Pulling Outward but Reacting Inward: Mechanically Induced Symmetry-Allowed Reactions of *cis*- and *trans*-Diester-substituted Dichlorocyclopropanes

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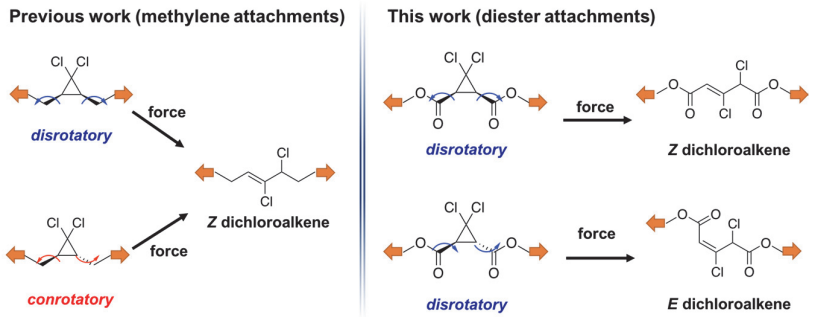

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Abstract The mechanically induced symmetry-allowed disrotatory ring-openings of *cis*- and *trans*- *gem*-dichlorocyclopropane (*g*DCC) diesters are demonstrated through sonication and single-molecule force spectroscopy (SMFS) studies. In contrast to the previously reported symmetry-forbidden conrotatory ring-opening of alkyl-tethered *trans*-*g*DCC, we show that the diester-tethered *trans*-*g*DCC primarily undergoes a symmetry-allowed disrotatory pathway even at the high forces (>2 nN) and short time scales (ms or less) of sonication and SMFS experiments. The quantitative force-rate data obtained from SMFS data is consistent with computational models of transition state geometry for the symmetry allowed process, and activation lengths of 1.41 ± 0.02 Å and 1.08 ± 0.03 Å are inferred for the *cis*-*g*DCC diester and *trans*-*g*DCC diester, respectively. The strong mechanochemical coupling in the *trans*-*g*DCC is notable, given that the directionality of the applied force may appear initially to oppose the disrotatory motion associated with the reaction. The stereochemical perturbations of mechanical coupling created by the ester attachments reinforce the complexity that is possible in covalent polymer mechanochemistry and illustrate the breadth of reactivity outcomes that are available through judicious mechanophore design.

Key words Woodward–Hoffmann, polymer mechanochemistry, structure-activity, *gem*-dichlorocyclopropane diester, sonication and single-molecule force spectroscopy

Mechanical forces in stretched polymers have been used to direct electrocyclic reactions down pathways that are typically "forbidden" by the Woodward–Hoffmann rules,[2] broadening our understanding of structure-activity relationships and laying the foundation for the use of mechanochemically accelerated reactions in stress-responsive materials.[3, 4] Examples of force-directed electrocyclic reactions began with the seminal work of Moore and co-workers, who demonstrated that mechanical force applied through *cis* pulling attachments leads to the symmetry-forbidden disrotatory ring opening of benzocyclobutene (BCB) derivatives.[5] Subsequent computational and experimental studies of electrocyclic ring openings of cyclobutene (CBE),[6-8] *gem*-dihalocyclopropanes (*g*DHCs),[6, 7] and epoxides[9] have provide additional insights into symmetry-forbidden mechanical reactivity manifolds.

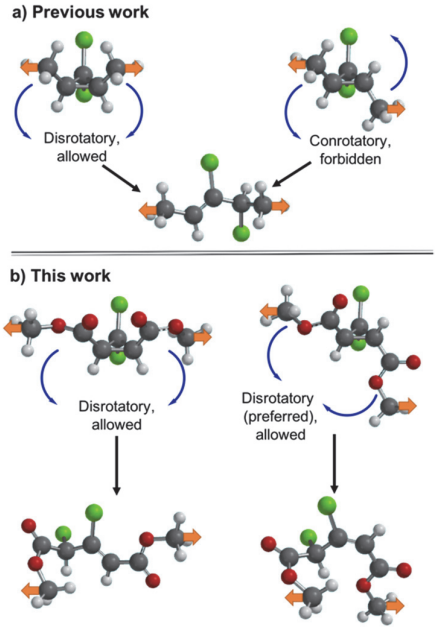

Figure 1. (a) Previously reported disrotatory and conrotatory pathways of mechanochemical reactions of *cis*- and *trans*- *g*DCC respectively, and (b) symmetry-allowed disrotatory pathways of *cis*- and *trans*- *g*DCC diesters featured in this work. Trans pulling in the *trans*-*g*DCC diester primarily leads to the disrotatory ring opening and the formation of (*E*)-2,3-dichloroalkene, in contrast to the reaction pathway of alkyl-tethered *trans*-*g*DCC.

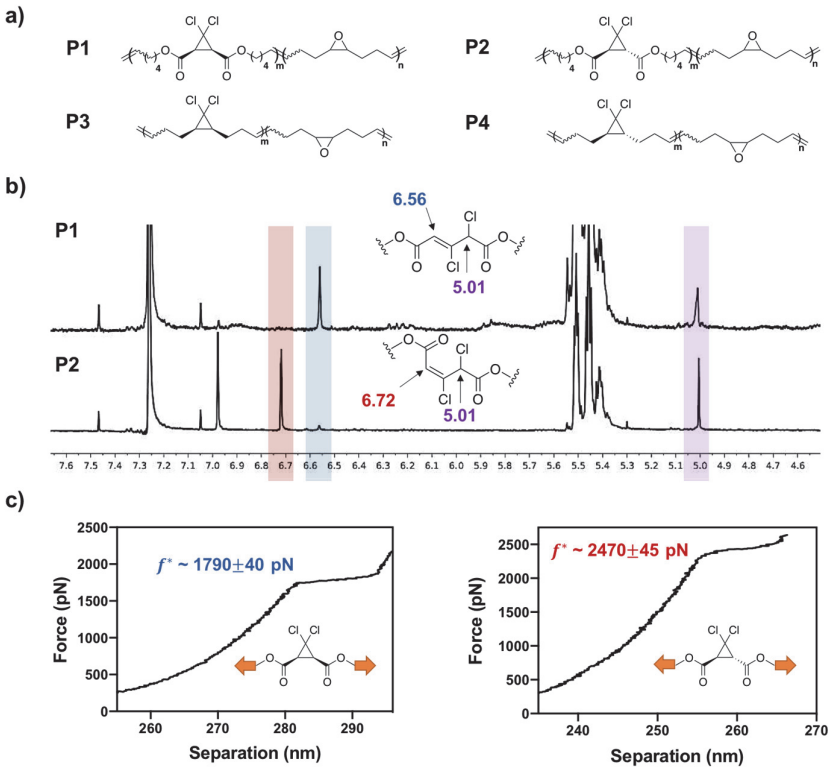

Figure 2 (a) Ring-opening metathesis (ROMP) polymers characterized in this work (**P1** and **P2**) and previous work (**P3** and **P4**). (b) Partial ^{1}H NMR (500 MHz, $CDCl_3$) of **P1** and **P2** after sonication (120 min) and peaks assigned to products of (*Z*)- and (*E*)- 2,3-dichloroalkene; ratio of (*E*)- and (*Z*)- isomers determined to be 10:1 from peak integrations in **P2** sonication. (c) Representative force-extension curves of **P1** and **P2** obtained by SMFS at a retraction velocity of 300 nm/s.

The aforementioned demonstrations tempt a broad generalization: delivering force via *cis*-substituted systems will lead to disrotatory ring opening, whereas pulling through *trans* substituents will result in conrotatory ring opening, as shown in Figure 1a for the mechanically coupled ring opening of *gem*-dichlorocyclopropane (*g*DCC) mechanophores studied previously by Wang et al.[6] Recent work,[10] however, has hinted that exceptions to this generalization might be more common than expected, even at very large (nN) forces that accelerate reaction rates by several orders of magnitude. Here, we report and quantify an extreme example of reactivity that proceeds predominately through a disrotatory pathway even as very large forces are applied via *trans* attachments. Specifically, we find that when ester groups are used as pulling attachments placed on the scissile cyclopropane bond, the kinetics of both the *cis*- and *trans*-*g*DCC diester ring opening are consistent with symmetry-allowed disrotatory pathways under mechanical loads (Figure 1b). We find the disrotatory reactivity of the *trans*-*g*DCC to be especially noteworthy, because it occurs at among the highest forces (>2.4 nN) that have been experimentally quantified for mechanophore activation.

For sonication and SMFS studies, multi-mechanophore polymers **P1** (M_n: 98 kDa) and **P2** (M_n: 85 kDa) were synthesized via entropy-driven ring-opening metathesis copolymerization (structures shown in Figure 2a).[11] An epoxidized cyclooctadiene comonomer was used in order to introduce a reactive site for strong adhesion of the polymer analyte to the cantilever tip of an Atomic Force Microscope (AFM), as reported previously.[4, 12] The incorporation of mechanophores in **P1** (14 mol% of repeat units) and **P2** (23 mol% of repeat units) were determined by ^{1}H NMR spectroscopy (see details in ESI). **P1** and **P2** were first subjected to pulsed ultrasonication for 120 min (in both cases, 2 mg/mL in THF, 1 s on/1 s off, see ESI for details). As shown in Figure 2b, ^{1}H NMR indicates that only (*Z*)-2,3-dichloroalkene products were generated from disrotatory ring openings of *cis*-*g*DCC diesters in **P1**, while mechanical activations of *trans*-*g*DCC diesters in **P2** gave mostly (*E*)-2,3-dichloroalkenes; the ratio of *E*- to *Z*- isomers was determined to be 10:1 from relevant peak integrations. The formation of the *E* product from the *trans*-*g*DCC indicates that the ring is opening through a preferential disrotatory reaction mechanism. This apparent misalignment in reaction pathway and the intended direction pulling in the *trans*-*g*DCC diester was unanticipated, and our initial hypothesis was that the cyclopropanes are sufficiently reactive that only low forces are necessary to trigger the reactions – at no force, the disrotatory pathway dominates, and if minimal forces are involved then that selectivity would be unlikely to be perturbed.

This hypothesis led us to quantify the force-coupled reactivity using SMFS. **P1** and **P2** were each independently deposited onto a silicon substrate, and SMFS was conducted in toluene following procedures that have been reported previously.[12, 13] Representative force-extension curves of **P1** and **P2** are shown in Figure 2c. All pulls that reached forces up to a given value (~1700 pN for **P1**, ~2400 pN for **P2**) exhibited a characteristic plateau region in the force curve, where the polymer is lengthening as a result of the irreversible ring-opening of the cyclopropane mechanophores. This observation (emphatically) voided the "low force reactivity" hypothesis, as the transition force of 2400

pN for the *trans-g*DCC is among the highest observed in a covalent mechanochemical reaction by SMFS.

force, at the very high forces involved in sonication, and at the intermediate but still quite high forces experienced in the SMFS experiments.

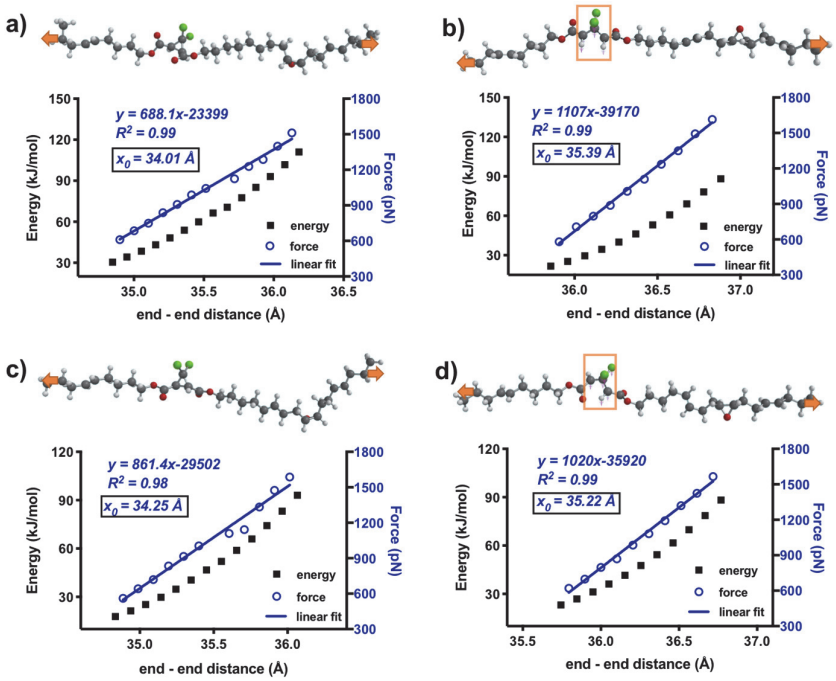

Figure 3 Energy profiles and force-extension curves (from CoGEF calculations) of the (a) ground state, (b) transition state of *cis-g*DCC diester (with cyclopropane structure in orange box geometrically locked), and the (c) ground state, (d) transition state of *trans-g*DCC diester. The blue circles represent the calculated force (from two adjacent square points, $(dE_2\text{-}dE_1)/(dx_2\text{-}dx_1)$) as a function of the calculated end to end distance (from two adjacent square points, $(x_1+x_2)/2$) and the blue lines represent the linear fit. The contour lengths x_0 presented for each structure are obtained by extrapolating force-distance curve to zero force.

The polymer contour length before (L_i) and after (L_f) this plateau was determined by fitting the pre- and post-plateau regions of the curve with an extended freely jointed chain model (e-FJC) according to literature precedent. The experimentally observed polymer extension (L_f/L_i) is compared to the extension that is predicted based on computational modelling, to verify that the width of the plateau is consistent with the activation of the disrotatory reaction observed by sonication. As seen in Table 1, the observed extension of L_f/L_i = 1.035 ± 0.006 for the *trans*-mechanophore system in **P2** matches well with the value of 1.036 calculated for conversion to the (*E*)-2,3-dichloroalkene, whereas the computed L_f/L_i = 1.064 for conversion to the (*Z*)-isomer is a poor fit of the experiment. The agreement in experimental (1.039 ± 0.009) and calculated (1.035) change in contour length for **P1** is similarly consistent with the formation of the (*Z*)-2,3-dichloroalkene. Thus, the disrotatory mechanisms of both stereoisomers appear to dominate the reactivity manifold at zero

To evaluate the force-rate relationship and quantify the mechanochemical coupling, the force curves were fit with computed force-free activation energies ($\Delta G^{\ddagger}$) and a truncated quadratic "cusp" model of the force-coupled potential energy surface.[14] The cusp model has proven to be well suited for similar analyses of ring openings of *g*DHCs in which the stereochemistry of pulling and the directionality of the reaction are nominally well aligned (*cis* pulling to disrotatory motion, *trans* pulling to conrotatory motion).[6, 15] Here, $\Delta G^{\ddagger}$ was determined by energy optimizations (DFT B3LYP/6-31G(d)) of the ground and transition states (located using the Synchronous Transit-Guided Quasi-Newton method,[16] see ESI for details).[17] Values of $\Delta G^{\ddagger}$ were calculated to be 44.0 kcal/mol and 45.4 kcal/mol for the symmetry-allowed disrotatory process of the *cis-* and *trans-g*DCC diester, respectively (Table 1). From these data, the high forces associated with the reaction of the disrotatory *trans-g*DCC diester reflect in large part the higher $\Delta G^{\ddagger}$ compared to that of the *trans-*

Table 1. SMFS Data of P1 and P2, Including Transition Forces, Force-Free Activation Energies, Force-Free Activation Length $\Delta x^{\ddagger}$ and the Relative Extension L_f/L_i (Obtained from Fitting SMFS Curves and Modeling).

	f^* (pN)	$\Delta G^{\ddagger}$ (kcal/mol)	cusp $\Delta x^{\ddagger}$ (Å)	modeled $\Delta x^{\ddagger}$ (Å)	SMFS L_f/L_i	modeled L_f/L_i
P1	1790 ± 40	44.0	1.41 ± 0.02	1.38	1.039 ± 0.009	1.035
P2	2468 ± 45	45.4	1.08 ± 0.03	0.97	1.035 ± 0.006	1.036

*g*DCC with methylene attachments (38.1 kcal/mol). The greater activation energy is attributed to the electron withdrawing esters destabilizing a transition state with allyl-cation-like character.

The geometries of their transition states involving a concerted ring opening/chloride migration of mechanism were calculated and compared to experiment.[6] Each fit of the experimental force-extension curve gives a force-free activation length, $\Delta x^{\ddagger}$, which we interpret as the extension along the polymer backbone that accompanies the change from the ground state to the transition state.[17] The experimental values of $\Delta x^{\ddagger}$ obtained in this way are 1.41 ± 0.02 Å and 1.08 ± 0.03 Å for **P1** and **P2**, respectively (Table 1), as compared to 1.38 Å and 0.97 Å obtained by models of *cis*- and *trans*-*g*DCC diesters and their disrotatory transition states (Figure 3a, b, d and e; geometric constraints added on cyclopropane rings). One of course cannot prove a mechanism, but, as with the stereochemistry of the product, the kinetics of force-coupled *cis*- and *trans*-*g*DCC diester ring openings are consistent with symmetry-allowed, disrotatory ring openings.

It is possible in theory that the mechanism proceeds through a homolytic bond scission in the cyclopropane ring, followed by rapid chloride migration. We cannot conclusively rule this mechanism out, but it seems unlikely because discrete diradical intermediates are likely to compete with rapid rotation of the pulling arms under force (as inferred previously from the behavior of cyclobutane mechanophores),[18] leading to a predominance of the minor alkene isomer. Also, the transition state structure inferred from the kinetics is within experimental uncertainty of that calculated for the concerted reaction, and similarity in molecular structure implies a likelihood of similarity in electronic structure.

The force involved in the SMFS reactivity of **P2**, well in excess of 2 nN, is large enough that the overwhelming majority of experimentally characterized mechanochemical reactions would have undergone complete conversion long before the onset of measurable reactivity here. Under that high tension, the diester-tethered *g*DCC reacts via a predominately disrotatory process even when pulled through *trans* attachments. Disconnections between simplified views of mechanochemical coupling and the reality of the reaction outputs are increasingly appreciated,[19] and the results here provide an additional example of the risk associated with assuming that reactivity will follow a specific pathway that is most intuitively associated with the direction implied by an applied force. A deeper understanding of the factors governing force-coupled reactivities is instructive for both the development of polymer mechanochemistry as a useful methodological tool for synthesis, and as a component of materials systems with stress-responsive function, including stress sensing,[20] self-healing/strengthening[21] and material toughening.[22]

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Supporting Information

YES.

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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(23) **Typical Experimental Procedure for the Synthesis of multi-mechanophore polymers P1 and P2:** 50 mg *cis*-macrocycle (0.15 mmol) and 105 mg mono-epoxidized cyclooctadiene (0.85 mmol), or 84 mg *trans*-macrocycle (0.25 mmol) and 93 mg mono-epoxidized cyclooctadiene (0.75 mmol), were dissolved in 0.15 mL dry DCM and deoxygenated with N_2 for 10 min. 1.0 mg (0.0012 mmol) Grubbs second generation catalyst was dissolved in 1 mL DCM and deoxygenated for 20 min. 0.1 mL of the Grubbs catalyst solution was transferred to the monomer solution via a syringe. The viscosity of the solution increased after 30 min. and stirring ceased quickly. 0.2 mL of DCM was added to the solution to allow the stirring to continue and the reaction was allowed to proceed for another 2 h. The reaction was quenched with 1 mL of ethyl vinyl ether and stirred for an hour. The reaction was then precipitated in methanol, redissolved in DCM and reprecipitated in methanol and dried on a vacuum line. ^{1}H NMR (500 MHz, $CDCl_3$) of **P1:** δ 5.52 – 5.41 (m, 14H), 4.22 – 4.11 (m, 4H), 2.94 – 2.91 (m, 12H), 2.81 (s, 2H), 2.24 – 2.13 (m, 25H), 1.70 – 1.64 (m, 4H), 1.68 – 1.42 (m, 36H); ^{1}H NMR (500 MHz, $CDCl_3$) of **P2:** δ 5.54 – 5.41 (m, 9H), 4.21 – 4.18 (m, 4H), 3.05 (s, 2H), 2.93 – 2.91 (m, 6.7H), 2.23 – 2.11 (m, 18H), 1.70 – 1.45 (m, 18H).