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Journal:	<i>Organic Chemistry Frontiers</i>
Manuscript ID	QO-RES-02-2019-000262
Article Type:	Research Article
Date Submitted by the Author:	18-Feb-2019
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Mechanical Generation of Isocyanate by Mechanically Induced Retro [2+2] Cycloaddition of a 1,2-Diazetidione Mechanophore

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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The encapsulation of guests in supramolecular capsules has long been used to trap reactive intermediates and enhance or reduce the kinetic stability of reactants, and alter the products of chemical reactions that occur within the capsule interior. In recent years, multiple studies have shown that variations of normal reactivity patterns can be induced by trapping reactants under tension, for example along a backbone of an overextended polymer chain, in a manner that is fundamentally very different from, but reminiscent of, encapsulation. Here, we describe the formation of a mechanochemically generated isocyanate *via* a mechanical retro [2+2] cycloaddition of a 1,2-diazetidione (DAO) mechanophore. A single DAO mechanophore is incorporated into the chain center of a poly(methyl acrylate) (PMA) backbone *via* single electron transfer-living radical polymerization (SET-LRP). Mechanical activation of the DAO *via* ultrasonic sonication leads to the formation of isocyanate and imine products, as supported by trapping experiments using 9-(methylaminomethyl)anthracene labelling and ^1H NMR spectroscopy. Further, we examine the relative mechanical susceptibility of chain-centered DAO mechanophores through a variety of methods, and evaluate the advantage and disadvantage of each.

We have found tremendous inspiration in the work of Julius Rebek, in ways that subtly (perhaps often even without our realization of it) but profoundly colour our thinking about a wide range of chemical problems. Consider Rebek's pioneering work on supramolecular capsules and cavitands, such as those constructed with hydrogen bonding.^{1, 2} Those efforts have led to a rich range of systems-level behaviours, including insights into the fundamental forces that guide molecular recognition in host-guest complexes,³⁻⁵ emergent properties and dynamics of multi-component assemblies,^{2, 6, 7} and methods to trap reactive intermediates,⁸ catalyse reactions,^{9, 10} and bias the selectivity of well-established reactions in new ways.¹¹

A similar mix of new and useful molecular behaviours with additional opportunities to study the fundamental underpinnings of chemical reactivity in new ways can be found in the area of covalent polymer mechanochemistry, where recent advances have demonstrated the potential of force-responsive motifs (mechanophores) to signal the onset of high material strains,¹²⁻¹⁴ report molecular level damage in materials,¹⁵⁻¹⁹ and respond to high stresses with triggered bond forming reactions that enhance mechanical properties (i.e., stress-strengthening).²⁰⁻²⁵ The latter is facilitated by mechanically unveiled reactive functional groups (e.g. *ortho*-quinodimethide,^{23, 26} cyanoacrylate/acrylate,^{21, 27} ruthenium/platinum catalyst,^{28, 29} NHC carbene,³⁰ ketene³¹) that can participate in subsequent reactions at overloaded/damaged regions to promote self-

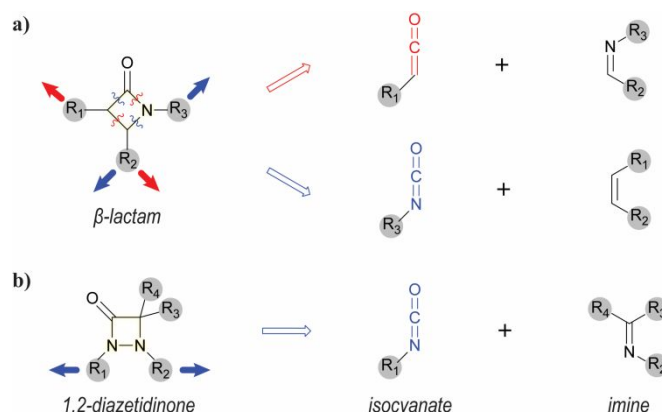


Figure 1. a) Mechanical generation of ketene or isocyanate from β -lactam mechanophore by altering pulling handles on the four-member ring; b) 1,2-diazetidione as mechanophore to produce isocyanate.

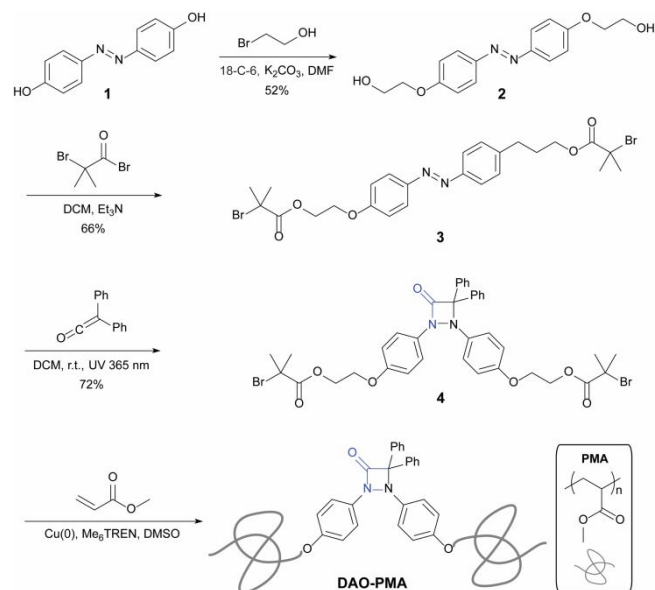
healing/strengthening. The development of new mechanophores in which can undergo facile generation of reactive functionalities remains as a challenging and yet a charming research topic.

Here, we explore mechanically assisted reactivity in the context of the generation of isocyanates. Isocyanates and related reactive functional groups³²⁻³⁴ have been extensively exploited as essential building blocks for industrial products including polyurethane elastomers, foams, polymer modification³⁵ and waterborne paints.³⁶ They are therefore appealing targets for mechanochemistry, but to the best of our knowledge the mechanically assisted activation of latent isocyanate functionality has yet to be reported. To that end, we were inspired by recent work by Robb and Moore, who reported the mechanochemical cycloreversion of a β -lactam-

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Electronic Supplementary Information (ESI) available: Synthesis detail, GPC characterization, NMR spectra. See DOI: 10.1039/x0xx00000x

Scheme 1. Synthetic route for poly(methyl acrylate) with chain-centered single 1,2-diazetidione mechanophore

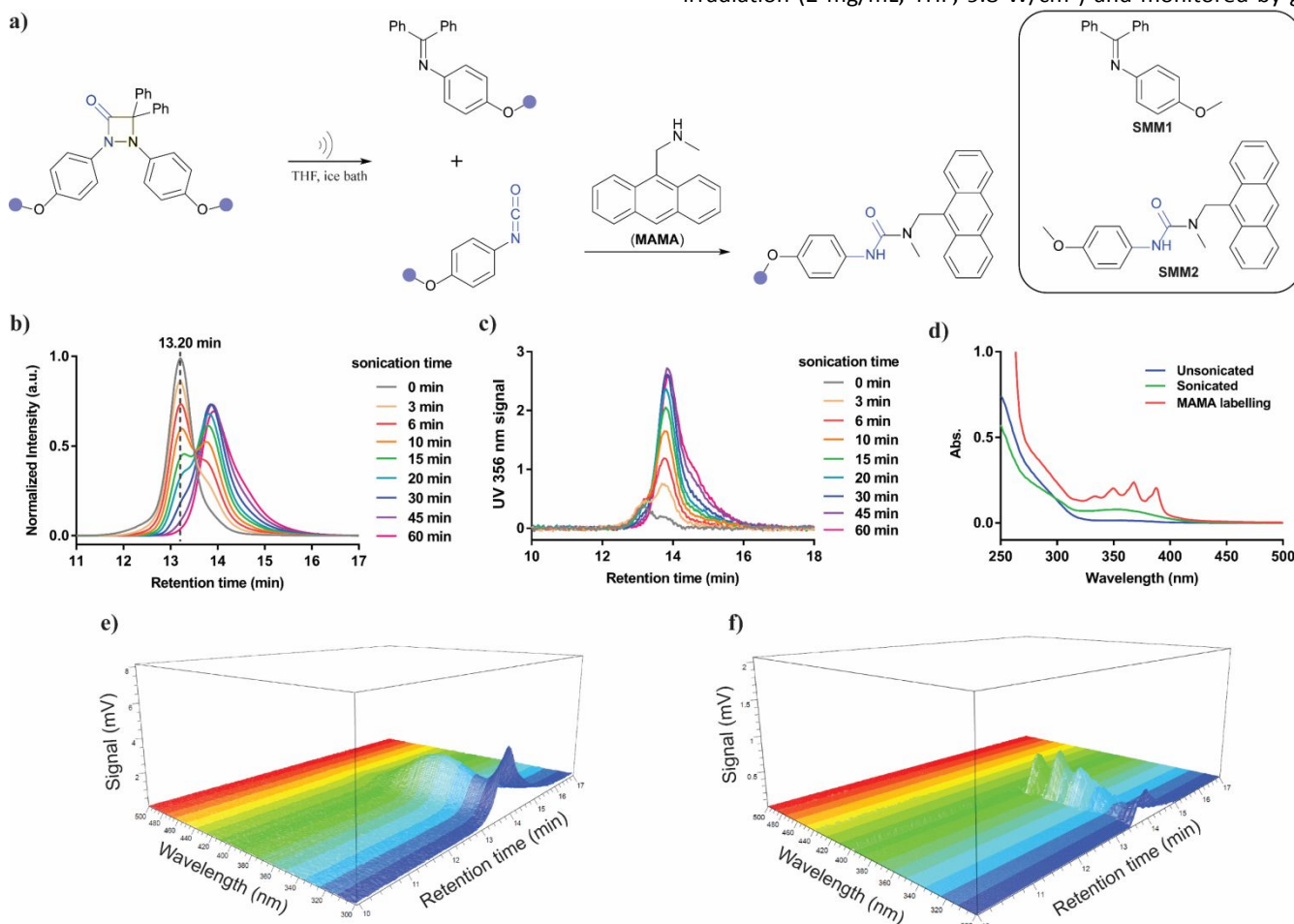


based mechanophore (Figure 1a, pulling handles at R_1 and R_2) to produce a ketene that was subsequently trapped with *iso*-

same mechanophore by pulling handles through R_2 and R_3 would lead to an isocyanate product (Figure 1a). The preparation of the requisitely substituted β -lactam, however, is somewhat arduous. We were therefore gratified to notice that an analogous 1,2-diazetidione (DAO) can be synthesized from facile addition of ketene to *cis*-azobenzene^{37, 38}, which we expected could be used to generate isocyanate through mechanical force applied to substituents on the two N atoms (Figure 1b).

To test out hypothesis, we employed a chain-centered, single mechanophore polymer strategy, as has been widely applied with a wide range of mechanophores. The synthesis of the desired polymer is shown in Scheme 1. Bisphenol azobenzene **1** was prepared using variations of reported procedures (see Supporting Information) and modified in two steps to give **3** in moderate yield. The [2+2] cycloaddition of *cis*-azobenzene with diphenyl ketene (generated *in situ*)^{38, 39} gave the desired DAO mechanophore **4**. Subsequent single electron transfer-living radical polymerization (SET-LRP) provided polymer **DAO-PMA** (number average molecular weight $M_n = 98.0$ kDa, polydispersity $\mathcal{D} = 1.13$).

We tested the mechanical reactivity of DAO by pulsed ultrasonication. **DAO-PMA** was subjected to ultrasonic irradiation (2 mg/mL, THF, 9.8 W/cm²) and monitored by gel-



butanol *in situ*.³¹ A low trapping efficiency was observed, probably due to the highly reactive nature of ketene. We hypothesized that a mechanochemical cycloreversion of the

permeation chromatography (GPC) coupled to refractive index (RI), multi-angle light scattering (MALS), and UV-vis photodiode array (PDA) detectors. As shown in Figure 2b, GPC traces reveal

a gradual decrease of the incipient polymer peak and concomitant emergence of a daughter polymer peak with increasing sonication time. After 60 min sonication, the incipient polymer peak has effectively disappeared, and several pieces of evidence (*vide infra*) indicate that chain scission occurs via the expected cycloreversion shown in Figure 1b.

The formation of imine species under sonication is supported by increasing absorbance at 356 nm (Figure 2c) since generated imine has a characteristic shoulder absorption peak at 356 nm (Figure 2d), consistent that expected based on the UV-vis spectrum of small molecule model SMM1 (Figure S3).

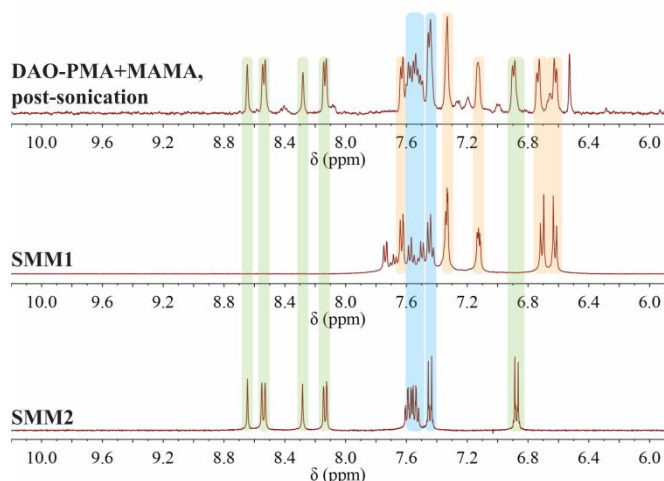


Figure 4. ^1H NMR spectra (DMSO- d_6 , 500 MHz) comparison of model molecules SMM1 and SMM2 and MAMA labelled DAO-PMA polymer after purification.

Moreover, the signal from GPC-coupled PDA detector shows the characteristic shoulder peak in the absorption spectrum around 356 nm (Figure 1e) at retention times that correspond to the elution of the daughter fragment. Further evidence from ^1H NMR is consistent with the mechanical activation of DAO and formation of the imine functionality (Figure S1).

The desired formation of phenyl isocyanate is more difficult to detect, due to its transience as a result of its reactivity with water and any other protic and/or nucleophilic species that might be either present in trace amounts or generated during sonication. We therefore used 9-(methylaminomethyl)anthracene (MAMA) as a labelled trapping molecule. **DAO-PMA** polymer was subjected to sonication in the presence of MAMA (1000 equivalent) and 5 μL dibutyltin dilaurate (DBTDL) as catalyst. After 60 min sonication, the M_n of the polymer is reduced from 98 to 35 kDa. The PDA signal of the GPC trace reveals absorption at retention times of 13–16 min, which correspond to the elution of the daughter fragments (Figure 2f). The UV-vis absorption spectrum in the range of 320–420 nm is consistent with a MAMA adduct of the expected isocyanate, as confirmed by spectroscopy of the model molecule SMM2 (Figure S3). To further confirm that MAMA is covalently attached to the daughter polymer, the sonicated polymer was purified by five rounds of methanol precipitation to completely remove any excess MAMA. The resulting polymer was dissolved and characterized by UV-vis and ^1H NMR spectroscopy. The UV-vis of MAMA labelled

polymer (Figure 1d) presents a same absorption pattern as model molecule SMM2 (Figure S3), while the ^1H NMR spectrum shows a mixture of peaks that are characteristic of the expected products, as confirmed by spectroscopy of model compounds SMM1 and SMM2 (Figure 3). Integration of the product ^1H NMR peaks provides an estimate that $\sim 80\%$ of the DAO mechanophore is converted to isocyanate and trapped by MAMA (Figure S2). As a control, an identical solution of **DAO-PMA**, MMAA and DBTDL was allowed to sit without sonication for 60 min before analysis; no evidence for activation or MAMA binding is observed in the UV-vis signal associated with the elution of the polymer (Figure S4, S5).

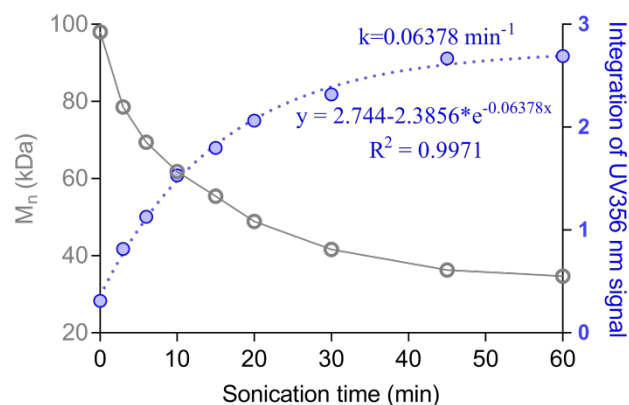


Figure 3. The evolution of molecular weight (M_n) and integration of GPC-UV356nm signal of DAO-PMA polymer during sonication.

The fact that the molecular weight is reduced by more than 50% means that the average chain is broken more than once, and yet the scission of DAO is not quantitative. This raises an interesting question as to how best quantify the mechanochemical susceptibility of the DAO mechanophore. Typically, single mechanophore polymers such as **DAO-PMA** are characterized by the reaction kinetics, and in particular the kinetics of chain scission, during sonication. Here, we applied several kinetic models to quantify the ultrasonication-mediated degradation behaviors of **DAO-PMA**. The most commonly applied framework for chain scission kinetics is given by equation (1),

$$\frac{1}{M_{n(t)}} - \frac{1}{M_{n(0)}} = kt \quad (1)$$

Where $M_{n(t)}$ is the molecular weight at time t ; $M_{n(0)}$ is the initial molecular weight and k is the rate constant.

Eq. (1) can be traced back to Casassa's theory in 1949.⁴⁰ It was cited by Jellinek and Haward in 1950^{41, 42} and then, for the first time, used by Nelapa to analyze the degradation of cellulose under shear force in 1977.⁴³ Later, it was used by Malhotra⁴⁴ in extensive studies of polymer degradation under sonication through presumably nonspecific homolytic scission. In 2011, Kryger et al. applied eq. (1) to the kinetics of scission in single mechanophore paper⁴⁵ providing a quantitative basis upon which to evaluate the relative mechanical susceptibility within a family of mechanophores.

The fact that eq. (1) is based on M_n raises an interesting question, in that, as noted previously, not all events that reduce

M_n involve the scission of the mechanophore whose behavior we are trying to quantify.⁴⁶ Therefore, the kinetics of chain scission do not necessarily match the kinetics of mechanophore activation.

Because DAO provides a UV signal of activation that is independent of change in molecular weight, the system at hand provides an opportunity to evaluate the suitability of eq. (1) for this polymer and mechanophore combination. We can obtain a direct measure of DAO scission from the UV-vis absorption signal of the imine by fitting the change in absorption at 356 nm to a first-order exponential decay. We denote the resulting rate constant k_{product} as it results from quantifying the products of DAO scission.

We also considered a third method, based on the change in peak height of the parent polymer peak in the GPC data, to calculate the mechanical degradation rate. This method was reported by Florea⁴⁷ and later used by Boydston to compare the chain scission rates of linear and star polymers.⁴⁸ Because we have adequate resolution of our parent and daughter peaks, we also performed a kinetic analysis of the change in peak height of the RI signal that is attributed to the parent polymer (retention time at 13.20 min, Figure 1b) to obtain what we denote k_{RI} . Finally, a variant of this method was employed, in which we deconvoluted the GPC traces into overlaying parent and daughter peaks, as previously performed by Boydston (for details, see Supporting Information).⁴⁸ The degradation rate constants were then calculated from peak intensity (k_{peak}) and area (k_{area}) of the resolved parent polymer peak (Figure S11).

Table 1. DAO-PMA activation rate constants obtained from various methods

Casassa	Product	Florea	Deconvolution	
$k_{\text{MW}} \cdot 10^5$ ($\text{Da}^{-1} \text{min}^{-1}$)	$k_{\text{product}} \cdot 10^2$ (min^{-1})	$k_{\text{RI}} \cdot 10^2$ (min^{-1})	$k_{\text{peak}} \cdot 10^2$ (min^{-1})	$k_{\text{area}} \cdot 10^2$ (min^{-1})
4.6 ± 0.25	6.4 ± 0.36	5.6 ± 0.23	5.4 ± 0.12	5.0 ± 0.07

The mechanophore activation rates obtained from the various methods are shown in Table 1. Notably, the rate constant retrieved from Casassa's method involves the possibility of multiple events per chain, rather than a 1:1 conversion of reactant (parent polymer) to product (daughter fragment). The intrinsic difference in its meaning is reflected in the units of the rate constant, and we put aside discussion of k_{MW} for the moment. A comparison of the remaining kinetic parameters is more revealing. The values of the other four rate constants are generally consistent, with a maximum difference of only 30%, but the apparent rate constant for product formation (k_{product}) is slightly, yet statistically significantly, greater than the rate constants inferred from changes in molecular weight (k_{peak} , k_{area} , and k_{RI}). It is tempting to simply ascribe the admittedly modest difference to experimental uncertainty, but given that the data are obtained from the same reaction, and all rate constants depend only on the relative (and not absolute) signal as a function of time, we consider the possibility that the difference is real and its likely implications.

In particular, the difference in rate constants boils down to the idea that DAO scission comes to completion prior to the end

of chain scission chemistry. The relative extent of DAO scission vs. overall chain scission makes clear that there is some off-target rupture taking place. If non-DAO scission occurred only in direct competition with DAO scission, however, and each chain broke only up to a single time, then the half-life for each process would be identical and the measured rate constants should match. A shorter half-life (greater k) for DAO scission instead implies that the chain scission reactions continue to occur even as the DAO scission has effectively stopped. In other words, some population of the parent polymers might be cleaved first at the DAO, and then subsequently undergo a second scission within a daughter fragment.

As the data in Table 1 suggest, the implications of such processes might often be modest, or even barely detectable, but these possibilities are worth bearing in mind, especially since they might be hidden by dispersity even for fairly well controlled polymerizations such as those employed here. Since rate constants of chain scission are often used to compare different mechanophores, and since those mechanophores are necessarily in different polymers, slight differences in polymer molecular weight and/or dispersity might contribute to differential behavior that complicates the desired comparison. It therefore seems prudent to monitor the scission of single mechanophore polymers by multiple methods whenever possible, using techniques that are specific to the mechanochemical reaction of interest as well as to the scission of the polymer chain in general.

Conclusions

Harkening back to Rebek's pioneering work on encapsulation complexes that have so inspired our thinking in polymer mechanochemistry, the use of mechanophore-specific signals is reminiscent of the ability to distinguish ¹H NMR signals of host, encapsulated guest, and unencapsulated guest that so empowered the thermodynamic, kinetic, and mechanistic investigations in those systems. While the ideas presented here are unlikely to surprise anyone working in the field of polymer mechanochemistry, we are not aware that they have been spelled out previously in the literature, and the new DAO mechanophore disclosed here presented a valuable opportunity to do so. In addition, the mechanochemical reactivity of DAO itself might be quite useful, as the isocyanate and, to a lesser extent, imine products formed from DAO cycloreversion are potentially useful as building blocks in stress-adaptive materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This manuscript is based on work supported by the National Science Foundation (CHE-1808518 to S.L.C.). Y.L. is grateful to the Duke University Department of Chemistry for a Burroughs

Wellcome Graduate Fellowship. We thank Dr. Peter Silinski and Dr. George Dubay for mass spectrometry analysis.

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