LLNL-JRNL-663754

Inducing and Quantifying Forbidden Reactivity with Single Molecule Polymer Mechanochemistry

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November 5, 2014

Nature Chemistry

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Inducing and Quantifying Forbidden Reactivity with Single Molecule Polymer Mechanochemistry

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Forbidden reactions, such as those that violate orbital symmetry effects as captured in the Woodward-Hoffman rules, remain an ongoing challenge for experimental characterization, because when the competing allowed pathway is available, the reactions are intrinsically difficult to trigger. Recent developments in covalent mechanochemistry have opened the door to activating otherwise inaccessible reactions. Here, we report single-molecule force spectroscopy studies of three mechanically induced reactions in which mechanical force is used to accelerate and observe reactivity in real time, and the forces for activating these reactions in both the symmetry allowed and symmetry forbidden pathways are compared. Just 'how forbidden' a reaction is can therefore be quantified, and the answer is shown to be highly variable and case-specific. To induce reactions on the ~0.1 s time scale of the experiments, for example, the forbidden ring opening reactions of benzocyclobutene, *gem*-difluorocyclopropane, and *gem*-

dichlorocyclopropane require approximately 130 pN less, 560 pN more, and 1,000 pN more force, respectively, than their corresponding allowed analogs. The results provide the first experimental benchmarks for mechanically induced forbidden reactions, and in some cases suggest revisions to prior computational predictions.

Molecules have multiple potential reaction pathways from which to choose, with each possibility comprising its own set of associated nuclear motions. The reactions that are observed therefore represent the outcome of a competition between the preferred pathway and any of a number of other possibilities. The factors that govern such selectivity include Woodward and Hoffman's orbital symmetry rules,[1] which capture the direction of concerted nuclear motion in electrocyclic reactions.[2] The Woodward-Hoffman rules are similar to many structure-activity relationships that are used to understand and predict chemical reactivity, in that although the structural, energetic, and dynamic details of a preferred pathway can often be gleaned from a variety of mechanistic studies, those of the paths not chosen often remain difficult to characterize by direct experimental study.[3,4]

Recently, Moore and co-workers have demonstrated that the direct application of sufficient mechanical force, delivered via polymer mechanochemistry, can be used to literally pull open a *cis*-benzocyclobutene (BCB) via disrotatory molecular motions that are "forbidden" by the Woodward-Hoffman rules and opposite to those in the normally observed, conrotatory pathways.[5] Subsequently, a few other symmetry forbidden reactions have also been mechanically activated, including the conrotatory ring opening of *gem*-dihalocyclopropanes (*g*DHCs)[6,7] and the disrotatory ring opening of epoxides.[8] These experimental demonstrations have motivated theoretical studies[9-11] and suggest the possibility of using force to not only activate reaction pathways that do not otherwise occur, but also to directly characterize reaction potential energy surfaces that are typically inaccessible experimentally. Here, we report the use of single-molecule force spectroscopy[12-14] to observe three mechanically triggered forbidden reactions as they occur in real time. In all three cases, symmetry allowed analogs are examined for comparison, providing a direct measure of just how "forbidden" each reaction is.

The three reactions chosen for this study are the electrocyclic ring opening reactions of BCB, *gem*-difluorocyclopropane (*g*DFC) and *gem*-dichlorocyclopropane (*g*DCC) (Figure 1). Similar to a simple cyclobutene, BCB reacts via a 4 π electron system, in which conrotatory ring opening is the symmetry allowed pathway and disrotatory ring opening is forbidden.[1,15] Thus, 1,2-dimethyl substituted BCBs will react at elevated temperatures to give *ortho*-quinodimethide (*o*QDM) products, the stereochemistry of which is determined by the stereochemistry of the reactants; the conrotatory ring opening of *cis*-substituted BCB generates an (*E,Z*)-*o*QDM, whereas the *trans*-substituted BCB leads to the (*E,E*) isomer. In contrast, the electrocyclic ring openings of *g*DFC[16,17] and *g*DCC[18,19] behave as effectively 2 π electron processes in which disrotatory pathways are favored. In the case of *g*DFC, this disrotatory ring opening leads to a 1,3-diradicaloid transition state and subsequent re-closure to a *g*DFC stereoisomer unless it is trapped mechanically,[13] whereas *g*DCC irreversibly forms a *2,3*-dichloroalkene product (Figure 1c) via C-C bond scission and chloride migration.[18]

Results and Discussion

For the SMFS studies, polymers with multiple mechanophores embedded along the backbone were synthesized (Figure 2). Epoxides increase the adhesion force between the polymer analyte and the tip of an atomic force microscope (AFM),[14] and they were incorporated via either co-polymerization with mono-epoxidized cyclooctadiene (**P1a** and **P2**) or post-synthetic epoxidation with *meta*-chloroperoxybenzoic acid (**P1b**, **P3-8**). Polymers were deposited on a surface, and the AFM tip was brought into contact and then retracted at a velocity of 300 nm/s. In cases where sufficiently high adhesion forces were obtained, a plateau was observed in the force-extension curve. The maximum attachment force prior to rupture varied from pull to pull, but each of the eight polymer types was characterized by either a single (**P1-4**, **P6-7**) or two distinct (**P5**, **P8**) plateau forces (f^*),[20] similar to those observed in previously reported multi-mechanophore polymers.[14] The transition and its corresponding f^* reflect the identity of the embedded mechanophore; that is, f^* is consistent for all pulls of a given type of polymer, and does not change with mechanophore content (**P1**, 1500 ± 60 pN; **P2**, 1370 ± 80 pN; **P3**, 1290 ± 50 pN; **P4**, 1820 ± 70 pN; **P5**, 1280 ± 70 pN, 1840 ± 80 pN; **P6**, 1330 ± 70 pN; **P7**, 2300 ± 100 pN; **P8**, 1290 ± 60 pN, 2290 ± 90 pN).

A representative force-separation curve for **P1**, bearing *trans*-BCB functionality along the main chain, is shown in Figure 3a. The changes in contour length at the plateau were obtained by fitting the pre- and post-transition force curves to a modified freely jointed chain model as described previously.[14] The relative extensions obtained are proportional to the mechanophore content in the copolymer, and match those calculated for the quantitative conversion of *trans*-BCB along the polymer backbone to the (*E,E*) isomer of the ring opened *o*QDM, as shown in Figure 1 (see Supplementary Information for a comparison of the observed and calculated extensions). We therefore ascribe the transition to the conrotatory ring opening of *trans*-BCB. Similarly, **P2**, which contains *cis*-BCB in its repeating unit (Figure 2), exhibits a plateau whose width corresponds to the disrotatory ring opening of *cis*-BCB to give the same, now disallowed, (*E,E*) isomer of *o*QDM; formation of the (*E,Z*) isomer is not consistent with the measured extensions (see Supplementary Information). The force spectroscopy therefore captures a glimpse of symmetry forbidden reactions occurring in real time within a single polymer molecule, and offers the first opportunity to quantify that force-induced reactivity and to compare it to symmetry allowed analogs.

In that context, it is interesting to note that the symmetry forbidden reactivity in **P2** occurs at a lower force (f^* ~ 1370 pN) than the symmetry allowed reactivity in **P1** (f^* ~ 1500 pN). Modelling shows that any differential "lever arm effect"[14] due to the differences in polymer backbone between **P1** and **P2** is negligible (see Supplementary Information), and so the lower f^* in **P2** reflects greater mechanochemical reactivity of *cis*-BCB than *trans*-BCB. Similar relative activities at high forces have been implicated by the greater addition of maleimides to the *cis* isomer of force-activated BCBs in pulsed sonication experiments[5] and predicted in some computations[21] (but not others[9]), where it is attributed to more efficient mechanochemical coupling in the *cis* pulling. The single molecule force spectroscopy (SMFS) data can be compared with previous calculations by noting that f^* corresponds to the force at which the velocity of chain extension is comparable to that of tip-surface reaction, which here involves reaction half-lives of ~100 ms.[13] At its value of f^*, the relevant force-coupled free energies of activation at room temperature for each mechanophore are therefore ~16 kcal/mol. Ribas-Arino *et al.*[21] have calculated force-modified potential energy surfaces for both *cis*-BCB and *trans*-BCB pulling, and the forces necessary to achieve 16 kcal/mol activation energies are ca. 1700 pN and 1800 pN, respectively. The relative value of f^* for *cis*-BCB is measured here to be 130 pN lower than *trans*-BCB (compared to ~100 pN predicted), and the roughly 300 pN differences in absolute values between the observed and predicted forces are likely due to the positive activation entropy of the reaction[22] and polymer backbone effects,[14] neither of which was included in the prior calculations.

Polymers **P3-5** provide an opportunity to look at the complementary case of *g*DFC, in which disrotatory ring opening is allowed and conrotatory ring opening is forbidden. Similar to BCB, previous work on *g*DFCs has shown that mechanical forces generated by pulsed ultrasound can be used to induce the ring opening reactions of both the cis and trans isomers to give the same *s-trans/s-trans* 1,3-diradicaloid transition state, and that this diradicaloid can be trapped under tension as a global minimum on the force-coupled potential energy surface.[13] To quantify this reactivity, **P3** (all *cis*-*g*DFC), **P4** (all *trans*-*g*DFC) and **P5** (copolymer of *cis*-*g*DFC and *trans*-*g*DFC) (Figure 2) were synthesized,[23] and their force-induced ring opening was characterized by SMFS. Force curves for these three polymers are shown in Figure 4. As with **P1** and **P2**, the measured changes in contour lengths for both the *cis*- and *trans*-*g*DFCs match the results obtained from modeling of *cis*- and *trans*-*g*DFC opening to a trapped *s-trans/s-trans-1,3*-diradical (see Supplementary Information). The plateaus in Figure 4a and 4b are therefore attributed to the symmetry allowed disrotatory ring opening of *cis*-*g*DFC and symmetry forbidden conrotatory ring opening of *trans*-*g*DFC, respectively.

As for BCB, the SMFS data can be compared to prior computational results on both the allowed and forbidden pathways. The force curves were fit [13,14] using previously reported force-free activation energies [17] and the cusp model [24] to describe the force-rate relationship (see Supplementary Information). 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 has been shown previously to be well suited for the allowed ring openings of other dihalocyclopropanes.[14] Each fit provides a force-free activation length $\Delta x^{\square}$ that corresponds to the extension along the polymer backbone that accompanies the change from ground state to transition state.[14] As seen in Table 1, the values of $\Delta x^{\square}$ obtained from the fits are within 0.02 Å of those calculated by modelling the previously reported ground and transition state structures [13] embedded within a polymer under tension (see Supplementary Information).

While the *g*DFC reactivity proceeds through its trapped *1,3*-diradicaloid transition state, the exact fate of that transition state here is uncertain. When trapped for short (< μs) times in the absence of reactive partners, the *1,3*-diyl persists and then rapidly closes to regenerate *g*DFC when the force is released.[13] Under the conditions of the SMFS experiments, however, the ring opening is irreversible, as seen in hysteresis and repeated force-extension curves on a single polymer (see Supplementary Information). We are obviously unable to characterize the ultimate product of this transformation, but we have observed that the trapped 1,3-diyls react with nitroxides,[13] or with oxygen when ambient air is introduced into sonication experiments. The trapping times are much longer in SMFS than sonication (> ms vs. < μs), and so we attribute the irreversible transformation here to reaction with oxygen, which we cannot exclude from the experimental environment.

Like *g*DFC*, g*DCC opens through a preferred disrotatory process, but within a more complex reaction mechanism in which the ring opening is coupled to chloride migration to give a 2,3-dichloroalkene product. As seen in the force curves for **P6** (f^* = 1330 pN),[14] the force necessary to drive the mechanochemical ring opening of *cis*-*g*DCC on the SMFS time scale is comparable to that required for *cis*-*g*DFC (1290 pN), and as with *cis*-*g*DFC the value of Δx□ obtained from the fits is within 0.02 Å of the calculated one (Table 1).

Limited mechanistic information regarding the forbidden, conrotatory reactivity of *g*DCC is available, and in fact prior computational work has concluded that the trans pulling of *g*DCC, unlike *g*DFC, still results in a disrotatory process.[18] SMFS of polymer **P7** (*trans*-*g*DCC in the repeating unit) provides an opportunity to look at the mechanistic consequences of trans pulling on *g*DCC, and a representative force curve is shown in Figure 4e. The observed kinetics of mechanically coupled *trans*-*g*DCC ring opening, however, are not consistent with the predicted disrotatory ring opening. Fitting the force curves using the same procedure and cusp model that was applied successfully to the other *g*DHCs gives a value of $\Delta x^{\ddagger} = 0.83$ Å; this value differs substantially and significantly from the value of 0.41 Å obtained by modeling *trans*-*g*DCC and its disrotatory transition state (see Supplementary Information). Looked at another way, the previous calculations on the disrotatory process predict a force plateau that is much higher than that observed here. As the force increases in the AFM experiment, therefore, another process turns on before the disrotatory ring opening, and we conclude that this process is the symmetry forbidden conrotatory ring opening reaction, similar to *trans*-*g*DFC.

Consistent with this conclusion, we note that the relative extension at the plateau matches that of the conversion from *trans*-*g*DCC to *Z*- isomer of the *2,3*-dichloroalkene; substantial formation of the *E*-isomer is not consistent with the measured extension (see Supplementary Information). This result agrees with the formation of *Z*-alkene products observed previously in sonication experiments,[6] and is in line with the expectations for a conrotatory ring opening of the *trans*-*g*DCC. Disrotatory ring opening, however, generates a mixture of *E*- and *Z*-alkenes.[19] While the applied force could bias the chloride migration, molecular dynamics simulations found that force-coupled disrotatory ring opening of *trans*-*g*DCC leads to 40%-60% of the *E*- isomer in the force range relevant to the SMFS studies.[18] The measured extensions therefore support that the experiments are probing the forbidden, conrotatory ring opening pathway.

The force spectroscopy results provide insights into transition state structures for both the allowed and forbidden reaction pathways. Within the allowed reactions, for example, f^* of *cis*-*g*DFC (1290 pN) is at or just below that of *cis*-*g*DCC (1330 pN), despite the fact that its force-free activation free energy is 4.4 kcal/mol higher (Table 1).[14,17] The lower force threshold points to greater mechanical leverage from a more extended transition state geometry in the *cis*-*g*DFC, a picture that is qualitatively consistent with the dissociative contribution of chloride migration leading to an earlier transition state in *g*DCC than observed in the fully splayed diradicaloid transition state of *g*DFC, and quantitatively consistent with the derived values of $\Delta x^{\square}$ reported in Table 1.

Additional, qualitative connections to reaction mechanism in the *g*DHCs are found in the differences in f^* for cis vs. trans pulling and highlighted in the force curves of **P5** (*cis*/*trans*-*g*DFC) and **P8** (*cis*/*trans*-*g*DCC). Whereas the allowed reactions have similar values of f^*, the difference in f^* for the forbidden vs. allowed reaction in *g*DCC (~1000 pN) is much greater than that of *g*DFC (~560 pN). The differences validate qualitative notions related to reactivity in these systems. Whereas the 2 π electron character of *g*DFC has been attributed to the electron withdrawing effects of the electronegative fluorines,[25] the partial dissociation of chloride in the ring opening of gDCC provides greater propenyl cation character, and it therefore should be expected to have more 2 π (vs. 4 π) electronic character and, as a result, a greater orbital symmetry bias toward the disrotatory process. The differential forces observed are consistent with this expectation.

Conclusions

These studies provide the first quantitative data for the mechanical acceleration of symmetry forbidden reactions, and the results from the two BCB polymers constitute the first demonstration of a force-coupled symmetry forbidden reaction that is faster than its force-coupled symmetry allowed counterpart. The ability to quantitatively probe otherwise forbidden reactions provides a rare opportunity to interrogate the structures of the transition states that regulate those pathways. This capacity complements other uses of mechanical forces to probe reaction mechanisms[26] and the otherwise "invisible" transition states associated with non-rate determining steps of multi-step reactions.[27] More generally, the agreement observed here between experimental and computational (when available) structures and transition state energies, for both symmetry allowed and symmetry forbidden reactions, complements studies using molecular force probes[28] and supports the broad generality of the chemomechanical framework[29] to reaction dynamics. Looking ahead, we note that the conrotatory ring opening reaction of *g*DCC involves a force of >2 nN, which we believe to be the greatest measured force ever tied to a covalent chemical mechanism other than homolytic bond scission,[30] and the ability to probe behaviour at very high forces is likely to aid the discovery of similar, previously unobserved reactivity patterns.

METHODS

Polymer preparation. Polymers with multiple mechanophores embedded along the backbone were synthesized and epoxides were incorporated to increase the adhesion force between the polymer analyte and the tip of an AFM.[14] The synthesis procedure and characterization data are described in details in the Supplementary Information.

SMFS. Polymers were deposited on a silicon substrate surface, and the AFM tip was brought into contact and then retracted at a velocity of 300 nm/s. In cases where sufficiently high adhesion forces were obtained, a plateau was observed in the force-extension curve. The maximum attachment force prior to rupture varied from pull to pull, but each of the eight polymer types was characterized by either a single or two distinct plateau forces (f^*),[31] similar to those observed in previously reported multi-mechanophore polymers.[14] The force-extension curve data were fit using previously published methods developed by Boris B. Akhremitchev.[13] The theoretical extension of the polymers and the theoretical activation length ($\Delta x^{\square}$) were modelled using the method described previously.[14]

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Supplementary Information is available in the online version of the paper.

Acknowledgements: This material is based on work supported by the U.S. Army Research Laboratory and the U.S. Army Research Office under grant W911NF-12-1-0337. S.L.C. acknowledges partial support from NSF MIRT (DMR-1122483). The authors thank B. Akhremitchev for providing the original force-extension modeling code. Part of this work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-ACS2-07NA27344. (LLNL-JRNL-663754)

Author Contributions J.W. and S.L.C. conceived and designed the experiments. J.W and H.M.K. performed the synthesis. T.B.K. collected the AFM data. Z.N. and A.L.R. performed the crystallography. M.T.O and T.J.M performed the calculation of the transition states. J.W. and S.L.C. analysed the data and wrote the manuscript.

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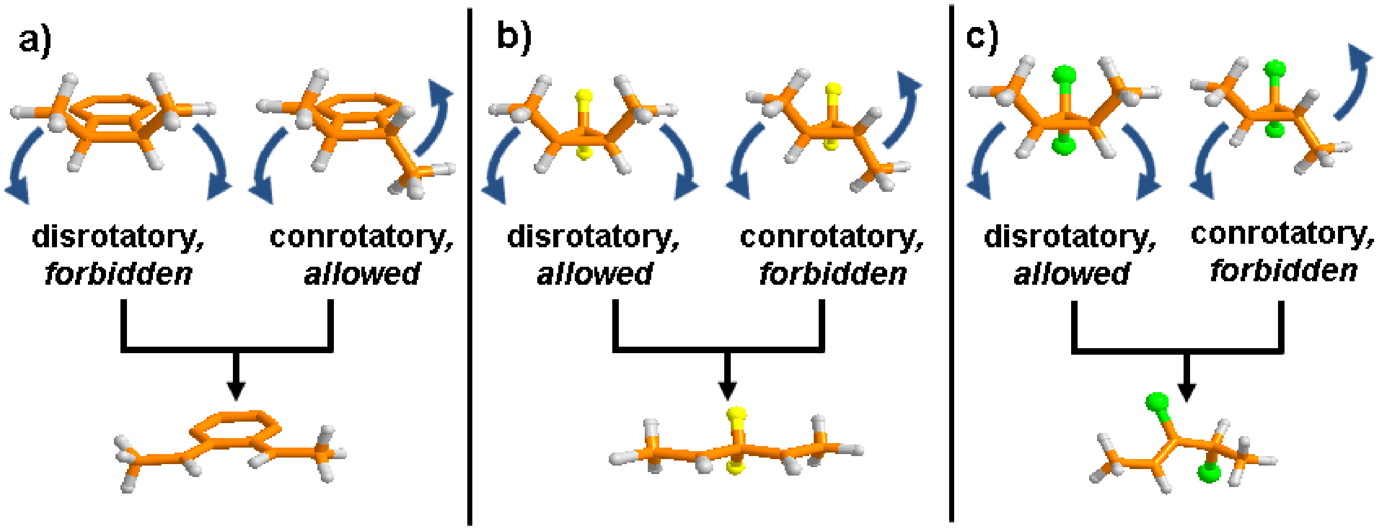
Table 1. The activation free energies of *g*DHCs and the activation length $\Delta x^{\square}$ obtained by fitting AFM curves with cusp model and by modelling the ground states and transition states.

	$\Delta G^{\square}$ (kcal/mol)	$\Delta x^{\square}$ (cusp) (Å)	$\Delta x^{\square}$ (modeling) (Å)
cis-*g*DFC (dis)	40.6[a]	1.53±0.04	1.55
trans-*g*DFC (con)	45.8[b]	1.38±0.05	1.37
cis-*g*DCC (dis)	36.2[c]	1.28±0.05	1.27
trans-*g*DCC (dis)	38.1[d]	0.83±0.07	0.41

a,b) from ref 13; c) from ref 10; d) derived from the $\Delta G^{\square}$ of *cis*-gDCC (36.2 kcal/mol) and the reported difference of $\Delta G^{\square}$ (1.9 kcal/mol) between *trans*-gDCC and *cis*-gDCC.(ref 15)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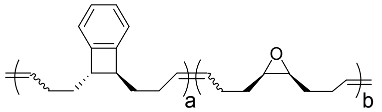
P1a



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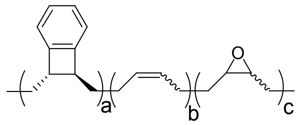

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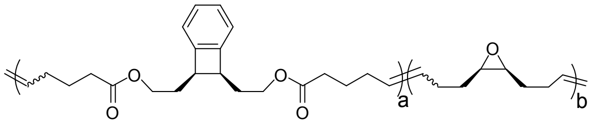

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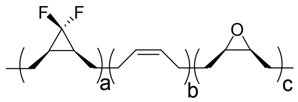

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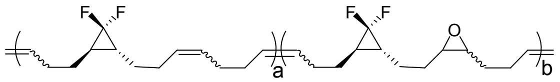

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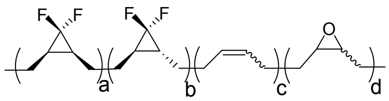

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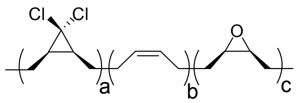
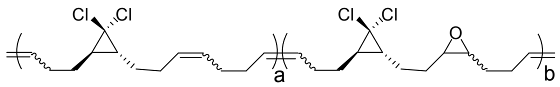
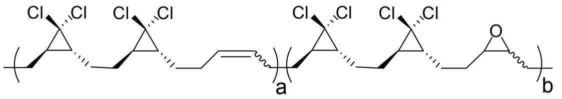


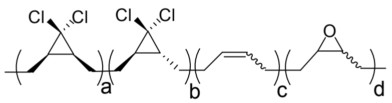
P7a

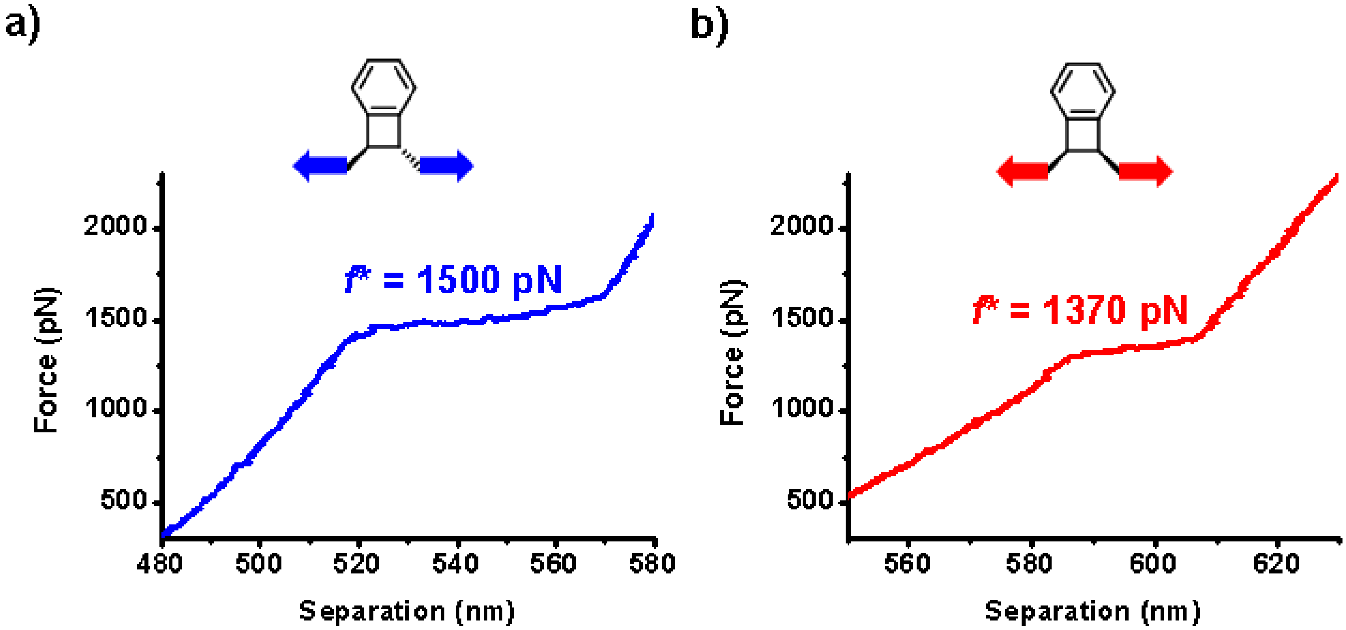


P7b



P8




a)
f* = 1500 pN
Force (pN)
2000
1500
1000
500
480
500
520
540
560
580
Separation (nm)
b)
f* = 1370 pN
Force (pN)
2000
1500
1000
500
560
580
600
620
Separation (nm)

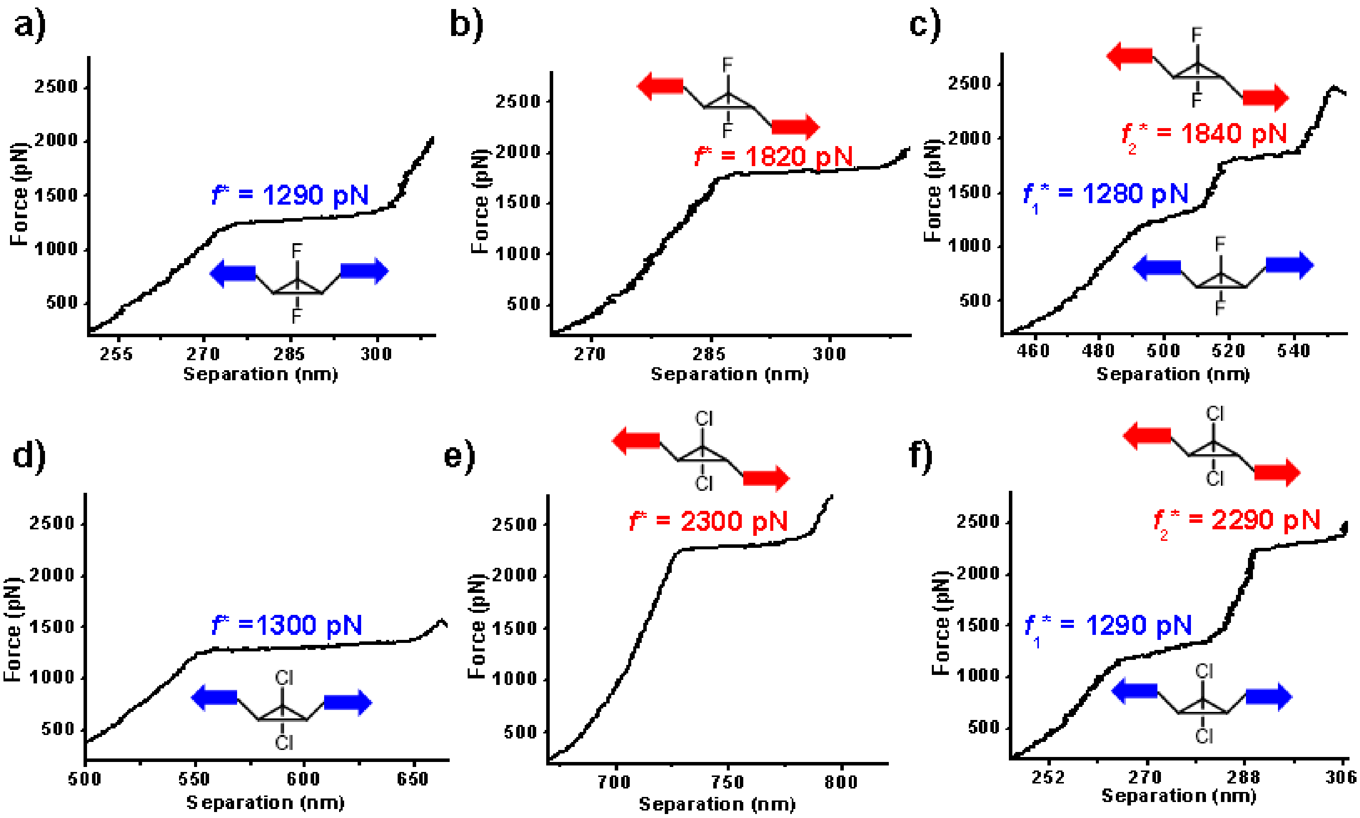


Figure legends

Figure 1. Disrotatory and conrotatory pathways of three mechanically activated reactions studied in this work. The reactants are "pulled" via a tensile force transmitted through the methyl substituents. Depending on the reactant and direction of applied force, the induced nuclear motion (blue arrows) is either allowed or forbidden based on orbital symmetry rules. Reactions: (a) benzocyclobutene to *ortho*-quinodimethide, (b) *gem*-difluorocyclopropane to *2,2*-difluoro-*1,3*-diyl, and (c) *gem*-dichlorocyclopropane to *2,3*-dichloroalkene. Note that in each of the three cases, disrotatory pulling of the *cis*- diastereomer leads to the same product as conrotatory pulling of the *trans*- diastereomer.

Figure 2. Polymers employed in this work. The specific content parameters *a*-*d* for each polymer tested are provided in the Supplementary Information.

Figure 3. Representative plateaus in the force-extension curves of (a) **P1** (*trans*-BCB in the repeating unit) and (b) **P2** (*cis*-BCB in the repeating unit). The plateau widths match those expected of the conrotatory ring opening of *trans*-BCB and disrotatory ring opening of *cis*-BCB, respectively. The values of f^* are the mid-points of the plateaus taken from each individual pull. For complete force curves, see Supplementary Information. Pulling directions are shown with blue (allowed pulling) and red arrows (forbidden pulling).

Figure 4. Representative plateaus in the force-extension curves of: (a) **P3** (*cis*-*g*DFC in the repeating unit); (b) **P4** (*trans*-*g*DFC in the repeating unit); (c) **P5** (copolymer of *cis*- and *trans*-*g*DFC); (d) **P6** (*cis*-*g*DCC in the repeating unit; data taken from ref. 8); (e) **P7** (*trans*-*g*DCC in the repeating unit); and (f) **P8** (copolymer of *cis*- and *trans*-*g*DCC). The values of f^* are the mid-points of the plateaus taken from each individual pull, and f_1^* and f_2^* corresponding to the first and second transition, respectively, in force curves of polymers with two types of mechanophore. For complete force curves, see Supplementary Information. Pulling directions are shown with blue (allowed pulling) and red arrows (forbidden pulling).