JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

A Remote Stereochemical Lever Arm Effect in Polymer Mechanochemistry

Junpeng Wang,[†] Tatiana B. Kouznetsova,[†] Zachary S. Kean,[†] Lin Fan,[‡] Brendan D. Mar,[‡] Todd J. Martínez,*[,‡] and Stephen L. Craig*[,†]

[†]Department of Chemistry, Duke University, Durham, North Carolina 27708, United States
[‡]Department of Chemistry, Stanford University, Stanford, California 94305, United States

Supporting Information

ABSTRACT: Molecular mechanisms by which to increase the activity of a mechanophore might provide access to new chemical reactions and enhanced stress-responsive behavior in mechanochemically active polymeric materials. Here, single-molecule force spectroscopy reveals that the force-induced acceleration of the electrocyclic ring opening of *gem*-dichlorocyclopropanes (*g*DCC) is sensitive to the stereochemistry of an α-alkene substituent on the *g*DCC. On the ~0.1 s time scale of the experiment, the force required to open the *E*-alkene-substituted *g*DCC was found to be 0.4 nN lower than that required in the corresponding *Z*-alkene isomer, despite the effectively identical force-free reactivities of the two isomers and the distance between the stereochemical permutation and the scissile bond of the mechanophore. Fitting the experimental data with a cusp model provides force-free activation lengths of 1.67 ± 0.05 and 1.20 ± 0.05 Å for the *E* and *Z* isomers, respectively, as compared to 1.65 and 1.24 Å derived from computational modeling.

Covalent polymer mechanochemistry has provided access to new reactivity and material properties, including biasing reaction pathways,[1] trapping structures that correspond to force-free transition states,[2,3] releasing small molecules[4] and protons,[5] activating latent catalysts,[6,7] and providing access to stress-reporting[8,9] and stress-strengthening[10] materials and electro-mechano-chemical soft display devices.[11] The ability to tune, and in particular to enhance, the activity of a given mechanophore[1] should be useful in almost all of these contexts. Here, we show that the remote stereochemistry of coupling between a *cis*-substituted *gem*-dichlorocyclopropane (*g*DCC)[12] mechanophore and the polymer chain that delivers force to the *g*DCC has a substantial impact on mechanophore activity, lowering by >30% (0.4 nN) the force necessary for reactivity on the 100 ms time scale. The stereochemical influence over mechanical response occurs without a measurable influence on the force-free reactivity of the mechanophore, representing a molecular strategy through which force-free and force-enhanced reactivity can be decoupled.

Single-molecule force spectroscopy (SMFS) has been used productively to study covalent mechanochemistry,[13−16] and we have combined SMFS and multi-mechanophore polymers to quantify the force-accelerated electrocyclic ring-opening reactivity of a series of mechanophores, such as *gem*-dihalocyclopropanes (*g*DHCs)[17−19] and benzocyclobutene.[19] The application of this approach to stereochemical coupling beyond the mechanophore is shown in Figure 1. The *g*DCCs

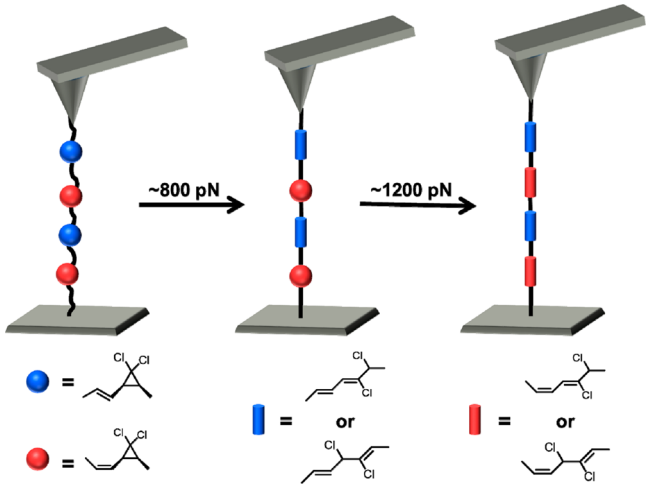

Figure 1. Pictorial representation of the SMFS experiment. The *E* (blue) and *Z* (red) α-alkene stereoisomers open in sequential transitions at ~800 and ~1200 pN, respectively.

are embedded along a polymer backbone via two different stereochemical attachments (red and blue spheres, Figure 1), and the sequential opening of the isomers is observed via the structural transitions that accompany their respective rearrangements. The substrate polymer **4** (Figure 2A) is formed by ring-opening metathesis polymerization (ROMP)[20,21] of co-monomers of *g*DCC-bearing cyclooctene **2** and epoxycyclooctene **3**, in which the epoxides are mechanically inactive in the force range of interest but increase the attachment force between the tip of the atomic force microscope (AFM)[18] and the polymer analyte.[18] The ROMP yields a mixture of stereoisomers at the α-alkene substituent on the *g*DCC. Polymers are deposited on a surface, and the AFM tip is brought into contact and then retracted at a velocity of 300 nm/s (see Supporting Information). In all cases where sufficiently high adhesion forces were obtained, two plateaus[22] (plateau forces f^* = 780 ± 40 and 1160 ± 60 pN, taken from

Received: September 16, 2014
Published: October 16, 2014

   dx.doi.org/10.1021/ja509585g | J. Am. Chem. Soc. 2014, 136, 15162−15165

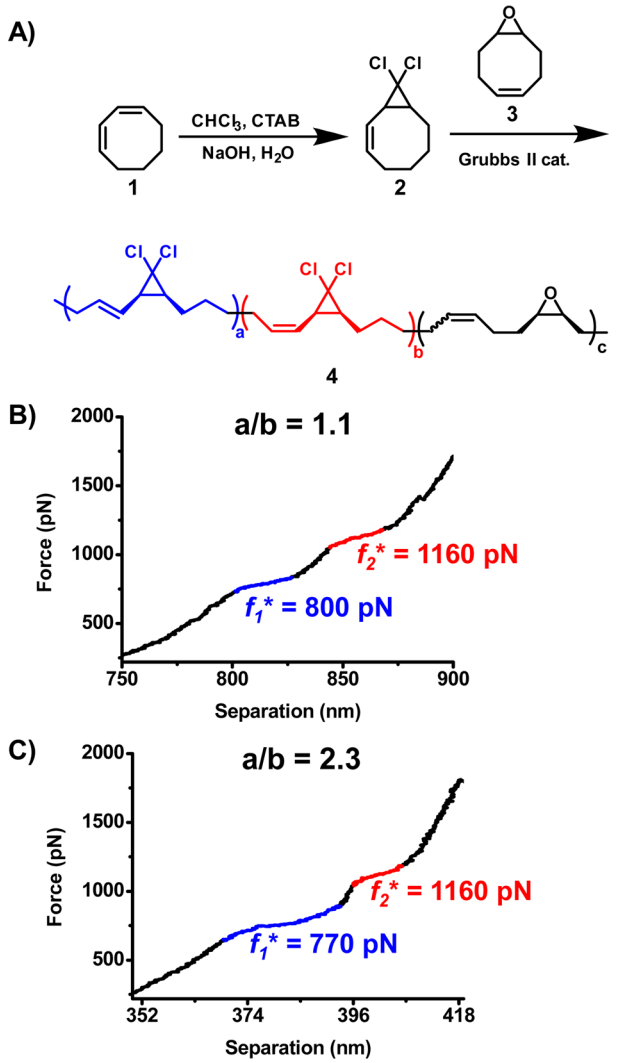

Figure 2. Synthesis of multi-mechanophore polymer **4** (A). Representative force curves of **4** with *a*:*b* = 1.1:1 (B) and 2.3:1 (C) obtained by SMFS at a retraction velocity of 300 nm/s. The blue and red regions of the plateaus are determined by inspection and provided to guide the eye only. Actual changes in contour length are determined by fitting the pre- and post-transition regions of the force curves to extended freely jointed chain models.

the midpoint of the transition[23]) were observed in the force–extension curve (Figure 2B,C), in contrast to the single plateau (f^* = 1330 pN) observed previously in *g*DCC polymers that do not have an α-alkene.[18]

Similar to the force curves of other multi-mechanophore embedded polymers,[18] the two plateaus are both structurally and kinetically consistent with the two α-alkene stereoisomers coupled to the ring opening of *g*DCC to 2,3-dichloroalkene products indicated in Figure 1. Structurally, the relative plateau lengths match those expected based on modeling the conversion of *g*DCCs to 2,3-dichloroalkenes. The ratio of *E* to *Z* isomers in **4** obtained after 30 min of ROMP is 1.1:1 (^{13}C NMR), and computational modeling predicts 4.0% extension upon ring opening of the *E* isomer and 2.9% extension in the case of the *Z* isomer. In comparison, fits to the experimental force curves provide extensions of 3.8 ± 0.5% and 2.9 ± 0.3% for the first and second transition, respectively. Polymerization of **2** under equilibrium conditions (24 h) yielded polymer **4** with an increased *E*:*Z* ratio of 2.3:1.[24−26] The plateau forces are effectively unchanged, but new fractional extensions of 7.3 ± 0.5% and 2.6 ± 0.4% at ∼770 and ∼1160 pN, respectively, vary with *E*:*Z* content as expected (7.5% and 2.3%, respectively, based on modeling).

The plateau forces are influenced by the actual length of the trapped polymer subchain, and so the kinetics of the differential reactivity is quantified by fitting each force curve independently, using force-free activation energies obtained from thermolysis experiments (see Supporting Information) and employing the cusp model[27] to describe the force−rate relationship. The cusp model accounts for changes in the shape of the reaction potential energy surface as a function of force, including the position of the transition state, and it has been shown previously to be well suited for the ring openings of dihalocyclopropanes.[18] Each fit provides a force-free activation length $\Delta x^{\ddagger}$ that corresponds to the extension along the polymer backbone that accompanies the change from ground state to transition state.[18] The values of $\Delta x^{\ddagger}$ obtained from the fits are consistent across multiple samples taken on multiple days (see Supporting Information), including individual polymers of different lengths and α-alkene *E*:*Z* content (see Table 1).

As with their fractional extensions, the differential kinetics of the two transitions can be related back to the α-alkene stereochemistry. Force-free activation lengths are determined by modeling the ground and transition state structures embedded within a polymer under tension applied by imposed geometric constraints (CoGEF[28] calculations), and extrapolated back to zero force (Figure 3). The activation lengths obtained from the computational modeling for the *E*- and *Z*-α-

Table 1. SMFS Data of Polymer 4, Including Plateau Forces, Extensions in Contour Length (Observed and Theoretical), and Activation Lengths (Obtained from Fitting SMFS Curves and Modeling) for Different Contents of *E* and *Z* Isomers

			L_f/L_i		$\Delta x^{\ddagger}$ (Å)	
polymerization time (h)	mechanophore/α-alkene content[a]	f^* (pN)	SMFS[b]	modeling[c]	SMFS	modeling
0.5	23% *E* isomer	800 ± 40	1.038 ± 0.005	1.040	1.65 ± 0.03	1.65
	21% *Z* isomer	1160 ± 50	1.029 ± 0.003	1.029	1.21 ± 0.04	1.24
24	40% *E* isomer	770 ± 40	1.073 ± 0.005	1.075	1.68 ± 0.05	1.65
	18% *Z* isomer	1160 ± 70	1.026 ± 0.004	1.023	1.20 ± 0.05	1.24

[a]Determined from ^{1}H NMR and ^{13}C NMR. [b]Ratio of contour length after plateau to that before plateau; the contour length is obtained by fitting the pre- and post-transition force curves to a modified freely jointed chain model as described previously.[18] [c]Ratio of contour length after plateau to that before plateau; the contour length is obtained by modeling (for details, see Supporting Information). All data were obtained at a retraction velocity of 300 nm/s.

dx.doi.org/10.1021/ja509585g | J. Am. Chem. Soc. 2014, 136, 15162−15165

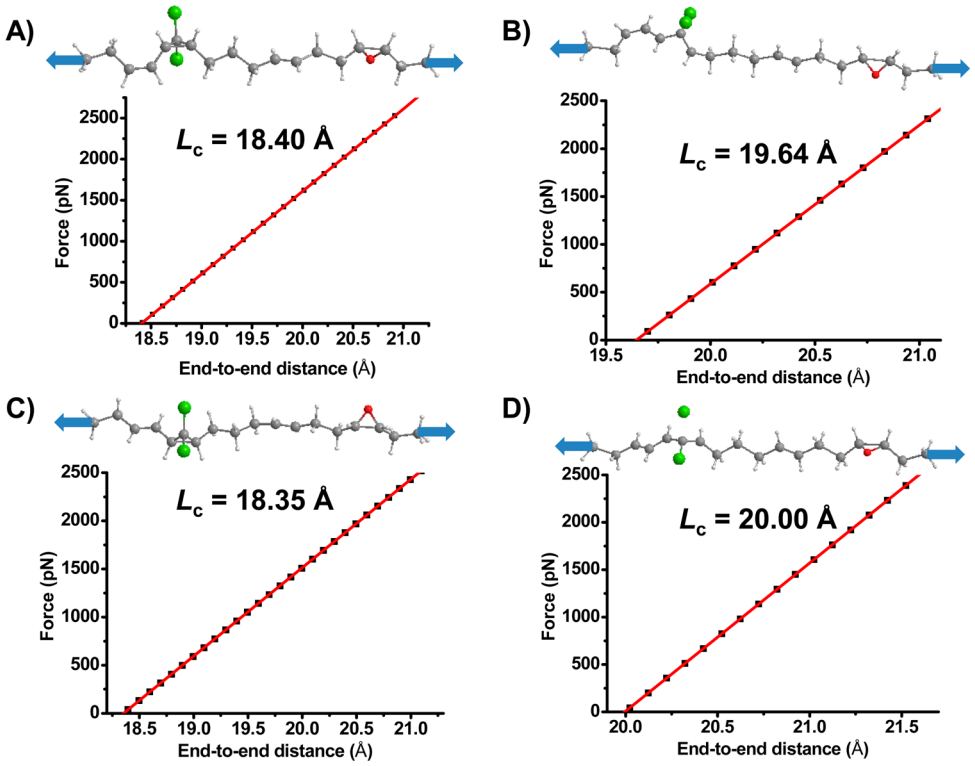

Figure 3. Force−distance curves of *Z*-alkene-*g*DCC ground state (A), *Z*-alkene-*g*DCC transition state (B), *E*-alkene-*g*DCC ground state (C), and *E*-alkene-*g*DCC transition state (D). The contour lengths L_c shown for each structure are obtained by extrapolating the force−distance curve to zero force.

alkene-bearing *g*DCCs are 1.65 and 1.24 Å, respectively, as compared to 1.67 ± 0.05 and 1.20 ± 0.05 Å determined from the experimental fits.

The extent of precision in the agreement is likely somewhat fortuitous, given the qualitative assumption of a cusp model to capture the effect of force on the positions of the ground and transition states, but even the relative values confirm the influence of the α-alkene stereochemistry. The difference in the force-coupled kinetics is effectively entirely due to enhanced mechanochemical coupling in the *E* isomer; calculations confirm the expectation that the stereochemistry of the α-alkene has no significant effect on the thermal barrier of the force-free electrocyclic ring opening of *g*DCC (see Supporting Information).

Relative to its *Z* isomer, the *E* isomer of the α-alkene therefore acts as a phenomenological "lever", in that it provides a greater mechanical advantage for a given applied force. Here, a stereochemical mutation, three bonds removed from the bond that is breaking, increases by almost 40% how the extension of the polymer chain is coupled to the torqueing motions that accompany the disrotatory *g*DCC ring opening. This structural perturbation is more subtle than, but just as effective as, incorporating *cis*-1,3-cyclopentyl connections along the polymer backbone on both side of the *g*DCCs, as reported previously.[18] Looking ahead, this and similar stereochemical handles might be useful for tuning mechanochemical activity[29] essentially independently of force-free thermal reactivity. While different theoretical approaches have been applied to explore covalent polymer mechanochemistry,[30,31] our results underscore the importance of considering remote structural effects in the analysis,[32,33] as the differences here would not be revealed in a theoretical analysis of a subset of atoms that did not extend out at least three bonds from the active mechanophore.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic details; NMR and GPC-MALS characterization; AFM experiments; thermolysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

todd.martinez@stanford.edu
stephen.craig@duke.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based on work supported by the U.S. Army Research Laboratory and the Army Research Office under grant W911NF-12-1-0337 and the National Science Foundation (DMR-1122483). The authors thank B. Akhremitchev for providing the original force−extension modeling code.

■ REFERENCES

(1) Hickenboth, C. R.; Moore, J. S.; White, S. R.; Sottos, N. R.; Baudry, J.; Wilson, S. R. *Nature* **2007**, *446*, 423.
(2) Lenhardt, J. M.; Ong, M. T.; Choe, R.; Evenhuis, C. R.; Martinez, T. J.; Craig, S. L. *Science* **2010**, *329*, 1057.
(3) Klukovich, H. M.; Kean, Z. S.; Ramirez, A. L. B.; Lenhardt, J. M.; Lin, J.; Hu, X.; Craig, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 9577.
(4) Larsen, M. B.; Boydston, A. J. *J. Am. Chem. Soc.* **2013**, *135*, 8189.

(5) Diesendruck, C. E.; Steinberg, B. D.; Sugai, N.; Silberstein, M. N.; Sottos, N. R.; White, S. R.; Braun, P. V.; Moore, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 12446.
(6) Piermattei, A.; Karthikeyan, S.; Sijbesma, R. P. *Nat. Chem.* **2009**, *1*, 133.
(7) Tennyson, A. G.; Wiggins, K. M.; Bielawski, C. W. *J. Am. Chem. Soc.* **2010**, *132*, 16631.
(8) Davis, D. A.; Hamilton, A.; Yang, J.; Cremar, L. D.; Van Gough, D.; Potisek, S. L.; Ong, M. T.; Braun, P. V.; Martinez, T. J.; White, S. R.; Moore, J. S.; Sottos, N. R. *Nature* **2009**, *459*, 68.
(9) Chen, Y.; Spiering, A. J. H.; KarthikeyanS; Peters, G. W. M.; Meijer, E. W.; Sijbesma, R. P. *Nat. Chem.* **2012**, *4*, 559.
(10) Ramirez, A. L. B.; Kean, Z. S.; Orlicki, J. A.; Champhekar, M.; Elsakr, S. M.; Krause, W. E.; Craig, S. L. *Nat. Chem.* **2013**, *5*, 757.
(11) Wang, Q.; Gossweiler, G. R.; Craig, S. L.; Zhao, X. *Nat. Commun.* **2014**, *5*, 4899.
(12) Lenhardt, J. M.; Black, A. L.; Craig, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 10818.
(13) Grandbois, M.; Beyer, M.; Rief, M.; Clausen-Schaumann, H.; Gaub, H. E. *Science* **1999**, *283*, 1727.
(14) Wiita, A. P.; Ainavarapu, S. R. K.; Huang, H. H.; Fernandez, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 7222.
(15) Schmidt, S. W.; Beyer, M. K.; Clausen-Schaumann, H. *J. Am. Chem. Soc.* **2008**, *130*, 3664.
(16) Schmidt, S. W.; Pill, M. F.; Kersch, A.; Clausen-Schaumann, H.; Beyer, M. K. *Faraday Discuss.* **2014**, DOI: 10.1039/C3FD00119A.
(17) Wu, D.; Lenhardt, J. M.; Black, A. L.; Akhremitchev, B. B.; Craig, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15936.
(18) Klukovich, H. M.; Kouznetsova, T. B.; Kean, Z. S.; Lenhardt, J. M.; Craig, S. L. *Nat. Chem.* **2013**, *5*, 110.
(19) Wang, J.; Kouznetsova, T. B.; Niu, Z.; Ong, M. T.; Klukovich, H. M.; Rheingold, A. L.; Martinez, T. J.; Craig, S. L. *Nat. Chem.* **2014**, submitted.
(20) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
(21) Hillmyer, M. A.; Laredo, W. R.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 6311.
(22) Marszalek, P. E.; Oberhauser, A. F.; Pang, Y.-P.; Fernandez, J. M. *Nature* **1998**, *396*, 661.
(23) The plateau forces reported here are taken from visual inspection. The kinetic analyses, including extensions and activation lengths, are obtained by fitting the entire force curve as described in the Supporting Information.
(24) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903.
(25) Thorn-Csányi, E.; Ruhland, K. *Macromol. Symp.* **2000**, *153*, 145.
(26) Tuba, R.; Grubbs, R. H. *Polym. Chem.* **2013**, *4*, 3959.
(27) Hummer, G.; Szabo, A. *Biophys. J.* **2003**, *85*, 5.
(28) Beyer, M. K. *J. Chem. Phys.* **2000**, *112*, 7307.
(29) Kean, Z. S.; Niu, Z.; Hewage, G. B.; Rheingold, A. L.; Craig, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 13598.
(30) Ong, M. T.; Leiding, J.; Tao, H.; Virshup, A. M.; Martínez, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 6377.
(31) Ribas-Arino, J.; Shiga, M.; Marx, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 4190.
(32) Tian, Y.; Boulatov, R. *ChemPhysChem* **2012**, *13*, 2277.
(33) Akbulatov, S.; Tian, Y.; Boulatov, R. *J. Am. Chem. Soc.* **2012**, *134*, 7620.