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Spotlights on Recent *JACS* Publications

THE AVENUE TO ANDITOMIN

Ikuro Abe and co-workers elucidate the complete biosynthetic pathway for the fungal natural product anditomin (DOI: 10.1021/ja508127q). Natural products are rich sources of architecturally complex compounds with potential therapeutic or commercial applications. This fungal meroterpenoid, first isolated in 1981, boasts a unique, highly oxygenated bridged ring system, the construction of which is not readily apparent.

To delineate the biosynthesis of anditomin, the authors identify the anditomin gene cluster by whole genome sequencing of the fungus *Emericella variecolor*. They characterize the functions of all 12 enzymes identified and determine the structures of the corresponding intermediates along the biosynthetic pathway. This process illuminates several intriguing transformations, including an unprecedented skeletal reconstruction by a nonheme iron-dependent dioxygenase to create the bridged ring, and another complex oxidative rearrangement in the last step of the synthesis, also by a dioxygenase.

The approach used in this study can be applied to the investigation of various other highly complex and intricate natural products. Deciphering these pathways can reveal novel biosynthetic transformations that can be borrowed and manipulated for the creation of new compounds with diverse biological properties.

Eva J. Gordon, Ph.D.

REGIOCHEMISTRY'S STRONG EFFECTS ON TRANSISTOR PERFORMANCE

The success of next-generation flexible electronic devices will be driven in part by the development of solution-processed polymer organic semiconductors with high charge carrier mobility. Currently, the best materials are polymers composed of electron-rich and electron-poor co-monomers, which are polymerized to yield materials with a small optical band gap. There are, however, applications where a small band gap is not desirable, but previous attempts to create polymers with wider band gaps have typically fallen short in terms of performance.

A team of researchers led by Martin Heeney set out to create high-performing conjugated polymers with a wider band gap, and they now report the synthesis and characterization of three novel polythiophene isomers with high charge carrier mobility (DOI: 10.1021/ja508798s). The molecules are the same in every way except for the placement of their side chains—a seemingly minor regiochemical difference that turns out to affect the molecules' structure, conjugation length, propensity to aggregate in solution, and ultimately optoelectronic properties and performance in field effect transistors. The researchers attribute the dramatic differences in behavior to differences in torsional twisting along the polymer backbone, with enhanced planarity associated with the best performance.

Christine Herman, Ph.D.

WARMING UP TO STRUCTURE DETERMINATION WITH EPR SPECTROSCOPY

Elucidating the structures, and thus the mechanism of function, of some of the most interesting biological molecules—membrane proteins and very large proteins—is difficult or impossible using traditional approaches. One emerging structure-determination method that can tackle these challenging proteins involves tagging the proteins at various locations with "spin labels", which light up on electron paramagnetic resonance (EPR) spectra and allow researchers to determine the interspin distances. However, the approach cannot measure distances beyond around 20 Å at physiological temperatures, and such longer-range distance information is critical for determining a protein's fold.

To overcome this limitation, researchers sometimes perform EPR spectroscopy at cryogenic temperatures, 50−80 K, which optimizes spin relaxation times, boosting distance measurements to 80 Å. Questions remain, though, about whether frozen proteins maintain physiologically relevant structures. Now, Wayne Hubbell and colleagues have developed spin labels with improved relaxation parameters, and a 5-residue loop that binds paramagnetic copper (DOI: 10.1021/ja5083206). The researchers incorporate the labels into loop regions of proteins and are able to measure interspin distances of around 40 Å at physiological temperatures. The approach is compatible with cryogenic experiments as well, offering an opportunity to validate the low-temperature structures.

Erika Gebel Berg, Ph.D.

THE MULTIPLE LIVES OF A SWITCHABLE CATALYST

Switchable catalysts are those whose activity can be turned on and off, or whose stereoselectivity can be reversed, as a result of structural changes triggered by external stimuli, such as chemicals and light. Although a number of switchable catalysts have been synthesized, few can go beyond the scope of one specific type of reaction.

Following their recent discovery of a rotaxane-based switchable organocatalyst for the thiol-Michael addition, David A. Leigh and colleagues continue to explore its capability in activating carbonyl compounds (DOI: 10.1021/ja509236u). The catalyst masks and exposes an amine catalytic center through a macrocycle by acid and base modulation, respectively, and shows distinct on/off activity in iminium, enamine, tandem iminium−enamine, and trienamine catalyses.

The researchers have for the first time demonstrated multiple activation modes of a switchable catalyst, providing valuable insights into behaviors of its different states in various types of reactions. This study also opens avenues for the design of advanced switchable catalytic systems, where multistep reaction sequences may be choreographed by programming the "on" and "off" states of catalysts.

Xin Su, Ph.D.

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NEW IMAGING MOLECULE TO TRACK THE PRODUCTION OF REACTIVE OXYGEN SPECIES INSIDE CELLS

Reactive oxygen species, also known as ROS, are important biological molecules involved in metabolism. However, errors in their production have been implicated in various diseases, such as Alzheimer's disease, diabetes, and certain forms of cancer. Unfortunately, researchers lack a selective and sensitive way to accurately track the production of ROS as it happens inside cells.

Now Christopher J. Chang and colleagues have developed a new molecule, called peroxy-caged-[^{18}F]fluorodeoxy thymidine-1 (PC-FLT-1), to detect the production of hydrogen peroxide, a type of ROS, inside live cells (DOI: 10.1021/ja509198w). The investigators designed PC-FLT-1 so that it is taken up by cells and cleaved by hydrogen peroxide to release a radioactive molecule. The radioactive molecule acts as a tracer for a clinical technique known as positron emission tomography (PET). PET measures the tracer's concentration inside the body and compiles the data to generate three-dimensional images.

By using a cancer cell model and an oxidative-stress cell model, Chang and colleagues demonstrate that the amount of radiation emitted from the cleaved PC-FLT-1 is directly proportional to the amount of hydrogen peroxide produced inside the cells. The investigators say one of the next steps is to test the tracer in clinical settings.

Rajendrani Mukhopadhyay, Ph.D.

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