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COMMUNICATION

Alkyne Mechanochemistry: Putative Activation by Transoidal Bending

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We investigated the use of mechanical stress to bend carbon-carbon triple bonds. Formation of an isoquinoline after reaction with a benzyl azide trap points towards a nucleophilic addition mechanism, differentiating mechanochemical *trans*-bending of π bonds from the typical reactivity observed for *cis*oidal bending of triple bonds in strained cyclic alkyne.

Modern polymer mechanochemistry serves not only to study the mechanical degradation of polymer chains under stress, but also to explore new approaches to drive productive chemical change.¹ Potential applications of non-degradative polymer mechanochemistry are in the development of self-healing² and self-reinforcing³ materials as well as other interesting uses, such as detection of the stress history in a material,⁴ changing the energy plane of chemical reactions to obtain products inaccessible by thermal mechanisms,⁵ pre-catalyst activation⁶ and more.

The design of new mechanochemically responsive functional molecules (mechanophores) has mostly focused on the stretching of weak bonds; however, Boydston and Craig have recently demonstrated mechanochemical bond scission based on angle bending of bicyclic compounds.⁷ The energy involved in chemical bond stretching is significantly higher than the energy necessary to bend bond or dihedral angles.⁸ An interesting, still unexplored mechanochemical reaction, is the bending of π bonds. Given the recent success of the “copper-free click-chemistry”⁹ where the azide-alkyne Huisgen cycloaddition¹⁰ is significantly accelerated by using a *cis*-bent carbon-carbon triple bond, we decided to study if *trans*-bending of a triple bond would lead to enhanced reactivity.

Theoretical studies showed that during pyramidalization of the triple bond, the energy of the anti-bonding π^* is significantly reduced while the energy of the π orbital remains mostly unchanged, suggesting that the distorted triple bond could react as an electrophile or a di-radical.¹¹ *Trans*-bent alkynes were observed in the solid state study of *ortho*-substituted phenyl acetylenes as well as *peri*-substituted naphthalenes (Fig. 1).¹² However, the bending angles

were much smaller compared to the angles in strained cyclooctynes.¹³ Here, we investigate the use of mechanical stress to bend alkynes to larger angles.

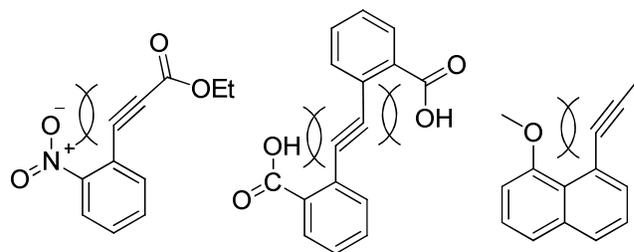


Fig. 1. Some examples of *trans*-bent alkynes previously studied by solid-state crystallography.¹²

Following polymer extension, a chain-centered triple-bond is expected to be tilted with respect to the force axis, and therefore *trans*oidal bending is expected (Fig. 2a). As a first step to test this notion, we used DFT calculations to simulate the stretching of a model triple bond to examine the deformation state prior to bond scission. Model alkyne **1** was studied using the CoGEF (constrained geometries simulate external force) technique.¹⁴ In the minimized structure, deformation up to a 26° angle ($180^\circ - \alpha$) between the force vector and the triple bond is observed; therefore, stretching in the direction of the force vector should lead to bending of the angles in the triple bond away from linearity and towards a *trans*-bending mode (Fig. 2). The terminal carbons in the molecule were constrained at increasingly higher distances, and the energy, as well as the two $-\text{H}_2\text{C}-\text{C}\equiv\text{C}-$ angles were measured for each step. Before any bond scission event, the $-\text{H}_2\text{C}-\text{C}\equiv\text{C}-$ angle bends to a minimum of 163.5° at relatively low energies. At this point, the force vector and the triple bond are almost aligned (Fig. 2b). Further stretching leads to a fast energy increase towards bond scission, while the bond angle does not change. While 163.5° is larger compared to the angles observed in cyclooctynes (152-162°),¹³ this result indicates that significant bending of the triple bond occurs before bond scission.

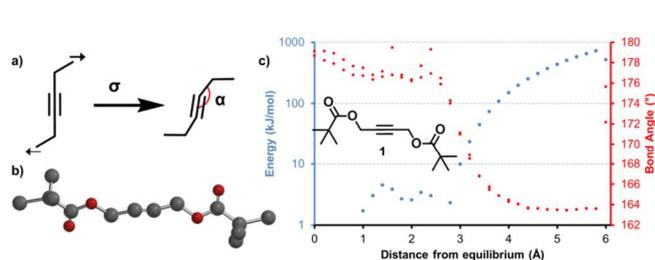
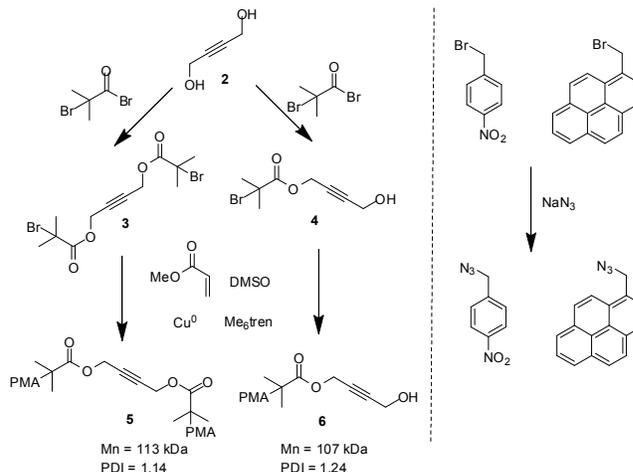


Fig. 2. a) Mechanochemical trans-bending of triple bond (σ represents applied stress). b) Stretched **1** from DFT calculations. c) CoGEF calculations of model compound **1**, where energy (blue) and $-\text{C}\equiv\text{C}-\text{CH}_2-$ bond angles (red) are shown.

If trans-bent alkynes react similarly to cis-bent alkynes, a Huisgen cycloaddition between a polymer chain-centered alkyne with a trapping azide would produce a 1,2,3-triazole attached to the polymer at the 4,5 positions. An understanding of the mechanochemical stability of the product is needed prior to starting experimental testing, given that Bielawski and co-workers demonstrated the mechanochemical retrocycloaddition of 1,2,3-triazoles attached to polymers at the 1,4 and 1,5 positions.¹⁵ We therefore calculated the CoGEFs profiles for a model triazole, stretching in the direction of the 1,4 vector and the 4,5 vector (see the ESI). The previously demonstrated retrocycloaddition occurs clearly in the first case in a concerted manner, where two bonds are cleaved in a single step, and the energy of the system decreases. However, when the force is applied along the direction of the 4,5 vector, a single bond is cleaved, and only at a much higher energy, causing a ring opening reaction without scission of the polymer chain.

A poly(methyl acrylate) (PMA) containing a chain-centered triple bond (**5**) was prepared by SET-LRP¹⁶ (Scheme 1). For control experiments, a similar PMA having the triple bond at the end of the chain was prepared. The alkyne at the end of the chain in **6** is not affected by ultrasound's solvodynamic shear forces, and therefore should be mechanochemically unreactive toward the trap. As traps, 4-nitrobenzyl azide and 1-(azidomethyl)pyrene were prepared.



Scheme 1. Synthesis of polymers and azide traps used in the study.

Solvodynamic shear from an acoustic field was used to induce strain in the polymer chain, since during this type of elongational flow unfolding of the chain is expected, leading to a narrow distribution of angles between the force vector and the triple bond (in the solid state all angles are possible).^{1c,17} A dilute solution of polymer **5** (1 mg/mL) and 4-nitrobenzyl azide (12000 equiv. to triple bond) in acetonitrile was prepared and sonicated at 6-9 °C. GPC analysis showed incorporation of the trap to the polymer as evidenced by the presence of a polymer peak at the UV-detector following absorption at 280 nm (Fig. 3a). When the solution of polymer and azide is left standing for 3 days at room temperature (no sonication), no peak at 280 nm is observed (Fig. 3b), indicating the reaction is not thermal. Comparison of the UV spectra of the sonicated and non-sonicated polymers (obtained from the PDA detector in the GPC), shows the addition of a new absorption band between 250-300 nm, which is also present in the UV-spectra of the trap azide, indicating the trap is chemically linked to the polymer (Fig. 3c). To reinforce this result, we repeated the experiment with 1-(azidomethyl)pyrene as a trap. Again, the sonicated polymer shows incorporation of the trap, clearly observed by the addition of the four typical absorption bands of the pyrenyl group to the polymer spectra (Fig. 3d and 3f). An

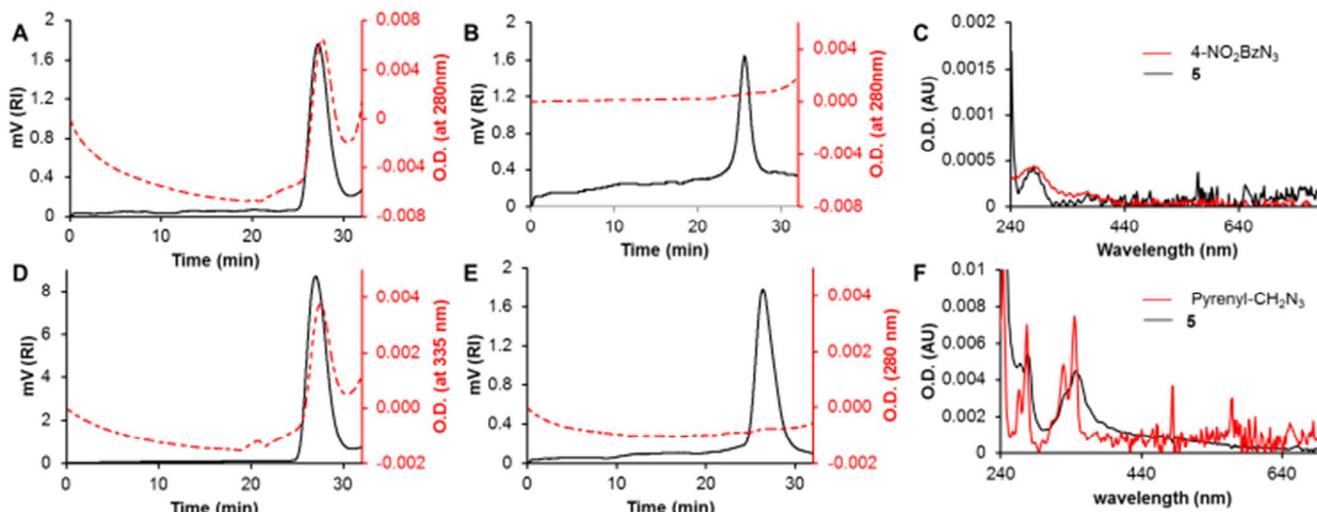
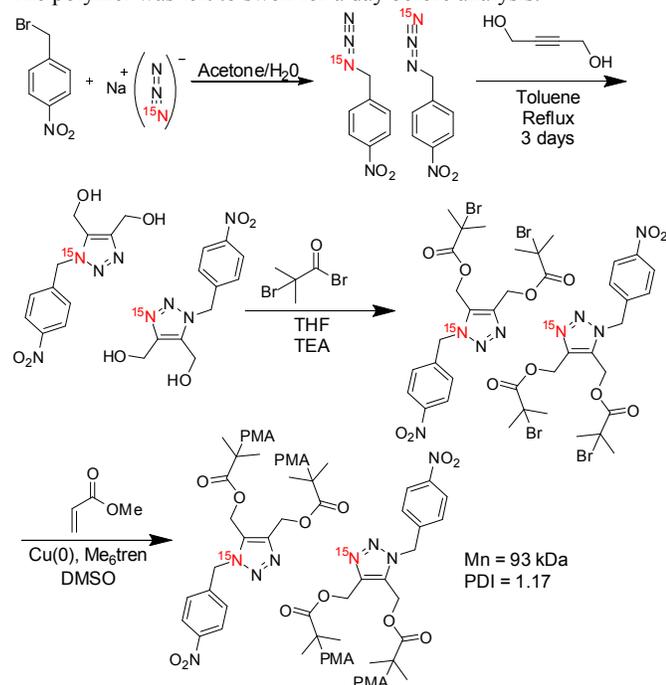


Fig. 3. a) GPC traces of **5** after sonication with 4-nitrobenzyl azide ($M_n = 67.8$ kDa, PDI = 1.30). b) GPC trace of **5** and 4-nitrobenzyl azide after 3 days at room temperature. c) UV spectrum of 4-nitrobenzyl azide (red) and **5** (black) after sonication with 4-nitrobenzyl azide (RT = 28.3 min). d) GPC trace of **5** after sonication with 1-(azidomethyl)pyrene ($M_n = 70.1$ kDa, PDI = 1.24). e) GPC trace of control polymer **6** after sonication with 1-(azidomethyl)pyrene ($M_n = 63.9$ kDa, PDI = 1.31). f) UV spectrum of 1-(azidomethyl)pyrene (red) and **5** (black) after sonication with 1-(azidomethyl)pyrene (RT = 28.3 min).

incorporation of 14.4% was calculated using the 344 nm absorption of pyrene (see the ESI). When control polymer **6** (having a triple bond at the end of the chain, which is not mechanically stressed) is sonicated with the 1-(azidomethyl)pyrene trap under similar conditions, no incorporation of the pyrenyl trap is observed (Fig. 3e), supporting that the reaction is mechanochemical (not thermal) and occurs at the triple-bond site. Interestingly, polymers with Mw below 30 kDa are typically used as controls, since they do not undergo chain scission during sonication.¹⁷ However, when **5**_{small} (30 kDa, see the ESI) is sonicated with the 4-nitrobenzyl azide trap, incorporation is still observed, albeit without chain scission.

Finally, we set out to study the product formed by the mechanochemical reaction using ¹⁵N isotope labelling and ¹⁵N NMR spectroscopy to identify the mechanochemically generated product. A ¹⁵N labelled trapping azide was prepared by reaction of 4-nitrobenzyl bromide with sodium azide-1-¹⁵N, producing two isotopic products, where the ¹⁵N labelled nitrogen can be either bound to the carbon or terminal (Scheme 2). Polymer **5** was sonicated with the labelled 4-nitrobenzyl azide and analyzed by ¹⁵N NMR. However, given the low sensitivity of ¹⁵N NMR combined with the extremely low concentration of the labelled atoms (a single atom per polymer chain), no peaks were observed even after two days of data collection. Therefore, we decided to use gel-phase NMR¹⁸ to reduce the scan time while working at a high polymer concentration. The NMR sample was in turn prepared by weighting 200 mg dry polymer in an NMR tube, and adding 0.5 mL of CDCl₃. The polymer was left to swell for a day before analysis.



Scheme 2. Synthesis of ¹⁵N labelled azide trap and model labelled polymer.

Searching the literature, we were surprised to find a single example of gel-phase NMR using ¹⁵N.¹⁹ Furthermore, important experimental details such as the delay time used were not provided. Measuring T₁ and T₂ directly is not possible using our polymer with a single labelled nitrogen per chain. To choose an appropriate delay and acquisition time, we decided to use T₁ and T₂ values determined experimentally from a ¹⁵N-labelled protein in a gel.²⁰ The actual values for our experiment are likely smaller; however, the values from Jürgen Sassa *et al.* significantly decrease our measurement time. Also the extra delay time would be plenty for complete decay.

Delay and acquisition times were set to 175 ms and 115 ms, respectively. After two days, we were able to obtain a ¹⁵N signal with a reasonable signal to noise ratio (Fig. 4a).

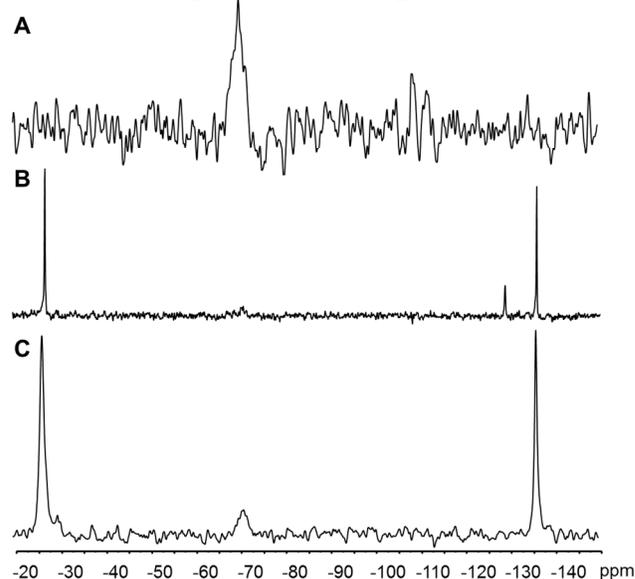


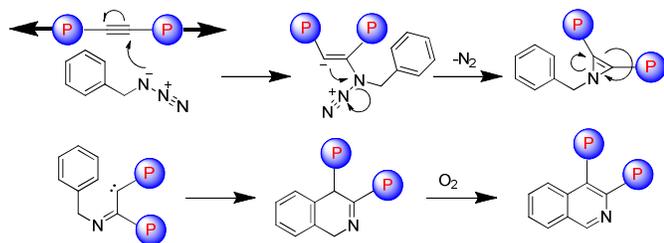
Fig. 4. ¹⁵N NMR of a) **5** after sonication with labelled 4-nitrobenzyl azide; b) model polymer with chain-centered labelled 1,2,3-triazole; and c) model polymer (Mn = 93 kDa, PDI = 1.17) with chain-centered labelled 1,2,3-triazole after sonication (1 mg/ml, pulsed ultrasound 0.5 s on, 1.0 s off, 8.7 W/cm², 3 h). After sonication Mn = 50.8 kDa, PDI = 1.33.

To identify the product, we prepared model polymers with chain-centered labelled 1,2,3-triazole (Scheme 2). All labelled triazole model molecules presented two distinct ¹⁵N NMR signals, around -20 and -130 ppm, corresponding to the different possible positions of the ¹⁵N labelled nitrogen (Fig. 4b and ESI). On the other hand, polymer **5** sonicated with the ¹⁵N labelled 4-nitrobenzyl azide, showed a single peak at -69 ppm (indicating loss of N₂ during sonication). We identified other possible products by examining the extensive ¹⁵N NMR chemical shift study by Witanowski *et al.*²¹ Remarkably, few chemical functionalities exhibit signals at this chemical shift most are 6-membered aromatic heterocycles where the nitrogen atom is linked to two carbon atoms, such as quinolines and isoquinolines.

Interestingly, there are numerous examples in the literature on the radical and thermal decomposition of 1,2,3-triazoles yielding quinolines and isoquinolines.²² We considered the possibility of a secondary mechanochemical reaction giving such a product. To test this possibility, we sonicated the model polymer containing the chain-centered labelled 1,2,3-triazole. After purification of the polymer, a new small peak at -69 ppm could be observed by gel-phase ¹⁵N NMR (Fig. 4c).

Given that the -69 ppm peak is the only observed peak in the sonication of **5** with the labelled azide, and not a secondary peak as observed in the sonication of the triazole, it was clear to us that the mechanochemical reaction does not cause a Huisgen cycloaddition. Previous studies on bent triple bonds argue that the reduction in the energy of the π* orbital, without change in the π orbital, allows the alkyne to react as an electrophile. Scheme 3 presents a possible reaction mechanism to form isoquinoline. Interestingly, 1H-azirine was proposed as an intermediate in the pyrolysis of 1,2,3-triazoles to isoquinolines. According to the mechanism proposed by Gilchrist *et al.*, 1H-azirine undergoes ring opening to form the iminocarbene, which undergoes cyclization, leading to the formation of the 1,4-

dihydroisoquinoline which rapidly oxidizes by air to the isoquinoline product.^{22b}



Scheme 3. Possible mechanism for formation of iso-quinoline during mechanochemical reaction of alkyne with azide. “P” represents attachment to the polymer.

Conclusions

We have studied the mechanochemical trans-bending of the carbon-carbon triple bond. The reactive intermediates were trapped using azides during sonication, and adequate controls were used to rule out the possibility of thermal reactivity. While Huisgen cycloaddition reactions occur easily with cisoidal alkynes, ¹⁵N labelled traps pointed to isoquinolines and not 1,2,3-triazoles as products. Based on theoretical and experimental studies, we propose the bent and stretched alkyne reacts as an electrophile. An alternative mechanism was proposed to explain the formation of isoquinolines, based on previously proposed mechanisms for the photolysis and pyrolysis of 1-benzyl-1,2,3-triazoles, however, a mechanism involving sonochemically produced nitrenes or nitrenyl radicals cannot be discarded. This study points towards a new way to activate triple bonds, and further studies on electronic effects, as well as different nucleophiles and other electron rich dipoles are underway. This study also demonstrated the power of ¹⁵N gel-phase NMR as a key analytical technique to investigate the mechanism of mechanochemical reactions.

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Notes and references

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