

CHEMISTRY

Unclicking chemistry

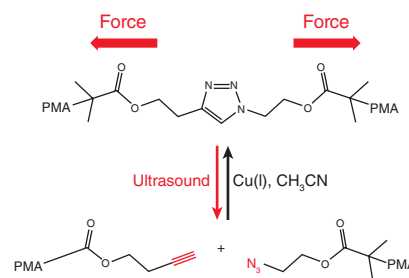
Mechanical force can revert the stable triazole product of the 1,3-dipolar cycloaddition back to the starting azide and alkyne components.

The click chemistry philosophy introduced by Nobel Prize laureate Barry Sharpless has been an enormously useful contribution to the synthetic chemistry community as well as to the chemical biology field. For a chemical transformation to be considered a click chemistry reaction, it must result in atom-economic bond formation, be highly efficient, be highly selective, be broadly applicable, use readily available starting materials, overwhelmingly form a single stable reaction product and proceed under mild conditions, ideally in water.

The ‘prince’ of click chemistry reactions is the copper(I)-catalyzed 1,3-dipolar cycloaddition, in which azide and alkyne moieties are coupled to form a highly stable 1,2,3-triazole-based product. This reaction has been particularly useful to the chemical biology field because of its bioorthogonal nature; azide and alkyne functional groups are not generally found in biological systems. Additionally, the reaction proceeds in water, and the triazole product is highly stable, making this reaction very useful for labeling a wide variety of biomolecules with various probes.

However, although the high stability of the triazole product is desirable in many applications, one limitation of this click reaction is that it cannot be cleanly reverted back to the original starting components using any known chemical transformation or through the application of heat to break the bonds. A simple and clean approach to undo the click reaction would certainly be desirable for synthetic chemistry and would possibly also be useful in biological experiments.

Christopher Bielawski of the University of Texas at Austin and his colleagues now report that the 1,3-dipolar cycloaddition reaction can be reversed by applying mechanical force. They show that by embedding the triazole product in a poly(methyl acrylate) polymer chain and applying ultrasound, they can regenerate the azide and alkyne precursors. Such application of ultrasound to polymer solutions induces the formation and implosion of cavitation bubbles, which exerts force on the molecules and eventually breaks the triazole ring in a couple of hours.



Reversing click chemistry. Applying ultrasound to a triazole embedded in a poly(methyl acrylate) (PMA) chain results in the regeneration of the alkyne and azide moieties. Reprinted with permission from the American Association for the Advancement of Science.

The researchers used a variety of spectroscopic and chemical labeling techniques to confirm that the triazole was cleanly broken into azide and alkyne moieties. Control experiments ruled out thermally induced cycloreversion. They determined optimal polymer molecular weights, triazole location in the polymer and sonication times. Finally, they showed that the uncoupled components could be ‘re-clicked’ with high efficiency by adding a copper(I) catalyst.

This unclicking reaction is an excellent example of how mechanical force can be used to break chemical bonds; it is not hard to imagine that this work will inspire other new chemical transformations. Bielawski also notes that the approach may find use in biological applications. “We do believe that mechanically facilitated cycloreversions could enable the development of novel bioconjugation and other chemical ligation techniques,” he says, though stressing that many substantial challenges lie ahead. “For instance, the need to use synthetic poly(methyl acrylate) to facilitate mechanical transformations could limit the scope of our methodology,” Bielawski explains. “However, we believe this is a solvable problem, as water-soluble polymers are known and have been used in other mechanically activated systems.” The researchers are also currently exploring how they can manipulate proteins via mechanical forces.

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RESEARCH PAPERS

Brantley, J.N. *et al.* Unclicking the click: mechanically facilitated 1,3-dipolar cycloreversions. *Science* **333**, 1606–1609 (2011).