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Spotlights on Recent *JACS* Publications

CARCINOGENIC DIMERIZATION MECHANISM REVEALED WITH MOLECULAR DYNAMICS

Ultraviolet rays in sunlight are a major cause of DNA damage, and one pathway by which this damage can occur is through a dimerization reaction of DNA pyrimidine bases thymine and cytosine. This damage can disrupt normal cellular processing of DNA and can lead to a variety of biological responses, including skin cancer.

The mechanism behind an important photodimerization reaction that forms cyclobutane thymine dimers has been found to occur in the singlet state in a computational study by Philipp Marquetand, Leticia González, and colleagues (DOI: 10.1021/jacs.6b06701). Cyclobutane thymine dimers are among the most frequently occurring class of structural damage found in UV-irradiated DNA.

This ultrafast dimerization reaction occurs on time scales of less than 1 ps. It has been previously explored experimentally with femtosecond spectroscopy and theoretically with quantum chemical calculations, but often with conflicting results. Using ab initio molecular dynamics, the authors show that the ultrafast photochemical dimerization occurs in the singlet state without participation of triplet states. Understanding the mechanism and factors that promote cyclobutane dimer formation in DNA will facilitate the development of methods and strategies to suppress this potentially harmful reaction.

Dalia Yablon, Ph.D.

A SIMPLE MIRROR-IMAGE SWAP YIELDS MORE-STABLE PROTEINS

A major goal in the design of proteins is increasing their stability, defined as the free energy difference between the folded and unfolded states. Because of the complexity of targeting the highly dynamic unfolded state, researchers most often attempt to increase protein stability by shoring up the folded state rather than destabilizing the unfolded one.

Now Daniel Raleigh, Carlos Simmerling, and colleagues have advanced efforts toward the latter strategy by investigating simple mutations of glycine to D-alanine at certain protein sites—including the C-terminal residue of α-helices (DOI: 10.1021/jacs.6b09511). This strategy can decrease the entropy of the unfolded state without substantially altering the stability of the folded state, thus increasing overall protein stability. With a combination of experimental, molecular dynamics, and free energy calculation approaches, Raleigh's team has developed an algorithm to predict the conditions under which these substitutions lead to overall protein stabilization. They find that this amino acid replacement is expected to stabilize proteins in 95% of cases, suggesting that it may be a broadly applicable tool for enhancing protein stability.

Deirdre Lockwood, Ph.D.

PROGRESS TOWARD ADVANCED MATERIALS: PROTEIN–ROTAXANE HYBRIDS

Rotaxanes are a class of mechanically interlocked molecules composed of a linear "axle" component that is threaded through any number of macrocyclic compounds, which are "locked" in place by the axle's bulky end groups. Despite mounting interest in rotaxanes for their possible applications in molecular nanotechnology, the bioconjugation of rotaxanes to proteins has not been previously demonstrated.

In a new report, researchers led by Matthew Francis describe the first synthesis of a protein–rotaxane hybrid molecule via an efficient thiol–ene bioconjugation protocol (DOI: 10.1021/jacs.6b10231). The synthesis occurs under mild aqueous conditions and is both rapid and near-quantitative. The team applies the chemistry to the formation of protein bioconjugates that contain mechanical bonds, which is the first step in the development of advanced materials based on protein–rotaxane hybrids. Going forward, the researchers say they will investigate the possibility that rotaxanes can be used as molecular switches to regulate the function of a protein, for example, by changing the protein's conformation or impacting the ability of substrates to access its active site.

Christine Herman, Ph.D.

GETTING SERIOUS ABOUT GRAPHENE AND CARBON NANOTUBE SILYLATION

A multitude of recent studies have reported successful covalent functionalization of synthetic carbon allotropes (SCAs) such as graphene and carbon nanotubes. However, few reports have focused on covalent silylation of these materials, despite the promise that organosilane functionalization holds for fine-tuning SCAs' electronic and physical properties. In a new study, Andreas Hirsch and co-workers introduce a novel and straightforward reductive silylation technique for graphene and carbon nanotubes based on a three-step protocol (DOI: 10.1021/jacs.6b09487).

Using potassium as an electron donor, the researchers first reduce the SCAs. Then, after ultrasonication to disperse intercalated components, they add silylating reagents such as trimethylsilyl chloride as electron trappers. Raman spectroscopy, mass spectrometric-coupled thermal gravimetric analysis, and optical and atomic force microscopy all provide evidence of successful reductive silylation of both graphene and carbon nanotubes using this technique. Interestingly, the two different SCAs show different manners of functionalization based on their topology: strain induced by initial placement of functional groups around nanotubes causes them to rearrange over time until they reach an equilibrium configuration, a process that is unnecessary for graphene flakes, in which strain is balanced by functional groups on both sides. The authors suggest that this study provides a new and versatile covalent organosilane functionalization strategy for SCAs.

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