JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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A Retro-Staudinger Cycloaddition: Mechanochemical Cycloelimination of a β-Lactam Mechanophore

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Supporting Information

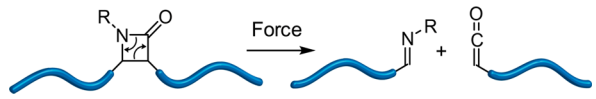
ABSTRACT: Mechanical activation of a β-lactam mechanophore using ultrasound induces a formal [2 + 2] cycloelimination reaction producing ketene and imine functional groups—the reverse reaction of the Staudinger cycloaddition. This transformation is predicted by computational modeling and verified by kinetics and UV−vis absorption measurements as well as polymer end-group analysis using ^{1}H and ^{13}C NMR spectroscopy. Addition of the β-lactam motif to the current repertoire of covalent mechanophores coupled with the diverse reactivity of the ketene functional group provides a promising new platform for achieving materials capable of autonomic self-healing behavior in response to external forces.

Polymer mechanochemistry provides a unique and powerful platform for generating diverse functionality in materials systems. During the past decade,[1] the emerging genre of covalent mechanochemistry has witnessed significant progress, establishing the activation of latent catalysts,[2] mechanoluminescence,[3] mechanochromism,[4] mechanically triggered polymer degradation,[5] and the generation of a variety of functional groups amenable to self-healing materials. In the last category, cyano-substituted cyclobutane[6] and *gem*-dihalocyclopropane[7] mechanophores are particularly promising, producing reactive cyanoacrylates and allylic halides, respectively. Polymer mechanochemistry has even demonstrated the ability to facilitate formally forbidden chemical transformations, i.e., the disrotatory electrocyclic ring opening of *cis*-1,2-disubstituted benzocyclobutene[8] and the conrotatory ring opening of *gem*-dihalocyclopropanes.[9]

Despite these remarkable achievements, the development of new mechanophores that expand upon the existing repertoire is a key objective. Mechanochemical generation of ketenes is one particular target that has remained elusive.[10] Ketenes are an incredibly versatile functional group that participate in diverse chemical transformations, including numerous electrophilic and cycloaddition reactions.[11] Hawker and co-workers have elegantly illustrated the utility of ketenes in polymeric materials by exploiting the thermal activation of Meldrum's acid derivatives for highly efficient functionalization and cross-linking.[12] The ability to generate ketenes mechanochemically would have important implications for materials systems that are capable of responding to mechanical forces and repairing damage autonomically.

Here we report a new mechanophore based on the β-lactam motif that undergoes a formal [2 + 2] cycloelimination under mechanical force to generate ketene and imine functional groups, i.e., a retro-Staudinger cycloaddition.[13] Staudinger first reported the cycloaddition reaction between an imine and a ketene to form a β-lactam in 1907.[14] Given the mechanochemical activity of other cycloaddition products (e.g., Diels−Alder adducts[15]) and four-membered-ring systems,[4a,6,16] we reasoned that the β-lactam ring may be capable of mechanically mediated cycloelimination to generate ketene and imine functional groups (Scheme 1).

Scheme 1. Generation of Ketene and Imine Functional Groups via Mechanochemical Cycloelimination of a β-Lactam Mechanophore



CoGEF calculations[17] were initially performed to evaluate the propensity for mechanochemical reactivity of the β-lactam motif (Figure 1). By artificially constraining the distance between two atoms and optimizing the relaxed geometry at distinct intervals of elongation using density functional theory (DFT), the mechanical fragmentation of a molecule can be modeled. The computational results indicate that mechanical elongation of the *cis*-β-lactam molecule causes an abrupt fragmentation that results unambiguously in the generation of ketene and imine groups. The energy maximum calculated for this transformation is 284 kJ/mol with a maximum force at rupture (F_{max}) of 3.47 nN. It is worth noting that these values are comparable to those for the cyano-substituted cyclobutane mechanophores reported previously (239−275 kJ/mol, F_{max} = 3.30−4.72 nN).[16b]

With the successful CoGEF predictions, we set out to synthesize a series of polymers to evaluate the mechanochemical activity of the β-lactam motif experimentally. The β-lactam core structure was synthesized in a single step via a Cu-catalyzed Kinugasa reaction between propargyl alcohol and *p*-benzyloxyphenyl-*N*-phenylnitrone (see the Supporting Information (SI) for details). Importantly, the resulting β-lactam was isolated exclusively as the cis diastereomer ($J_{3,4}$ = 5.9 Hz), excluding effects of the stereochemical configuration on the analysis of the mechanochemical properties. Deprotection of the phenol

Received: July 14, 2015
Published: August 21, 2015

DOI: 10.1021/jacs.5b07345
J. Am. Chem. Soc. 2015, 137, 10946−10949

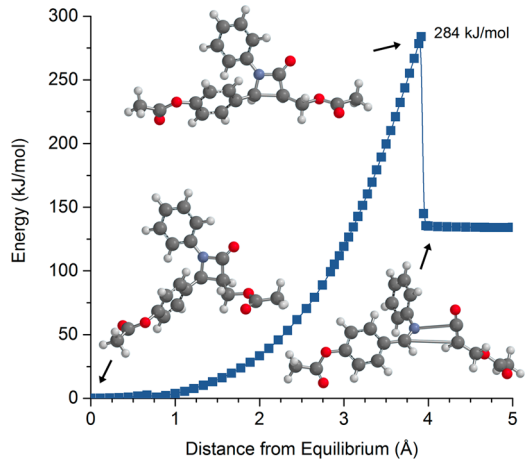
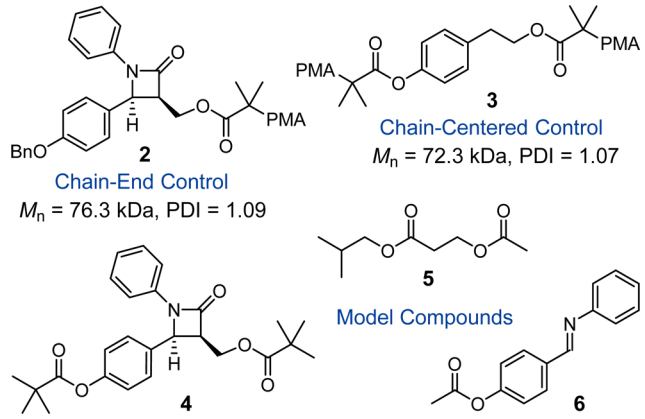


Figure 1. DFT calculations (CoGEF) for a *cis*-β-lactam mechanophore. Increasing the distance between the methyl groups ultimately triggers a [2 + 2] cycloelimination reaction to generate fragments containing ketene and imine functional groups. Calculations were performed at the B3LYP/6-31G* level of theory.

followed by esterification with α-bromoisobutyryl bromide furnished the bifunctional initiator, which was subsequently employed in the living radical polymerization of methyl acrylate using Cu wire/Me_6TREN in dimethyl sulfoxide to afford poly(methyl acrylate) (PMA) polymer **1** containing a chain-centered β-lactam unit (see Scheme 2 for the structure). Control polymers containing the β-lactam unit at the chain end (control **2**), which is not susceptible to mechanical forces during ultrasonication, and a chain-centered moiety with similar connectivity but lacking any cyclic structure (control **3**) were also prepared (Chart 1). All of the polymers in this study were synthesized with a number-average molecular weight (M_n) of 70−77 kDa and polydispersity index (PDI) of ≤1.09.

Mechanochemical activity was evaluated using pulsed ultrasonication (8.8 W/cm^2) in tetrahydrofuran (THF) at −10 °C. Polymer **1** showed a steady decrease in molecular weight as monitored by gel-permeation chromatography (GPC), with attenuation of the initial polymer peak (M_p = 75 kDa) and a concomitant increase of a new well-defined peak at approximately one-half the original molecular weight (M_p = 42 kDa) (see Figure S1 in the SI). After **1** was subjected to ultrasonication for 120 min, the overall M_n decreased from 70.9 to 49.6 kDa. In direct contrast, ultrasonic irradiation of chain-centered control polymer **3** under identical conditions resulted in substantially less chain cleavage, generating a poorly defined, low-molecular-weight shoulder in the GPC chromatogram and reducing M_n from 76.3 to 58.9 kDa. The significant difference in the mechanochemical activities of **1** and control **3** is highlighted when the rates of polymer cleavage are compared (Figure 2). The rate constant for ultrasonication-induced cleavage, k', was measured for both polymers with experiments performed in triplicate to ensure reproducibility and meaningful statistics. The

Chart 1. Structures of Control Polymers and Small-Molecule Model Compounds



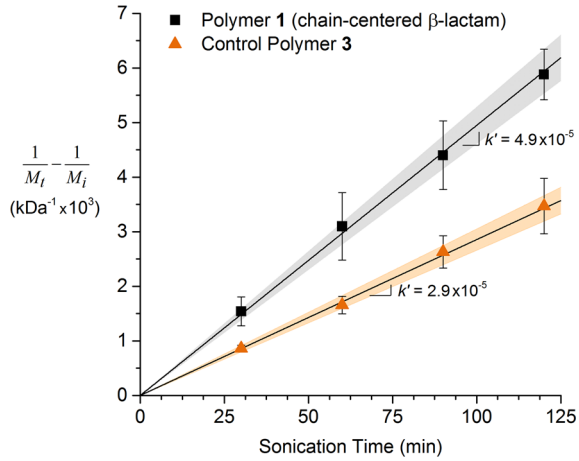
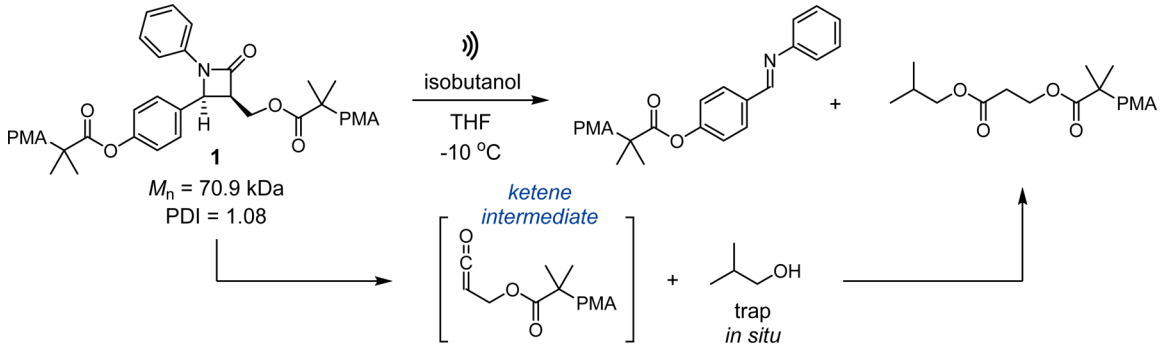


Figure 2. The rate of ultrasonication-induced chain cleavage, determined from the slope of the curve, is significantly faster for polymer **1** containing a chain-centered β-lactam unit than for control **3**. Measurements were performed in triplicate, and the error bars represent the standard deviation at each time point. The shaded regions represent the margins of error of the slopes at the 99% confidence interval.

Scheme 2. Ultrasonication of Polymer 1 Using Isobutanol To Trap the Mechanochemically Generated Ketene



DOI: 10.1021/jacs.5b07345
J. Am. Chem. Soc. 2015, 137, 10946−10949

rate constant measured for **1** ($k' = 4.9 \times 10^{-5}$ min^{-1} kDa^{-1}) is nearly 70% larger than that for control polymer **3** ($k' = 2.9 \times 10^{-5}$ min^{-1} kDa^{-1}), providing outstanding evidence of the mechanophore character of the β-lactam unit.

UV−vis and NMR spectroscopy were used to gain insight into the mechanochemical cleavage of **1** containing a chain-centered β-lactam mechanophore and provided evidence for the generation of ketene and imine groups via a cycloelimination mechanism. A large excess of isobutanol was employed during ultrasonication to trap the highly reactive ketene in situ according to Scheme 2. To support these measurements, three well-defined model compounds were synthesized with the structures displayed in Chart 1. The structures of the model compounds mimic the chain-centered β-lactam mechanophore (**4**), the isobutyl ester chain end expected from the reaction of a ketene with isobutanol (**5**), and the corresponding imine chain end (**6**).

GPC monitored with a UV−vis photodiode array detector showed the appearance of new absorption peaks between approximately 250 and 400 nm after ultrasonication of **1**, while the as-synthesized polymer exhibits no absorption at wavelengths >295 nm (Figure 3). Significantly, the absorption profiles of **1**

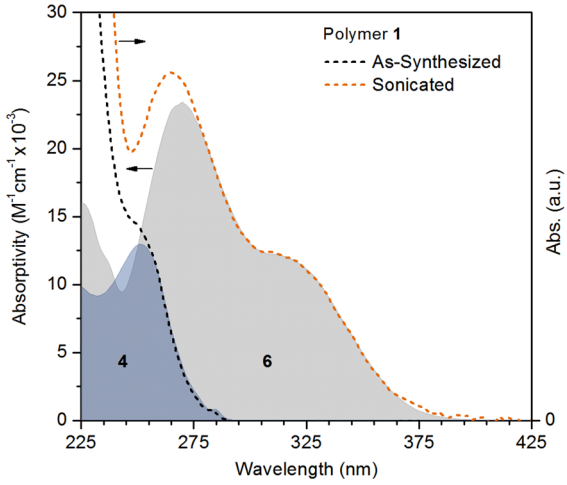


Figure 3. UV−vis absorption spectra of polymer **1** before and after ultrasonication and model compounds **4** and **6** (shaded curves) measured in THF. The spectra of **1** were acquired from GPC measurements and are scaled independently to illustrate their correlation with the spectra of the model compounds.

before and after ultrasonication match the UV−vis absorption spectra of model compounds **4** and **6**, respectively, indicating that the chain-centered β-lactam mechanophore is transformed into an imine group consistent with the proposed mechanism. The UV−vis spectrum of the chain-end control polymer **2** was unchanged after ultrasonic irradiation (see Figure S2), indicating that mechanical forces are indeed responsible for the observed changes in **1** and precluding alternative pathways such as thermal or photochemical activation.

Evidence for generation of both imine and ketene groups upon mechanochemical cleavage of **1** was provided by ^{1}H NMR measurements, which revealed the appearance of characteristic resonances corresponding to model compounds **5** and **6** after ultrasonication. A new singlet around 8.6 ppm representative of the imine methine proton is particularly diagnostic of this transformation, in addition to other distinctive aromatic resonances (Figure 4). Approximately 50% of the β-lactam mechanophores were converted into the corresponding imines

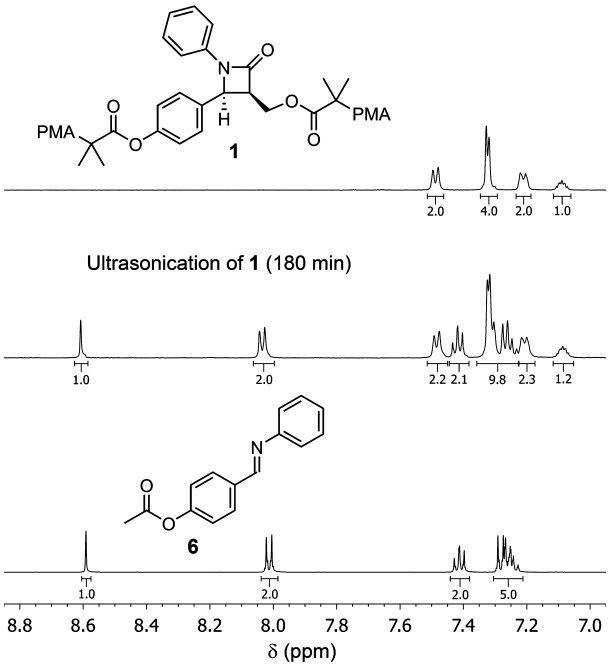


Figure 4. ^{1}H NMR spectra (500 MHz, acetone-d_6) of **1** before (top) and after (middle) ultrasonication for 180 min reveal the appearance of characteristic peaks consistent with a newly formed imine end group, represented by the NMR spectrum of model compound **6** (bottom).

after 180 min of ultrasonication, as determined by integration of the NMR signals. When this sample was analyzed by GPC using a refractive index detector, the relative peak areas indicated that approximately 65% of polymer chains were cleaved. The greater fraction of chain scission determined by GPC relative to imine formation determined by NMR likely originates from a distribution in the position of the mechanophore along the polymer chains, since significant deviation from the polymer midpoint has been shown to yield nonspecific chain scission and results in efficiency less than unity.[16e] In addition to imine signals, several new peaks indicative of the formation of the isobutyl ester end group are also apparent in the spectrum of **1** after ultrasonication, including doublets at 3.89 ppm (J = 6.4 Hz) and 0.94 ppm (J = 6.7 Hz) (see Figure S3). These new peaks are fully consistent with the spectrum of model compound **5**, which exhibits, among others, peaks at 3.87 ppm (d, J = 6.6 Hz, 2H) and 0.92 ppm (d, J = 6.7 Hz, 6H). Once again, these features were not observed in the ^{1}H NMR spectrum of chain-end control **2** after ultrasonication under identical conditions (see Figure S4).

In order to confirm the proposed mechanism of β-lactam cleavage, we conducted ^{13}C-labeling experiments in conjunction with NMR spectroscopy to support, in particular, the mechanochemical generation of a transient ketene group. Using a procedure similar to that for polymer **1**, an analogous β-lactam mechanophore was synthesized using $^{13}C_3$-labeled propargyl alcohol followed by installation of α-bromoester initiating groups and polymerization of methyl acrylate to afford polymer **1*** (M_n = 74.3 kDa, PDI = 1.07). Similarly, ^{13}C-labeled chain-end control polymer **2*** was also prepared (M_n = 76.7 kDa, PDI = 1.09). The proton-decoupled ^{13}C NMR spectrum of **1*** after ultrasonic irradiation for 180 min in the presence of isobutanol exhibits three new resonances at 34.3 ppm (dd, J = 58.2, 39.5 Hz), 61.1 ppm (d, J = 39.4 Hz), and 171.2 ppm (d, J = 58.1 Hz) (Figure 5). The splitting observed for these new peaks is fully consistent with the structure of the proposed isobutyl

DOI: 10.1021/jacs.5b07345
J. Am. Chem. Soc. 2015, 137, 10946−10949

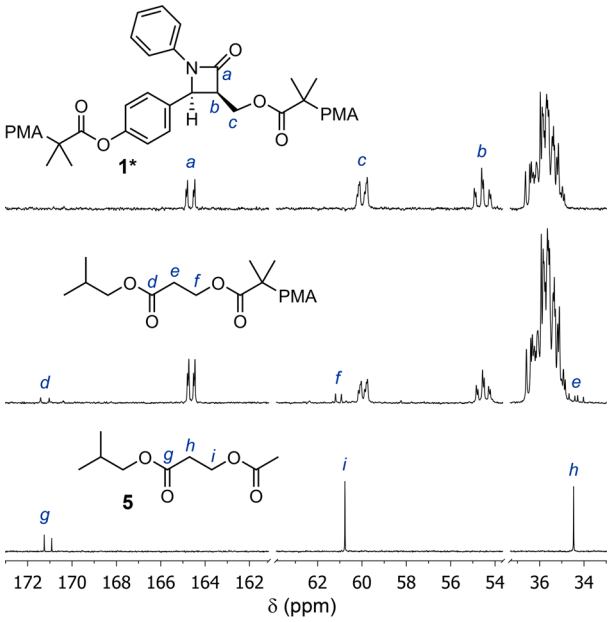


Figure 5. ^{13}C NMR spectra (acetone-d_6) of $^{13}C_3$-labeled polymer **1*** before (top, 125 MHz) and after (middle, 150 MHz) ultrasonication for 180 min reveal the appearance of three new resonances (labeled *d*, *e*, and *f*). These new peaks are consistent with the chemical shifts of model compound **5** (bottom, 125 MHz) and support the formation of an isobutyl propionate polymer chain end via reaction of a ketene intermediate with isobutanol. The three carbon atoms derived from propargyl alcohol (labeled *a*, *b*, and *c*) were ^{13}C-labeled.

propionate end group and also with the relevant chemical shifts associated with model compound **5**, which appear at 34.5, 60.8, and 171.3 ppm. The ^{13}C NMR spectrum of control polymer **2*** was unchanged after ultrasonic irradiation under identical conditions (see Figure S5).

In summary, we have demonstrated that the *β*-lactam motif represents a new mechanophore capable of generating ketene and imine groups via a mechanically facilitated formal [2 + 2] cycloelimination reaction—the reverse transformation of the Staudinger cycloaddition. This finding is supported by comparisons of sonication-induced chain cleavage rates, UV–vis absorption measurements, and end-group analysis using ^1H and ^{13}C NMR spectroscopy. In addition, these experimental results validate predictions from DFT calculations (CoGEF). In view of the diverse reactivity of ketene groups and their versatility in polymer and materials science, the *β*-lactam mechanophore has outstanding potential for a variety of applications, including self-healing materials capable of autonomic restoration of mechanical damage.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07345.

Crystallographic data for **6** (CIF)

Experimental details, synthetic procedures, NMR and UV–vis spectra, and GPC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by the National Science Foundation (CHE 1300313). M.J.R. gratefully acknowledges the Arnold and Mabel Beckman Foundation for a Beckman Institute Postdoctoral Fellowship.

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DOI: 10.1021/jacs.5b07345
J. Am. Chem. Soc. 2015, 137, 10946–10949