Chemists' HAT trick for greener chemical synthesis

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Creating new chemical compounds, such as new drugs, is not as simple as assembling one of those models with colored balls and sticks you might have seen in a beginning chemistry class. No, it's often a complex process with many steps and many chemical participants, some of which are toxic and environmentally hazardous.

One technique used in chemical synthesis is called hydrogen atom transfer, or HAT. It's a potentially powerful and versatile chemical tool, but technical constraints have limited its use. Now chemists at the University of Utah, Scripps Research, and their colleagues have borrowed a technique from the chemistry of energy storage to accomplish HAT with fewer chemicals and less cost.

"HAT stores the potential for incredibly useful transformations," says Samer Gnaim of Scripps Research, first author of a study reporting the researchers' findings. "By the introduction of a fundamentally new concept, these chemical challenges can be solved, establishing HAT as an approachable tool to the vast majority of organic chemicals in both industrial and academic settings."

The study is published in *Nature*.

"This is a classic example of the need for multi-disciplinary centers that bring organic chemists, electrochemistry and computational scientists together to address large problems in organic synthesis," says Minteer, distinguished professor of chemistry.

HAT's promises and challenges

HAT is a process that simply moves a hydrogen atom from one molecule to another. It's useful for making use of unsaturated carbon-carbon bonds—the most common useful chemical bond in organic chemistry—to create a wide array of new bonds such as carbon-carbon, carbon-oxygen, and carbon-nitrogen bonds. All of those are important steps in building complex molecules. Making new bonds from a carbon-carbon double bond is called "functionalization."

"The functionalization of such bonds is an attractive strategy to construct molecules and achieve molecular complexity in an efficient fashion," Gnaim says.

But as useful as it is, HAT has its drawbacks. The simple process of moving a hydrogen atom requires additional chemicals like oxidants and reductants to create an active catalyst, a compound that helps the reaction proceed. The oxidants and reductants are needed in large quantities, which makes it impractical to employ HAT on a large scale, and nearly impossible to be applied for industrial chemical processes.

Insight from energy storage

While chemists have been grappling with how to improve HAT, energy storage researchers have at the same time been developing a process that can help. Storing energy in the form of hydrogen involves converting positively charged protons into hydrogen molecules with the help of a cobalt hydride catalyst. It's the same kind of catalyst needed for the HAT process.

But the energy storage field has been able to build cobalt hydride catalysts using protons and electrons as stand-ins for oxidants and reductants—a completely different chemical process to achieve the same end product.

So Gnaim and his colleagues compared how the electrochemical process compares to conventional HAT chemistry by evaluating its performance in a wide range of organic chemistry reactions. The results were very encouraging. Using electrochemistry to create cobalt hydride catalysts was more sustainable and efficient, they found, and even made the process more precise and tunable.

What we can do now

The electrochemical process offered other benefits. It could be performed in small or large batches, without the complicating steps of removing all air or water from the process and left behind the need for expensive oxidants and reductants.

"Chemists are continuously seeking to expand the chemical reactivity to new spaces allowing the discovery of new transformations that can improve the discovery processes of new drugs," Gnaim says. "In our case, we can access new molecular motifs by using environmentally friendly and cheap substances relying on the use of classical HAT reactions and new transformations."

More information: Phil Baran, Cobalt-electrocatalytic HAT for functionalization of unsaturated C–C bonds, *Nature* (2022). DOI: 10.1038/s41586-022-04595-3.
www.nature.com/articles/s41586-022-04595-3

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