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Spotlights on Recent *JACS* Publications

MOLECULAR "PHOTOMAGNETIC CONDUCTOR" OFFERS NEW RESEARCH PERSPECTIVES

Molecular complexes that respond to light by adopting a different crystal structure have been synthesized and studied for a range of applications, such as optical devices or switches. These types of molecular crystals can change from being an insulator to a conductor when they are irradiated with light. Other materials may switch from a non-magnetic state to a magnetic state. At the base of these changes is a phenomenon known as molecular charge transfer, whereby cations and anions that form the molecular complex interact through the absorption of photons.

Now, Toshio Naito and co-workers report a molecular complex that simultaneously switches from a non-magnetic insulator to a magnetic conductor (DOI: 10.1021/ja306260b). This particular transformation of properties has not been seen before. By experimenting with a range of pairs of molecular anions and cations, the authors find a molecular crystalline material composed of bipyridinium cations and dithiolate anions $Ni(dmit)_2$ that proves to be a reversible "photomagnetic conductor". Under ultraviolet irradiation within a broad temperature range, the material changes from a diamagnetic semiconductor into a magnetic conductor, and it changes back to its original state when the UV light is removed. **Alexander Hellemans**

EPIPOLYTHIADIOXOPIPERAZINE ANTIVIRAL AND ANTIMALARIAL NATURAL PRODUCTS

A range of natural products effective against poliovirus and the parasite that causes malaria have been synthesized thanks to an improved method for the sulfenylation of 2,5-diketopiperazines developed by K. C. Nicolaou and co-workers (DOI: 10.1021/ja308429f). The researchers used elemental sulfur and sodium hexamethyldisilazide in tetrahydrofuran solvent to effect the stereo- and regioselective sulfenylation of a broad range of diketopiperazine substrates. These reaction conditions were used to synthesize four natural products and structurally related analogues of the epipolythiodioxopiperazine family.

The authors find that selected compounds have nanomolar potency in antiviral biological assays. The compounds are also active against the *Plasmodium falciparum* parasite that causes malaria in humans. Malaria caused by *P. falciparum* is particularly virulent, with much higher mortality rates than from other species. It presents a massive public health problem in sub-Saharan Africa, home to the vast majority of the estimated 300−500 million cases of malaria annually.

"By blending total synthesis of natural products of biological and medical interest with method development endeavors and chemical biology studies, the work described herein exemplifies the modern paradigm of natural product synthesis and underscores its relevance and importance to chemistry, biology, and medicine," the authors conclude. **Sonja Krane, Ph.D.**

ADJACENT TO THE TARGET SITE IS SPOT ON

Calpains, members of a family of enzymes called cysteine proteases, participate in a variety of cellular activities including cell movement, signaling events, and control of cell death. Inhibitors of calpains are drug leads for conditions such as cancer and diabetes and can also be used as molecular probes of calpain function. However, creating inhibitors that are specific for calpains over the other 140 or so cysteine proteases that exist in humans is a formidable challenge.

Rather than trying to compete with a large number of similar interactions, Greenbaum and co-workers create a peptide in the shape of a small helix that mimics a key region of a natural protein inhibitor of calpain called calpastatin (DOI: 10.1021/ja307599z). They incorporate a stabilizing element that assists the helix in nestling itself right into a spot just adjacent to where most other inhibitors bind. They also create derivatives of the stabilized helix that attach permanently to the enzyme, which can be used to explore calpain function. This clever strategy for the specific targeting of calpains can be extended to the design of inhibitors of other enzymes and protein−protein interactions as well. **Eva J. Gordon, Ph.D.**

NMR MAPS A BATTERY'S METAL

A future dominated by electric vehicles depends on the development of more powerful and long-lasting batteries. Of growing interest are batteries containing lithium iron manganese phosphates (LFMP), which are non-uniform materials. The structure of LFMPs is key to building batteries with enhanced energy storage capacity, yet it remains poorly understood. Normally, solid-state NMR would be an ideal method for assessing the structure and electrical properties of such compounds, but LFMP is difficult to study by NMR because it contains paramagnetic transition metals. The paramagnetic atoms push NMR signals well outside the normal chemical shift range and broaden signals beyond recognition.

Guido Pintacuda and colleagues develop a novel solid-state NMR experiment to overcome LFMP's paramagnetism (DOI: 10.1021/ja306876u). Called aMAT, the experiment includes state-of-the-art adiabatic pulse schemes and magic angle spinning. The researchers test the approach on LFMP compounds with varying ratios of iron to manganese. The location and intensity of signals in the resulting ^{31}P NMR spectra reveal information about the local environment around the phosphates, including their distance and orientation relative to nearby metal ions. The researchers generate high-resolution models of LFMP electron distribution by combining theoretical calculations with the NMR information. They hope to extend the method to the study of other compounds containing transition metals. **Erika Gebel, Ph.D.**

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PHOTOSYSTEM II: GETTING TO THE CORE OF PHOTOSYNTHESIS

Photosystem II, found in plants, algae, and cyanobacteria, is the only known enzyme in living organisms that captures photons to split water molecules into hydrogen and oxygen, a process called photodissociation. The oxygen-evolving complex (OEC), with four manganese atoms and one calcium atom at the core of the photosystem II enzyme, catalyzes the process and supplies the electrons for the reduction of photo-oxidized chlorophyll *a* in photosynthesis.

The structure of the OEC has been studied by X-ray diffraction, but the increasing availability of tunable monochromatic X-ray beams in synchrotron sources has encouraged the use of near-edge X-ray absorption fine structure techniques. These NEXAFS experiments have yielded high-resolution absorption spectra that can be correlated with functional groups and individual bonds in biomolecules, allowing researchers to obtain a more detailed structure of the OEC. Moreover, the data support earlier theories stating that the oxidation of water would require four intermediate steps, called S-transitions, of which the first three involve an oxidation of Mn(III) to Mn(IV).

Barbara Brena and co-workers confirm this hypothesis by applying density functional theory to model the four intermediate OEC structures (DOI: 10.1021/ja306794p). **Alexander Hellemans**

GAS-PHASE EXPLORATION OF PEPTIDE FOLDING

The proper folding of proteins is vitally important to human health, and misfolded proteins are suspected to be the cause of neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases. Scientists study the folding of small, simple polypeptides to develop rules that can then be applied to larger, more complex proteins. One important ingredient to the preferred folding of proteins is their local environment: they fold differently in aqueous environments, where peptide−water intermolecular bonds drive folding, than in nonpolar cell membranes, where intrapeptide hydrogen-bonding dictates the structures chosen.

A team led by Timothy Zwier at Purdue University use a gas-phase measurement technique—it more closely resembles the nonpolar environment of a cell membrane—to study short polyglycine chains (DOI: 10.1021/ja306652c). They find that the lowest energy conformation involves formation of a helix referred to as a mixed 14/16 helix, which alternates the direction of the intramolecular H-bonds in order to minimize the dipole moment of the peptide backbone. This structure is strongly preferred in the absence of solvent over structural motifs commonly seen in these types of simple peptides in aqueous solution.

This observation invites further investigation of these glycine-rich peptides in the nonpolar environment of cell membranes, where many proteins of biological relevance reside. **Polly Berseth, Ph.D.**

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