new hot papers - 2010

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Samuel H. Gellman talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Chemistry.

Photo credit: Dan Yang.

Article Title: Foldamers with Heterogeneous Backbones
Authors: Horne, WS; **Gellman, SH**
Journal: ACCOUNT CHEM RES
Volume: 41
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Page: 1399-1408
Year: OCT 2008
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SW: Why do you think your paper is highly cited?

Broad attention to this paper reflects increasing interest in "foldamers," which are oligomers that adopt specific biopolymer-like shapes. The foldamer concept constitutes the basis of a subfield of chemistry that has germinated and grown over the past 15 years or so.

Proteins are natural oligomers that fold in specific ways, and the specific shapes adopted by proteins are necessary for their biological functions. Many chemists have sought to extend this relationship between folding and function to unnatural oligomers, with the hope of achieving activities that are not accessible via more traditional molecular design strategies.

The account summarizes work from the preceding few years that has identified a very powerful and versatile new strategy for foldamer design.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

This paper is a short review that provides a synthesis of existing knowledge. The paper offers a concise introduction to a new approach for the design of molecules that can display unique structural and functional properties.

SW: Would you summarize the significance of your paper in layman's terms?

Proteins are the workhorse molecules in biology; proteins do nearly all of the heavy lifting, at the molecular level, within living organisms. Developing ways to mimic proteins with synthetic molecules could lead to new substances for important applications, such as new types of drugs to treat human diseases and new materials for solar energy harvesting.

"Foldamer research invites one to explore many fundamental questions relating to the way that bonding patterns within large molecules determine overall molecular shape."

SW: How did you become involved in this research, and were there any particular problems encountered along the way?

I was drawn to this research area by a deep desire to extrapolate from, and perhaps ultimately improve upon, the remarkable molecules that are found in living systems.

Organic chemists are very good at the design and synthesis of relatively small molecules that perform specific tasks, such as drugs, pesticides, and dyes. However, the central functional role of proteins in biology seems to teach us that larger molecules are intrinsically more powerful than small molecules.

Foldamer research represents an effort to extend the well-developed knowledge and techniques of organic chemistry to create new kinds of molecules that adopt specific shapes, which provide a basis for new approaches to function-based design. This area is very exciting, because the horizons are so vast, and there are so many high-impact goals to be achieved.

Foldamer research is technically challenging, because this type of work forces one to confront limitations in synthetic and predictive tools. For example, chemical synthesis of proteins, which requires stepwise introduction of many subunits in a precise order, is very challenging, and synthesis of unnatural oligomers of comparable size is even more difficult.

SW: Where do you see your research leading in the future?

Foldamer research invites one to explore many fundamental questions relating to the way that bonding patterns within large molecules determine overall molecular shape. However, the most vital goal for foldamer research, at this point, is to show why this family of molecules is worthy of study. Demonstrating worthiness will require showing how foldamers can be useful.

In my own view, which could turn out to be incorrect, the clearest path to utility is to show that foldamers can inhibit interations between specific pairs of biological macromolecules. It is widely recognized that inhibiting specific protein-protein associations can be very valuable medically, but that this goal is typically difficult to achieve, particularly via traditional small molecule-based medicinal chemistry.

Many in the foldamer community believe that this class of molecules offers unique opportunities for mimicry of protein recognition surfaces. Achieving this type of activity, in a variety of systems, is a major goal in my laboratory.

SW: Do you foresee any social or political implications for your research?

I do not see any political implications behind this work. If foldamer-based strategies truly deliver novel and effective medicinal agents, then this area of research will contribute to the betterment of human society.

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