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Accelerating a Mechanically Driven *anti*-Woodward–Hoffmann Ring Opening with a Polymer Lever Arm Effect

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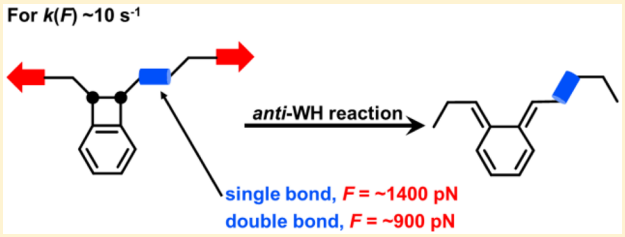
Supporting Information

ABSTRACT: Mechanical forces have previously been used to drive reactions along pathways that violate the orbital symmetry effects captured in the Woodward–Hoffmann rules. Here, we show that a polymer "lever arm effect" can provide a mechanical advantage in accelerating the symmetry forbidden disrotatory ring opening of benzocyclobutene (BCB). Addition of an α-*E*-alkene to the BCB mechanophore drops the force required to induce reactions on the ∼0.1 s time scale of single-molecule force spectroscopy experiments from 1370 to 920 pN.



The utility of a chemical reaction is constrained by its inherent selectivity, including that dictated by Woodward and Hoffmann's orbital symmetry rules,[1] which capture the direction of concerted nuclear motion in electrocyclic reactions.[2] The predictability and reliability of selective reactions provide great utility, for example, in rational chemical synthesis. In some cases, however, it might be desirable to steer a reaction in a direction different from its normal pathway, for example, to access an otherwise unattainable product. In the context of electrocyclic reactions, Moore and co-workers recently reported 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–Hoffmann rules and opposite to those in the normally observed, conrotatory pathway.[3] Other mechanically driven, symmetry forbidden reactions have since been reported, including the conrotatory ring opening of *gem*-dihalocyclopropanes (*g*DHCs)[4,5] and the disrotatory ring opening of epoxides,[6] and experiments have been supplemented by theoretical studies[7−9] and quantitative single-molecule force spectroscopy[10−12] (SMFS) studies of multiple, symmetry forbidden reactions.[13] The forces required to trigger forbidden reactions on a given time scale are intrinsically tied to the mechanophore and reaction of interest but can also be adjusted by the structure of the unreactive polymer backbone that is delivering the force.[12,14] We recently reported that an *E*-alkene, appended to the α position on a *gem*-dichlorocyclopropane (*g*DCC)[4] mechanophore, lowers by >30% (0.4 nN) the force necessary for *g*DCC reactivity on the 100 ms time scale of a SMFS experiment.[15] We expected that the same "lever arm" strategy should be applicable in the context of the symmetry forbidden, disrotatory ring opening reaction of the BCB mechanophore. Here, we report that introduction of an a-*E*-alkene to *cis*-substituted BCB leads to a reduction in the force required to obtain the necessary reactivity from 1370 to 920 pN (Figure 1).

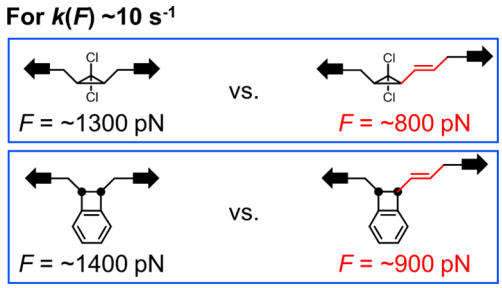


Figure 1. Lever arm effect of α-E-alkene in gem-dichlorocyclopropane (*g*DCC, top) and BCB (bottom) systems. On a time scale of 0.1 s, the introduction of the α-*E*-alkene decreases the force required for activating both systems by ∼500 pN.

We follow our previous strategy in which SMFS[16−19] is applied to multimechanophore polymers. This approach has been used successfully to quantify the force-accelerated electrocyclic ring opening reactivity of a series of mechanophores, such as *g*DHCs,[11−13] benzocyclobutene,[13] and spiropyran.[20] The synthetic procedure for making the polymer that contains both the mechanical leverage and BCB mechanophore is shown in Figure 2a. The BCBs were embedded along the backbone of polymer **3** via the ring opening methathesis polymerization (ROMP)[21,22] of comonomers of BCB-bearing monomer **1** and epoxy-cyclooctene **2**.

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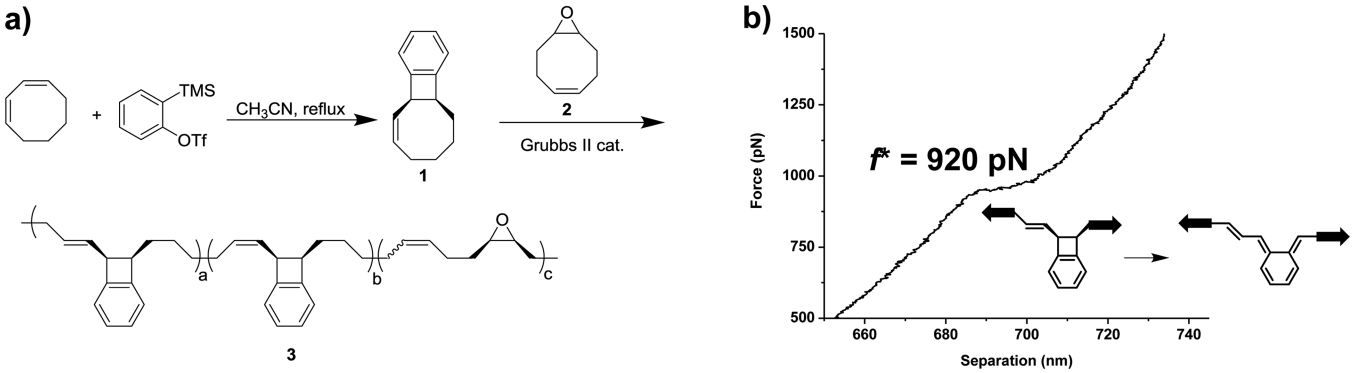

Figure 2. (a) The synthetic procedure of a multimechanophore polymer **3**. (b) A representative force curve of **3** obtained by SMFS at a retraction velocity of 300 nm/s. (As consideration of clarity, only the vicinity of the plateau part is shown. For the complete force curve, see Supporting Information, SI).

The epoxides were incorporated because they are mechanically inactive in the force range of interest but increase the attachment force between the tip of the atomic force microscope (AFM) and the polymer analyte.[12] Incorporation of **1** was inefficient, and the highest BCB content obtained was 18%. The ROMP yielded a mixture of stereoisomers at the α-alkene substituent on the BCB, with a ratio of *E*:*Z* = 3.5:1 (14% *E*-alkene and 4% *Z*-alkene), as determined by ^{1}H NMR. Polymers were deposited on a surface, and the AFM tip was brought into contact and then retracted at a velocity of 300 nm/s (the details have been described previously).[13] In all cases where sufficiently high adhesion forces were obtained, a plateau[23] (plateau force f^* = 920 ± 60 pN, as defined previously;[11,12] uncertainty reported as the standard deviation of mean) is observed in the force−extension curve (Figure 2b).

As we have observed in the force curves of other multimechanophore polymers,[12] the plateau is structurally consistent with the expected BCB ring opening reaction. The relative plateau length matches that expected based on modeling the conversion of *cis*-BCB to the expected (*E*,*E*)-*ortho*-quinodimethide (*o*QDM); conversion to the corresponding (*E*,*Z*) isomer that would result from the symmetry allowed conrotatory ring opening, on the other hand, is not consistent with the observed extensions. In combination with our previous studies of similar reactions,[13] we therefore ascribe the observed transition to the disrotatory ring opening of *cis*-BCB to give the symmetry disallowed, (*E*,*E*) isomer of *o*QDM. A second, much more subtle transition is observed at ∼1250 pN, and this transition likely corresponds to the ring opening of the small amount of *Z*-α-alkene-BCB (∼4% of polymer content). Because this structural feature is small, and since the difference in mechanochemical coupling effects between *Z*-α-alkene and *E*-α-alkene has been characterized previously,[15] we focus here on the lower-force transition that involves the *E*-alkene isomer.

Importantly, the symmetry forbidden reactivity in **3** occurs at a lower force (f^* = 920 pN) than that reported previously for *cis*-BCB in the absence of the α-alkene (f^* = 1370 pN). The associated mechanically coupled rate accelerations are substantial. Extrapolating the previously reported force-rate behavior of *cis*-BCB to a force of 920 pN, for example, shows that the introduction of the α-*E*-alkene leads to a rate enhancement in the symmetry forbidden ring opening of >1000-fold over the parent BCB mechanophore. As with prior demonstrations of α-alkene substituent effects in symmetry allowed electrocyclic reactions,[15] the dominant contribution to the enhanced reactivity is mechanical leverage. If one assumes that the α-alkene-bearing BCB and the original BCB have the same activation energy, the drop of 450 pN in f^* requires a ∼0.75 Å increase in the activation length (see SI), which is the length change from the reactant to the product along the vector of force.[12] According to previous calculations, the transition-state structures of the disrotatory ring opening of cyclobutene systems are highly expanded and very similar to the products.[24,25] We therefore use the change in polymer contour length associated with conversion of the reactant to the product to estimate the differential activation lengths. The contour lengths of the reactant and product were modeled, by CoGEF calculations,[26] using methods reported previously.[12] The modeling shows that the expected increase in the activation length due to the α-*E*-alkene is ∼0.63 Å. The enhanced mechanical leverage therefore accounts for >80% of the observed rate acceleration, with the difference due to the effect of the alkene on the force-free activation energy, similar to the *g*DCC system.[15] An independent measure of the change in force-free activation energy due to the alkene is obviously impossible to come by, as the disrotatory process does not occur under force-free conditions.

The SMFS data presented here constitute only the second quantitative study of force−activity relationships in reactions that are mechanically steered to proceed in a direction that opposes the Woodward−Hoffmann rules.[13] On a fundamental level, the agreement between the observed and expected (based on molecular modeling) decrease in force required, relative to the parent BCB system, supports the continued use of the same chemomechanical framework[27] for interpreting reactivity across both allowed and forbidden reactions. On a more practical level, lever arm effects are shown here to be a viable mechanism by which to improve access to otherwise forbidden, mechanically driven reactions. The ability to predict and exploit electrocyclic reactivity might therefore extend beyond the reactions covered by the Woodward−Hoffmann rules to include selected—and, more importantly, selective—examples of mechanically steered reactions that provide access to an even richer set of products and intermediates.

EXPERIMENTAL SECTION

General Methods. All of the starting materials and reagents are commercially available and used as received. All reactions were performed in dry solvent under N_2. For ^{1}H NMR and ^{13}C NMR analysis, the residual solvent peaks ($CDCl_3$ 7.26 ppm [^{1}H], 77.16 ppm [^{13}C]) were used as an internal chemical shift reference. All chemical shifts are given in ppm (δ) and coupling constants (J) in Hz as singlet

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(s), doublet (d), triplet (t), quartet (q), multiplet (m), or broad (br). Gel permeation chromatography (GPC) experiments were performed on an in-line two columns (10^4 and 10^3 Å) using THF (inhibitor free) as the eluent. Molecular weights were calculated using a multiangle light scattering (MALS) detector and interferometric refractometer (RI). The refractive index increment (d*n*/d*c*) values were determined by online calculation using injections of known concentration and mass.

Synthesis. *Mixture with (Z)-4b,5,6,7,8,10a-Hexahydrobenzo-[3,4]cyclobuta[1,2][8]annulene (1) as major component.* In a 100 mL round-bottom flask was added 5.0 g (16.8 mmol, 1 equiv) benzyne precursor 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, 5.5 g (50.4 mmol, 3 equiv) *cis,cis*-1,3-cyclooctadiene and 30 mL acetone nitrile. To the mixture was added 7.7 g (50.4 mmol, 3 equiv) cesium fluoride. The reaction mixture was allowed to stir under nitrogen at room temperature overnight. After 24 h of reaction, the mixture was poured into saturated sodium bicarbonate solution and filtered by suction filtration. The organic layer in the filtrate was collected, and the aqueous layer was extracted with hexane three times (20 mL × 3). The combined organic phase was washed with brine and water and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography with hexane as the eluent to yield a mixture of **1** and minor impurities (ene reaction products)[28] as a colorless oil (0.5 g, 16.1% yield). Attempts at further purification were unsuccessful, and since the impurities proved to have negligible reactivity in the ensuing polymerization, the as-obtained mixture was carried forward for subsequent polymerization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.18 (m, 2H), 7.17−7.11 (m, 1H), 7.09−7.02 (m, 1H), 5.83−5.69 (m, 1H), 5.60 (dd, J = 11.2, 3.8 Hz, 1H), 4.43 (m, 1H), 3.82−3.63 (m, 1H), 2.28−2.04 (m, 2H), 2.02−1.71 (m, 4H), 1.67−1.54 (m, 1H), 1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 127.4, 127.1, 121.6, 121.6, 52.6, 45.9, 32.3, 29.3, 27.7, 26.2. HRMS (ESI-TOF): calcd for $C_{14}H_{16}$([M − H]+) 183.1168, found 183.1166.

To further confirm the stereochemistry of BCB, **1** was epoxidized into 1a,2,3,4,5,5a,9b,9c-octahydrobenzo[3′,4′]cyclobuta[1′,2′:3,4]-cycloocta[1,2-*b*]oxirene (**4**) as a white solid (mp 45−50 °C). The X-ray crystallographic structure of **4** shows that it is *cis*-BCB (see SI). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.23 (m, 3H), 7.14 (d, J = 6.5, 1H), 3.67−3.47 (m, 2H), 3.17 (m, 1H), 3.04 (m, 1H), 2.40 (m, 1H), 2.27 (m, 1H), 2.15 (m, 1H), 2.00−1.90 (m, 1H), 1.68−1.51 (m, 1H), 1.46−1.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 145.0, 127.8, 127.7, 122.6, 121.5, 57.4, 56.8, 50.5, 46.4, 31.00, 29.6, 28.2, 24.2. HRMS (ESI-TOF): calcd for $C_{14}H_{16}O$ ([MH]+) 201.1274, found 201.1273.

The synthesis of monomer **2** was conducted by following a previously reported procedure.[29]

Polymer 3. A 0.12 g of the mixture with majority component **1** (0.64 mmol) and 0.58 g **2** (3.2 mmol) was added in a 1 mL scintillation vial. 2.0 mg (2.36×10^{-3} mmol) Grubbs second-generation catalyst[30] was added to the vial and allowed to stir. The viscosity of the solution increased over 30 min, at which point the stirring ceased quickly. 0.5 mL of DCM was added to the solution to allow the stirring to continue, and the reaction was allowed to proceed overnight. After 24 h of stirring, the reaction was quenched with 0.5 mL of ethyl vinyl ether and stirred for 1 h. The reaction was then precipitated in methanol, dissolved again in DCM, reprecipitated in methanol, and dried on a vacuum line. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.14 (m, 0.42H), 7.13−6.95 (m, 0.40H), 5.79−5.19 (m, 2.4H), 4.43 (t, J = 6.5 Hz, 0.04H), 4.13 (t, J = 5.9 Hz, 0.14H), 3.56 (q, J = 7.2, 6.0 Hz, 0.18H), 2.90 (t, J = 4.8 Hz, 2H), 2.46−1.82 (m, 4.6H), 1.80−1.04 (m, 5.7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.4, 131.2, 130.6, 130.1, 129.8, 129.5, 129.4, 127.4, 127.3, 126.9, 126.7, 123.2, 122.7, 122.3, 57.4, 57.4, 56.9, 56.5, 55.9, 50.8, 50.5, 48.6, 48.4, 48.3, 48.1, 32.5, 29.5, 27.9, 27.8, 27.7, 24.3. GPC-MALS: M_n = 159,000, PDI = 1.52, d*n*/d*c* = 0.130 mL/g. Polymer composition: a = 0.14, b = 0.04, c = 0.82.

SMFS. Details of the SMFS experiments have been described previously.[13] The spring constant of the AFM cantilever was calibrated in air, by applying the thermal noise method.[31] Polymer solution was absorbed on a silica substrate surface, which was brought into contact with an AFM tip and then retracted at a velocity of 300 nm/s. The experiments were performed in toluene at room temperature. Approach/retract cycles were repeated, and the force−extension curves were recorded and analyzed using homemade software.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01465.

NMR spectra, force curve fitting, theoretical modeling (PDF)

Crystal structure (CIF)

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Notes

The authors declare no competing financial interest.

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