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LETTERS

Biasing reaction pathways with mechanical force

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During the course of chemical reactions, reactant molecules need to surmount an energy barrier to allow their transformation into products. The energy needed for this process is usually provided by heat, light, pressure or electrical potential, which act either by changing the distribution of the reactants on their ground-state potential energy surface or by moving them onto an excited-state potential energy surface and thereby facilitate movement over the energy barrier. A fundamentally different way of initiating or accelerating a reaction is the use of force to deform reacting molecules along a specific direction of the reaction coordinate. Mechanical force has indeed been shown to activate covalent bonds in polymers, but the usual result is chain scission[1]. Here we show that mechanically sensitive chemical groups make it possible to harness the mechanical forces generated when exposing polymer solutions to ultrasound[2], and that this allows us to accelerate rearrangement reactions and bias reaction pathways to yield products not obtainable from purely thermal or light-induced reactions. We find that when placed within long polymer strands, the *trans* and *cis* isomers of a 1,2-disubstituted benzocyclobutene undergo an ultrasound-induced electrocyclic ring opening in a formally conrotatory and formally disrotatory process, respectively, that yield identical products. This contrasts with reaction initiation by light or heat alone[3], in which case the isomers follow mutually exclusive pathways to different products. Mechanical forces associated with ultrasound can thus clearly alter the shape of potential energy surfaces[4] so that otherwise forbidden or slow processes proceed under mild conditions, with the directionally specific nature of mechanical forces providing a reaction control that is fundamentally different from that achieved by adjusting chemical or physical parameters. Because rearrangement in our system occurs before chain scission, the effect we describe might allow the development of materials that are activated by mechanical stress fields.

We used the COGEF (COnstrained Geometries simulate External Force) method[5] computationally to determine the effects of molecular deformation on *trans* and *cis* 1,2-dimethoxybenzocyclobutenes. A profile of energy change relative to the ground state versus molecular elongation was produced for each isomer by systematically increasing the distance *d* between the methyl carbons while allowing all other atoms to fully relax (Fig. 1a). The energy and geometry at each deformation state was calculated at the B3LYP/6-31G* level of density functional theory. The calculations predict that the two isomers are distorted in a different rotational sense. In the *trans* isomer, the simulated extensional deformation induces a conrotatory torquing motion of the substituents, consistent with the atomic motions experienced for the thermally allowed pathway for ring opening[3] (Fig. 1b). In contrast, strain induces a disrotatory torquing motion of the substituents in the *cis* isomer[6], consistent with the Woodward–Hoffman allowed photochemical pathway for ring opening. These simulations predict that the mechanically activated processes are proceeding along thermally allowed and disallowed pathways for the *trans* and *cis* isomers, respectively[3]. Assuming these calculations accurately describe the geometric and electronic changes that accompany the action of extensional deformation, a formal disrotatory ring opening is predicted for *cis* benzocyclobutene (BCB). The presence of reaction products that result from the conrotatory ring opening of the *trans* isomer and from disrotatory ring opening of the *cis* isomer would strongly indicate that a mechanochemical process is in operation.

To test these predictions experimentally, we incorporated bifunctional BCB units **1** and **2** into well-defined, link-functionalized polymers[7] (LFPs) (Fig. 2). Using this preparation, only a single mechanophore—the putative mechanochemically active unit—is incorporated into the centre of each polymer chain. The incorporation of the mechanophores into polymers is necessary to study their mechanochemical behaviour because small molecules are largely inert to mechanical forces[8]. To carry out the synthesis, the carboxylic acid functions of **1** or **2** were coupled to α-methoxy-ω-amino poly (ethylene glycol) (mPEG)[9]. This synthesis yielded a series of polymers **3** and **4**, which contained the *trans*-BCB linker and the *cis*-BCB linker respectively, in weight-averaged molecular masses of $M_w = 4$, 10, 20, 40 and 60 kDa.

Having only a single BCB unit per 40 kDa polymer chain requires sensitive analytical techniques to observe reactivity at this specific site. *N*-(1-pyrene)-maleimide **5** (ref. 10) was used as a dienophile trap; the pyrene label allows the reaction to be monitored by gel permeation chromatography (GPC) using an ultraviolet (UV) detector. The strength of the UV signal is normalized against that obtained from a refractive index (RI) detector. Each polymer molecule contains only a single BCB unit, so cycloaddition of dienophile **5** and the *ortho*-quinodimethide (*o*QDM) diene generated by ring opening will result in one pyrene chromophore per polymer chain (Fig. 2).

It has previously been demonstrated that the application of ultrasound to dilute solutions of LFPs can be used to fragment a polymer chain at a single specific site[9]. The action of ultrasound on polymer molecules is generally thought to be mechanical, owing to frictional forces generated by the relative movement of solvent and macromolecules resulting from collapse of cavitation bubbles[2]. A dilute solution of the 40 kDa LFP **3** or **4** was sonicated in acetonitrile in the presence of a 500-fold excess of **5**. After sonication, each polymer was analysed by GPC, monitoring the UV absorbance at 345 nm, a wavelength at which the starting polymer has no absorbance but the pyrene label strongly absorbs. It was found that the UV signal significantly increased relative to the RI signal in both polymers **3** and **4** (Fig. 3a and b). This result suggests that the pyrene-labelled dienophile was incorporated into both LFPs, a particularly interesting result in the case of **4** given the calculated predictions. Significantly, these results were obtained for reactions conducted at approximately 6–9 °C, a temperature range for which the rate of thermal ring opening is negligible.

Several control experiments were carried out. There was no increase in UV absorbance when LFP **3** was manipulated exactly as described

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above, with the ultrasound omitted (Supplementary Information). This control experiment indicates that ultrasound is necessary for the observed response. A PEG homopolymer of M_w 43 kDa containing no BCB linker was subjected to the same conditions as above. Although the UV absorbance increased slightly, it was by far less than for **3** or **4** (Fig. 3c). These observations indicate that the increased UV absorbance was due to a mechanically activated ring opening reaction, followed by cycloaddition of the *o*QDM intermediate with **5**.

Previous studies on ultrasound-induced polymer degradation have demonstrated a chain-length dependence on the rate of reaction[2,8,9]. In particular, longer chains experience larger solvodynamic shear forces and accelerated reaction rates. Assuming that force reduces the kinetic barrier to ring opening, larger forces will correlate to faster rates. A reaction promoted purely by thermal energy is not expected to have such a M_w dependence. The LFPs **3** and **4** with $M_w = 4, 10, 20$ and 60 kDa were sonicated in the presence of **5**. The UV/RI signal ratios at the elution time corresponding to the M_w of the LFP were monitored by GPC. It was found that for both LFPs **3** and **4**, the UV/RI signal ratio increased smoothly with increasing M_w above a threshold value of about 20 kDa (Fig. 3d). The increasing response with increasing M_w indicates that the reaction in both polymers is activated by a mechanical process. Interestingly, for a given M_w, *cis* LFP **4** was found to react to a greater extent than *trans* LFP **3** for all the M_w values studied above 20 kDa.

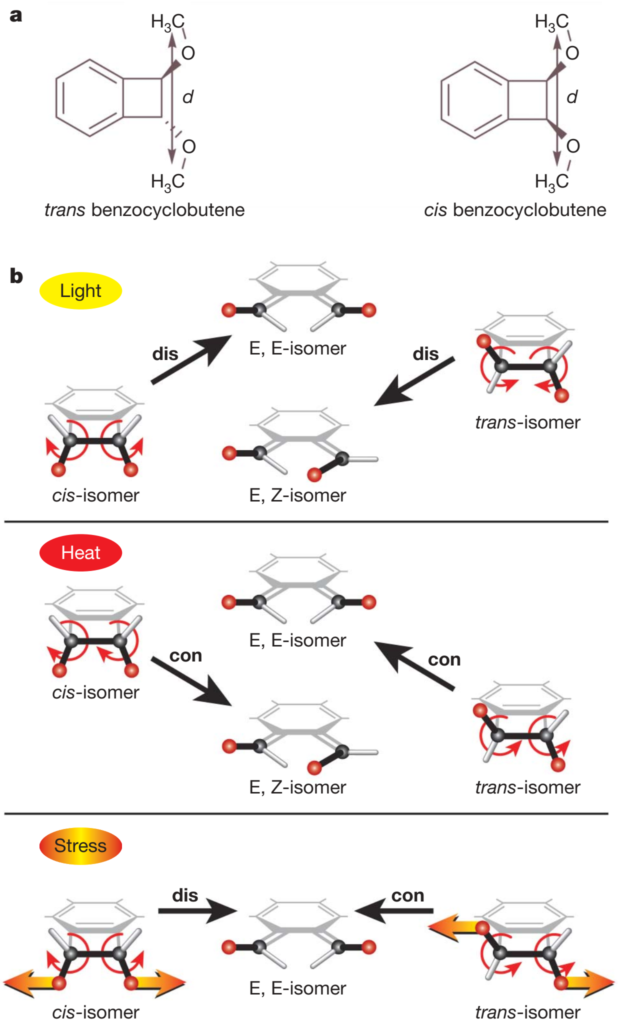

Figure 1 | Electrocyclic ring opening of benzocyclobutenes. The intermediate resulting from the electrocyclic ring opening of benzocyclobutenes depends on the method of activation and on the geometry of the molecule. **a**, To simulate mechanical tensile force, the distance *d* between the terminal methyl carbons of *trans* and *cis* 1,2-dimethoxybenzocyclobutene was systematically increased. At each step the geometry was minimized and the energy was calculated at the density functional theory B3LYP/6-31G* level. **b**, The expected pathways of photochemically activated and thermally activated electrocyclic ring opening of BCB, and the computationally predicted results of mechanically activated ring opening. Upon activation by light, the Woodward–Hoffman rules predict that both *cis* and *trans* BCB undergo disrotatory ('dis') ring opening. The *cis* isomer yields the E,E-*o*QDM intermediate, and the *trans* isomer yields the E,Z-*o*QDM intermediate (with *zusammen* double bond geometry). Upon activation by heat, both isomers undergo conrotatory ('con') ring opening. The *cis* isomer yields the E,Z-*o*QDM intermediate, and the *trans* isomer yields the E,E-oQDM intermediate. Activation by mechanical forces is predicted to induce a formal disrotatory ring opening in the *cis* isomer and a formal conrotatory ring opening in the *trans* isomer, such that both isomers are predicted to yield the same E,E-*o*QDM intermediate.

We also performed control experiments with PEG homopolymers of $M_w = 5, 10, 20, 26$ and 60 kDa. In this case, the UV/RI ratio of the unbroken chains[11] is independent of M_w (Fig. 3d). Furthermore, a 1:1 mol ratio mixture of 4 kDa LFP **4** and 43 kDa PEG was sonicated. No significant increase in the UV signal was observed (Supplementary Information). These results suggest that the linker must be embedded within a polymer and the M_w must be above the critical value to observe reactivity: mixing alone is not enough.

To determine the specific chemical structures of the pyrene-modified LFPs, and to investigate the stereochemical consequences of mechanical activation, we resynthesized pyrene-labelled maleimide **5**, enriched with ^{13}C isotope in the carbonyl positions. Polymers **3** and **4** (40 kDa) were subjected to ultrasound in the presence of $\mathbf{5^{13}C}$. After sonication, each polymer was analysed by ^{13}C nuclear magnetic resonance (NMR). It was found that both polymers **3** and **4** yielded a single resonance at δ 174.2 p.p.m. (Fig. 4a). That the polymers provided the same product was confirmed by examination of mixtures. When 1:1 mixtures of sonicated LFPs **3** and **4** were measured in either $CDCl_3$ or CD_3OD, only a single ^{13}C carbonyl peak was observed. Comparison of the ^{13}C NMR spectra obtained after sonication of LFPs **3** and **4** to model compound **6** indicated that the observed NMR signal is due to the Diels–Alder adduct, which results from endo addition of the maleimide to the E,E-*o*QDM intermediate (with *entgegen* double bond geometry) (Fig. 4b). Sonication of 43 kDa PEG under the same conditions yielded no detectable resonances in the carbonyl region.

The action of ultrasound on the *trans* BCB in polymer **3** induces a formal conrotatory ring opening to the *o*QDM intermediate, while the *cis* BCB in polymer **4** reacts via a formal disrotatory ring opening. That different modes of reactivity are observed for the two different isomers confirms that the activation is neither thermal nor photochemical but rather behaves according to COGEF simulations of mechanical activation.

The consequence of ultrasound-induced reactivity of LFPs **3** and **4** was compared to the products obtained under purely thermal conditions. The thermal reaction products were generated by reacting trap $\mathbf{5^{13}C}$ with polymer **3** in toluene at 105 °C and with polymer **4** in xylenes at 140 °C (ref. 12). ^{13}C analysis indicated that *trans* LFP **3** reacted smoothly with maleimide $\mathbf{5^{13}C}$ to give the same major product observed with polymer **3** and **4** under ultrasound conditions (Fig. 4a). The thermal reaction of polymer **4** did not yield any recognizable products. This result is consistent with previous reports[12] and our own experience on small-molecule model compounds that *cis*-1,2-diacetoxybenzocyclobutenes thermally degrade to a complex mixture.

To determine whether mechanical activation of the BCB linker may occur without polymer chain scission, polymer **3** was sonicated in the presence of maleimide trap $\mathbf{5^{13}C}$, yielding a bimodal GPC trace with peak molecular weights of 40 and 20 kDa, presumably corresponding to unbroken and broken chains. The 40 kDa polymer, separated from the 20 kDa byproduct by preparatory GPC, showed the characteristic UV increase of pyrene incorporation by cycloaddition. Furthermore, ^{13}C analysis revealed that the Diels–Alder adduct was

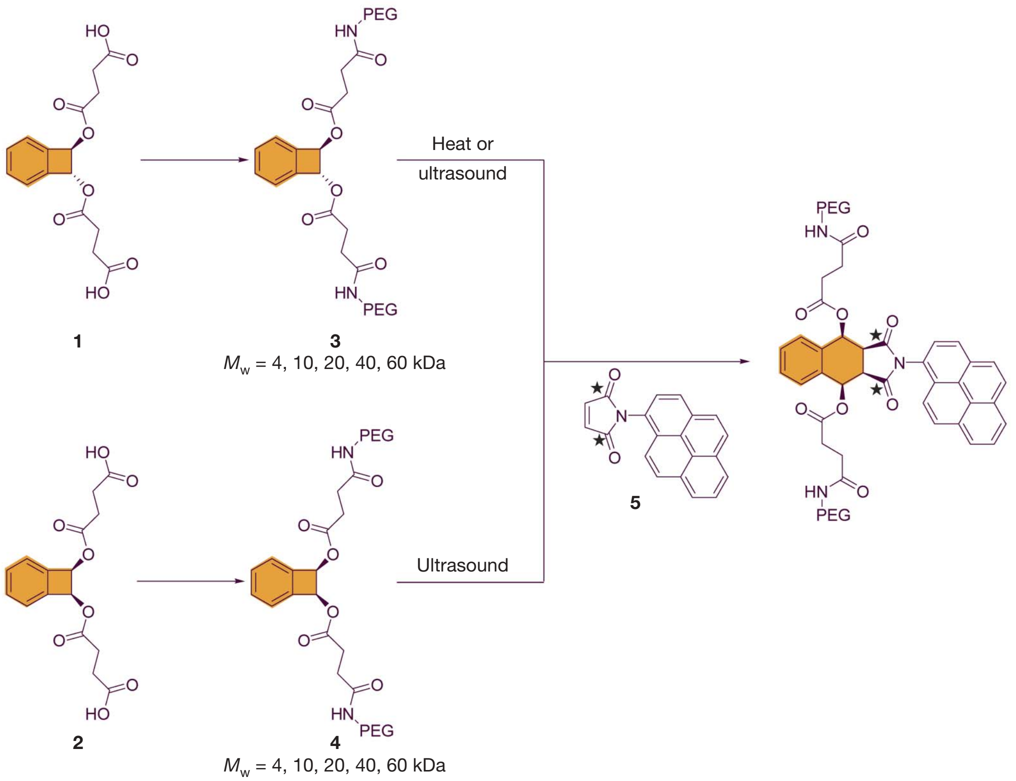

Figure 2 | Preparation and reaction of mechanosensitive polymers. Shown are the preparation of link-functionalized polymers **3** and **4** from bifunctional BCB units **1** and **2**, and the reaction of these polymers with maleimide trap **5**. For **5^{13}C**, the positions of the ^{13}C labels are marked with a star.

present in the uncleaved polymer strands (Supplementary Information). This observation demonstrates that the LFPs can be mechanically activated without fragmenting the backbone.

The findings can be summarized by considering the reaction coordinate diagrams shown in Fig. 4c and d. Mechanical forces perform work[8] on the *trans* BCB unit by deforming bond lengths and angles, which reduces the barrier of a formal conrotatory process and accelerates the reaction (Fig. 4c). For the *cis* isomer, mechanical force does work on the BCB unit to reduce the barrier for a formal disrotatory process, even though it is known to be the higher energy ring opening pathway[3,6] (Fig. 4d). This explanation is consistent with the computational studies, which suggested that elongational deformation would induce a disrotatory motion for the *cis* isomer rather than the thermally allowed conrotatory ring opening (Supplementary Information). The disrotatory process is favoured because the molecular deformation induced by force is nearly congruent with the deformation along the disrotatory reaction pathway.

In conclusion, we have shown that ultrasound can be applied to polymer solutions to accelerate and alter the course of chemical reactions. The effects of ultrasound are consistent with the intuitive effects of a mechanical force, which acts to bias the reaction pathway towards products that best relieve the applied force by directly altering the molecular potential energy surface. Although there are practical limitations to the use of mechanochemistry for controlling the outcome of chemical reactions, we expect that the procedures

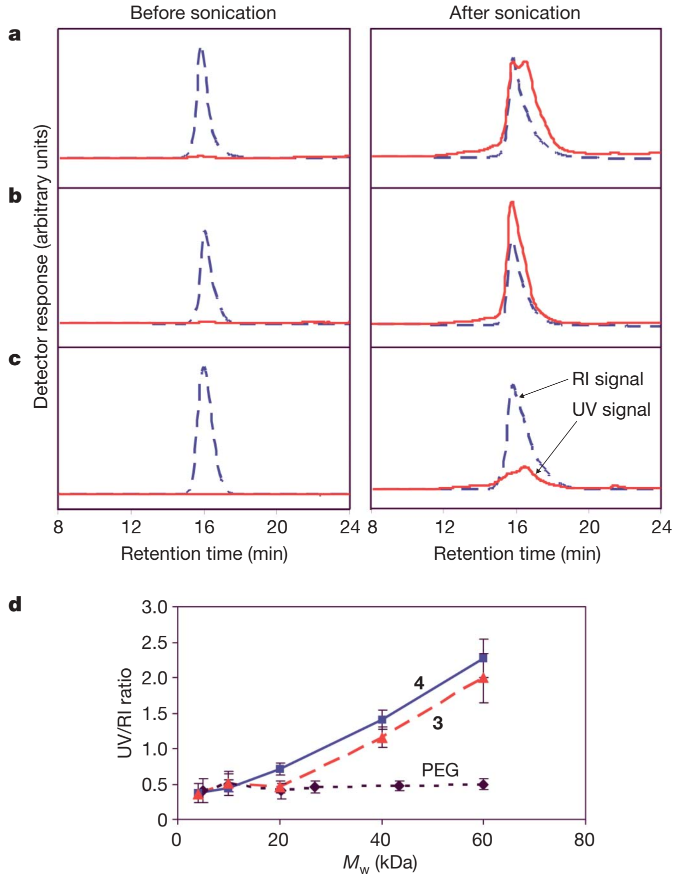

Figure 3 | Reaction of the mechanosensitive polymers. a–c, The top panels show GPC traces of the polymers before (left) and after (right) sonication. **a**, The 40 kDa *trans* polymer **3**. **b**, The 40 kDa *cis* polymer **4**. **c**, The 43 kDa PEG polymer. **d**, A plot of the ratio of the UV absorption to refractive index signal intensity versus polymer M_w for **3**, **4** and PEG. The increased UV absorption of LFPs **3** and **4** as a function of M_w is evidence that the ultrasound-induced reaction proceeds via mechanical activation. Error bars indicate the standard deviation observed for 2–4 independent trials.

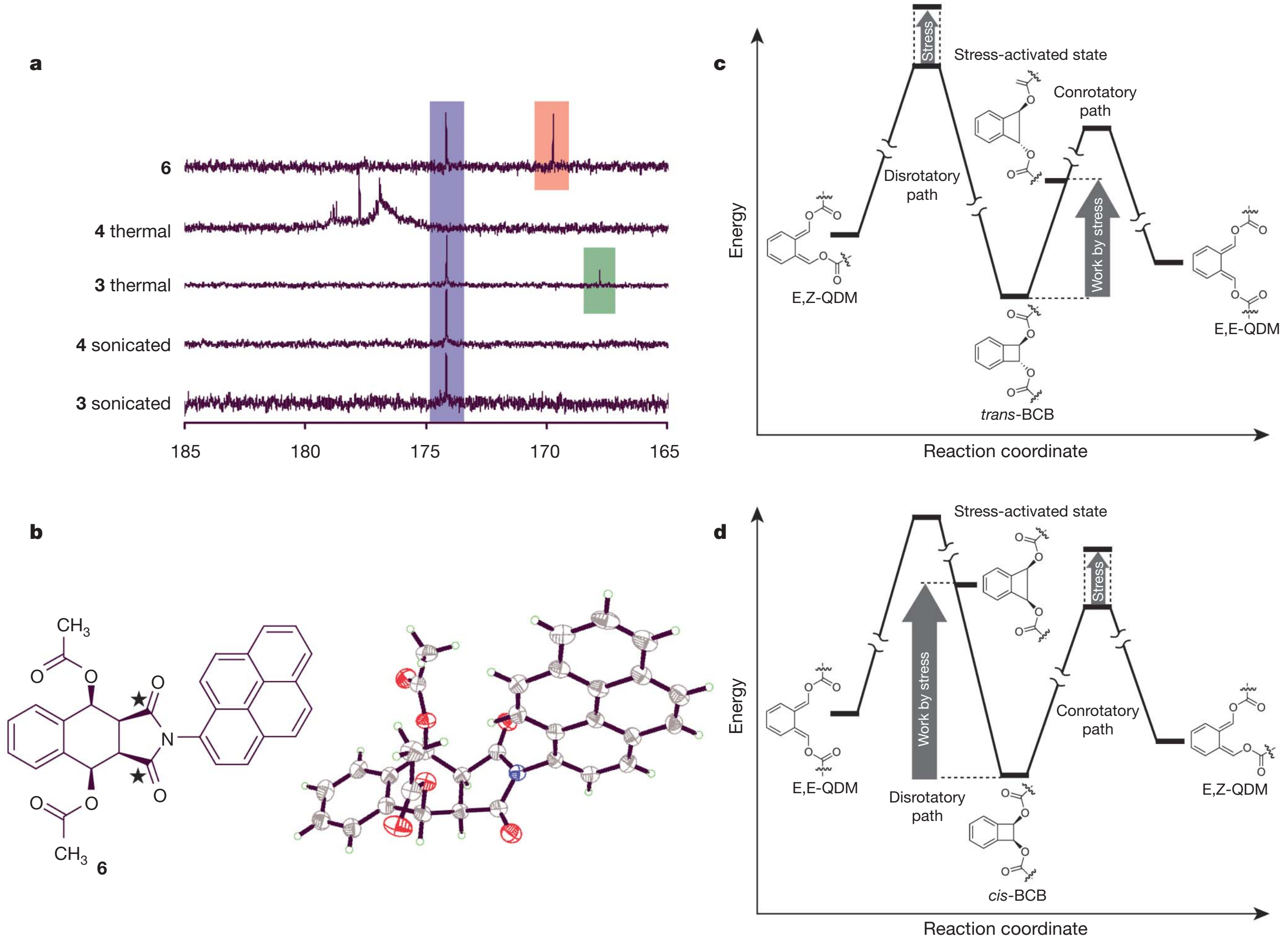

Figure 4 | Comparison of reaction products and pathways for *trans* and *cis* benzocyclobutenes induced by ultrasound and by heating. a, A portion of the ^{13}C NMR spectrum comparing the products formed from polymers **3** and **4** in the presence of **5^{13}C** by ultrasound and by thermal activation. Compound **6**, whose structure is confirmed by X-ray crystallography (**b**), exhibits a resonance at δ 174.2 p.p.m. (coloured blue) assigned to the Diels–Alder adduct resulting from endo addition of the maleimide dienophile to the E,E-*o*QDM intermediate (the carbon corresponding to the resonance at δ 174.2 is marked with a star). This resonance is not observed in the thermal reaction of polymer **4**. The resonance at δ 169.7 p.p.m. (coloured red) is assigned to the ester carbonyl in **6** at natural abundance. The resonance at δ 168.0 p.p.m. (coloured green) is due to *N*-pyrene-2,3-naphthimide, which occurs after thermal elimination of acid groups from the Diels–Alder adducts. **c**, In *trans*-BCB, mechanical force accelerates a formal conrotatory ring opening to the E,E-*o*QDM intermediate. **d**, In *cis*-BCB, mechanical force promotes a formal disrotatory ring opening to the E,E-*o*QDM intermediate even though the thermally allowed process is the conrotatory pathway. Additional transition states and intermediates may exist and are not shown[16].

reported here will be generally useful for discovering new mechanophores, the chemical reactivities of which are activated by external force.

METHODS

Sonication of polymers. To a solution of polymers **3** or **4** (0.75 mg ml^{-1}, 19 µM for 40 kDa polymer) in acetonitrile we added maleimide trap **5** (2.75 mg ml^{-1}). Approximately 12 ml of this solution was introduced into a Suslick cell[13]. A thermocouple and an argon line were threaded through the septa and placed in contact with the solution, ensuring that they did not touch the probe. The third side arm of the cell contained a septum. The cell was then wrapped in aluminium foil to exclude light. Argon was bubbled through the solution for 30 min before each experiment as well as during the experiment. The entire system was placed in an ice bath to maintain a temperature of 6–9 °C throughout sonication. The sample was then sonicated (pulsed on 0.5 s, off 1.0 s, at a frequency of 20 kHz and at an intensity of 8.73 W cm^{-2}) for a total time of 45 min (15 min sonication time). After sonication, the solvent was removed and the polymer sample was isolated by preparatory GPC. The concentrations used in all experiments were estimated to be below the critical overlap concentration for PEG[14,15].

Determination of UV/RI ratios. After isolation of the polymer, the molecular weight profile was recorded on a GPC equipped with three Waters Ultrastyragel preparatory GPC columns (10^4 Å, 10^3 Å and 500 Å) eluted with tetrahydrofuran, plumbed through a Waters 2487 UV detector, and a Waters 410 RI detector. The UV detector sensitivity was set to 4.00 aufs (absorbance units full scale), and the absorption for all experiments was monitored at 345 nm. The RI sensitivity was set to 8, and the temperature at the detector was kept constant with a thermostat set between 31.9–32.5 °C. After the profile was recorded, the area under the UV and RI curves for unbroken chains was measured using triSEC software (version 3.0, revision B.00.05, Viscotek). The baseline and integration limits were set to include the M_w range corresponding to the unbroken chains using the RI trace. The UV area was then measured without changing the position of the integration limits. The baseline in the UV trace was redrawn to include only the area within the integration limits.

^{13}C NMR experiments. For ^{13}C labelling experiments, the polymer of interest was sonicated as above with ^{13}C-labelled maleimide, **5^{13}C**. The polymer from two such runs was isolated by preparatory GPC and combined in an NMR tube with the appropriate solvent. The spectra were recorded on an instrument operating at a ^{13}C frequency of 125 MHz, with about 10–15 mg of polymer dissolved in 0.5 ml of solvent and 15,000–17,000 acquisitions.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Contributions J.S.M. conceived the BCB experiment. C.R.H. performed all experiments and initial computational analyses. J.B. performed the final computational analysis. S.R. Wilson performed the crystallography. N.R.S., S.R. White and J.S.M. directed the research and all authors wrote the manuscript.

Author Information The atomic coordinates for *cis*-1,2-bis [(3-carboxypropanoyl)oxy]-1,2-dihydrobenzocyclobutene **2** (accession number 628670), *N*-(1-pyrene)-2,3-naphthimide (accession number 628377), and 4,9-diacetoxy-2-(1-pyrenyl)-(3aR,4c,9c,9ac)-3a,4,9,9a-tetrahydro-benzo [f]isoindole-1,3-dione **6** (accession number 628671) have been deposited in the Cambridge Crystal Structure Database. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to J.S.M. (jsmoore@uiuc.edu).