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CHEMISTRY

Mechanically Throwing a Reaction into Reverse

Frank A. Leibfarth and Craig J. Hawker

When synthetic chemists are confronted with sluggish chemical transformations, they typically try to make the reaction go faster by increasing the temperature, pumping in more photons, or turning to specially designed catalysts. In many cases, these solutions also lead to unwanted side products that waste valuable reactants, which has led to a search for simpler strategies for speeding up chemical reactions. On page 1606 of this issue, Brantley *et al.* (1) report the selective activation of covalent bonds through mechanical force and observed totally different reactivity compared with thermal or photochemical activation of the same reaction. By pushing, or in this case literally pulling, the reactions down different pathways, they explore novel concepts for synthesizing organic molecules.

Brantley *et al.* targeted the most popular version of “click” chemistry, which is the rapid and selective assembly of molecular modules into larger units under mild condi-

tions. Click chemistry encompasses a number of robust, efficient reactions that can be run in complex environments (for example, under physiological conditions) and has emerged as a focus in synthetic chemistry because of its simplicity and broad applicability (2). In this particular case, the copper (Cu)-catalyzed azide, alkyne cycloaddition (CuAAC) reaction, creates a 1,2,3-triazole ring, which is an extremely robust functional group that is largely unaffected by most thermal and chemical treatments. Indeed, this high stability has been exploited in biology (e.g., labeling biomolecules) and materials science (e.g., linking polymer chains) (3, 4).

The challenge addressed by Brantley *et al.* was to make the reaction reverse, or “unclick,” a task made all the more difficult by the stability of the triazole ring. At first glance, this feat may seem straightforward: just heat the triazole to elevated temperatures and let entropy, which would favor dissociation, take over. However, even when heated to nearly 300°C for extended periods of time, the triazole ring proved to be robust, and no reaction was observed. Instead, Brantley *et al.* used a very simple method: They incorporated the triazole ring

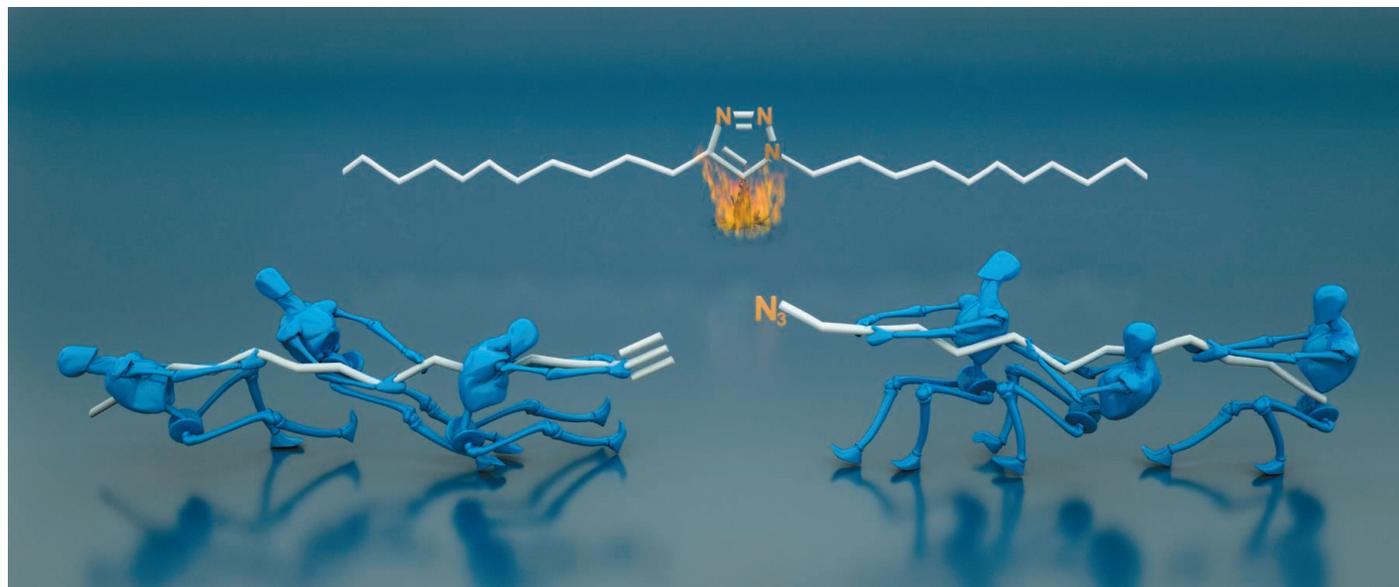
A traditionally irreversible reaction that led to very stable chemical bonds could be reversed by pulling the molecule apart in solution with mechanical forces.

into long polymer chains and mechanically extended the dissolved molecules by means of an ultrasound technique. The formation of bubbles in solution (cavitation processes) exerted force on the molecules, and after 2 hours the triazole rings were cleanly broken.

This nascent field of mechanochemistry exploits the ability to mechanically direct chemical reactions down thermally or photochemically inaccessible pathways and effectively allows for distinctive ways to modulate chemical reactivity (5, 6). In this regard, the use of mechanical force by Brantley *et al.* led to a transformation that is altogether new: the conversion of highly inert 1,2,3-triazoles to their corresponding azide and alkyne precursors. Such selective bond activation may be used to minimize undesirable reactivity and enhance the rate of transformations that are otherwise prohibitive, and the CuAAC reaction represents an excellent platform for demonstrating reactivity control. Previous attempts at reversing this reaction used harsh thermal or photochemical conditions and led to a multitude of unwanted by-products.

The surprising ability to convert triazoles into their constituent precursors by mechanical means and then use the reactiv-

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Pulled apart. Schematic representation of the cycloreversion of a 1,2,3-triazole ring to afford reactive azide and acetylene that is only accessible through mecha-

nochemistry (front). This chemistry is not accessible through other strategies, such as thermal reaction (back).

ity of the resulting azide and alkyne groups through normal synthetic methods is an outstanding example of how new transformations may be achieved through the assistance of mechanical force, and how they may be coupled with traditional strategies for covalent bond formation. These results also challenge some fundamental assumptions that are usually made about chemical reactions. For example, the principle of microscopic reversibility posits that chemical reactions proceed in the forward and reverse directions along the same reaction coordinate. However, the mechanism of the metal-catalyzed click reaction is undoubtedly different from that of the mechanically facilitated reverse reaction. Thus, mechanical-activation processes that force molecules to adopt conformations closer to that of a dissociated state could play important roles in determining molecular stabil-

ity as well as the ability to generate reactive groups under mild conditions.

Indeed, before the work of Brantley *et al.*, it was widely believed that the 1,2,3-triazole rings could not undergo clean cycloreversion. Because they can, it follows that materials relying upon triazoles for mechanical strength may experience failure if subjected to the appropriate stress. These failure events may actually enable the use of simple chain stretching and other mechanical events to do useful chemistry.

The discovery of uncommon and unknown chemical means to drive chemical reactions may also obviate the need for specially designed catalysts and enable researchers to develop simple and powerful synthetic pathways for making molecules using processes that can now only be imagined. One of the most lasting outcomes from this work may in fact be its influence

on the way that synthetic chemists make and break covalent bonds. The problem of side products is a familiar one in chemistry, despite the maturity of the discipline, and is one reason why a reevaluation of the direction and focus of how synthetic chemistry is done has been warranted (7). Instead of turning up the heat, mechanical force should be considered as an alternative tool to manipulate molecules.

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MICROBIOLOGY

Pyrazinamide—Old TB Drug Finds New Target

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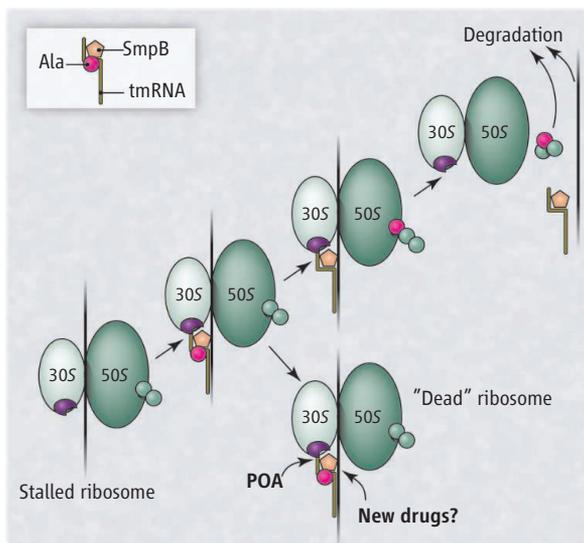
More than 60 years after the discovery of pyrazinamide (PZA), a drug that is a mainstay of combination therapy for tuberculosis (TB), researchers have finally uncovered a mechanism of action that is convincing and novel. On page 1630 of this issue, Shi *et al.* (1) show that PZA inhibits trans-translation, a key cellular process for managing damaged proteins and “rescuing” nonfunctioning ribosomes, in *Mycobacterium tuberculosis*. The finding identifies a potentially promising target for new drugs.

The story of PZA’s development bears retelling. In the 1940s, in the early days of TB therapy, French doctor Vital Chorine observed (2) that mycobacteria were inhibited by nicotinamide, a water-soluble vitamin in the vitamin B group. This led investigators to synthesize and test small libraries of nicotinamide analogs, including isoniazid and PZA. Although PZA showed negligible activity against *M. tuberculosis* in laboratory cultures, it was especially potent

in mice infected with TB. This discrepancy led to the realization that PZA was considerably more active in vitro at acidic pH (3) and gave rise to the idea that the drug targets a subpopulation of TB bacteria that are semidormant and residing in an acidified niche. Although researchers didn’t understand PZA’s mechanism of action, the drug’s

introduction into clinical use played a major role in shortening the duration of TB therapy from 9 to 6 months.

Like isoniazid, another frontline TB drug, PZA is a prodrug (a biologically inactive compound that must be metabolized to produce an active compound) with a very narrow spectrum of activity, killing only



Translational switch. Upon trans-translation, stalled ribosomes restart protein synthesis after binding of the Ala-charged tmRNA complex to RpsA (purple). Incorporation of the Ala residue is followed by a C-terminal peptide tag, also encoded by tmRNA, that flags the restarted hybrid protein for degradation. POA prevents RpsA from recognizing tmRNA. In some bacteria, the quality control imparted on proteins and mRNA by trans-translation is an essential process; in others, its perturbation severely alters stress responses, pathogenesis, and development (6). For these reasons, trans-translation is now an attractive, validated target for new drugs.

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