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Stereochemical effects on the mechanochemical scission of furan-maleimide Diels-Alder adducts

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Clarifying the correlation between the chemical structure of mechanophores and their mechanical reactivity informs the design of mechanochemical systems. One specific correlation that has received much recent attention is that between stereoisomerism and mechanical reactivity. Here, we report previously unobserved differences in the mechanical reactivity of furan-maleimide Diels-Alder (DA) stereoisomers. We evaluated the internal competition between the mechanically triggered retro-DA reaction and the mechanochemical ring opening of *gem*-dichlorocyclopropane mechanophores in the pulsed sonication of polymer solutions. The relative extent of the two sonomechanochemical reactions in the same polymer shows that the *endo* DA isomer exhibits greater mechanical lability than its *exo* isomer. This result contrasts with recent measurements of the relative rates of scission in a similar system and points to potential enhanced sensitivity obtained through the use of internal competition as opposed to absolute rates in assessing mechanical reactivity in sonication studies.

The Diels-Alder (DA) reaction of furan and maleimide has become an empowering tool for polymer chemistry.¹ For example, Wudl *et al.* and Min *et al.* utilized it as the basis for thermally re-mendable polymers,^{2, 3} and McElhanon and co-workers have used it as the cross-linker for thermally responsive dendrimers.⁴ The furan-maleimide motif was further exploited by Shoichet *et al.* in a DA cross-linked hydrogel for tissue engineering.⁵ In all of these examples, the DA adducts fulfil a load-bearing, structural role that relies on the mechanical stability of the adduct. The activation energy of the retro-Diels-Alder (rDA) reaction, however, is around 25 kcal/mol,⁶ much lower than the homolytic dissociation energy of the conventional carbon-carbon covalent bond, and so one would expect that the DA adducts would be mechanically labile relative to the rest of the covalent structure of the polymers and networks. This has been proven to be true, and mechanically induced rDA reactions have been implicated in linear polymers,⁷ surface-tethered brush

polymers⁸ and cross-linked polymeric networks,³ and they as related reactions have been coupled to photochemical reactivity.^{9, 10}

A critical mechanistic question is the influence of the adduct stereochemistry on the susceptibility of the mechanically induced rDA reaction. Stevenson *et al.* recently compared the mechanical reactivity of four furan-maleimide DA regio- or stereo- isomers.¹¹ By comparing the relative rates of the polymer chain scission, they found that whereas regioisomeric effects in the attachment of the adduct to the polymer main chain are substantial (distal attachments are relatively inert, while proximal attachments are mechanically labile), *endo* and *exo* stereoisomers had no detectable impact on the rate of scission in the adducts with proximal attachments. The sensitivity of rate measurement to subtle differences in mechanical reactivity, however, is not clear. As it is unlikely that the two stereoisomers are truly identical in reactivity, we sought a more sensitive measure of their mechanical susceptibility.

Our approach was to exploit the competition between the mechanochemical scission of DA adducts and the non-scissile ring opening reaction of *gem*-dichlorocyclopropane (*gDCC*) mechanophores to probe the relative mechanical lability of DA stereoisomers under pulsed sonication (Figure 1a), as we have found to be useful in studies of other scissile mechanophores measurements.¹² Polymers **P1-3** were synthesized using carbodiimide polyesterification methodology of Moore and Stupp,¹³ in which diols of each DA isomer (or a non-DA adduct diol control) and *gDCC* were copolymerized with glutaric acid for approximate three days (Figure 1b, see ESI for procedures). The largely random nature of the copolymerization is supported by thermal degradation experiments (see ESI for details). The molecular weights of **P1** ($M_{n,0}$ = 160 kDa) and **P2** ($M_{n,0}$ = 110 kDa) after thermal degradation through the rDA reaction are determined to be 2.7 kDa and 2.8 kDa, respectively, versus 2.0 kDa and 2.1 kDa expected for a completely random polymerization. Comparatively, the expected molecular weights of the *gDCC* block in the corresponding diblock copolymers (once the small molecular rDA fragments has been removed) would be 122 kDa and 81 kDa, respectively. To quantify the relative

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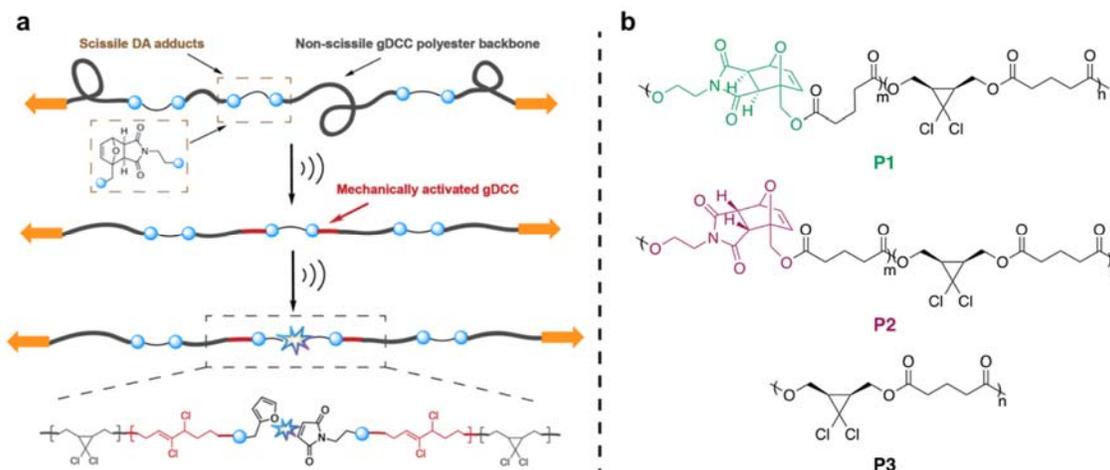


Figure 1 (a) The strategy of studying the competition between the mechanochemical scission of scissile mechanophores and the non-scissile ring opening of gDCC mechanophores. (b) The chemical structures of synthesized polymers **P1**, **P2** and **P3**. Polymers **P1** and **P2** contain scissile DA adducts and non-scissile gDCC mechanophores. Polymer **P3** only contains gDCC mechanophores.

mechanical reactivity of each isomer, we plotted the fraction of gDCC of the scission cycle¹⁴ (SC ; $SC = [\ln(M_{n,0}) - \ln(M_{n,t})]/\ln 2$) and obtained the slope (Φ_i) of the linear fit to the data. $M_{n,t}$ is the number average molecular weight as a function of sonication time t , and it was obtained by size exclusion chromatography with multiangle light scattering (SEC-MALS). The magnitude of Φ_i reports the relative mechanical reactivity of the most scissile bond along the polymer backbone; larger Φ_i implies a mechanically stronger bond. Because it reflects an internal competition, we have found that Φ_i is independent of many of the experimental factors that influence scission rates (polymer concentration, sonication power, temperature and solvent).¹⁵ The magnitude of Φ_i does depend, however, on initial molecular weight,¹⁵ and so we synthesized **P1-3** at a range of initial number-averaged molecular weight ($M_{n,0}$) to allow us to account for any molecular weight dependencies (shown in Table 1). The polymers were dissolved in THF at a concentration of 2 mg/mL and the pulsed ultrasound (20 kHz, 8.0 W/cm², 1s ON/ 1s OFF) was used to generate high extensional flows and mechanical forces along the polymer backbone.¹⁶ The solution was maintained at 6–9 °C with an ice bath, and reactions were carried out under a nitrogen atmosphere (see ESI for details and additional data).

The internal competition shows that the *endo* stereoisomer is more mechanically labile. As seen in Figure 2a, when the polymers

Table 1. Feed ratio of DA monomers, $M_{n,0}$, Φ_i , and R^2 values of **P1 1-3** and **P2 1-3**

	DA ratio (mol %)	$M_{n,0}$ (kDa)	Φ_i	R^2
P1-1	20	77	0.19	0.977
P1-2	21	160	0.14	0.984
P1-3	20	220	0.086	0.963
P2-1	20	72	0.087	0.917
P2-2	20	83	0.084	0.951
P2-3	20	110	0.072	0.946

are made from a similar ratio of DA adducts and similar $M_{n,0}$, the Φ_i

of **P1-1** is 0.19 ($R^2 = 0.977$), which is more than twice as large as that of **P2-1**, $\Phi_i = 0.087$ ($R^2 = 0.917$). As seen in Figure 2b, this trend is observed across a range of $M_{n,0}$. The values of Φ_i for polymers **P1 1-3** are 0.19 (77 kDa), 0.14 (160 kDa), and 0.086 (220 kDa), respectively, whereas Φ_i for polymers **P2 1-3** are 0.087 (72 kDa), 0.084 (83 kDa), and 0.072 (110 kDa) respectively.

To further validate our findings, we also measured the molecular weight of **P1** ($M_{n,0} = 53$ kDa, DA monomer content: 20 mol%) and **P2**

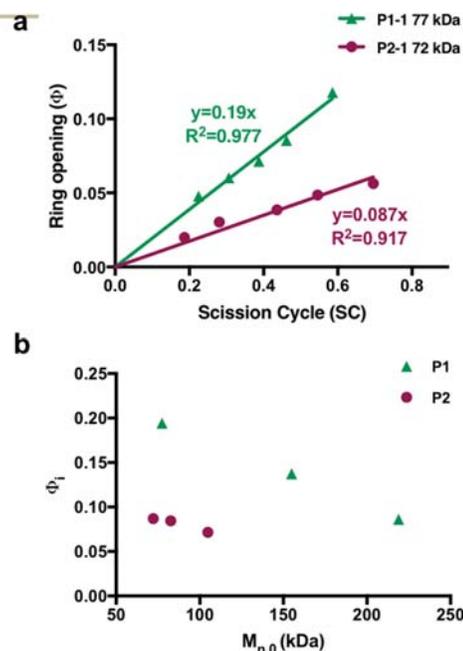


Figure 2 (a) The Linear fitting of the portion of gDCC ring opening (Φ) and scission cycle (SC) of **P1-1** and **P2-1**; Slope value: Φ_i ; Green solid line represents **P1-1** degradation ($\Phi_i = 0.19$, $R^2 = 0.977$) while red solid line represents **P2-1** degradation ($\Phi_i = 0.090$, $R^2 = 0.954$). (b) The Φ_i of **P1** and **P2** determined at three $M_{n,0}$. Green triangle and red round points represent **P1** and **P2**, respectively.

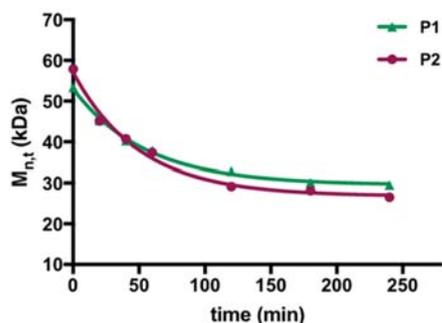


Figure 3 Decrease of $M_{n,t}$ of **P1** and **P2** as a function of sonication time t . The $M_{n,4h}$ are determined from the average of three runs of SEC experiments, which are 30 kDa and 27 kDa for **P1** and **P2**, respectively. The solid lines are exponential fits of the data, whose functions are $M_{n,t} = 23.5 \cdot e^{-0.018t} + 29.5$ ($R^2 = 0.99$) and $M_{n,t} = 30.3 \cdot e^{-0.020t} + 26.8$ ($R^2 = 0.99$) for **P1** and **P2**, respectively.

($M_{n,0} = 58$ kDa, DA monomer content: 20 mol%) after 4 h sonication, denoted as $M_{n,4h}$. Under our conditions, 4 h is sufficient to reach an apparent limiting molecular weight that varies undetectably with further sonication time. The magnitude of $M_{n,4h}$ offers a complementary measure of the relative mechanical susceptibility of covalent bonds incorporated within the polymer chain; weaker bonds lead to a lower $M_{n,4h}$.¹² Figure 3 shows the $M_{n,t}$ change of **P1** and **P2** as a function of sonication time, and the $M_{n,4h}$ of **P1** and **P2** are measured to be 30 kDa and 27 kDa respectively, consistent with

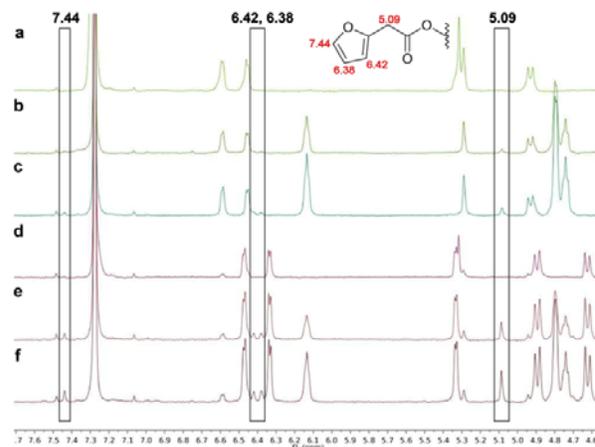


Figure 4 The ^1H NMR (500 MHz) stacking diagrams of the polymer **P1** ($M_{n,0} = 160$ kDa) before sonication (a) and after sonicated for 1h (b) and 2h (c), and the polymer **P2** ($M_{n,0} = 110$ kDa) before sonication (d) and after sonicated for 1h (e) and 2h (f).

a slightly greater mechanochemical lability of the *endo* isomer relative to the *exo* isomer. As the polydispersity (PDI) narrows as $M_{n,t}$ decreases with increasing sonication time (see ESI for SEC traces and PDI change), the degradation rate of longer polymers is larger than that of shorter polymers and scissions of daughter chains can be neglected in a kinetic analysis for comparative purposes.^{17, 18} Thus, we fit the change in $M_{n,t}$ change with sonication time t to a first-order exponential decay ($dM_{n,t}/dt = k_d (M_{n,t} - M_{lim})$). Rate constants k_d of DA bond scissions of **P1** and **P2** were determined to be $1.8 \times 10^{-2} \text{ min}^{-1}$

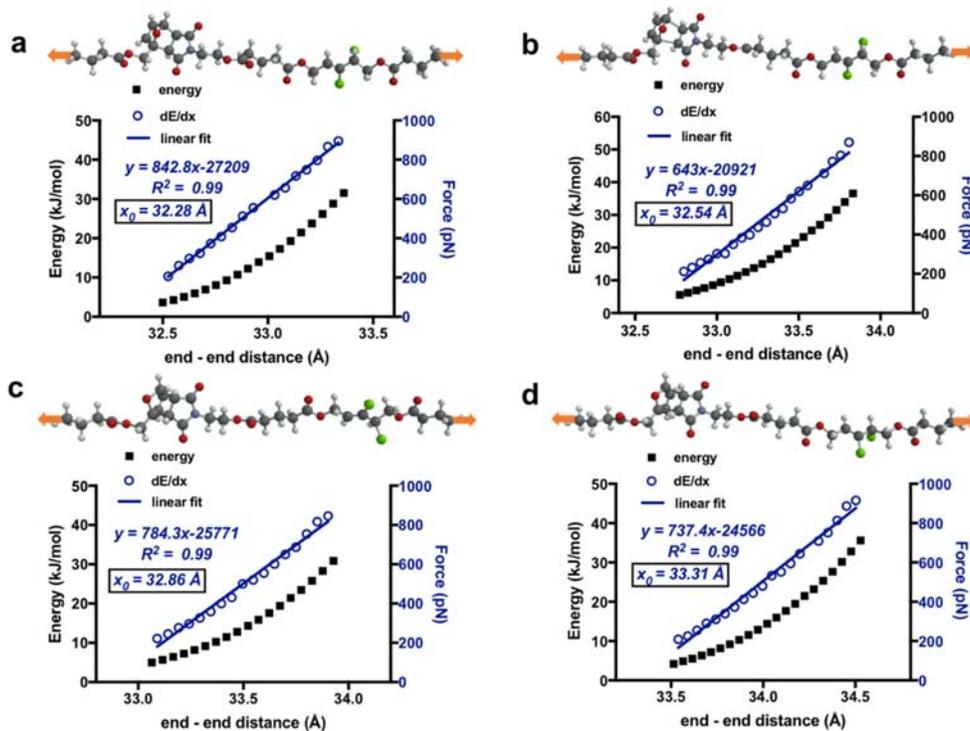


Figure 5 CoGEF of (a) ground state of *exo* isomer, (b) transition state of *exo* isomer, (c) ground state of *endo* isomer and (d) transition state of *endo* isomer. The black square points represent the relative energy as a function of end to end distance. The deep blue circles represent the calculated force (from two adjacent square points, $(dE_2 - dE_1)/(dx_2 - dx_1)$) as a function of the calculated end to end distance (from two adjacent square points, $(X_1 + X_2)/2$) and the deep blue lines represent the linear fit. x_0 is the force-free end to end distance when extrapolating the force to zero.

($R^2 = 0.99$) and $2.0 \times 10^{-2} \text{ min}^{-1}$ ($R^2 = 0.99$), respectively. This numerical similarity manifests the insensitivity of the kinetic analysis.

In comparison, we determined that Φ_i for control polymers **P3** is 0.63, 0.51, and 0.44 for $M_{n,0}$ of 140, 160, and 200 kDa, respectively (see ESI for details). The larger Φ_i of **P3** shows that the DA adducts are mechanically weaker than the rest of covalent structures along the polymer backbone. In addition, the ^1H NMR spectra of polymers **P1** and **P2** following 2 h of sonication (Figure 4) have peaks at $\delta = 7.44, 6.42, 6.38$ and 5.09 ppm that are characteristic of the expected furan product of the retro-DA reactions, which further supports the mechanical lability of the DA adducts.

These observations are consistent with expectations based on computational modelling. We computed the force-free activation energy (ΔG^\ddagger) and the force-free activation lengths (Δx^\ddagger) of the rDA reactions of two stereoisomers. ΔG^\ddagger is determined by energy optimization (DFT B3LYP/6-31G(d))¹⁹ of the ground and transition states (located using the Synchronous Transit-Guided Quasi-Newton method,²⁰ see ESI for details), and found to be 24.8 kcal/mol for the *exo* isomer and 22.6 kcal/mol for the *endo* isomer. Thus, the rDA reaction of the *endo* isomer is ~ 2.2 kcal/mol more facile than that of the *exo* isomer. In addition, the optimized ground and transition states were computationally embedded within a short 2,3-dichloroalkene-bearing chain. The length of each as a function of force was determined using CoGEF¹⁹ calculations. The lengths were extrapolated to zero force (Figure 5), and the differences in length between transition and ground state (Δx^\ddagger) were calculated to be 0.26 Å for the *exo* isomer and 0.45 Å for the *endo* isomer. Δx^\ddagger corresponds to the extension along the polymer backbone that accompanies the change from ground state to transition state along the reaction path of interest, and it is an indicator of mechanochemical coupling.²¹⁻²³ The larger Δx^\ddagger calculated for the *endo* isomer indicates that its rDA reaction is better coupled to a force of tension in the pendant chains, and so both the intrinsic reactivity and the mechanochemical coupling of the *endo* isomer favour its mechanical lability relative to that of the *exo* isomer.

In conclusion, the results presented here suggest the mechanical lability of furan-maleimide rDA adducts depends on stereochemistry to an extent that has been hidden from prior analyses. Furan-maleimide couplings are increasingly popular tools in the construction of load-bearing polymers, and so these stereochemical effects – while subtle – might manifest in bulk behaviour, including fracture of networks formed through the DA chemistry. More generally, the system employed here presents a potentially valuable case study, in that the difference in mechanical reactivity of the two stereoisomers eludes detection even by very careful kinetic measurements of chain scission rates.¹¹ Such kinetic analyses have proven to be quite valuable in revealing relative mechanochemical behaviour in a range of prior studies,^{17, 24-26} but we speculate that internal competitions similar to that employed here might therefore be broadly useful for quantifying mechanochemical behaviour in other systems for which increased sensitivity is desirable.

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Conflicts of interest

There are no conflicts to declare.

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TOC

An internal competition between mechanochemical reactions unveils the relative mechanical reactivity of furan-maleimide Diels-Alder (DA) stereoisomers.

