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Spotlights on Recent *JACS* Publications

FINDING THE FRICTION IN FOLDING PEPTIDES

A protein molecule must have proper shape and structure in order to support the biochemical processes of life. To clarify the forces at work behind how proteins achieve their final, functional conformation, physicist Roland Netz and colleagues ran protein-folding simulations to evaluate the effects of friction within the molecule itself (DOI: 10.1021/ja211494h).

The researchers looked at short peptide chains—$(GlySer)_4$ and Ala_8—in a protein-folding simulation designed to monitor internal friction forces by altering solvent viscosity, which also has a significant effect on protein-folding dynamics. To fully account for the effect of solvent—but not alter equilibrium properties or free energies—the researchers designed the simulation to reduce and increase viscosity by rescaling the solvent mass.

If a hypothetical peptide lacks inhibitory forces as the solvent viscosity approaches the vanishing point, the peptide should fold almost instantaneously. But in these simulations, folding never reaches that near-instantaneous point because of the effects of internal friction. The researchers identified kinetic traps caused by the formation of temporary hydrogen bonds within Ala_8, adding more time to the peptide's folding process.

This simulation sheds light on the complex internal forces at work during protein folding, which could aid in protein design and offer insight on diseases caused by misfolded proteins, such as Alzheimer's disease. **Kenneth J. Moore**

FIRST-TIME DEMONSTRATION OF FOUR-COMPONENT INTERWOVEN MOLECULES

For the first time, the quantitative formation of a four-component pseudorotaxane-like complex has been demonstrated by Pablo Ballester and co-workers (DOI: 10.1021/ja301900s). Rotaxanes are a class of supramolecular structures composed of mechanically interlocked molecules, and their assembly from multiple components remains challenging. Scientists are interested in rotaxanes and other interlocking molecules for their potential to serve as stimuli-responsive molecular machines, switches, and shuttles for applications ranging from biology to nanoelectronics.

The new four-component pseudorotaxane-like complex is composed of a linear molecule that threads itself through a macrocycle and is held together by an ion pair. The polyatomic anions used in the study participate in hydrogen bonding and drive the self-assembly of the complex. The team is currently working on a synthetic approach to "cap" the ends of the linear pseudorotaxanes generated by this method to yield highly stable, mechanically interlocked rotaxane molecules. **Christine Herman, Ph.D.**

CHASING AN ELUSIVE INTERMEDIATE IN CARBENE CATALYSIS

Tomislav Rovis and co-workers successfully captured analogues of the elusive "Breslow intermediate" by reacting a thiamine mimic with an iminium ion in place of the native aldehyde substrate (DOI: 10.1021/ja302031v). The researchers built a triazolylidene carbene catalyst to mimic the reactive portion of thiamine and reacted it with a nitrogen-containing iminium ion, which has electronic reactivity similar to that of an aldehyde.

In 1958, chemist Ronald Breslow had proposed that thiamine reacted with an aldehyde to form a catalytic intermediate that transforms the aldehyde into a reactive acyl anion equivalent. But re-creating this key "Breslow intermediate" in the laboratory has been difficult. Previously, a synthetic heterocyclic carbene catalyst similar to thiamine reacted with an aldehyde as predicted, but the product lacked the activity required to prove the product was in fact a functional Breslow intermediate. When combined with an iminium ion, the Rovis group's catalyst forms the nitrogen analogue of the Breslow intermediate as a yellow solid in 68% yield. The structure of the intermediate was confirmed using X-ray crystallography, and the formation was found to be reversible under acidic conditions.

Many enzymes catalyze their specific molecular transformations with the help of the vitamin thiamine. This stable, functional analogue of the Breslow intermediate is the most direct evidence that this intermediate is part of carbene catalysis involving aldehyde substrates. **Melissae Fellet, Ph.D.**

FIGURING OUT PROTEIN FOLDING

A clever new approach for exploring protein folding has been reported by James Petersson and co-workers (DOI: 10.1021/ja2113245). They devised a method for creating synthetic proteins that differ just slightly from their natural counterparts, in that certain oxygens atoms in the protein are replaced with sulfur atoms. This replacement allows the use of a technique called fluorescence quenching to monitor changes in protein structure during folding. The authors demonstrate the utility of this approach by synthesizing and tracking the folding of α-synuclein, a protein implicated in Parkinson's disease.

Not just strings of amino acids, proteins are complex structures whose three-dimensional configurations are inextricably intertwined with their functions. In fact, cells come equipped with highly sophisticated protein folding processes to ensure that newly generated proteins are arranged properly in space. Unfortunately, the protein folding process can go awry, which can result in globs of aggregated proteins that not only do not function properly but can actually cause harm. Indeed, misfolded proteins are a hallmark of several neurological diseases, including Alzheimer's and Parkinson's disease.

The approach described in this study offers an exciting and generally applicable new tool for exploring the protein folding process. This method could also help in the design of new drugs for the various human diseases that are linked to protein misfolding. **Eva J. Gordon, Ph.D.**

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