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Force Transduction Through Distant Force-Bearing Regioisomeric Linkages Affects the Mechanochemical Reactivity of Cyclobutane

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Abstract:

Fundamental understanding of mechanochemical reactivity is important for designing new mechanophores. Besides the core structure of mechanophores, substituents on a mechanophore can affect its mechanochemical reactivity through electronic stabilization of the intermediate or effectiveness of force transduction from the polymer backbone to the mechanophore. The latter factor represents a unique mechanical effect in considering polymer mechanochemistry. Here, we show that regioisomeric linkage that is not directly adjacent to the first cleaving bond in cyclobutane can still significantly affect the mechanochemical reactivity of the mechanophore. We synthesized three non-scissile 1,2-diphenyl cyclobutanes, varying their linkage to the polymer backbone via the *o*, *m*, or *p*-position of the diphenyl substituents. Even though the regioisomers share the same substituted cyclobutane core structure and similar electronic stabilization of the diradical intermediate from cleaving the first C-C bond, the *p* isomer exhibited significantly higher mechanochemical reactivity than the *o* and *m* isomers. The observed difference in reactivity can be rationalized as the much more effective force transduction to the scissile bond through the p-position than the other two substitution positions. These findings point to the importance of considering force-bearing linkages that are more distant from the bond to be cleaved when incorporating mechanophores into polymer backbones.

Introduction

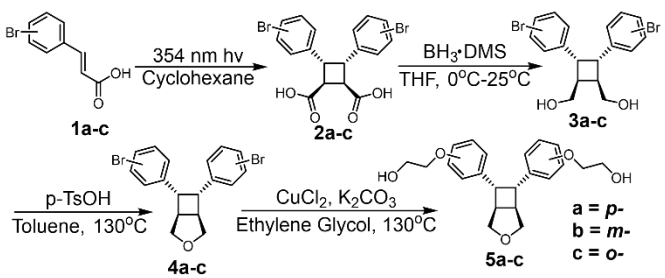
Pulling on a strand of polymer with embedded force-responsive units, mechanophores, has been shown to reveal mechanochemically activated reactivities that follow different mechanisms and reaction trajectories from thermally or photochemically activated pathways.[1-5] Much of the research into the fundamentals of mechanochemistry has focused on how electronic, steric, and stereochemical factors influence the reactivity of mechanophores as these parameters are the main drivers of reactivity in thermal or photochemical reactions.[6-13] Many studied mechanochemical reactions involve the homolytic cleavage of a C-C bond to generate diradical species in the first step of mechanoactivation. The extent of electronic stabilization of the formed diradical intermediates can impact the mechanochemical reactivity.[7-8]

An additional factor unique to mechanochemical reactions is the transmission of force to the targeted scissile bond. Force transmission can be greatly impacted by the molecular structures. Varying the attachment points of force-bearing substituents to the core mechanophore structures often affects the effectiveness of force transduction.[6, 14-23] The studied mechanophores include spiropyrans,[6, 14, 17] naphthopyrans,[15, 18] Diels-Alder adducts,[10, 16] cubane,[19] coumarin dimers,[23] and fused cyclobutane structures.[21-22] Pulling at positions on the mechanophore that poorly couple the applied force to the targeted first bond to be cleaved results in reduced or no mechanical reactivity. For example, De Bo and coworkers reported that pulling from proximal positions on furan-maleimide adducts results in retro-Diels Alder reaction, while pulling from distal positions inhibits mechanoreactivity;[16] Craig and coworkers showed that only pulling at vicinal carbons of cubane results in its mechanoactivation.[19]

Less intuitively, Craig and coworkers discovered that the structure of force-transducing substituents at the same locations of dihalocyclopropane mechanophore can also affect the threshold force for mechanoactivation.[24-26] For example, a polynorbornene backbone structure lowers the force required to ring open the backbone-embedded epoxide[24] or dihalocyclopropanes[25] as compared to with a more flexible backbone. Stereochemistry of the substituents can also affect the mechanochemical reactivity. Craig and coworkers reported that *E* backbone alkenes can lower the threshold force for *gem*-dichlorocyclopropane (gDCC) activation more than *Z* alkenes.[27] A *syn* arrangement of the force-transducing substituents on dihalocyclopropane and cyclobutane decreases the threshold force required to break the first bond in the mechanophore.[7, 12, 28-29] These interesting effects are deemed geometric or mechanical rather than electronic in nature. Further probing these mechanical effects requires looking at connectivity that is not immediately adjacent to the core of the mechanophore, as non-local polymer structure is implicated in force transmission.[30].

Diphenyl substituents on cyclobutane have recently been shown to significantly lower the threshold force for cyclobutane ring-opening as compared to dialkyl or diester substituents,[8, 31] thus making diphenyl cyclobutane a promising low-force mechanophore system. We were curious if connecting the phenyl substituents to the polymer strands via the *o*, *m*, or *p* positions would affect the mechanochemical reactivity. Varying such a distant linkage from cyclobutane could change the trajectory of force being applied to the phenyl groups, which projects onto the first cleaving C-C bond of the cyclobutane. To probe this question, we designed a set of non-scissile, regioisomeric diphenyl cyclobutanes that differ only in the location of polymer attachment on the phenyl substituents. We observed a striking effect among the regioisomers in their mechanochemical reactivity, and used computational modeling to rationalize the difference in the effectiveness of force transduction. This finding points to the necessity of considering linkages that are more distant from the scissile bond in a mechanophore for efficient force coupling in order to develop mechanophores with more sensitive force responses.

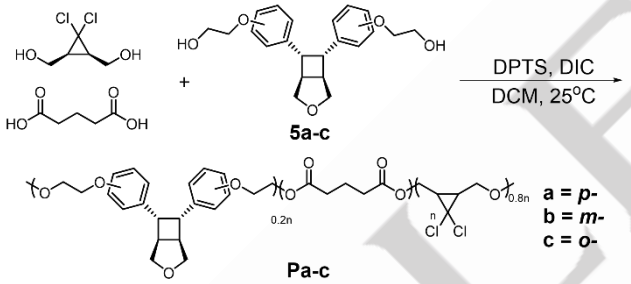
Results and Discussion



Scheme 1. Synthesis of diphenyl oxabicyclo[3.2.0]heptane regioisomers **5a-c**.

We targeted a simple bicyclic oxabicyclo[3.2.0]heptane structure to render the cyclobutane mechanophore a non-scissile design. The synthesis began with photodimerization of bromocinnamic acid. Crystals of *o*, *m*, or *p*-bromocinnamic acid were irradiated under 354 nm light as a suspension in cyclohexane. All the three regioisomers yielded the cyclobutane structures **2a-c** with *syn*-diphenyl substituents quantitatively and diastereoselectively on a multi-gram scale. Reduction of the carboxylic acids to alcohols with BH_3·DMS was followed by condensation of the resulting diol at 130°C to generate oxabicyclo[3.2.0]heptanes **4a-c**. **4a-c** were then coupled with ethylene glycol in the presence of $CuCl_2$ as a catalyst to yield diols **5a-c** as white solids. Diols **5a-c** were recrystallized to obtain high purity for use in polycondensation to synthesize multimechanophore polymers with diphenyl cyclobutane units connected through the *o*, *m*, or *p* position of the phenyl substituents.

gDCC is an extensively studied mechanophore that undergoes ring opening reaction to yield 2,3-dichloroalkene.[32] Because the rate and extent of mechanophore activation depend on the chain length of the mechanophore-containing polymers[33] and it is difficult to control molecular weight in polycondensation, we chose gDCC as an internal standard to also be incorporated into polymers as reported in other studies in order to compare the degree of activation for the three regioisomers.[10, 34-36] Thus, the ratio of mechanoactivation for cyclobutane relative to gDCC can be used to compare the reactivity difference among the three isomers embedded in polymers with different lengths. Cyclobutane diol **5a-c** (0.2 eq.), gDCC diol (0.8 eq.), and glutaric acid (1.0 eq.) were copolymerized through polycondensation using DPTS and DIC and yielded random copolyesters **Pa-c** with M_n of 35-90 kDa (Scheme 2).



Scheme 2. Synthesis of multi-mechanophore polymers containing diphenyl cyclobutane and gDCC.

Solutions of **Pa-c** in toluene were sonicated and analyzed by NMR spectroscopy, using previously described small molecule analogs as reference structures.[37] As sonication time increased, there was a growth of several new signals in the aromatic region as well as new alkene signals that corresponded to the ring-opened form of the diphenyl cyclobutane (Figure 1 and Figure S14-19). These signals were integrated and compared with the signals corresponding to ring-opened gDCC relative to the integration of peaks for gDCC and the cyclobutane mechanophore before sonication to give an activation ratio of cyclobutane/gDCC.

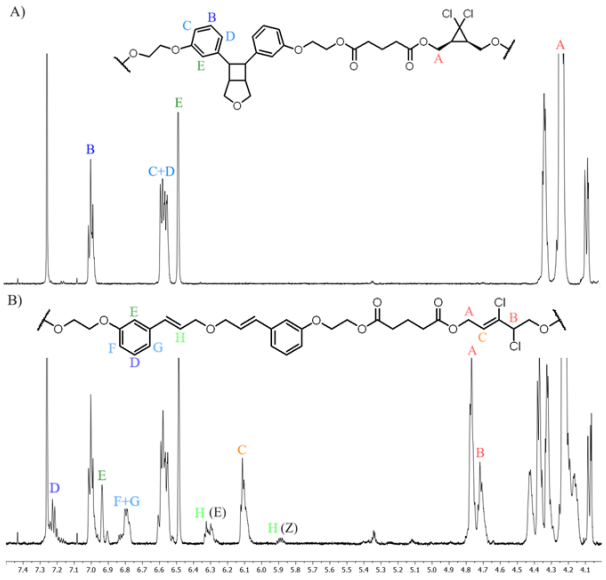


Figure 1. Comparison of ^{1}H NMR spectra for a copolymer containing the *m*-diphenyl cyclobutane and gDCC with A) before sonication and B) after 60 minutes of sonication.

Throughout the course of sonication, the *m* and *o* isomeric diphenyl cyclobutanes in polymers **Pb** and **Pc** were activated less than gDCC, giving similar cyclobutane/gDCC activation ratios of 0.79±0.14 and 0.66±0.06, respectively. In contrast, the *p* isomer in **Pa** was activated more than gDCC. **Pa** gave a cyclobutane/gDCC activation ratio of 1.67±0.22 (Figure 2). This result indicates a much higher mechanochemical reactivity of the *p* isomer than the *o* and *m* isomers.

We assigned the configuration of the mechanochemically generated dienes by comparing their ^{1}H NMR signals to those of reported reference compounds. Both the *m* and *p* isomers showed two sets of alkene peaks with the majority being the *E* alkenes.[37] The formation of *Z* alkenes suggests stereoreversion in the lifetime of the diradical intermediate during the mechanochemical ring-opening of cyclobutane. The *o* isomer formed only a single detectable stereochemical product, *E*,*E*-diene. This corresponds to retained stereochemistry from the *exo*-cyclobutane connected to the polymer chain through *syn*-diphenyl substitution. Electronic stabilization of the diradical species and force-imparted nonstatistical dynamic effects have both been invoked to rationalize the stereochemical product distribution in reported mechanochemical ring-opening reactions.[28, 38-39] A detailed exploration of origins of the stereochemical product distribution for these three isomers requires comprehensive computation and is beyond the scope of this work, but the observed difference shows the impact of subtle structural variation on product distribution for even a relatively simple mechanochemical reaction.

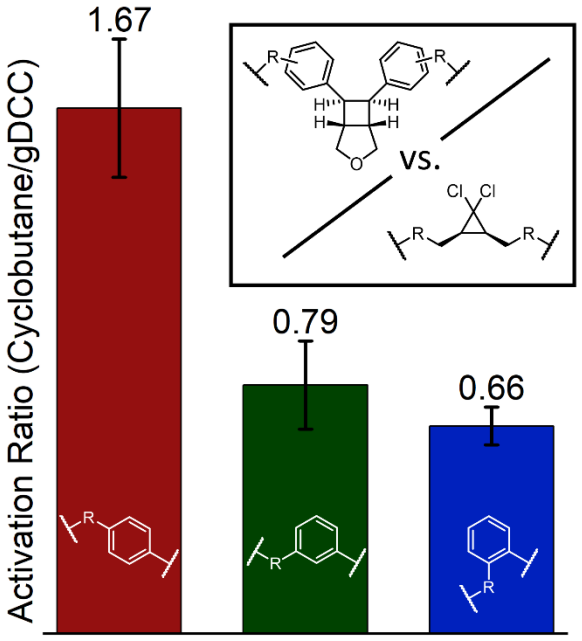


Figure 2. Measured activation ratios of cyclobutane/gDCC for *p*, *m*, *and o* diphenyl cyclobutane isomers.

To give insight into the origin of reactivity differences in the three isomers, we used a recently introduced tension model of bond activation (TMBA).[40] The TMBA model predicts threshold activation forces through a bivariate fit of two key parameters that affect mechanochemical reactivity: the change in energy from the force-free ground state to the diradical intermediate, ΔE, and the linear spring constant or resistance to cleavage of the target bond, k_{eff}. The ΔE value is used as a measure of the strength of the bond where stronger bonds have a larger ΔE value, while k_{eff} is used as a measure of the force sensitivity of scissile bond where a smaller k_{eff} value corresponds to smaller forces needed to elongate the scissile bond to a unit length.

To find ΔE, the energies of ground state and diradical intermediate were calculated at the B3LYP/def2-tzvpp level of theory. To obtain the diradical intermediate energies, the structures were optimized first in the triplet state, and then energies were calculated in the singlet state under a broken symmetry operation. Using the triplet state, rather than singlet state, for the initial geometry optimization facilitated convergence to a diradical stationary point without convergence on closed-shell structures. Following this analysis, ΔE was found to be 40 kcal/mol for the *m* isomer, moderately higher than that for the *o* and *p* isomers, which is in the range of 30-33 kcal/mol. This result indicates slightly reduced stabilization of the diradical due to the lack of resonance effect in the *m* isomer. But this difference in electronic stabilization of the diradical intermediate for the *m* vs *o*/*p* isomers does not account for the observed difference in reactivity for the *p* vs *o*/*m* isomers.

Table 1. Calculated mechanical sensitivity, k_{eff}, and the ΔE between the ground state and diradical intermediate of the scissile bond of 1,2-diphenyl cyclobutane isomers, and their semi-empirically predicted threshold force, F_{pred}, values, using the TMBA model.[40]

isomer	k_{eff} (nN/Å)	ΔE (kcal/mol)	F_{pred} (nN)
p	8.62	32.5	0.70
m	19.38	39.9	1.41
o	25.00	30.7	1.47

We then calculated the k_{eff} of the first C-C bond to be cleaved in cyclobutane. The diphenyl cyclobutane structures were first optimized under force-free conditions at the B3LYP/6-31G* level, and then optimized under an external force ranging from 1.5-2.5 nN in 0.05 nN increments at the B3LYP/6-31G* level of theory. Although the three isomers have almost the same C1-C2 bond length under force-free conditions of 1.59-1.60 Å, the *p* isomer exhibited significantly more elongated C1-C2 bond length under 2.5 nN force of 1.785 Å than the *m* and *o* isomers at 1.665 Å and 1.650 Å, respectively (Figure 3). The bond lengths were plotted as a function of the applied force, and k_{eff} was obtained from a linear fit of external force as a function of bond length (Figures S2-S4). The calculated k_{eff} of the *p* isomer was 9.2 nN/Å, while k_{eff} values for the *m* and *o* substituted isomers were 19.8 and 23.2 nN/Å, respectively (Table 1). The more than halved k_{eff} for the *p* isomer indicates higher mechanical sensitivity to applied forces that distort the molecule, particularly for the scissile bond in the rate limiting step. The TMBA model provides a semi-empirical correlation between the predicted threshold forces and previously reported threshold forces measured by single molecular force spectroscopy (SMFS) under the same constant velocity loading rate of 300 nm/s for a variety of mechanophores, including many cyclobutane-based ones. Therefore, we applied this model to calculate the threshold forces for the isomers. As expected, the *p* isomer has the lowest predicted threshold force (0.73 nN), in line with the experimentally determined threshold force of a similar diphenyl cyclobutane structure (0.67 nN).[41] The *m* and *o* compounds in contrast had predicted threshold forces almost twice those of the *p* isomer (1.43 nN, 1.38 nN) (Table 1). gDCC has a reported measured threshold force of 1.33 nN by SMFS under the same conditions,[25] placing it between the *p* isomer and the *m, o* isomers in terms of the mechanochemical reactivity. Despite the very different strain rates and forces accessed during constant velocity SMFS experiments and ultrasonication, the ordering between experimentally measured threshold force for gDCC and the semi-empirically predicted threshold forces for the three isomers studied here reproduced the experimentally observed reactivity trend determined from activation ratios in ultrasonication of mechanophore copolymers.

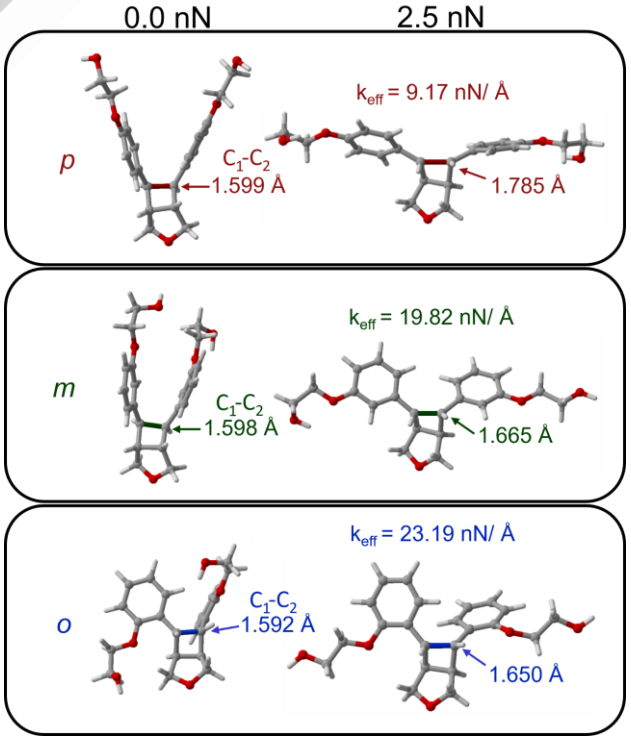


Figure 3. Calculated cleaving bond length in cyclobutane under 0.0 and 2.5 nN force and k_{eff} for the *p*, *m*, and *o* isomers.

Conclusion

Using a set of *syn* 1,2-diphenyl cyclobutanes for which the attachment points to the polymer backbone are at the *o*, *m*, or *p* position of the phenyl substituents, we show that the *p* isomer gives substantially greater mechanochemical reactivity, even though these substitutions are distant from the scissile bond of the fused cyclobutane mechanophore. Computational investigations reveal that polymer backbone linkage through the *p* position results in more effective force transduction onto the scissile bond of cyclobutane (more facile bond elongation with increasing applied forces), which accounts for the observed enhanced mechanochemical reactivity of the *p* isomer.

This work demonstrates a mechanical, rather than electronic or steric, effect in polymer mechanochemistry. It is therefore important to consider the chemically passive linkages that are immediate or remote to the core mechanophore structures when designing new mechanophores and integrating the mechanophores into polymeric systems that target macroscopic force-response originating from molecular mechanochemical reactivity. It is also interesting to investigate whether the same favorable mechanical transduction exists for other mechanophore structures and other transannular linkages to the scissile bond of the mechanophores in the future.

Supporting Information

The authors have cited additional references within the Supporting Information.

Acknowledgements

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Keywords: mechanochemistry • mechanochemical reactivity • force transduction • cyclobutane • regioisomer

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