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Regiochemical Effects on Molecular Stability: A Mechanochemical Evaluation of 1,4- and 1,5-Disubstituted Triazoles

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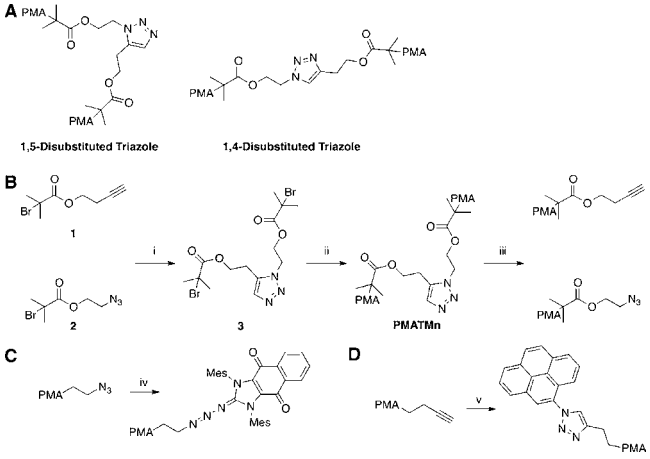
Supporting Information

ABSTRACT: Poly(methyl acrylate) chains of varying molecular weight were grown from 1,4- as well as 1,5-disubstituted 1,2,3-triazoles. Irradiating acetonitrile solutions of these polymers with ultrasound resulted in the formal cycloreversion of the triazole units, as determined by a variety of spectroscopic and chemical labeling techniques. The aforementioned reactions were monitored over time, and the rate constant for the cycloreversion of the 1,5-disubstituted triazole was measured to be 1.2 times larger than that of the 1,4-disubstituted congener. The difference was attributed to the increased mechanical deformability of the 1,5-regioisomer as compared to the 1,4-isomer. This interpretation was further supported by computational studies, which employed extended Bell theory to predict the force dependence of the activation barriers for the cycloreversions of both isomers.

The burgeoning field of polymer mechanochemistry, wherein exogenous forces are directed to chemical functionalities in an anisotropic manner through polymer actuators, offers opportunities to precisely direct chemical reactions down specific pathways.[1] As a result, mechanical forces have been shown to facilitate a number of intriguing, and often novel, transformations.[2] For example, we recently demonstrated that mechanochemical approaches could effect the formal [3+2] cycloreversion of 1,4-disubstituted 1,2,3-triazoles, a process that is challenging to access using other stimuli (thermal, photochemical, etc.).[2g] We hypothesized that the 1,5-disubstituted isomers[3] of the aforementioned triazoles might also be susceptible to cycloreversion under mechanical activation (Scheme 1A). Furthermore, we reasoned that 1,4- and 1,5-disubstituted triazole mechanophores presented an opportunity to explore regiochemical effects on molecular stability using polymer mechanochemistry. Although stereochemistry has been shown to influence mechanochemical transformations,[2e,4] there have been no reports demonstrating how mechanical processes are influenced by the regiochemistry of the polymers attached to the mechanophores. Beyond enriching the field of mechanochemistry,[5] such an endeavor was envisioned to provide insight that would be beneficial for the rational design of new mechanophores[1] as well as force-responsive materials.

Our experimental efforts began with the synthesis of a 1,2,3-triazole bearing polymerization initiators at the 1- and 5-ring positions (Scheme 1B). The regioselective cycloaddition of **1** and **2** was facilitated using [Cp*(PPh$_3$)$_2$RuCl] as a catalyst in tetrahydrofuran (THF), and the corresponding bifunctional initiator **3** was isolated in good yield (79%). Subsequent Cu-mediated living radical polymerization of methyl acrylate (MA) from **3** afforded triazole-centered poly(MA) (PMA) with a number-average molecular weight (M_n) dictated by the initial monomer-to-initiator ratio (**PMAT**$_{M_n}$, where the subscript indicates the M_n in kDa; see Table 1).

Scheme 1. Relevant Structures, Syntheses, and Controls[a]



[a](A) PMA-functionalized triazole mechanophores. (B) i, [Cp*-(PPh$_3$)$_2$RuCl], THF; ii, MA, Me$_6$TREN, Cu^0, DMSO; iii, ultrasound (pulsed, 1 s on and 1 s off; 9.7 W cm^{-2} power intensity; 9 °C). (C) iv, **NQMes** (10 equiv), THF, rt, 24 h. (D) v, 1-azidopyrene (10 equiv), CuI (0.1 equiv), MeCN, 85 °C, 24 h.

Upon the synthesis of the aforementioned polymers, their susceptibility to mechanical activation was explored. Ultrasound irradiation of a 10 mg mL^{-1} solution of **PMAT**$_{81}$ in CH$_3$CN at 9 °C for 5 h (active sonication time) resulted in a reduction of the polymer M_n by approximately half (cf., M_n = 81 kDa presonication vs 42 kDa postsonication), as determined by gel permeation chromatography (GPC, Figure 1A).

Anticipating that the aforementioned reduction in M_n indicated mechanical activation of the triazole moiety, we sought to characterize the expected azide and terminal alkyne products of the proposed cycloreversion reaction. 1,3-Dimesitylnaphthoquinimidazolylidene (**NQMes**), a stabilized carbene known[6] to form characteristic acyclic triazene products upon reaction with organoazides, was explored as a means to

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Table 1. Selected Polymer Molecular Weight Data

	presonication		postsonication		
polymer[a]	M_n (kDa)	PDI[b]	M_n (kDa)	PDI	sonication time[c] (h)
PMAT$_{156}$	156	1.4	80	1.5	2
PMAT$_{81}$	81	1.4	42	1.3	5
PMAT$_{42}$	42	1.3	20	1.4	5
PMAT$_{27}$	27	1.4	14	1.6	7
PMAT$_{19}$	19	1.4	19	1.3	7

[a]**PMAT** refers to the 1,5-disubstituted triazole-centered PMA, and the subscript gives the approximate value of M_n in kDa. [b]Polydispersity index (PDI) was calculated as PDI = M_w/M_n, where M_w is the weight-average molecular weight. M_n and M_w were determined as their polystyrene equivalents using GPC (eluent = THF). [c]Actual duration of ultrasonication (pulse sequence: 1 s on, 1 s off).

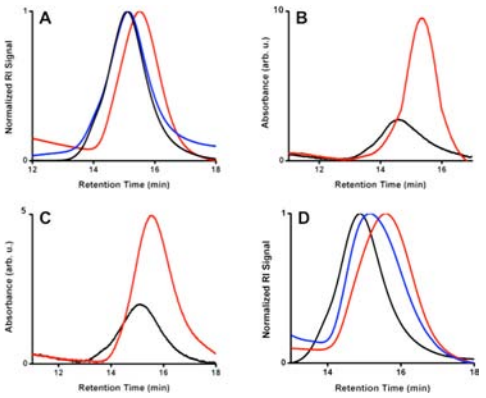

Figure 1. (A) GPC traces showing the scission of **PMAT$_{81}$** (black) upon sonication (red). No chain scission was observed when **PMAT$_{81}$** was heated in diphenyl ether (220 °C) for 24 h (blue). (B) GPC traces (visualized with UV detection at 315 nm) showing an increased absorption for the postsonicated **PMAT$_{81}$** after treatment with **NQMes** (red) compared to the presonicated **PMAT$_{81}$** (black) at the same concentration. (C) GPC traces (visualized with UV detection at 345 nm) showing an increased absorption for the postsonicated **PMAT$_{81}$** upon treatment with 1-azidopyrene (red) compared to the presonicated **PMAT$_{81}$** (black) at the same concentration; see text for additional details. (D) GPC traces showing the scission of **PMAT$_{81}$** (black) under sonication (red) and re-formation of the triazole through Cu-mediated click chemistry (blue).

selectively label, and thus identify the presence of, mechanically liberated azides (Scheme 1C).[2g] In this experiment, the material obtained following the sonication of **PMAT$_{81}$** was dissolved in THF and treated with excess **NQMes** (10 equiv). The isolated product was consistent with the expected triazene, as determined by GPC aided with UV detection at 315 nm.[2g] For comparison, no change in the material's absorption properties was observed after treatment of presonicated **PMAT$_{81}$** with **NQMes** under otherwise identical conditions (Figure 1B). In parallel, efforts were directed toward labeling mechanically liberated terminal alkyne moieties using 1-azidopyrene (Scheme 1D). After irradiating **PMAT$_{81}$** with ultrasound, the resulting product was treated with excess 1-azidopyrene (10 equiv) in the presence of CuI at 85 °C for 24 h. GPC analysis of the material isolated from this reaction mixture revealed a characteristic pyrene absorbance at 345 nm (Figure 1C). In contrast, GPC analysis of the material obtained after treating presonicated **PMAT$_{81}$** with 1-azidopyrene under otherwise identical conditions did not show an increased absorption at the aforementioned wavelength. Collectively, these results suggested to us that the expected products of the proposed cycloreversion were generated upon ultrasound irradiation of 1,5-disubstituted triazoles embedded within PMAs.

To further demonstrate that the polymeric products of mechanical activation contained azido and alkynyl termini, efforts were directed toward coupling the postsonicated materials using Cu-catalyzed [3+2] cycloaddition chemistry. Upon ultrasound irradiation of a CH_3CN solution of **PMAT$_{81}$**, the isolated material was first analyzed by GPC (M_n = 42 kDa), dissolved in CH_3CN (10 mg mL^{-1}), and then heated to 85 °C for 24 h in the presence of excess CuI (30 equiv). Consistent with a successful coupling reaction, the molecular weight of the polymer product was measured to be nearly twice that of its starting material (M_n = 79 kDa) and nearly identical to that of presonicated **PMAT$_{81}$** (Figure 1D).

The mechanical component of the observed reactivity was verified through a number of control experiments. Importantly, the cycloreversion was found to have a characteristic molecular weight dependence,[1,2a−d,g,4,7] as only higher molecular weight polymers (i.e., M_n > 19 kDa) underwent activation (Table 1). Furthermore, cycloreversion was not observed when **PMAT$_{81}$** was heated in diphenyl ether at 220 °C for 24 h (Figure 1A); additional experiments confirmed that thermal effects were negligible (SI). Collectively, these results demonstrated that cycloreversion was only observed upon mechanical activation of triazole-centered PMAs.

During the course of our studies, the activation of 1,5-disubstituted triazoles embedded in polymers of M_n = 27 kDa was observed. This was a surprising result because we previously found that analogous low mol. wt. polymers containing the 1,4-regioisomer did not undergo mechanical activation.[2g] To quantify this difference in reactivity, the rate constants for mechanical activation of both isomers embedded within polymers of similar initial molecular weight (M_n = 90 kDa) were measured. The polymers were individually subjected to ultrasound irradiation as described above, and the change in the M_n of each polymer was monitored using GPC as a function of sonication time.[4a] The corresponding rate constants were measured to be k(1,5-triazole) = 3.22 × 10^{-5} min^{-1} and k(1,4-triazole) = 2.76 × 10^{-5} min^{-1} (Figure 2).[8]

In an effort to explain the differences in the aforementioned rate constants, we first reasoned that the 1,5-triazole was more responsive to mechanical activation in part because the vicinal polymer attachments were localizing the mechanical forces

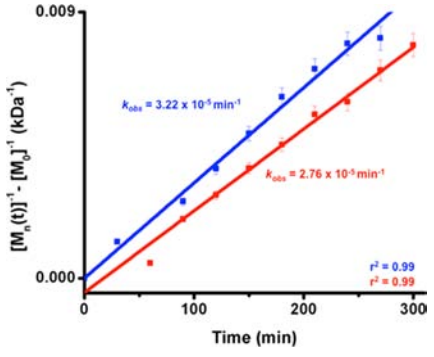

Figure 2. Plots of the change in M_n versus time used to measure the rate constants for the cycloreversions of 1,5-disubstituted (blue) and 1,4-disubstituted (red) triazoles. Each regioisomer was embedded within a PMA (M_n = 90 kDa) and subjected to ultrasound irradiation.

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generated under ultrasound to a smaller region of the heterocycle (i.e., the N_1-C_5 bond). In contrast, the polymers attached to the 1,4-regioisomer translated mechanical energy across the heterocyclic scaffold, effectively requiring additional force to facilitate the cycloreversion process. We also reasoned that (1) the N_1-C_5 bond should be more susceptible to mechanical deformation than the N_3-C_4 bond due to the rigidity imposed by the π-character in the N_2-N_3 bond and (2) the N_1-C_5 bond of the 1,5-regioisomer should be slightly weakened as a consequence of steric congestion.

To explore these viewpoints more quantitatively, we employed electronic structure calculations to probe the mechanically induced cycloreversion processes. In particular, we used the recently described extended Bell theory[9] (EBT), which offers a computationally inexpensive alternative to methods that explicitly include the effect of mechanical stress[2f,10] or strain[11] on molecular potential energy surfaces. Regardless, EBT accurately predicts mechanochemical reactivity using standard geometry optimizations and saddle point searches performed for mechanically unperturbed molecules.[9] The method also determines the force dependence of the activation barrier for a given transformation using only two parameters. The first parameter is the change in distance between the two atoms to which the force is applied in going from the reactant state to the transition state (TS). If this distance increases, then applying an elongational force across those two atoms should lower the overall reaction barrier.[12] Conversely, if this distance decreases at the TS, then applying an elongational force should retard activation. The second parameter is the difference in the molecular compliance between the TS and the reactant state, which determines the curvature of the force dependence of the activation barrier. Thus, EBT generalizes the classic Bell model,[13] which assumes that the barrier is linearly dependent on the force. While this method requires that the applied force not be too large, the amount of information that can be extracted from such a relatively simple set of calculations makes EBT attractive for evaluating mechanochemical phenomena.

EBT calculations for the triazole cycloreversions were performed with the NWCHEM package[14] using density functional theory,[15] employing the 6-31G* basis set[16] and the B3LYP exchange-correlation energy functional (SI).[17] Triazoles featuring 1,4- and 1,5-dimethyl substituents (**TA1** and **TA2**, respectively; Figure 3) were initially chosen for the *in silico* evaluation of the cycloreversion processes. In the case of **TA1**, the N_1 and C_4 atoms were considered to be the points to which the pulling forces were applied, as we reasoned that these nuclei would simulate the translation of mechanical force to the triazole moiety. Similarly, the N_1 and C_5 atoms were treated as the pulling points for EBT analysis of **TA2**. To determine which set of pulling points would more readily facilitate the triazole cycloreversion, the internuclear distances between the aforementioned atoms in **TA1** and **TA2** were calculated in the reactant and TS geometries. As expected, the change in distance between the pulling points in **TA2** was larger than the corresponding change between the pulling points in **TA1** (0.93 Å for **TA2** vs 0.62 Å for **TA1**). Thus, **TA2** was predicted to be more susceptible to mechanical activation than **TA1** (*vide infra*; Figure 3). By extension, the 1,5-disubstituted triazoles should respond to mechanical forces (i.e., undergo mechanical cycloreversion) more readily than their 1,4-disubstituted congeners, which was consistent with the experimental observations previously discussed.

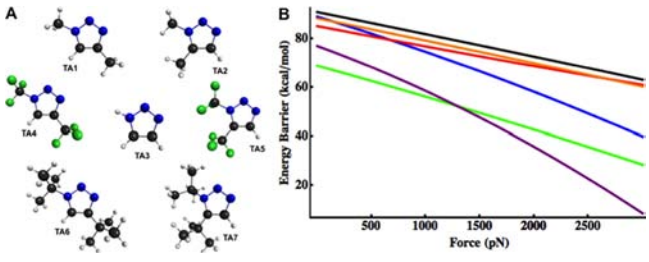

Figure 3. (A) Reactant state geometries of **TA1**-**TA7**. Legend: C, black; H, white; F, green; N, blue. The figure was prepared using MacMolPlt.[18] (B) Force curves for **TA1** (black), **TA2** (blue), **TA4** (red), **TA5** (green), **TA6** (orange), and **TA7** (violet). "Energy barrier" refers to the predicted activation energy for the cycloreversion of the corresponding triazole.

The intrinsic reactivity of the 1,2,3-triazole was explored through the evaluation of an analogue bearing only hydrogen substituents, and therefore devoid of steric bulk or highly perturbing electronic effects (**TA3**; Figure 3). As in the aforementioned calculations, the change in the N_1-C_5 distance in going from the reactant state to the TS was larger than the corresponding change in the N_1-C_4 distance (0.85 vs 0.60 Å), consistent with the hypothesis that direct bond activation in the 1,5-regioisomer (in contrast to force translation across the 1,4-regioisomer) facilitates the cycloreversion process by pulling the triazole into a TS geometry necessary for the retro-[3+2] reaction. Since stereoelectronic effects were negligible in **TA3**, the result also suggested to us that the N_1-C_5 bond is inherently more susceptible to mechanical deformation than the N_3-C_4 bond, which could result from the rigidity imposed by the N_2-N_3 bond (*vide supra*). Collectively, these data further supported the conclusion that 1,5-disubstituted triazoles were intrinsically more susceptible to mechanical activation than their corresponding 1,4-regioisomers.

Having explored the intrinsic susceptibility of 1,4- and 1,5-disbustituted triazoles to mechanical activation, the response of the cycloreversion energy barrier to exogenous forces was probed using EBT. Figure 3 shows the predicted changes in the reaction barriers for the cycloreversions of **TA1** (black) and **TA2** (blue) as a function of force, hereafter referred to as force curves (FCs). A series of functionalized triazole analogues (**TA4**-**TA7**; Figure 3) were also evaluated computationally in the manner previously discussed (*vide supra*) to elucidate electronic or steric effects on the cycloreversion process. Importantly, the zero force barriers corresponding to cycloreversions of the 1,5-regioisomers were lower than those of the analogous 1,4-regioisomers in all cases. Building on this result, we sought to draw a comparison between predicted trends in cycloreversion and known triazole reactivity. We reasoned that electron deficient triazoles should undergo cycloreversion more readily than electron rich analogues, as electron deficient triazoles are known to participate in the Dimroth rearrangement.[19] Toward this end, the zero force barriers to cycloreversion for bis(trifluoromethyl)-substituted triazoles (**TA4** and **TA5**) and dimethyl-substituted triazoles (**TA1** and **TA2**) were compared. As expected, the activation energies for the cycloreversions involving the dimethylated isomers (E_a = 90.7 kcal/mol for **TA1**; E_a = 88.9 kcal/mol for **TA2**) were found to be larger than those for the analogous trifluoromethyl congeners (E_a = 85.0 kcal/mol for **TA4**; E_a = 68.7 kcal/mol for **TA5**). Since this result conformed to our prediction, we

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turned our attention to an evaluation of steric effects on the cycloreversion processes.

To explore the role of sterics, the cycloreversions of dimethyl substituted triazoles were compared to bis(*tert*-butyl) analogues (**TA6** and **TA7**). We reasoned that the relative differences between the zero force energy barriers for each set of analogues would reveal the extent to which steric congestion influenced the cycloreversion processes. In accord with this assessment, the difference between the aforementioned barriers for the cycloreversions of **TA1** and **TA2** (ΔE_a = 1.87 kcal/mol) was calculated to be smaller than that of **TA6** and **TA7** (ΔE_a = 11.37 kcal/mol). This result also demonstrated that the steric interactions present in the 1,5-disubstituted triazoles were increasing the overall molecular compliances, as evidenced by the appreciable curvature of the FC calculated for **TA7**. Indeed, the FCs for all of the 1,5-analogues evaluated exhibited greater curvature than those of the corresponding 1,4-isomers. It should also be noted that **TA7** exhibited the largest force dependence of all the derivatives analyzed using EBT, as evidenced by the precipitous decrease in activation energy for its cycloreversion under increasing force (Figure 3). Collectively, these results indicated that, in combination with the intrinsic deformability of the N_1-C_5 bond, steric congestion rendered the 1,5-regioisomer more susceptible to mechanical activation than the 1,4-regioisomer.

In summary, we have shown that 1,5-disubstituted triazoles undergo a mechanically facilitated cycloreversion to afford azide and terminal alkyne moieties. The products of the cycloreversion were identified through reaction with small molecule labels as well as spectroscopic and chromatographic characterization. A variety of control experiments ruled out thermal effects and indicated that mechanical forces were responsible for the observed reactivity. The rate of cycloreversion was found to be 20% greater for the 1,5-disubstituted regioisomer than for its 1,4-congener, which was explained by a combination of increased molecular compliance and direct bond activation in the case of the former. In a broader context, these results show that the relative regiochemistry of the polymer attachments on a mechanophore must be considered when evaluating or designing mechanochemical systems.

■ ASSOCIATED CONTENT

Supporting Information

Syntheses, experimental procedures, computational methods, and analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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