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Spotlights on Recent *JACS* Publications

HOW BIOPOLYMERS STRETCH

The structural and mechanical properties of proteins are intimately linked with their function. During blood clotting, the protein fibrinogen undergoes proteolytic conversion to monomeric fibrin which, in turn, polymerizes and forms three-dimensional filamentous networks, the scaffold for blood clots and thrombi. The elasticity of the fibrin polymer is important, for example, to stop bleeding, but the molecular-scale changes that accompany the mechanical deformations of fibrin are not understood.

To gain new insight into fibrin structural dynamics, Valeri Barsegov, John Weisel, and co-workers have performed theoretical studies to explore the stretching of fibrin and fibrinogen at the molecular level (DOI: 10.1021/ja3076428). Using a computational method called all-atom molecular dynamics simulations accelerated on graphics processors, they have discovered that fibrin(ogen) stretching is accompanied by the conversion of one structural state, an α-helix, to another, a β-strand. The triple α-helix unwinds to facilitate formation of the more extended β-sheet structure. These insights into the molecular underpinnings that guide this remarkable structural and phase transition may provide clues into how fibrin and other α-helical proteins that experience similar structural changes respond to stress. **Eva J. Gordon, Ph.D.**

NONCONVENTIONAL INTERACTIONS SPOTTED BETWEEN HALOGENS AND CARBONYLS

An interaction that was once believed to occur exclusively between biomacromolecules has now been observed in a synthetic environment. Researchers led by Werner M. Nau demonstrate for the first time a perpendicular halogen bond between a halogen atom and a carbonyl group inside a molecular container (DOI: 10.1021/ja3102902).

The perpendicular halogen bond only recently emerged as a peculiar yet important interaction thought to be unique to biomolecular interactions, such as that of the thyroid hormone receptor and its ligand thyroxin. In the study, the research team characterized the interactions between diiodine or dibromine and the molecular container known as cucurbituril. They combined experimental, statistical, and computational analyses to demonstrate that perpendicular halogen bonds are not limited to carbonyl groups in proteins, but rather can extend to amides and esters in synthetic small-molecule systems. The findings in this study offer hope that researchers may be able to exploit this nonconventional interaction between halogens and carbonyl groups for applications in crystal engineering, functional materials, and, in particular, drug design. **Christine Herman, Ph.D.**

WARMING PROTEINS FROM THE INSIDE OUT

Protein behavior depends on the protein's composition and the temperature. In a study of the protein camphor-bound cytochrome P450 (P450cam), researchers have characterized what happens sequentially to a protein when it is heated from very cold temperatures. They found that, perhaps surprisingly, the hydrophobic core of the protein is the first to "wake" upon heating.

A team led by Jeremy C. Smith at Oak Ridge National Laboratory in Tennessee examined P450cam using a high-flux backscattering spectrometer to measure neutrons scattered through dry and hydrated forms of P450cam at different temperatures (DOI: 10.1021/ja3097898). The technique allowed them to measure the protein's internal movement, characterized by the mean square displacement (MSD), on picosecond to nanosecond time scales. The researchers found that both the dry and hydrated forms of P450cam made sharp transitions in MSD as their temperature passed through 140 and 160 K. The hydrated protein made another transition between 180 and 200 K.

The team verified a computer simulation of the protein against their measurements and then used the simulation to examine how different molecular side chains within the protein responded to temperature changes. They concluded that, at low temperatures (100−160 K), hydrophobic and aromatic side chains in the core begin to move more, and that around 180−220 K in the hydrated sample the hydrophilic side chains on the surface activate. **Lucas Laursen**

HIGHLY SELECTIVE REMOTE CONJUGATE ADDITION

Takashi Ooi and co-workers have developed a highly selective method of carbon−carbon bond formation (DOI: 10.1021/ja310209g). Their reaction is based on the Michael addition, a stalwart in organic chemistry textbooks and laboratories that allows the 1,4 conjugate addition of carbon nucleophiles to electron-deficient alkenes.

Now, the researchers have effected 1,6 and 1,8 conjugate addition reactions in a regio-, diastereo-, and enantioselective fashion. The vinylog and unprecedented bis-vinylog of Michael addition are remarkable in that the standard 1,4 addition to activated di- or trienes is generally favored. To overcome this preference, a chiral P-spiro triaminoiminophosphorane catalyzes the reaction of an azalactone with either δ-substituted dienyl *N*-acylpyrroles or ζ-substituted trienyl *N*-acylpyrroles.

High levels of regio- and stereocontrol are crucial in the synthesis of natural products and other pharmaceutically important molecules. The authors conclude that the new reaction method provides a novel way of "coping with the selectivity issues associated with the conjugate addition of prochiral enolates to prochiral electron-deficient polyenes". **Sonja Krane, Ph.D.**

MOLECULAR ORIGINS OF LIGHT-DRIVEN CIRCADIAN RHYTHMS

Melanopsin is a light-responsive protein in vertebrate retinas. Signals from this protein activate the brain's biological clock, which controls the daily mental, physical, and behavioral cycles of circadian rhythms. Melanopsin is challenging to purify and

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thus hard to study in-depth. Even its basic properties, like the wavelength of light that it absorbs best, are difficult to pin down.

Sivakumar Sekharan, Victor Batista, and Jennifer Wei report the first homology structural model of the binding site of mouse melanopsin (DOI: 10.1021/ja308763b). They use the model to investigate the molecular changes that affect light absorption of melanopsin. To build their new model, the scientists started with the known crystal structure of the invertebrate squid rhodopsin. They then changed amino acids in the protein binding site so its sequence matched that of mouse melanopsin. Finally, they calculated the structure of the mutated protein, using the known structure as a starting point for the optimization.

The scientists compared the structures of squid and bovine rhodopsin and mouse melanopsin and identified mutations responsible for different wavelength absorptions among the three proteins. Understanding the molecular origins of melanopsin's light reponse can help scientists optimize light therapy for circadian rhythm disorders. **Melissae Fellet, Ph.D.**