

Mechanochemistry of Cubane

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ABSTRACT: We report the mechanochemical reactivity of the highly strained pentacyclic hydrocarbon cubane. The mechanical reactivity of cubane is explored for three regioisomers with 1,2-, 1,3-, and 1,4-substituted pulling attachments. Whereas all compounds can be activated thermally, mechanical activation is observed via pulsed ultrasonication of cubane-containing polymers only when force is applied via 1,2-attachment. The single observed product of the force-coupled reaction is a thermally inaccessible *syn*-tricyclooctadiene, in contrast to cyclooctatetraene (observed thermally) or a pair of cyclobutadienes that would result from sequential cyclobutane scission. We further quantify the mechanochemical reactivity of cubane by single molecule force spectroscopy, and force-coupled rate constants for ring opening reach $\sim 33\text{ s}^{-1}$ at a force of $\sim 1.55\text{ nN}$, lower than forces of $1.8\text{--}2.0\text{ nN}$ that are typical of conventional cyclobutanes.

Before it was first accomplished in 1964, the synthesis of the now paradigmatic molecule cubane (Figure 1) was

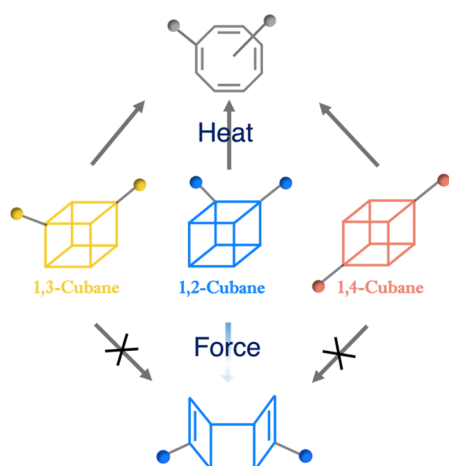


Figure 1. Mechanical and thermal pathway of 1,2-cubane, 1,3-cubane, and 1,4-cubane.

largely considered to be impossible.¹ Because of its remarkable structure and symmetry,² cubane is attractive both from a fundamental perspective and because of its wide range of applications in energetic materials,^{3,4} medicines,^{5,6} and polymer chemistry.^{7,8} Among its notable characteristics is a strain energy of 162 kcal/mol (20 kcal/mol C),⁹ in comparison to 26 kcal/mol in cyclobutane (6.5 kcal/mol C).¹⁰ Despite its enormous internal strain, cubane shows good kinetic stability, with temperatures of up to $200\text{ }^{\circ}\text{C}$ required for thermal decomposition on the time scale of days.^{11–13}

These features, as well as cubane's heralded position in the physical organic canon, attracted our attention. The growing mechanochemistry of cyclobutane, including fused cyclobutanes,^{14–17} suggested that cubane is an excellent candidate

for a mechanophore. Mechanophores are stress-responsive functional groups, often embedded in polymers or bulk materials. Upon external stress, mechanophores exhibit specific chemical responses, such as mechanochromism,^{18–20} mechanocatalysis,^{21,22} small molecule release,^{23–25} stress-strengthening,^{19,26} or novel reactions.^{27–30} To the best of our knowledge, cubane mechanochemistry has yet to be investigated, and we therefore wondered whether cubane could be activated efficiently through application of mechanical force. If so, what are the pathway and product(s) of its dissociation? How does the reactivity depend on pulling geometry, and how does it compare to reported cyclobutane mechanophores? In addition, because cubane comprises multiple cyclobutane substructures, does its mechanochemistry involve multiple reactions and ultimate dissociation of the cubane structure, or do changes in energetics and mechanochemical coupling halt reaction progress at an intermediate stage?

The necessary pulling attachments for mechanical coupling can be displayed through one of three regiochemistries: 1,2-, 1,3-, and 1,4-substitution (blue, yellow, and red in Figure 1, respectively). At temperatures above $200\text{ }^{\circ}\text{C}$, cubane isomerizes to cyclooctatetraene on accessible time scales, a product that can be further converted to bicyclooctatriene and dihydropentalenes with prolonged heating.^{11,12,31} *syn*-Tricyclooctadiene is believed to be an early intermediate along this isomerization pathway, although it has not been observed experimentally because of its rapid conversion to cyclooctatetraene at the elevated temperatures required for its (much slower) formation.^{11,12,31}

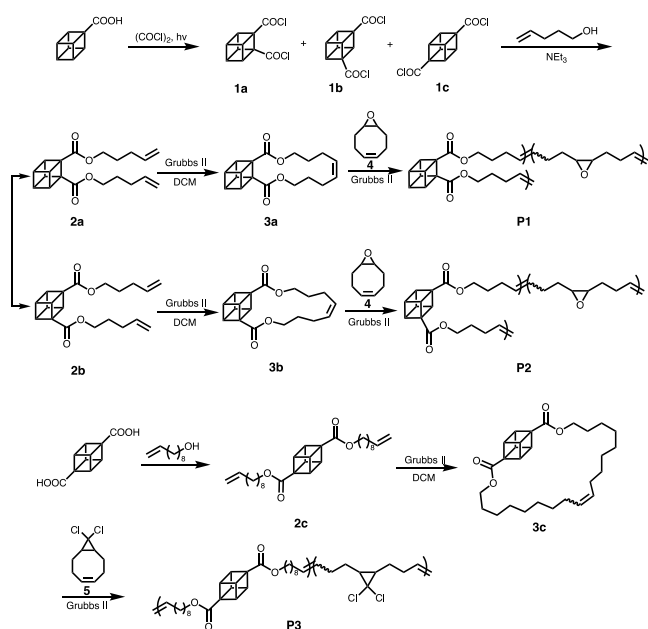
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As shown in Scheme 1, cubane copolymers were synthesized from commercially available cubane-1-carboxylic acid. When

Scheme 1. Synthesis of Polymers P1, P2, and P3



irradiated in the presence of oxalyl chloride, the monosubstituted cubane was converted to three disubstituted acyl chlorides **1a**, **1b**, and **1c** in an approximately 3:6:1 ratio.³² The mixture was esterified to dienes with 4-penten-1-ol. Pure **2a** and **2b** were isolated with careful separation by column chromatography, and they were converted into their corresponding polymerizable macrocycles **3a** and **3b** through ring-closing metathesis (RCM). For the 1,4-substituted cubane, we employed a different route with increased arm length to close the ring through RCM, yielding **3c**.

Thermolysis of 1,2-cubane and 1,4-cubane shows that these complexes are quite stable under heating. Even at 140 °C, the reaction proceeds on the time scale of hours (see the Supporting Information). The activation energy for 1,2-cubane obtained from rate constants is 32.4 kcal/mol and 35.3 kcal/mol for 1,4-cubane. The same set of products (cyclooctatetraenes) are formed through thermolysis of 1,2- and 1,4-cubane.

We synthesized polymers with multiple repeats of cubane through a strategy inspired by entropy driven ring-opening metathesis polymerization (ED-ROMP),^{33,34} as employed previously for the synthesis of multi-mechanophore polymers.³⁵ To test the mechanochemical reactivity via sonication studies and single-molecule force spectroscopy (SMFS), we prepared copolymers of 9-oxabicyclo[6.1.0]non-4-ene (epoxy-COD) and cubane. The epoxide comonomer is employed to increase the adhesion of the polymers to the cantilever tips in SMFS, and it is mechanically inactive under the forces achieved in these experiments.^{28,36} The cubane diene derivatives **3a** and **3b** were incorporated into polymers **P1** ($M_n = 72$ kDa, 12 mol % **2a**) and **P2** ($M_n = 84$ kDa, 4 mol % **2b**), respectively. Macrocycle **3c** was copolymerized with (Z)-9,9-dichlorobicyclo[6.1.0]non-4-ene (**5**) to yield **P3** ($M_n = 48$ kDa, 17 mol % **2c**).

Pulsed ultrasonication (1 s “on” and 1 s “off”) of **P1**, **P2**, and **P3** was conducted in deuterated tetrahydrofuran (THF-*d*₈) at a

concentration of 1.7 mg/mL. The ¹H NMR spectra of the reaction mixture following sonication showed no observable conversion of the cubane moieties in **P2** and **P3**; only ring-opening of the internal standard gDCC was observed in the case of **P3** (see the Supporting Information). Sonication of **P1**, however, leads to both a decrease in the relative integration of the peaks assigned to cubane ($\delta = 3.9$ –4.2 ppm) and the appearance of new peaks labeled in Figure 2. Several pieces of

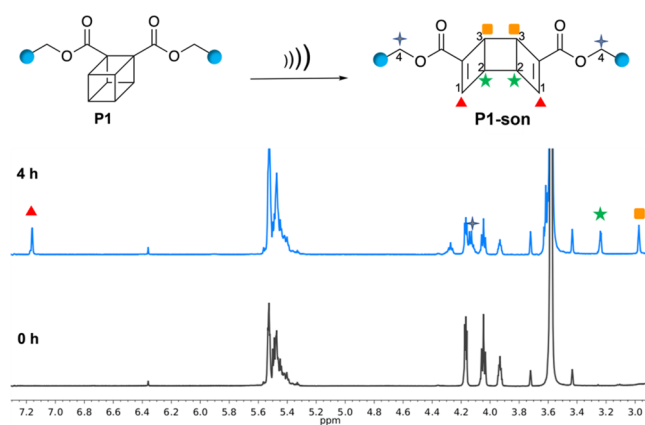


Figure 2. ¹H NMR spectra (THF-*d*₈, 500 MHz) of **P1** before and after 4 h of sonication and individual peaks assigned to the converted portion of product **P1-son**. The peak at $\delta = 3.62$ following sonication is consistent with trace THF-*h*₈ picked up from the sonication vessel and is not associated with the polymer product (see Figures S5 and S9, Supporting Information).

spectroscopic evidence support the assignment of these peaks to the protons of *syn*-tricyclooctadiene derivative (**P1-son**, Figure 2). First, the chemical shifts of peaks at 7.16 (d), 4.12 (m), 3.24 (q), and 2.97 (t) ppm are similar to those of previously reported similar structures.^{37–39} Second, the peaks display the expected relative integrations of 1:2:1:1. Third, the ¹H–¹H correlation spectrum (COSY) shows cross-peaks between the resonances at $\delta = 7.16$ and $\delta = 3.24$ and between $\delta = 3.24$ and $\delta = 2.97$. Finally, the configuration of the tricyclooctadiene is assigned as *syn* because we observe that proton 2 ($\delta = 3.24$) is split as an apparent quartet due to through-space 1,3-coupling with the *cis* hydrogen on the far corner of the central cyclobutane. This additional coupling is not expected for the *anti*-tricyclooctadiene.

As shown in Figure 3, prolonged ultrasonication leads to more activation of the 1,2-cubane mechanophore as well as a decrease in polymer molecular weight due to accumulated chain scission events along the polymer chain. Sonication of polymer **P1** for 4 h reduces its molecular weight from the initial 72 kDa to 22 kDa. The limiting molecular weight of multimechanophore polymers is correlated to the force required to break the polymer,⁴⁰ and the molecular weight reduction in **P1** is indistinguishable from that of the mechanically inactive **P2**, supporting the noncissile nature of the 1,2-cubane activation. We further quantified the activation of 1,2-cubane by the relative integration of the ¹H NMR peaks of product **P1-son** to that of the cubane starting material. The analysis shows that the conversion in **P1-son** reaches 57% relative to initial 1,2-cubane content after 4 h of sonication. No activation is observed in the sonication of **P2** or **P3**.

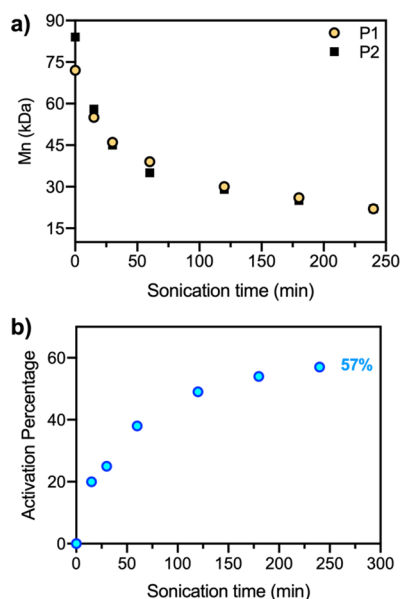


Figure 3. (a) Molecular weight change of the polymers **P1** and **P2** with sonication time. (b) Conversion of 1,2-cubane to *syn*-tricyclooctadiene with sonication time, as quantified by ^1H NMR.

We employed SMFS methods developed by our lab^{27,28,36,41} to further quantify the force-coupled reactivity of 1,2-cubane. Representative force extension curves of **P1** are overlaid in Figure 4. The force curves feature a characteristic plateau of f^*

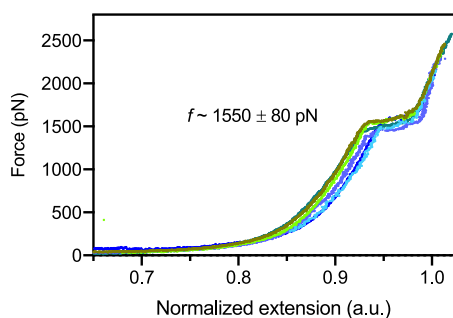


Figure 4. Normalized force–extension curves of **P1** in toluene at a retraction velocity of 300 nm/s.

$\sim 1550 \pm 80$ pN, which we attribute to the ring-opening of 1,2-cubane to *syn*-tricyclooctadiene and concomitant extension of the polymer backbone. The SMFS traces permit a kinetic analysis of the reaction, and the slope of rate versus force curve reports the force sensitivity of the rate in terms of an activation length, $\Delta x^\ddagger$. We have shown previously that $\Delta x^\ddagger$ can be interpreted as the change in contour length along the polymer backbone as the reaction moves from its ground to transition state. The empirical $\Delta x^\ddagger$ of 0.82 Å observed for cubane is consistent with the expectation of a rate determining, initial homolytic scission of the C1–C2 bond. The position of the transition state of the force-free reaction can be estimated by accounting for the changes in $\Delta x^\ddagger$ with force. One potentially reasonable approximation is to use a truncated quadratic (“cusp”) model^{42–44} to estimate the force-dependent change in $\Delta x^\ddagger$. While not employed in homolytic scissions such as that inferred here, the cusp model has been used successfully in electrocyclic ring-openings, especially of *gem*-dihalocyclopropanes. Its use here (see the Supporting Information for details)

gives a force free activation length of 0.91 Å, again consistent with that expected for a rate-determining step of initial homolytic bond scission.

A reasonable mechanism for the mechanochemical 1,2-cubane ring-opening starts with the rate-determining scission of the C–C bond adjacent to the pulling attachments, forming a short-lived biradical that quickly undergoes subsequent C–C scission to generate the *syn*-tricyclooctadiene as a mechanically stable product. The fact that *syn*-tricyclooctadiene is not further broken under mechanical treatment is notable, as like its cubane precursor it possesses a central cyclobutane with pulling attachments that emanate from adjacent positions. The absence of a second cycloreversion can be rationalized on two fronts. First, scission of the central cyclobutane would lead to two cyclobutadiene products in a reaction that, due in considerable part to the antiaromaticity of cyclobutadiene, is similarly endothermic to homolytic bond scission ($\Delta H_{\text{rxn}} = 87$ kcal/mol at B3LYP/6-31G* level of DFT calculations). Second, in addition to the high barrier associated with this cycloreversion, the reaction path for the cycloreversion suffers from poor mechanochemical coupling. Li and Houk have observed that the concerted retro-cycloadditions as well as any biradical pathways that might be involved in cyclobutadiene dimerization (and its reverse) are stabilized by secondary orbital interactions of the delocalized pi systems, which favors highly parallel arrangements of the developing cyclobutadienes.⁴⁵ As a consequence, the extension associated with lengthening the scissile bond(s) is not fully transmitted to the coupled polymer extension but is significantly offset as the $\text{C}_{\text{scissile}}\dots\text{C}_{\text{scissile}}\dots\text{C}_\alpha$ bond angles decrease during bond scission; in other words, the two cyclobutene walls of the *syn*-tricyclooctadiene gradually tilt toward each other as the bond lengthens, and they ultimately “snap” toward a nearly parallel arrangement when the $\text{C}\dots\text{C}_{\text{scissile}}$ bond breaks. The key point is that the first bond breaking allows the coupled stress in the overstretched polymer attachment to relax much more in the first step (blue points, Figure 5) than in the second (gray points). For example, Figure 5 shows how the separation between alpha carbons changes as a function of scissile C–C bonds for the observed first and unobserved second cyclobutane scission in a presumed stepwise, biradical pathway. Similar effects are expected for concerted (e.g., retro-[4 + 2])

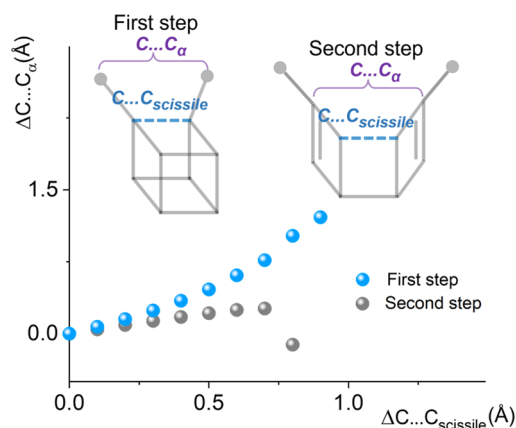


Figure 5. Calculated $\Delta\text{C}\dots\text{C}_\alpha$ changes as a function of $\Delta\text{C}\dots\text{C}_{\text{scissile}}$ for the observed first and unobserved second cubane scission. DFT calculations (B3LYP, 6-31G*) performed by fixing the $\Delta\text{C}\dots\text{C}_{\text{scissile}}$ bond length and minimizing the remaining structure.

reactions.⁴⁵ The same framework explains the mechanical stability of the 1,3- and 1,4-disubstituted cubane derivatives, as the associated change in length for attachments at the positions is much smaller during bond scission than is observed in the 1,2 isomer (see the [Supporting Information](#)).

This observation of new reactivity in an iconic molecule such as cubane is unsurprisingly accompanied (at least for us) by an enjoyable tinge of nostalgia, but not to the exclusion of prospective opportunities. The mechanochemistry of cubane is nuanced relative to its cyclobutane mechanophore predecessors. The same requirement of 1,2-disubstituted pulling attachments is observed, but activation is easier than found in isolated cyclobutanes, and here only a single cyclobutane within the fused multicyclic system reacts. As a result, mechanical activation leads smoothly to the corresponding *syn*-tricyclooctadiene, a product that eludes isolation upon thermal activation and otherwise requires rhodium(I) catalysis for its generation.⁴⁶ Simple computational models of mechanochemical coupling show how the structure of what might be described as a three-dimensional cluster-type mechanophore⁴⁷ contributes to the observed behavior and has inspired us to think about how molecular designs that lead to similar types of opening and unfolding might be harnessed to access otherwise hard-to-reach intermediates. In addition, cyclobutane mechanophores have been used to probe structure–activity relationships in macroscopic networks,^{19,48,49} and cubane offers similar mechanochemical reactivity but with lower force, smaller molecular extension, products with different subsequent reactivity, and greater exothermicity than are otherwise available among the cyclobutane family.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.2c10878>.

General experimental details; synthetic details; sonication experiments; thermolysis experiments; single molecule force spectroscopy (SMFS) experiments; computational analyses (output files available at DOI: <https://doi.org/10.7924/r47h1r86c>); NMR spectra ([PDF](#))

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Author Contributions

L.W. and X.Z. contributed equally to this paper.

Notes

The authors declare no competing financial interest.

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