at $f_{\max} \geq 2.5$ nN because chains with $f_{\max} < 2.5$ nN don't affect the

bulk composition. Consequently, currently eqs. 1-3 are empirically indistinguishable from eqs. 15-17, which describe the evolution of the segment only after its f_{\max} reaches 2.5 nN, with the segment length, λ_o , and its center, δ_o , at the stretching time, t_o , when $f_{\max} = 2.5$ nN being additional model parameters.

$$\lambda_{os} = 1 - (1 - \lambda_o)e^{-k_s \Delta t} \quad (\text{eq. 15})$$

$$\delta = 0.5 - 0.5(1 - \delta_o)e^{-(k_s + k_d)\Delta t} \quad (\text{eq. 16})$$

$$f_{\max} = (\alpha + \beta t_o + \beta \Delta t)\lambda_{os}^2 \quad (\text{eq. 17})$$

These additional parameters increase the computational cost of fitting eqs. 15-17 without affecting the outcome as evidenced by eqs. 15-17 producing the same microenvironment-averaged reaction-probability distributions (Fig. 6a-b) as eqs. 1-3 using the values of λ_o , δ_o and t_o derived from parameterized eqs. 1-3 (Extended Data Fig. 4c and 4e). Consequently, the capacity of our model to reproduce the measurements quantitatively is not predicated on its assumption that overstretched segments originate at a terminus.

Eq. 1 is the integral form of eq. 18, in which the instantaneous rate of elongation of λ_{os} is proportional to the instantaneous fraction of the backbone that is not overstretched with a time-independent k . However, the available experimental data are likely insufficient to rule out more complex rate laws. For example, the rate constant that increases with t (eq. 19) yields an integral form (eq. 20) that can be approximated with a linear combination of eq. 1. Because reacting chains populate diverse microenvironments, any model requires a distribution of parameters to reproduce measured bulk mechanochemistry and a single distribution of k_s (Extended Data Fig. 5) is indistinguishable from a sum of distributions of k_i without additional currently-unavailable data. The same argument applies to k_d .

$$\frac{\partial \lambda_{os}}{\partial t} = k(1 - \lambda_{os}) \quad (\text{eq. 18})$$

$$\frac{\partial \lambda_{os}}{\partial t} = (\gamma + vt)(1 - \lambda_{os}) \quad (\text{eq. 19})$$

$$\lambda_{os} = 1 - e^{-t(\gamma + 0.5vt)} \approx 1 - a_1 e^{-b_1 t} - (1 - a_1)e^{-b_2 t} \quad (\text{eq. 20})$$

Eq. 1 is also derivable from finding that fractional extensions of linear chains in flows increase approximately linearly with their Hencky strains until close to full extension,⁷ and the approximately exponential dependence of the Hencky strain of a fluid element in the proximity of an imploding bubble on single μs residence timescale, based on the Keller–Miksis model³² and some plausible parameter values. In this approach, k_s , is expected to scale not with the time-dependent fluid strain-rate, $\dot{\epsilon}(t)$, but $\log_e(\dot{\epsilon}(t))$.

Method Section References

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Data availability: the data discussed in the main text and the SI are tabulated in the Supplementary

data file suppdata.mat

Code availability: This work used a simplified version of the previously reported Matlab code for simulating the composition of a sonicated solution, provided in the Supplementary information along with the instructions for use. The full code with examples of input/output datasets is available at <https://datacat.liverpool.ac.uk/1697/>