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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Spotlights on Recent *JACS* Publications

MOLECULAR DYNAMICS SIMULATIONS TOWARD EARLY ALZHEIMER'S DETECTION

Birgit Schiøtt and colleagues find that 13 different imaging agents used to detect amyloid fibrils share a common mechanism of binding with the protein aggregates (DOI: 10.1021/ja405530p).

In amyloid diseases such as Alzheimer's and type 2 diabetes, proteins misfold and are deposited as amyloid fibrils. Researchers want to find ways to detect the fibrils in living patients to diagnose Alzheimer's disease, but it has been challenging to develop noninvasive approaches. Although small-molecule imaging agents that bind amyloid fibrils offer promise for noninvasive detection, researchers know little about their binding mechanism.

Now Schiøtt's group has used molecular dynamics simulations to study the binding of a model of an amyloid fibril with 13 different small-molecule imaging agents. They find that these ligands all bind in an orientation parallel to the fibril, although their binding position varies depending on the side chains of the fibril and the specific ligand. The work could potentially help researchers design better imaging agents for early diagnosis of Alzheimer's disease. **Deirdre Lockwood, Ph.D.**

METAL-CONTAINING CORES YIELD NANOSTRUCTURED MATERIALS

Inspired by elegant examples of supramolecular architectures in nature, researchers led by Feihe Huang and Peter Stang present a new route to building diverse metal-containing nanostructures and hydrogels from simple synthetic precursors (DOI: 10.1021/ja406877b). The method comes complete with a set of design rules that enable researchers to tune and predict the resulting materials.

The team looks to a class of precursor molecules known as rhomboids—amphiphilic molecules containing a metallacyclic core and both hydrophilic and hydrophobic regions that enables them to aggregate into higher-order structures known as supra-amphiphiles. They find that by controlling three parameters—precursor concentration, reaction time, and composition of the hydrophilic moieties decorating the parent molecules—they can create zero-dimensional micelles, one-dimensional nanofibers, or two-dimensional nanoribbons from the same two amphiphilic precursors. They can then prompt these nanoscale constructs to aggregate at high concentrations into three-dimensional metallohydrogels.

This work is a significant step toward the rational design of structurally complex, aggregation-based nanostructures for potential applications as functional soft materials in biological systems and materials science research. **Christine Herman, Ph.D.**

PING-PONG-PLAYING SAMS

Enzymes called radical *S*-adenosylmethionine (SAM) methylthiotransferases (MTTs) catalyze the attachment of a small chemical entity, called a methylthio group, to large biomolecules such as proteins and transfer RNAs. Though not entirely understood, this type of modification is part of a growing number of RNA and protein modifications with important biological functions, and may be a preliminary step in the biosynthesis of certain sulfur-containing biomolecules. While investigating the catalytic mechanism of two MTTs, RimO and MiaB, Squire Booker and co-workers (DOI: 10.1021/ja4048448) discover that the enzymes use an unexpected, ping-pong-like sequence of events to transfer methylthio groups to their substrates.

Using a variety of biochemical techniques and enzyme activity assays, the authors determine that rather than inserting sulfur into the substrate and then simply capping the sulfur with a methyl group from SAM, the enzymes catalyze the transfer of a methyl group from SAM to an iron–sulfur cluster present in the enzyme. The methyl group is then transferred from the cluster to the substrate.

Given that similar ping-pong-like reactions have recently been discovered in other subclasses of radical SAM enzymes, these findings suggest that this may be a general reaction mechanism used by this important enzyme family. Further characterization of the mechanism of MTTs and other radical SAMs will enhance our understanding of the functional consequences of their activity. **Eva J. Gordon, Ph.D.**

DETERGENT SCRUBS AWAY RELEVANT MEMBRANE PROTEIN STRUCTURE

Membrane proteins are notoriously difficult to study because their structure, and thus their function, depends on interactions with the fatty molecules that flank the proteins under physiological conditions. Scientists have attempted to simulate membrane conditions in test tubes with detergents, but it has not been clear whether the proteins look and act the same in detergents as they do in a membrane. To address this question, Bruno Miroux, François Dehez, and colleagues have developed a strategy to study how the structure of a membrane protein—mitochondrial uncoupling protein 2 (UCP2)—is altered by detergents (DOI: 10.1021/ja407424v).

UCP2 is linked to type 2 diabetes and other diseases, making the protein an important target for drug development. Scientists previously solved a structure of UCP2 in the detergent dodecylphosphocholine (DPC) by nuclear magnetic resonance spectroscopy. In this study, Dehez's team performs molecular dynamics simulations on UCP2's NMR structure in a membrane-like environment and in DPC.

In the DPC simulation, UPC2 maintains the loose pore-like structure that has been observed by NMR. However, UPC2 rapidly collapses into a compact structure in the membrane-like environment. This suggests, the authors say, that DPC severely alters the structure and function of UPC2, calling into question the biological relevance of membrane protein structures determined under unnatural conditions. **Erika Gebel Berg, Ph.D.**

Published: October 9, 2013

dx.doi.org/10.1021/ja410056x | *J. Am. Chem. Soc.* 2013, 135, 14895–14895