Mechanically Throwing a Reaction into Reverse
Frank A. Leibfarth, et al.
Science 333, 1582 (2011);
DOI: 10.1126/science.1210892

This copy is for your personal, non-commercial use only.

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by clicking here.

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines here.

The following resources related to this article are available online at www.sciencemag.org (this information is current as of October 26, 2011):

Updated information and services, including high-resolution figures, can be found in the online version of this article at:
http://www.sciencemag.org/content/333/6049/1582.full.html

A list of selected additional articles on the Science Web sites related to this article can be found at:
http://www.sciencemag.org/content/333/6049/1582.full.html#related

This article cites 7 articles, 3 of which can be accessed free:
http://www.sciencemag.org/content/333/6049/1582.full.html#ref-list-1
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. 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 conditions. 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 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
Pyrazinamide—Old TB Drug Finds New Target

Stewart T. Cole

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 a tuberculosis-specific drug validates a new target for broad-spectrum antibiotics.

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.