Mimicking enzymes, chemists produce large, useful carbon rings

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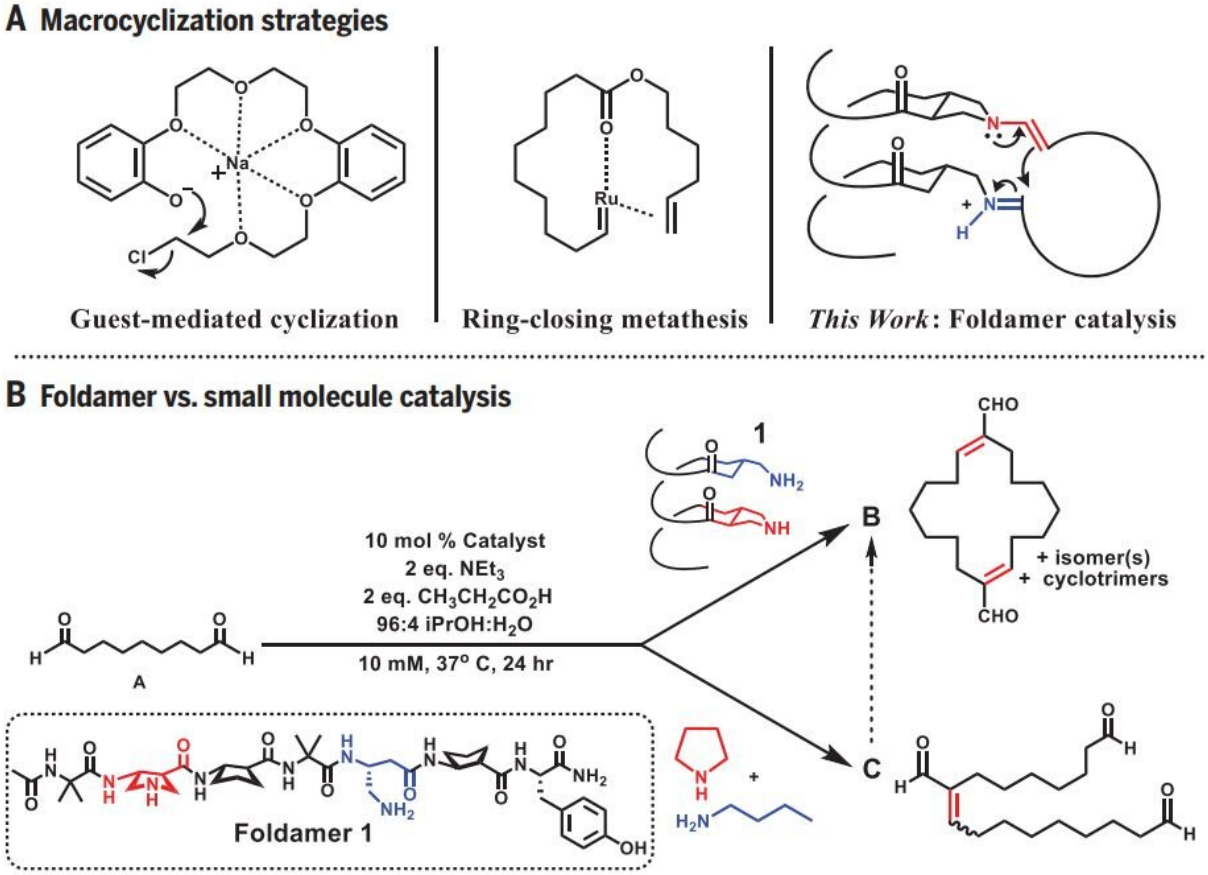

Macrocyclization strategies. (A) Prior approaches and foldamer approach to macrocyclization. (B) Divergent reactivity: Foldamer versus small-molecule catalysis. eq., equivalent(s). Credit: *Science* (2019).DOI: 10.1126/science.aax7344

Drawing inspiration from nature, University of Wisconsin-Madison chemists have discovered an efficient way to wrangle long, snaking molecules to form large rings—rings that form the backbone of many pharmaceuticals but are difficult to produce in the lab.

The work may represent preliminary progress toward deciphering just how enzymes, honed by evolution, so efficiently produce natural compounds. More immediately, the new method could help researchers synthesize drugs that have large ring backbones, such as those for hepatitis. The research is published Dec. 19 in the journal *Science*.

Nature prefers the disorder of a long, flexible molecule to the order of a rigid ring, which makes it notoriously difficult for chemists to coax large rings to form in the lab. "If the linear molecules get long enough, it's as if the ends don't know anymore that they're connected, and they're just as likely to bond with other molecules as they are to come together," says UW-Madison Professor of Chemistry Sam Gellman, the senior author of the report.

Yet biological enzymes can easily bring these ends together and form rings of all sizes. They accomplish this feat thanks to their complex, three-dimensional shapes that act as a specialized lock—the linear molecule fits into place like a key in just the right way for an organized reaction to take place.

To both study how enzymes work and mimic their abilities, Gellman's team turned to much smaller, three-dimensional protein-like molecules called foldamers that their lab has helped develop.

Because the foldamer has a three-dimensional shape that can grab on to the ends of the flexible precursor molecule, it greatly increases the odds that the ends find one another. At the same time, the foldamer catalyzes the right reaction that links the ends into a closed ring. The upshot is

straightforward and predictable synthesis of a challenging, and useful, molecular shape.

"As chemists, we see how extraordinarily effective enzymes are at doing reactions that are hard to accomplish in a flask, but we don't truly understand how they work," says Gellman. "If we learn how these small foldamer catalysts work, we may be able to build catalysts that are effective for many different reactions. Ultimately, perhaps we can bootstrap our way toward foldamers that have truly enzyme-like activity."

Graduate student and lead author Zebediah Girvin began the research by testing the abilities of a short, spiral-shaped foldamer. Girvin tried to use the foldamer to bend a linear molecule containing nine carbon atoms so it would form a ring. But instead of a ring of the expected size, Girvin got one twice as large—the result of two precursor molecules first joining and then closing the circle.

"This is a common situation in science. You try something and it doesn't work out the way you expected," says Gellman. "The challenge is to recognize when the surprising result is as interesting as the original goal, or even more interesting."

Guided by this serendipity, Girvin began testing how well the foldamer could produce the larger rings it seemed to prefer creating. He found that he could readily manufacture rings made up of 12 to 22 carbon atoms when the foldamer's reactive sites, where the ring closure occurs, were lined up with one another on one side. This orientation brought the two ends of diverse linear molecules close enough to fuse.

As a proof-of-concept for the new technique, Girvin synthesized the natural product robustol from scratch. Derived from the leaves of the Australian silky oak tree, robustol weighs in with a hefty 22-atom ring.

Gellman's team is most excited about the potential for foldamers to catalyze other useful reactions and possibly help unravel longstanding mysteries about how enzymes, nature's chemical virtuosos, produce the molecules required for life simply by arranging amino acid building blocks in the right shape. While those answers are years away, the ring-closing technique they've discovered could have more immediate use synthesizing drug candidates. The hepatitis C drug vaniprevir, which is used in Japan and in late-stage trials in the U.S., contains just this kind of large ring.

The real potential of foldamers stems from their diversity. Chemists can make a nearly infinite variety of foldamers in the lab because they have access to more building blocks than are found in natural proteins. This could allow chemists to build more useful catalysts, which led Gellman to patent certain foldamers and found the company Longevity Biotech to explore their therapeutic uses.

Going forward, that wealth of options will allow researchers to arrange these catalysts in shapes likely to be useful in unexpected ways. Only more research will tell.

"We don't really know what these catalysts are capable of yet," says Girvin. "It will take years to figure out their potential, and it's important that we cast a broad net and keep open minds about what we can accomplish with these new tools."

More information: "Foldamer-templated catalysis of macrocycle formation" *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aax7344

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