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# Reactivity and Mechanism of a Mechanically Activated *anti*-Woodward–Hoffmann–DePuy Reaction

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Supporting Information

**ABSTRACT:** Mechanical forces, applied via covalent polymer mechanochemistry, have been used to bias reaction pathways and activate otherwise inaccessible reactions. Here, single-molecule polymer mechanochemistry is used to induce the disrotatory outward ring opening of a *cis*-dialkyl substituted *syn*-chloro-*gem*-chlorofluorocyclopropane, in violation of the Woodward–Hoffmann–DePuy (WHD) rule. The forces required to trigger the *anti*-WHD pathway on the ~100 ms time scale of the experiment are about 200 pN greater than those involved in the WHD favored process (1290 vs 1500 pN). The kinetics are complemented by tension trapping experiments that suggest that the reaction proceeds along a reaction pathway that generates substantial diradicaloid character.

In recent years, covalent polymer mechanochemistry has been explored and applied in various contexts, including materials development,[1−5] elucidating reaction mechanisms,[6−10] catalysis,[11−14] proton and small molecule release,[4,15,16] and electro-mechanochemical soft display devices.[17] A unique feature of mechanochemistry is the potential to bias reaction pathways and activate reactions that are inaccessible by conventional thermal chemistry or photochemistry.[18] For example, Moore and co-workers have demonstrated that *cis*-benzocyclobutene (BCB) undergoes a formally symmetry-forbidden disrotatory ring opening reaction when the *cis*-BCB is embedded in the midchain of a polymer and subjected to high extensional forces through ultrasonication.[18] Other forbidden reactions, such as the conrotatory ring opening of *gem*-dihalocyclopropanes[8,19] and the disrotatory ring opening of a dialkyl epoxide,[9] have also been mechanically activated and characterized.

Single-molecule force spectroscopy (SMFS) has been used extensively to quantify mechanically activated reactions.[6,7,20−23] We have recently reported the SMFS study of three mechanically activated forbidden reactions in which the forces required to induce the symmetry-forbidden reactions were quantified and compared to their symmetry-allowed analogues.[24] Here we report the SMFS study of a mechanically activated *anti*-Woodward–Hoffmann–DePuy (WHD)[25−28] reaction of *syn*-chloro-*gem*-chlorofluorocyclopropane (*syn*-Cl-*g*CFC) (Figure 1), which, to the best of our knowledge, is the first real-time observation of this reaction class. As shown in Figure 1, under force-free conditions, *syn*-Cl-*g*CFC undergoes disrotatory ring opening in an *inward* fashion, providing

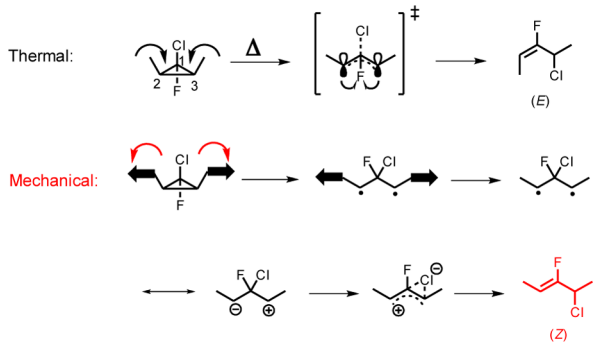


**Figure 1.** Proposed mechanisms for thermal and mechanical activation of dimethyl-*gem*-chlorofluorocyclopropane. Thermally the methyl groups undergo inward disrotation, during which the electrons of the breaking C2–C3 bond donate to the *anti*-bonding orbital of the C–Cl bond to assist the breakage of the C–Cl bond and form the *E*-alkene product, following WHD rule. Mechanically pulling on the methyl groups forces the rotation outward, although this disfavors the cleavage of the $Cl^-$ anion, violating WHD rule. During the mechanically activated ring opening reaction, *syn*-Cl-*g*CFC first opens into a diradical, which then undergoes ion separation to form the *Z*-alkene product.

stereoelectronic assistance to the C–Cl bond cleavage, as predicted by the WHD rule. The application of sufficient mechanical forces to the *syn* alkyl substituents, however, is expected to alter the torquoselectivity[29] of the reaction, literally pulling the *g*CFC along the *anti*-WHD disrotatory *outward* ring opening pathway.[30]

In order to not only induce but quantify that reactivity using SMFS, we exploit the methodology of incorporating multiple mechanophores on a polymer backbone, which has allowed us to quantify the force-coupled reactivities of *gem*-dihalocyclopropanes[31,32] and benzocyclobutene.[24] The synthetic procedure employed is shown in Figure 2a. Chlorofluorocarbene was generated by $CHFCl_2$ and NaOH under phase transfer conditions[33,34] and added to 1,5-cyclooctadiene, resulting in *gem*-chlorofluorocyclopropanated cyclooctadiene, which is a mixture of isomers **1** (alkyl groups in the *syn*-position with respect to the chlorine atom) and **2** (alkyl groups in the *anti*-position) in a ratio of 7:3 (Figure 2a). Solvolysis[35] in ethanol in the presence of silver nitrate selectively consumed **2**, and unreacted **1** was then successfully isolated from the resulting product mixture. Ring opening metathesis polymerization (ROMP)[36,37] of **1** and the mixture of **1** and **2** yielded polymers

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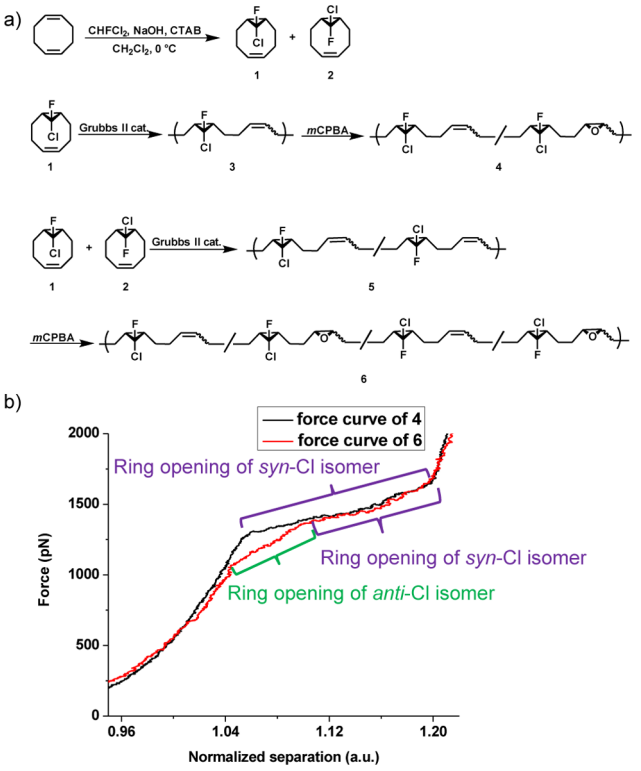


**Figure 2.** (a) Synthetic scheme of polymers **4** (*syn*-Cl-*g*CFC in the repeating unit) and **6** (containing the mixture of *syn*- and *anti*-Cl-*g*CFC in a ratio of 7:3). (b) Representative force curves of **4** and **6** obtained by SMFS at a retraction velocity of 300 nm/s. The force curves are normalized to the stress-bearing subchain's contour length at 500 pN.

**3** (containing only *syn*-Cl-*g*CFC) and **5** (containing *syn*-Cl-*g*CFC and *anti*-Cl-*g*CFC in a ratio of 7:3), respectively (Figure 2a). Epoxidation increases the adhesion force between AFM tip and the polymer analyte,[32] presumably through the formation of covalent bonds.[38] Here, epoxides were incorporated by postsynthetic epoxidation of **3** and **5** with *meta*-chloroperoxybenzoic acid (*m*CPBA), yielding **4** and **6**, respectively, for SMFS study.

The polymers were deposited on a surface, and the AFM tip was brought into contact and then retracted at a velocity of 300 nm/s (see Supporting Information, SI). Figure 2b shows representative force curves of **4** and **6**. The force curve of **4** features a plateau (plateau force $f^* = 1500 \pm 70$ pN, taken from the midpoint of the transition) that is similar to that observed in other *g*DHCs.[31,32] The contour length extensions associated with the plateau were obtained by fitting the pre- and post-transition force curves to a modified freely jointed chain model as described previously.[32] The relative extensions match those calculated for the quantitative conversion of *syn*-Cl-*g*CFC to the *Z*-alkene, as would result from the expected disrotatory outward rotation (Figure 1). The force curve thus captures the real-time observation of the mechanically activated *anti*-WHD reaction.

The force curves obtained for **6** (30% *anti*-Cl and 70% *syn*-Cl) are more nuanced, suggesting two different transitions associated with the stereoisomers. Support for the presence of a second transition is found by overlaying the force curves obtained for **4** and **6** (Figure 2b). First, we note that the two polymers have the same percentage of extension at the plateau. This reveals that both *anti*-Cl and *syn*-Cl isomers formed the *Z*-alkene product during the transition, which is consistent with the results of previous sonication experiments (see SI),[30] and further supports a disrotatory outward ring opening from *syn*-Cl-*g*CFC. Second, the presence of two regimes of response in **6** is made evident by an early, lower force transition that is attributed to the *anti*-Cl isomer, as discussed below.

Thermolysis experiments show that the force-free activation free energies for the disrotatory outward ring opening of *anti*-Cl-*g*CFC and disrotatory inward ring opening of *syn*-Cl-*g*CFC are 37 and 41 kcal/mol, respectively (see SI). These two reactions both follow WHD rule, and the difference between their activation energies is mainly caused by the steric effects. Since no significant *anti*-WHD disrotatory outward ring opening is detected for *syn*-Cl-*g*CFC at 210 °C (see SI), the activation energy difference between the outward and inward ring opening for *syn*-Cl-*g*CFC is at least 4 kcal/mol (providing a selectivity ratio of 100:1 at 210 °C). So the activation energy difference for disrotatory outward ring opening of the two isomers is ≥8 kcal/mol. The SMFS data provides an opportunity to directly compare the forces required to activate the two disrotatory outward ring opening reactions. As seen in Figure 2b, despite the large gap between thermal barriers, the requisite forces for *syn* and *anti* isomers are quite similar. The relatively small force gap implies a more efficient mechano-chemical coupling from a more extended transition state for the ring opening of *syn*-Cl-*g*CFC.

This is confirmed by a more quantitative analysis on the kinetics. The similarity in activation energies (37 vs 36 kcal/mol) and transition forces (1290 vs 1330 pN) for *cis-anti*-Cl-*g*CFC and *cis*-dialkyl-*gem*-dichlorocyclopropane (*cis*-*g*DCC) suggests that the activation length for *cis-anti*-Cl-*g*CFC is close to that of *cis*-*g*DCC (1.28 Å).[32] The force curve for **4** was fit using a cusp model[39] for the reaction potential energy surface. This model has previously been shown to be a good approximation for other dihalocylopropane systems.[24,32,40] Here, it provides an activation length for the *syn*-Cl isomer of ≥1.52 Å (see SI), which is comparable to that of *cis-gem*-difluorocyclopropane (*cis*-*g*DFC, 1.53 Å).[24] We therefore envision that this *anti*-WHD reaction might involve a transition state with considerable diradical character (Figure 1), as is the case in the isomerization of *g*DFC.[8]

We demonstrated previously that the diradical transition state of *g*DFC isomerization can be mechanically converted into a global minimum on the force-coupled potential energy surface, allowing the "tension trapped" diradicaloid to react with a nitroxide radical.[8] Evidence of the diradicaloid is obtained by sonicating a *g*DFC polymer solution with coumarin−2,2,6,6-tetramethylpiperidine-1-oxyl (CT), leading to the addition of the UV-active CT moieties along the polymer backbone.[8] The same methodology was applied here to polymers **3** and **5**, and quantification by UV absorption reveals significant incorporation of CT, similar to what was observed for *g*DFC (Figure 3). Note that in the early stage of the sonication, the amount of CT incorporated per new generated chain for *syn*-Cl-*g*CFC is close to that observed in *g*DFC. As sonication continues, the incorporation of CT onto *syn*-Cl-*g*CFC increases more slowly than onto *g*DFC. This trend is consistent with the difference in the two reaction outcomes. Whereas each *g*DFC can be activated multiple times due to the reversibility of the ring opening, each *syn*-Cl-*g*CFC can only be activated once, as it is irreversibly transformed into the ring opening 2-fluoro-3-chloro-alkene product. In addition, the incorporation of CT into **6** is lower than that into **4**, indicating


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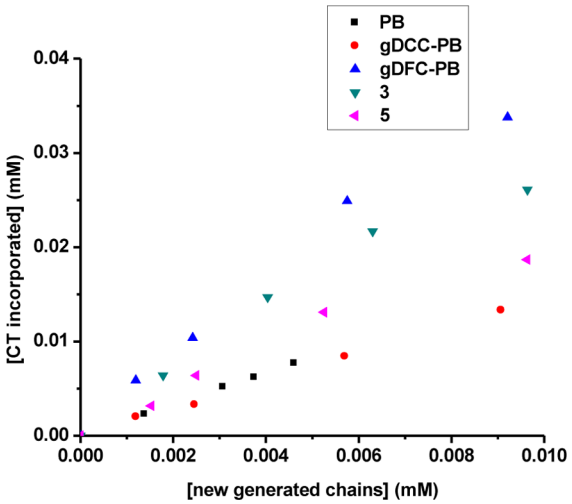


**Figure 3.** Sonication of PB, *g*DCC-PB, *g*DFC-PB, and polymers **3** and **5** with CT, respectively (1 mg/mL in THF, 6−9 °C, $N_2$ atmosphere). The concentration of the incorporated CT was plotted against the concentration of newly generated chains. The concentration of incorporated CT was determined from the UV absorbance of the polymer, and the concentration of newly generated chains was determined from the change of the molecular weights (for details, see SI).

that the ring opening of the *anti*-Cl-*g*CFC has less diradicaloid character and more charge separation, as is typically invoked in the ring opening of *g*DCC.[19] Taken together, the nitroxide trapping experiments support an *anti*-WHD transition state whose character is more similar to that of *g*DFC isomerization than *g*DCC ring opening, in agreement with activation lengths inferred from the SMFS studies.

The single molecule polymer mechanochemistry experiments reported here not only induce a reaction that violates the torquoselectivity predicted by WHD rules but also provide the first quantified measure of the WHD effect in the context of polymer mechanochemistry. Both the kinetic analysis and tension trapping experiments shed light on the ring opening mechanism, suggesting substantial diradicaloid character in the *anti*-WHD process relative to the WHD analogue. The latter is representative of an opportunity, afforded by polymer mechanochemistry, in that the reactions proceed from very similar reactants to give the same product, but do so through reaction mechanisms that are sufficiently different as to provide an avenue for differential reactivity, here captured in the modification of the polymer chain by a radical trap.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06168.

Synthetic details; NMR and GPC-MALS characterization; AFM experiments; modeling data (PDF)

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### Notes

The authors declare no competing financial interest.

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