Mechanochemistry

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Mechanical Reversibility of Strain-Promoted Azide–Alkyne Cycloaddition Reactions

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Abstract: *Mechanophores, that is, molecules that show a defined response to force, are crucial building blocks of mechanoresponsive materials. The possibility of mechanically induced cycloreversion for a series of triazoles formed via strain-promoted azide–alkyne cycloaddition reactions was investigated by density functional theory calculations, and these triazoles were compared to the 1,4- and 1,5-regioisomers formed in the reaction of an azide with a terminal alkyne. We show that cycloreversion is in principal possible and that the pulling geometry is the most important parameter that determines the probability of cycloreversion. We further compared triazole stability to the mechanical stability of polymers that are frequently used as force transducers in mechanochemical experiments and identified DIBAC (azadibenzylcyclooctyne) as a promising mechanophore for future applications.*

Cycloaddition between azides and alkynes has become an indispensable reaction in materials chemistry. It enables the functionalization of polymers and surfaces as well as the synthesis of gels and macromolecular architectures.[1] Mechanically-induced cycloreversion of the 1,2,3-triazole unit was proposed recently and would allow the straightforward synthesis of mechanoresponsive materials, with the triazole as a highly versatile mechanophore.[2] Successful cycloreversion would combine self-healing with self-reporting properties in one material, allowing triazole reformation as well as detection of the liberated azide or alkyne in a chromogenic or fluorogenic reaction.[3] Using density functional theory (DFT) calculations, we investigated the feasibility of mechanically induced cycloreversion for a series of triazoles formed from strained alkynes in a strain-promoted azide–alkyne cycloaddition (SPAAC) reaction.[4]

Mechanically induced cycloreversion of triazoles formed from terminal alkynes has been investigated previously using DFT calculations.[2,5] The product of the copper-catalyzed azide–alkyne cycloaddition reaction (CuAAC; 1,4-substituted regioisomer; Figure 1a),[6] was compared to the 1,5-regioisomer formed in the ruthenium-catalyzed reaction (RuAAC; Figure 1a).[7] Cycloreversion was proposed for both regioisomers, with a slightly higher probability for the 1,5-regioisomer.[2] Efficient, mechanically induced cycloreversion of the 1,4-regioisomer has, however, been questioned subsequently in a different and more accurate simulation approach,[5] and the experimental feasibility of cycloreversion for both regioisomers remains speculative.

With the aim of understanding possible differences between the 1,4- and the 1,5-regioisomers, we compared the CuAAC and RuAAC reaction products (Figure 1a) with a number of triazoles formed from strained alkynes (Figure 1b). SPAAC reactions yield both regioisomers with equal probability.[8] Furthermore, the availability of these different

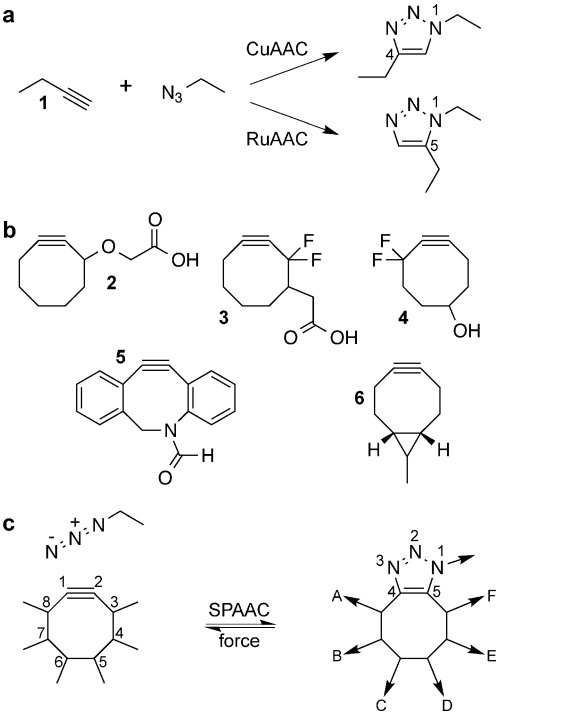

Figure 1. Experimental design. a) 1,2,3-triazoles formed in the CuAAC or RuAAC reactions. b) The strained cyclooctynes used as model systems for investigating cycloreversion. c) Possible pulling geometries of triazole ring systems formed through the SPAAC reaction. For cycloreversion both the N1–C5 and the N3–C4 bonds need to be broken. Since the SPAAC reaction forms two regioisomers with equal probability, the same cyclooctyne was used to simulate the **A** and **F** (ALO, **2**), **B** and **E** (DIFO3, **3**), and **C** and **D** (DIFO, **4**; DIBAC, **5**) pulling positions on the cyclooctyne ring. In addition, a symmetric molecule (BCN, **6**) was considered, where the force is simultaneously applied to atoms 5 and 6 of the cyclooctyne ring.

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cyclooctynes allows testing of the influence of the cyclooctyne ring and its substituents on the mechanical stability of the formed triazoles.

For our study, we chose the experimentally well-characterized strained alkynes ALO[8a] (**2**), DIFO3[8b] (**3**), DIFO[9] (**4**), DIBAC[10] (**5**), and BCN[11] (**6**). Our main selection criteria were reactivity in SPAAC reactions[4] and the position of the linker on the cyclooctyne ring. Every cyclooctyne in this set has a different linker attachment site (Figure 1b,c). These attachment sites allow the coupling of a polymer to act as a force transducer in mechanochemical experiments such as ultrasound polymer mechanochemistry[2] or single molecule force spectroscopy.[12] Considering the different linker attachment sites and regioisomers, we were able to investigate all relevant and experimentally feasible pulling geometries on the cyclooctyne ring (Figure 1c and Figure 2).

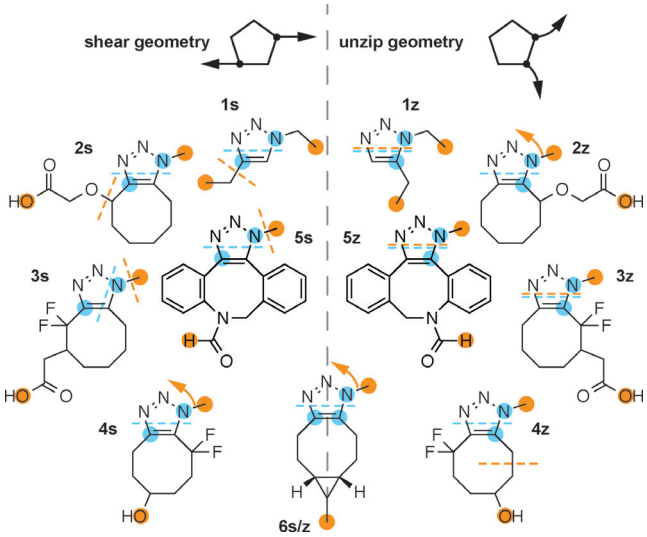

Figure 2. Results of the pre-screening calculations (6-31G basis set) using terminal (orange dots) or internal (blue dots) anchor atoms. The dashed lines show the rupture position and the arrows indicate relocation of the linker.

To simulate the action of an external pulling force, we employed the COGEF (COnstrained Geometries simulate External Force) approach.[13] Using this approach, two anchor atoms (e.g., the terminal atoms of the linkers) are chosen. During the simulation, these atoms are moved further apart from each other, step by step, thereby mimicking a quasistatic mechanochemical experiment. The structural response of the molecule is followed until the point of bond rupture and the equilibrium energy of the molecule is calculated under this geometry constraint. In this way, a potential is obtained that describes the energy of the molecule as a function of separation distance between the two anchor atoms. This COGEF potential forms the basis for modeling thermally activated and mechanically assisted bond breaking, as will be described in more detail below.

The calculations were performed using Gaussian orbitals as implemented in the NWChem package.[14] We employed the B3LYP hybrid functional together with the 6-31G or 6-31++G basis sets since this combination has already been applied to triazole molecules in the absence of an applied force.[8c,15] More importantly, this combination of DFT functional and basis set has been demonstrated to provide a good compromise between accuracy and computational cost for characterizing the mechanical rupture of covalent bonds in polyatomic molecules (see the Supporting Information for details).[16] To select the most promising candidate molecules, we first performed a set of pre-screening calculations with the computationally cheaper 6–31G basis set. In the first round of pre-screening calculations, the anchor atoms were chosen such that they represent the terminal atoms of the linkers (i.e., the experimentally relevant pulling positions) and the molecule was stretched until the first bond ruptured (Figure 2, orange labels; see Movies in the Supporting Information).

Cycloreversion, as indicated by the orange and blue dashed lines in Figure 2, was observed for the 1,5-regioisomer (**1z**) as well as for the corresponding pulling geometries of DIFO3 (**3z**) and DIBAC (**5z**). In all other cases, a different bond ruptured or the linker attachment site was relocated to a different ring atom of the cyclooctyne ring, which we consider a simulation artifact (see the Supporting Information). In the second round of pre-screening calculations, the anchor atoms were located on the triazole unit itself (internal anchor atoms), thus eliminating the linker effects and forcing ring opening (Figure 2, blue labels). When using internal anchor atoms, triazole cycloreversion occurred for all molecules tested except for DIFO3 (**3s**), thus indicating that cycloreversion is the preferred reaction when considering the triazole unit only.

Having obtained a first hint that cycloreversion is possible for triazoles based on DIFO3 (**3z**), DIBAC (**5z**), and terminal alkynes (**1z**), we focused on these three reactions and performed a quantitative analysis of the rupture forces by using the more accurate 6-31++G basis set. Following the approach of Beyer et al.,[13,17] we modeled bond rupture with a Morse potential, utilizing parameters obtained from the simulated global COGEF potential. These parameters (Figure S1 and Tables S1, S2 in the Supporting Information) were subsequently used in a standard Arrhenius-type model to describe the thermally activated and mechanically assisted bond rupture process. Applying bond rupture probability theory, the most probable rupture forces were calculated as a function of the externally applied force for a given loading rate. To mimic the conditions used in ultrasound polymer mechanochemistry,[18] a loading rate of 10^8 nN s^{-1} was used (see the Supporting Information for details).

Table 1 summarizes the most probable rupture forces of the bonds broken in the simulations. Clearly cycloreversion is the most probable pathway for **1z** ($F_{1z(T)} = 4.09$ nN), **3z** ($F_{3z(T)} = 4.25$ nN), and **5z** ($F_{5z(T)} = 4.11$ nN). In contrast, the triazoles **1s**, **3s**, and **5s** rupture at forces $F_{s(I)} > 7$ nN, as can be seen when pulling on the internal anchor atoms. For **1s**, **3s**, and **5s**, linker rupture is significantly more likely ($F_{1s(T)} = 4.09$ nN; $F_{3s(T)} = 4.96$ nN; $F_{5s(T)} = 5.01$ nN) and cycloreversion appears experimentally impossible. This result is in line with previous DFT simulations[5] and single-molecule force spectroscopy experiments of **1s**,[12] which suggest that mechan-

Table 1: Most probable rupture forces for the different triazoles, calculated for a loading rate $r = 10^8$ nN s^{-1} (see Section 2.2 in the Supporting Information).

	Shearing		Unzipping	
	$F_{s(T)}$ [nN][a]	$F_{s(I)}$ [nN][a]	$F_{z(T)}$ [nN][a]	$F_{z(I)}$ [nN][a]
1 (terminal alkyne)	4.09 (linker rupture)[b]	7.95 (cycloreversion)	4.09 (cycloreversion)	4.65 (cycloreversion)
3 (DIFO3)	4.96 (linker rupture)[b]	8.94 (cycloreversion)	4.25 (cycloreversion)	5.16 (cycloreversion)
5 (DIBAC)	5.01 (linker rupture)[b]	7.32 (cycloreversion)	4.11 (cycloreversion)	4.29 (cycloreversion)

[a] The anchor atoms were chosen on the terminal atoms of the linkers (terminal, T) or directly on the triazole ring (internal, I). [b] Linker rupture, that is, a bond is broken that is not part of the triazole or cyclooctyne ring.

ically induced cycloreversion is very rare[12] or is not a purely mechanochemical effect.[5]

The above results suggest that triazole cycloreversion should be experimentally possible for **1z**, **3z**, and **5z**. In a typical ultrasound experiment, long polymer chains are coupled at both terminal anchor atoms. Shear forces, generated by imploding cavitation bubbles, stretch these polymers, thereby applying a pulling force on the whole molecule. Cycloreversion consequently competes with rupture in the attached polymer chains. To compare the mechanical stability of the triazole units **1z**, **3z**, and **5z** with that of frequently used polymers, we carried out independent simulations for polytetrahydrofuran (pTHF)[19] and polymethacrylate (PMA)[2,20] (see the Supporting Information).

When comparing the forces required for cycloreversion ($F_{1z(T)} = 4.09$ nN; $F_{3z(T)} = 4.25$ nN; $F_{5z(T)} = 4.11$ nN) and rupture in the attached polymer chains, a similar trend is observed for **1z**, **3z**, and **5z** (Figure 3 and Figures S3–S7). The weakest bond in pTHF ruptures at a force of $F_{pTHF} = 4.49$ nN, which lies above the force required for cycloreversion in all three cases. The triazole unit is the weakest bond in the system and cycloreversion should be experimentally possible. In contrast, the triazoles **1z**, **3z**, and **5z** are mechanically stronger than PMA ($F_{PMA} = 3.70$ nN), so cycloreversion will most likely not occur when PMA is used as the force transducer.

Our calculations not only aid in designing mechanochemical experiments but also reveal that cycloreversion requires significantly lower forces when atoms N1 and C5 are mechanically loaded instead of atoms N1 and C4 (Table 1). This observation is easily explained when considering the pulling geometry. When the force is applied at the N1 and C4 atoms (**1s**, **3s**, **5s**) the force acts on both the N1–C5 and N3–C4 bonds simultaneously and the molecule is sheared apart. In contrast, the N1–C5 and N3–C4 bonds are loaded sequentially when the force is applied at the N1 and C5 atoms (**1z**, **3z**, **5z**) and the bonds are separated one by one in a zipper-like fashion. This geometry effect is frequently observed in larger biological systems, for example, the mechanical separation of DNA[21] or β-strands in proteins.[22] It appears to be a general principle that also applies to the mechanical rupture of covalent bonds in ring structures. Overall, this result highlights the importance of the pulling geometry, which is far more important for determining the rupture pathway than the nature of the substituents and the exact position where the force transducer is coupled to the molecule.

In summary, we have shown that the mechanically induced cycloreversion of RuAAC and SPAAC reactions is in principle possible. The most crucial parameter defining the rupture pathway, and consequently the feasibility of cycloreversion, is the direction of the applied force that acts on the triazole unit. Most importantly, we have identified DIBAC as a promising strained alkyne that we predict to undergo cycloreversion under experimental conditions. Since DIBAC is also one of the most reactive strained alkynes currently used in coupling experiments, it has many characteristics of a mechanophore and may, once experimentally characterized, find application in mechanoresponsive materials.

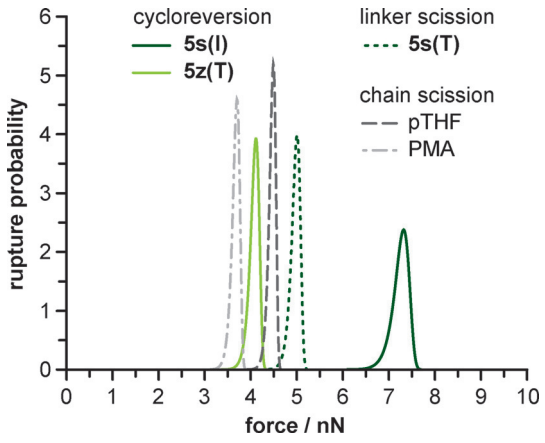

Figure 3. Rupture probability distribution as a function of applied force for DIBAC-based triazoles (**5s**, **5z**) and the reference polymers pTHF and PMA.

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