

## NEWS OF THE WEEK

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## ORGANIC CHEMISTRY

## PEPTIDE SYNTHESIS REINVENTED

Versatile amide-forming reaction could transform field of biomolecular synthesis

**S**IGNIFICANT NEW REACTIONS for the synthesis of basic organic functional groups don't come down the pike every day, even from experienced synthetic chemists. But a new type of amide-forming ligation chemistry conceived by a team led by an assistant professor of chemistry just starting out in his career does indeed seem to fall into the significant category.

Jeffrey Bode and coworkers at the University of California, Santa Barbara, discovered the amide-forming ligation and demonstrated its utility for joining short peptides (*Angew. Chem. Int. Ed.*, published online Jan. 17, dx.doi.org/10.1002/anie.200503991) and for the iterative synthesis of  $\beta$ -peptide oligomers (*J. Am. Chem. Soc.* 2006, 128, 1452). "We discovered the reaction while working on new ways to synthesize amides from nitrones," Bode says.

The near-ideal reaction creates amide linkages between  $\alpha$ -keto carboxylic acids and N-alkylhydroxylamines. It is near ideal because it's chemoselective (works in the presence of other functional groups, including other types of amines and carboxylic acids); it proceeds in water without catalysts or other reagents; and it's fairly "green" or atom economical, its sole by-products being water and carbon dioxide.

"It's a real potential breakthrough," says chemistry professor Stephen B. H. Kent of the University of Chicago, a specialist in the chemical synthesis of proteins.

"When people start using the reaction, warts could appear. But to my mind, it's the most promising new chemistry for chemical protein synthesis in at least a decade."

Chemical protein synthesis is important for dissecting the molecular basis of protein function and for protein-inspired nanofabrication, but it has been hampered by limitations in the available synthetic reactions, Kent notes. For example, native chemical ligation, a reaction Kent and others developed in the early 1990s, generally requires a cysteine at the end of one of the peptide fragments to be combined.

The development of a versatile amide-forming ligation that dispenses with such limitations has been a long-standing goal in the field of protein synthesis. "What you want is to be able to ligate at any, or almost any, pair of amino acids, and the chemistry of Bode and coworkers promises that," Kent says. "Further work will be required. They're very cautious in their claims and appropriately so. But from what they've shown, the approach does promise that it will work for a variety of amino acid pairs."

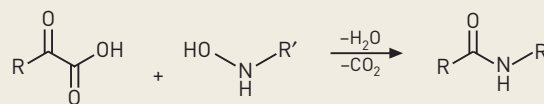
Such a technique "could be extremely important and, in fact, transforming for the field," Kent says. "It would allow all sorts of flexibility in chemical tactics, so you'd be able to make much bigger proteins" than is currently possible.

The reaction is "creative and



**LIGATORS** The team that developed the new chemoselective amide-forming ligation chemistry includes (from left) Kyle D. Baucom, Bode, Nancy Carrillo, Justin A. Russak, and Eric A. Davalos.

unexpected," says chemistry professor Samuel H. Gellman of the University of Wisconsin, Madison, a specialist in the synthesis of  $\beta$ -peptides and peptide-inspired foldamers. "It reveals an entirely new and nonobvious way to generate the carboxamide linkage in the presence of many other functional groups."



**LIGATION** The reaction Bode and coworkers developed is a deceptively simple decarboxylative condensation of an  $\alpha$ -keto carboxylic acid and an N-alkylhydroxylamine that yields an amide product. The researchers are currently trying to elucidate the reaction mechanism.

The discovery "opens the prospect of the reaction being used for peptide coupling and other fragment condensations, which is still a huge challenge in syntheses of longer polypeptides and proteins," Gellman adds. "The novelty of the accomplishment is likely to inspire other chemists. It already has me thinking."—STU BORMAN