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Force–Reactivity Property of a Single Monomer Is Sufficient To Predict the Micromechanical Behavior of Its Polymer

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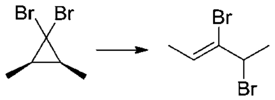
Ⓢ *Supporting Information*

ABSTRACT: We demonstrate an accurate prediction of the micromechanical behavior of a single chain of cyclopropanated polybutadiene, which is governed by rapid isomerization of the cyclopropane moieties at ~1.2 nN, from the force–rate correlation of this reaction measured in a small series of increasingly strained macrocycles. The data demonstrate that a single physical quantity, force, uniquely defines the dynamics across length scales from >100 to <1 nm and that strain imposed through molecular design and that imposed by micromanipulation techniques have equivalent effects on the kinetics of a chemical reaction. This represents a new method of screening potential monomers for applications in stress-responsive materials that could also facilitate atomistic interpretations of single-molecule force experiments.

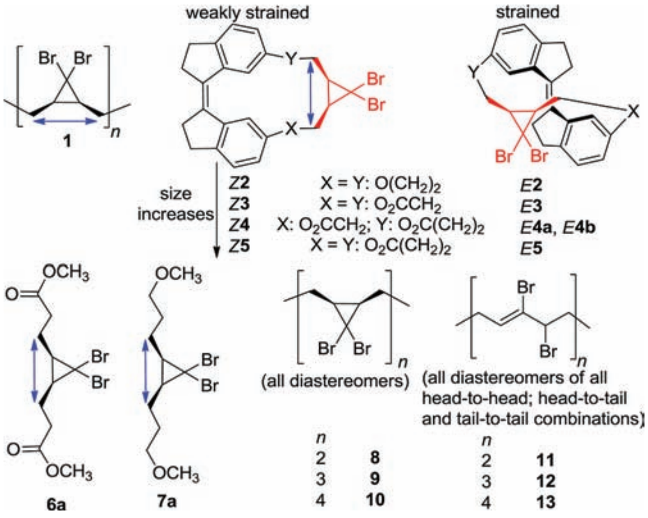
Stretching a polymer can significantly change the reactivity of its constituent monomers.[1] Such changes are thought to contribute to the response of polymeric materials to external loads and the behavior of polymers in shear flows.[2,3] Understanding these phenomena at the molecular level and designing new stress-responsive,[2,4] photoactuating,[5] and other energy-transducing materials require a means of extrapolating the kinetics of a localized reaction in a stretched polymer from that of a suitable small-molecule reactant.[6]

The effect of stretching a polymer on the reactivity of its monomers is typically quantified as a correlation between the reaction rate and the force needed to stretch the polymer. For a few localized reactions, such rate–force correlations can be measured in single-molecule force experiments. To date, the results of such experiments could not be predicted a priori (e.g., from the reactivity of individual monomers).[2] Here we demonstrate that a force–rate correlation measured for a series of increasingly strained macrocycles **2**–**5** (Scheme 1) allows an accurate prediction of the previously reported[7] experimental force-induced extension of poly(*cis*-dibromocyclopropane) (**1**) (Scheme 1), which is dominated by strain-induced acceleration of reaction 1. In contrast, the standard model of chemomechanical kinetics[8] failed to reproduce this force–extension behavior.[7] These results establish the equivalency of kinetic effects resulting from strain imposed by molecular design and by micromanipulation techniques. Establishing such a homology[9] across the "length gap" separating traditional chemistry and covalent mechanochemistry has been a long-standing goal of the field.[2,10,11]



(1)

Scheme 1. Molecular Structures of the Studied Compounds[a]



[a]In definitions of X and Y, the leftmost atom is stilbene-bound. *E*4**a** and *E*4**b** are diastereomers. The local coordinates are defined by blue arrows. Schemes S6 and S7 list the isomers constituting **8**–**13**.

We studied the force-dependent ring-opening of *gem*-dibromocyclopropane because (1) the reaction may form the basis of new types of stress-responsive polymers of unprecedented toughness[2,4,12,13] and (2) among force–extension behavior derived from single-molecule force measurements, that of polymer **1** is unique because it reflects the reaction of thousands of monomers, that is, it represents the ensemble-averaged reactivity of cyclopropane in a microscopically strained sample.[7] To quantify the rate of reaction 1 as a function of the restoring force of an individually strained cyclopropane moiety, we measured the ring-opening kinetics of cyclopropane in macrocycles **2**–**5**. The molecular architectures of such macrocycles mimic the distribution of restoring forces of reactive sites in stretched polymers[10] and allow such forces to be varied systematically in small increments and over a sufficiently large range to obtain accurate trends.

Scheme 2 shows the syntheses of the *Z* isomers of macrocycles **2**–**5**. Irradiating a micromolar solution of each *Z*

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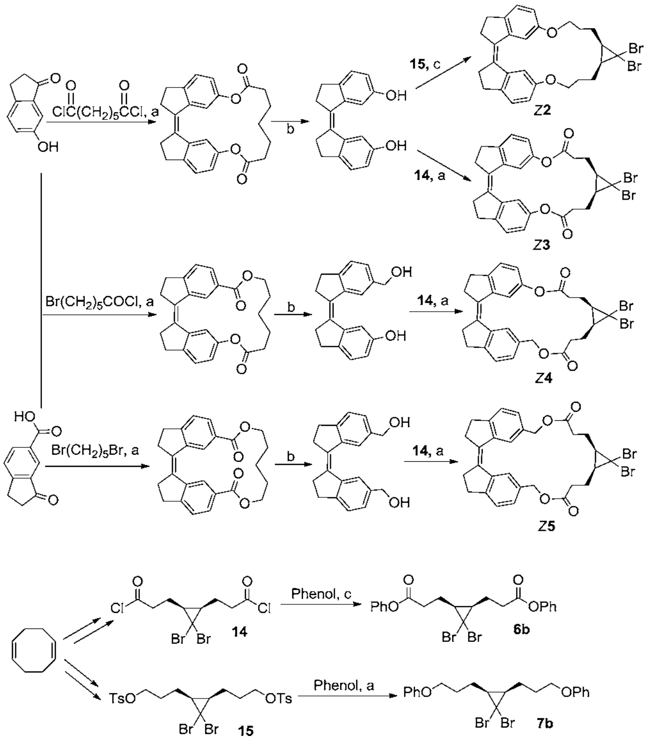
Scheme 2. Syntheses of Compounds 2−7[a]



[a]Conditions: (a) K_2CO_3, Bu_4NBr, DMF; (b) $LiAlH_4$, THF; (c) Et_3N, $CHCl_3$. See Scheme S1 for full details.

analogue in hexanes at 375 nm yielded a photostationary state containing up to 60% *E* isomer [Table S2 in the Supporting Information (SI)]. We used both the photostationary states and isolated *E* isomers in kinetic studies. We measured the activation parameters of reaction 1 by heating ~40 μm solutions of **2**−**7** in anhydrous deoxygenated $CH_3O(CH_2)_2CN$ in the dark to 100−140 °C (*Z* isomers) or 60−140 °C (*E* isomers) for at least two reaction half-lives and analyzing the composition by HPLC. ^{1}H NMR spectroscopy and high-resolution mass spectrometry confirmed the clean conversion of the dibromocyclopropanes into 2,3-dibromoalkenyl moieties. The measured activation parameters are summarized in Table 1.

To extrapolate the measured kinetics of reaction 1 in macrocycles **2**−**5** to the micromechanical behavior of polymer **1**, we calculated at the B3LYP/6-311+G* level of density functional theory in the gas phase (1) the restoring force of the local coordinate of the reactive moiety, f_l, in each macrocycle (blue arrows in Scheme 1) and (2) the relationship between f_l and the constraining force f acting on the C atoms of the terminal CH_3 groups of polymer **1** of an arbitrary length. The suitability of the B3LYP/6311+G* level for this reaction is supported by the good agreement between the calculated and measured activation parameters of reaction 1 for compounds **2**−**7** (mean absolute deviation 0.8 kcal/mol; Table 1).[14−16]

Table 1. Key Parameters of Compounds 1−7

	experimental		B3LYP/6-311+G* calculated		
	$\Delta G^{\ddagger\circ\ a}$	$\Delta\Delta G^{\ddagger\ a}$	$\Delta G^{\ddagger\circ\ a}$	$\langle q_l \rangle$ (Å)	$\langle f_l \rangle$ (pN)
*Z*2	29.3 ± 0.2	1.5 ± 0.4	32.1	3.249	40
*Z*3	29.3 ± 0.1	3.6 ± 0.5	31.2	3.271	150
*Z*4	31.1 ± 0.1	1.8 ± 0.3	31.6	3.252	100
*Z*5	29.9 ± 0.1	3.0 ± 0.3	30.3	3.272	165
*E*2	27.2 ± 0.1	3.6 ± 0.3	28.3	3.320	210
*E*3	26.5 ± 0.1	6.4 ± 0.3	27.3	3.361	400
*E*4a	28.2 ± 0.1	4.7 ± 0.3	29.4	3.347	360
*E*4b	29.6 ± 0.2	3.3 ± 0.3	30.4	3.279	175
*E*5	30.9 ± 0.2	2.0 ± 0.3	32.2	3.261	110
6	32.9 ± 0.5		33.1	3.219	
7	30.8 ± 0.3		30.9	3.230	

[a]Values in kcal/mol. For **6** and **7**, the experimental $\Delta G^{\ddagger\circ}$ values are for **6b** and **7b** (Scheme 2) and the calculated values are for **6a** and **7a**. For macrocycle **2** (ether stilbene−cyclopropane link), $\Delta\Delta G^{\ddagger}$ is defined relative to the standard free energy of activation of unconstrained (i.e., stilbene-free) strap **7b** [i.e., $\Delta\Delta G^{\ddagger}(\mathbf{2}) = \Delta G^{\ddagger\circ}(\mathbf{7b}) - \Delta G^{\ddagger\circ}(\mathbf{2})$]. For macrocycles **3**−**5** (ester stilbene−cyclopropane link), $\Delta\Delta G^{\ddagger}$ is defined relative to the standard free energy of activation of unconstrained (i.e., stilbene-free) strap **6b** [i.e., $\Delta\Delta G^{\ddagger}(n) = \Delta G^{\ddagger\circ}(\mathbf{6b}) - \Delta G^{\ddagger\circ}(n)$ for n = 3−5).

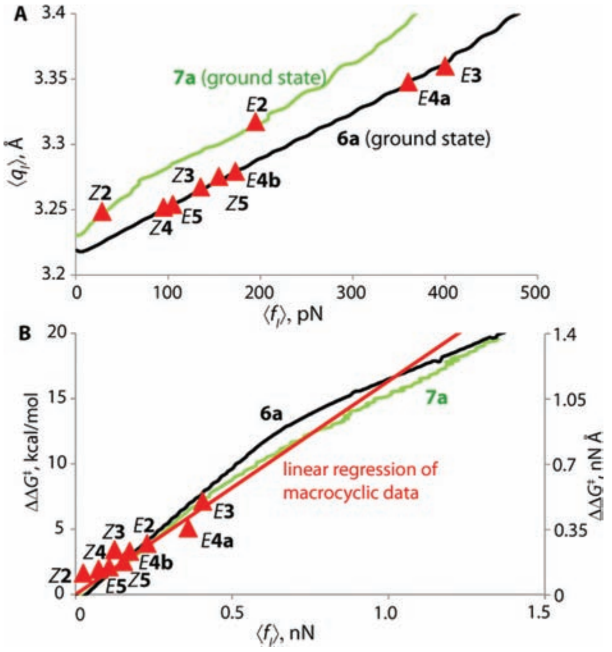


Figure 1. (A) Computed relationships between the ensemble-averaged length of a local coordinate of the cyclopropane moiety and its restoring force coupled to a constraining potential across the C atoms of the terminal CH_3 groups.[17] in derivatives **6a** and **7a** (black and green lines, respectively) and the ensemble-averaged lengths of the same local coordinate of the cyclopropane moiety in the ground states of macrocycles **2**−**5** (red ▲). (B) Relationships between the strain-induced barrier lowering and the local restoring force of the cyclopropane moiety in **6a** and **7a** (solid lines, calculated) and macrocycles **2**−**5** (red ▲, measured). Values of $\langle q_l \rangle$ and $\Delta\Delta G^{\ddagger}$ are listed in Table 1; the rest of the data are given in Tables S16 and S17.

We first calculated force−extension curves of conformational ensembles of cyclopropanes **6a** and **7a** (Scheme 1), applying to each conformer an identical force between the C atoms of the terminal CH_3 groups.[6,17] Derivatives **6** and **7** are analogues of macrocycles **2**−**5** without the constraining, stiff stilbene. These calculations yielded a correlation between $\langle q_l \rangle$, the length of the local coordinate *l*, and its restoring force $\langle f_l \rangle$. (Figure 1A). By comparing $\langle q_l \rangle$ in the ground state of each macrocycle to this correlation (Figure 1A), we obtained the corresponding local restoring forces (Table 1) and the relationship between the restoring force and the measured activation-energy lowering for each macrocycle (Figure 1B).

The slope of 1.12 Å for the linear regression of the force-dependent barrier lowering $\Delta\Delta G^{\ddagger}(f_l)$ for the macrocycles

(Figure 1B, red line) is similar to the previously reported coefficient of proportionality between the barrier lowering of reaction 1 in polymer **1** and the stretching force *f* applied to the polymer termini by an atomic force microscope (AFM). This fact is consistent with our quantum-chemical calculations of the relationship between local restoring and stretching forces (chemomechanical coupling) in *gem*-dibromocyclopropane oligomers (see below), which indicate that when stretched to forces above ~1 nN, polymer **1** acts as an almost ideal force transducer: the force applied at the termini of a ~100 nm long chain of polycyclopropane is nearly identical to the restoring force of the local coordinate *l* generated within an individual monomer (Scheme 1).

The slope of ~1.1 Å for the force−energy correlation is significantly less than the difference in the values of the local coordinate *l* in the strain-free ground and transition states, $\Delta\langle q_l\rangle_0$, of **6a**, **7a**, and **8** (1.40 Å), in violation of the minimal model of chemomechanics.[6,8,20] To understand the cause of this deviation, we calculated $\Delta\Delta G^{\ddagger}(f_l)$ in **6a** and **7a** by optimizing their transition states coupled to a massless, infinitely soft harmonic constraint.[17] The computed and extrapolated $\Delta\Delta G^{\ddagger}(f_l)$ values are in good agreement (Figure 1B), with the lower slopes resulting from the breakdown of two key assumptions of the minimal model: (1) the ensemble-averaged restoring force of the local coordinate of the transition state, $\langle f_l\rangle^{\ddagger}$, is considerably less than either the constraining force *f* (Table S16 and Figure S10) or the local force $\langle f_l\rangle$ in the ground state, and (2) the difference in the lengths of the local coordinate *l* in the ground and transition states, $\Delta\langle q_l\rangle$, decreases with the constraining force (Figure S11).

To extrapolate the macrocyclic data in Table 1 to the micromechanical behavior of polymer **1** (i.e., to predict its force−extension curve), one needs (1) the relationship between the local force of the cyclopropane moiety $\langle f_l\rangle$ and the force acting at the termini of polymer **1** and (2) the compliances of the end-to-end distance[10] of polymer **1** and its ring-opened isomer. To obtain these data, we optimized the ground states of dibromocyclopropane oligomers **8**−**10** and the corresponding dibromopentenes **11**−**13** constrained by an infinitely soft, massless harmonic potential at the C atoms of the terminal CH_3 groups.[17] Figure 2 shows the calculated ratio of the local restoring force to the constraining force, $\langle f_l\rangle/f$ (i.e., the chemomechanical coupling coefficient[6,19]) and the normalized extension $\langle q\rangle/q_0$ as functions of *f*. Since the $\langle f_l\rangle/f$ ratios for oligomers **8**−**10** are identical for $f > 750$ nm, we assumed the ratio to be independent of the polymer length (for weaker forces, reaction 1 is too slow, and the observed force−extension curves[7] are independent of $\langle f_l\rangle/f$). Finally, we estimated the harmonic compliances[10] of polymer **1** studied by Craig[7] by linear extrapolation of the compliances of the terminal C···C distances of complete conformational ensembles of **8**−**13** to the strain-free contour lengths of Craig's polymer (Figure S12), as was done previously for homologous series of constrained hydrocarbons.[10] The extrapolated compliances were 7.2 and 3.1 m/N for the cyclopropane and alkene isomers of the polymer, respectively, versus 7.7 and 2.9 m/N derived by linear regression of the experimental force−extension curve at 0.4−1 and 1.3−1.5 nN.

Figure 3 compares the experimental force−extension curve of polymer **1** reported by Craig with those calculated from the $\Delta\Delta G^{\ddagger}(f)$ correlations obtained by combining (1) $\Delta\Delta G^{\ddagger}(f_l)$ from linear regression of the macrocyclic data (red line in Figure 1B) or (2) average DFT-calculated $\Delta\Delta G^{\ddagger}(f_l)$ for **6a** and **7a** (Figure 2A) with the $\langle f_l\rangle/f$ ratios. The force−extension curves were computed by a recursive scheme using only the data from Figure 1B, the experimental extension rate of 3 μm/s, the polymer lengths at 1 and 1.5 nN (to estimate the polymer compliances[17] as described above), and the strain-free rate constant for ring opening of 3.1×10^{-11} s^{-1} (based on the $\Delta G^{\ddagger\circ}$ value of 32.2 kcal/mol calculated for dimer **8** at the B3LYP/6-311+G* level). The agreement between the measured force−extension curve and that derived from the macrocyclic data is remarkable, considering that the latter is based on an extrapolation of the cyclopropane reactivity over 11 orders of magnitude of the rate constant and an applied strain of over 100 nm.

In summary, we have demonstrated that the chemically driven micromechanical behavior of a polymer can be predicted with useful accuracy from two readily accessible pieces of data: (1) the kinetic stability of an isolated monomer as a function of the restoring force of one of its local coordinates (i.e., an intrinsic force−reactivity sensitivity of a monomer) and (2) the

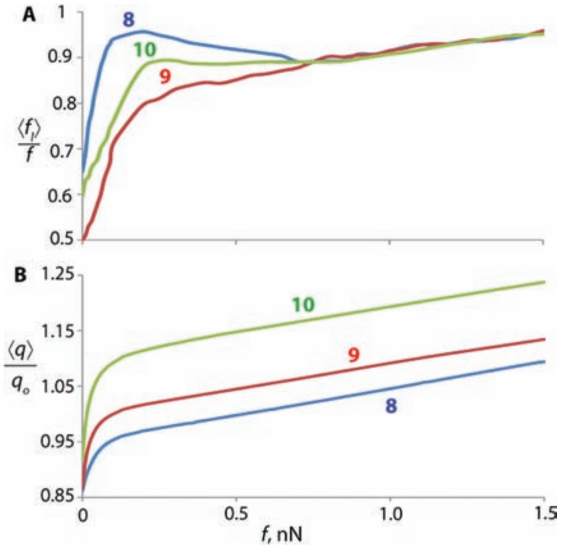


Figure 2. (A) Coupling between the local and constraining forces, $\langle f_l\rangle/f$, as a function of *f* for cyclopropane oligomers **8**−**10**. (B) Normalized extension of the terminal C···C separation vs *f* for **8**−**10**. The strain-free contour length q_0 was obtained by linear extrapolation of the harmonic part of the force−extension curves to zero force (Table S16).

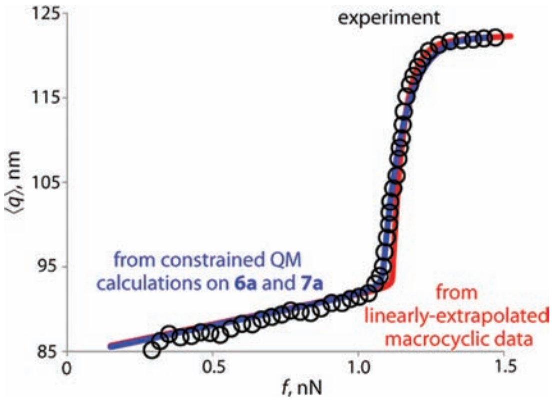


Figure 3. Measured (black ○, from Figure 1 of ref 7) and predicted (blue and red lines) force−extension curves for polymer **1**. Table S9 lists the data plotted here.

ratio of the local restoring force experienced by a monomer in its ground state to the stretching force applied at the termini of its polymer (the chemomechanical coupling coefficient). These findings are conceptually significant because they demonstrate the following:

1. A single physical quantity derived from a continuum description of matter (the stretching force, obtained from the bending of an AFM cantilever within Hooke's law) uniquely describes intrinsically atomistic dynamics (a chemical reaction). In other words, force provides a useful quantitative link between the continuum and atomistic models needed to describe the chemical response of soft matter to macroscopic loads.
2. The micromechanical behavior of a polymer ($>10^8$ molecular degrees of freedom) may not be an emergent property but rather may be determined uniquely by the properties of an isolated monomer ($<10^2$ degrees of freedom).

The ability to estimate the micromechanical behavior of a polymer from the intrinsic force−reactivity properties of an individual monomer would facilitate the development of new stress-responsive polymers,[1,11] the molecular interpretation of single-molecule force and elongational-flow experiments,[2,20] and experimental validation of theoretical and computational chemomechanical models.[6] For example, single-molecule force measurements are limited to reactions that result in an elongation of the polymer contour length by a minimum of several nanometers, whereas the intrinsic force−reactivity properties of almost any monomer or reactive site can be measured using a series of increasingly strained macrocycles.[6,10] Likewise, the computational design of polymers with specific micromechanical properties remains prohibitively expensive. In contrast, calculations of intrinsic force−reactivity correlations of individual monomers are much less resource-intensive and can be carried out at a high level of theory. Here we found excellent agreement between the force-dependent barrier lowering calculated for ensembles of simple cyclopropanes (**6a** and **7a**) and experimental $\Delta\Delta G^{\ddagger}(f)$ values. At present we lack sufficient empirical data to be confident that such an agreement is general, and for many reactions, optimizations of transition states coupled to a constrained potential remain challenging. The broad reaction scope and technical simplicity of measuring intrinsic force−reactivity properties of individual monomers using macrocyclic series could rapidly increase the number of reactions with known force−rate correlations. Such data will enable broad benchmarking of computational algorithms and identification of efficient and accurate strategies for quantum-chemical calculations of intrinsic force−reactivity properties of diverse monomers. Finally, our results suggest that intrinsic the force−reactivity property of a monomer and the chemomechanical coupling coefficient of its polymer are independent determinants of chemically driven micromechanical behavior and hence could be modified individually to maximize the diversity of mechanical properties available in polymers of the same chemical composition.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic procedures; spectroscopic characterization of macrocycles **2**−**5** and the intermediates; details of kinetic measurements and quantum-chemical computations; coordinates and energies of the optimized structures; and results of IRC calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) All converged transition-state structures passed the wave function stability test. Intrinsic reaction path (IRC) calculations (Figure S9) confirmed the concerted disrotatory mechanism of reaction 1 in broad agreement with prior work.[15,16]

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(17) The force was applied by defining an infinitely soft massless harmonic potential across the constrained distance. The infinitely long equilibrium distance q_0 of this potential (spring) ensured that it exerted force kq_0 (where k is the harmonic force constant) on any two points across which it was applied (e.g., terminal C atoms) irrespective of their equilibrium separation. In other words, the generated force was identical for all conformers of a constrained molecule regardless of their structural differences. In addtion, an infinitely soft constraining potential does not change the harmonic vibrational frequencies of the molecule, thus allowing the computation of thermodynamic properties from analytic molecular Hessians.[6] Single-molecule force experiments are often modeled by assuming that the macromolecule is stretched by an infinitely soft constraint.[18]

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