

Latest News

February 5, 2007
Volume 85, Number 6
p. 7

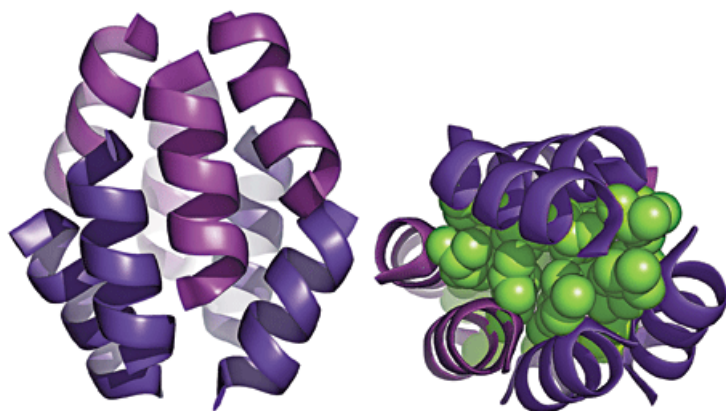
Foldamers

Synthetic Protein Mimics Real Thing

β -Amino acid-based assembly has hallmarks of a true protein

[Stu Borman](#)

IN THE CLASSIC TALE "Pinocchio," the wood-carver Gepetto made a puppet that turned out to act just like a real boy. In the same spirit of creativity, researchers have created the first nonprotein oligomer that has been verified experimentally to look and act much like a true protein (*J. Am. Chem. Soc.* **2007**, *129*, 1532).



Reprinted from *JACS* (both)

Ribbon diagram (top) of β -peptide bundle shows its overall architecture, and partially space-filling representation (bottom) shows how its β -homoleucine residues (green) form a well-packed hydrophobic core.

Nonproteins that act like proteins have long been sought for their potential use for a range of biomedical applications, including the design of proteinlike therapeutics that wouldn't be degraded by enzymes and could therefore be administered orally.

Chemistry professor [Alanna Schepartz](#) and coworkers Douglas S. Daniels, E. James Petersson, and Jade X. Qiu at Yale University have now created such a proteinlike structure, a β -peptide bundle. And they show that it exhibits several hallmarks of real proteins, including exceptional stability, an interior core of water-shunning amino acid side chains, and the ability to fold and unfold reversibly.

Schepartz and coworkers made the structure by synthesizing an oligomer from 12 β -amino acids, which are residues with backbones one carbon atom longer than those of natural α -amino acids. The oligomer forms a helix with three faces, a type not seen in natural (α -amino acid-based) proteins. The researchers designed the helix to display hydrophobic side chains on one face and hydrophilic side chains on the other two.

They found that the helices self-assemble into an octameric bundle. When the helices assemble, hydrophilic side chains become arrayed on the outside of the assembly and hydrophobic ones hide inside, similar to the arrangement of side chains in most natural proteins.

The ability to create such "foldamers," peptide- or proteinlike folded structures, has been pursued by several groups. For the most part, they've made helices. The Schepartz group's β -peptide bundle is a higher order structure, an assembly of helices.

Higher order β -peptide foldamers have been made before, but they either weren't fully characterized structurally or weren't as proteinlike as the β -peptide bundle. Extensive complementary interactions between hydrophilic side

chains on the bundle's surface help it adopt its discrete higher order structure, whereas earlier β -peptide foldamers tended to aggregate, Schepartz says.

The new JACS paper "describes the first higher order foldamer assembly to be characterized crystallographically," says chemistry professor [Samuel H. Gellman](#) of the University of Wisconsin, Madison. The β -peptide bundle "is an important step toward a long-term goal of creating nonnatural molecules with the structure, function, and complexity of proteins," he says.

"It's a major advance," says [William DeGrado](#), professor of biochemistry and biophysics at the University of Pennsylvania. Schepartz and coworkers "have succeeded in a spectacular manner. It's a first move toward the ability to design entirely novel biomimetic polymers from scratch." Demonstrating the ability to tailor-make such foldamers from three-dimensional models could be a focus of future efforts, he says.

The new findings are "what I've been waiting for," comments organic chemistry professor [Dieter Seebach](#) of the Swiss Federal Institute of Technology, Zurich. "We can now be sure that there will soon be enzymelike β -peptidic catalysts, which will be stable in a natural environment full of peptidases." That's the type of prediction a creative wood-carver might understand and appreciate.

Chemical & Engineering News

ISSN 0009-2347

Copyright © 2007 American Chemical Society