

Chemists illuminate elusive mechanism of widely used click reaction

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Scientists at The Scripps Research Institute (TSRI) have illuminated the mechanism at the heart of one of the most useful processes in modern chemistry. A reaction that is robust and easy to perform, it is widely employed to synthesize new pharmaceuticals, biological probes, new materials and other products. But precisely how it works had been unclear since its invention at TSRI more than a decade ago.

"These new findings allow us to exert greater control of the [reaction](#) and make it faster and more efficient under the most challenging conditions," said chemist Valery Fokin, an associate professor at TSRI, who was principal investigator for the new study. "The reaction-tracking techniques we developed here also can be applied to the study of other complex processes, both chemical and biological."

The report, which sheds light on the reaction known as copper-catalyzed azide–alkyne cycloaddition (CuAAC), on April 4 in *Science Express*, the advance online edition of the journal *Science*, and in the April 18, 2013 issue of the journal.

Classic Click Reaction

Fokin and his laboratory, and the laboratory of K. Barry Sharpless, a [Nobel laureate](#) and the W.M. Keck Professor of Chemistry at TSRI, reported the discovery of the CuAAC reaction in 2002. Danish researchers independently reported a similar reaction in the same year.

The reaction involves the use of copper compounds to catalyze the linkage of two functional groups, a nitrogen-containing azide and a [hydrocarbon](#) alkyne, to make a stable five-membered heterocycle, 1,2,3-triazole. Azides and alkynes are small [functional groups](#) that can be easily introduced into a wide variety of structures using chemical or [biological methods](#) without interfering with normal [biological processes](#).

The experimental simplicity and reliable performance of CuAAC under virtually all conditions, including in water and in the presence of oxygen, has made it a "go-to" method whenever covalent stitching of small man-made molecules or large [biopolymers](#) is needed, exemplified by protein and nucleic acid labeling, in vitro and in vivo imaging, drug synthesis and the forging of complex molecular architectures with surgical precision.

"Despite its many uses, the nature of the copper-containing reactive intermediates that are involved in the catalysis had not been well understood, in large part due to the promiscuous nature of copper, which rapidly engages in dynamic interactions with other molecules," said Fokin.

Previous studies had hinted that in the swirl of short-lived bondings and partings that occur during a given CuAAC reaction, not one but two copper-containing catalytic units—"copper centers"—are needed to help build the new triazole structure. To confirm this, Fokin and two of his graduate students, Brady Worrell and Jamal Malik, tried to reproduce key steps of the CuAAC catalytic cycle with either one or two copper atoms available. Analysis of the reaction course by tracking the heat given off by each reaction as well as product yield indicated whether it worked efficiently. "By monitoring the reaction in real time, we showed that both copper atoms are needed and established the involvement of copper-containing intermediates that could not be isolated or directly observed," said Worrell, who was the paper's first author.

In a second set of experiments, Worrell, Malik and Fokin introduced a pure isotope of copper—which differs slightly in mass from the isotope blend found in natural copper—as one of the two copper centers so that they could track their respective fates during the reaction. "We hypothesized that the two copper centers would have distinct roles, but found unexpectedly that their functions during key steps in the reaction are effectively interchangeable," said Malik.

New Linkages

The research reveals the popular CuAAC reaction in unprecedented detail. In addition to the fundamental insights into the chemistry of copper and its interactions with organic molecules, the techniques will lead to better understanding of many chemical and biological processes involving copper. The current study also enables development of new reactions that exploit weak interactions of copper catalysts with carbon-carbon triple bonds. In fact, based on the new findings, Fokin and his team have begun to devise new reactions in which one [copper](#) center can be replaced with a different element, to pursue complementary biocompatible and efficient techniques.

More information: "Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide–Alkyne Cycloadditions," *Science Express*, 2013.

Provided by Scripps Research Institute

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