

Spotlights on Recent JACS Publications

■ WATER-SOLUBLE FLUORESCENT PROBE WITH RECORD SENSITIVITY

Kari Rissanen and co-workers have developed a new fluorescent probe that lights up in the presence of nanomolar levels of inorganic pyrophosphate (PPi) in water (DOI: 10.1021/ja4128949). The probe—a simple terpyridine-Zn(II) complex—is the first water-soluble fluorescent PPi sensor to achieve this level of sensitivity under physiological conditions.

Having probes that report how much PPi is present could lead to improved cancer diagnostics, since PPi plays a key role in energy transduction, DNA replication, and other metabolic processes that are dysregulated in cancer cells. Previous PPi probes have suffered from poor water solubility and low sensitivity in water (micromolar levels), leaving researchers to rely on protein-based probes for PPi detection, which have their own limitations.

The new probe has a detectable fluorescence response at 20 nM and shows a 500-fold increase in fluorescence upon binding to PPi. Although the probe is selective for PPi over other ions, the researchers note a decrease in fluorescence in the presence of certain anions as well as competitive inhibition from other phosphate anions, including ATP. The team demonstrates the probe lights up the nuclei of HeLa cells and can be coaxed into a hydrogel and coated onto paper strips for low-cost pyrophosphate detection.

Christine Herman, Ph.D.

■ TWISTED CRYSTALS MAKE RIPPLES OF LIGHT

Often, the way light interacts with a material can provide valuable insight into its internal makeup. Spherulites are spherical semicrystalline regions in a material that may interact with light to form unusual color and reflection patterns. Banded spherulites appear like ripples in a pond during a gentle rainstorm—each concentric set of circles denotes a semicrystalline region. Banded spherulites have been studied in long-chain polymers, but they also appear in many other materials.

Alexander Shtukenberg, Bart Kahr, and colleagues study the optical and structural properties of banded spherulites in 21 molecular crystals, polymers, and minerals (DOI: 10.1021/ja5013382). The researchers find optical patterns that cannot be explained by the compounds' natural optical properties. They discover instead that the unusual light interactions result from misoriented, overlapping, and even twisting layers of thin crystalline sheets—like a twisted pile of water-logged plywood. From their extensive data, the researchers conclude that such concentric bands almost universally indicate helical twisting along crystalline branches, no matter what the type of material.

It is remarkable that materials with such different atomic structure and chemistry spontaneously align into similar patterns. These observations could help researchers better understand and exploit complex self-ordering in structures found in nature.

Jenny Morber, Ph.D.

■ REWRITING TEXTBOOKS: HEMOGLOBIN HAS NOT TWO, BUT NINE CONFORMATIONS

Many biochemistry students first learned about structure–function relationships in proteins via the classical two-state structure of hemoglobin. Now, a new study suggests that hemoglobin may have nine conformational states. Hemoglobin, a tetrameric protein, is often used to illustrate the concept of allosteric regulation: how the binding of a substrate to one subunit of a protein increases or decreases the affinity of other subunits for a substrate. In the classical model, when one subunit of hemoglobin binds oxygen, the overall structure shifts from a tense to a relaxed state that binds oxygen more strongly.

A couple decades ago, researchers started getting hints that there may be intermediate states in this transition, but capturing those structures proved difficult, and significant debate continues about the nature of hemoglobin's allosteric transitions. This study may help put some of those debates to rest.

Naoya Shibayama and colleagues use metal substitutions, a variety of conditions, and chemical cross-links to generate three hemoglobin crystals (DOI: 10.1021/ja500380e). Using X-ray crystallography, the researchers discover that each crystal contains hemoglobin in three different conformations, for a total of nine. Among them, they identify an intermediate state never before detected. The researchers next use O₂ equilibrium measurements in the crystals to assess the affinity of each conformation for oxygen, finding a stepwise pattern in moving from the more tense-like states to the new intermediate to the relaxed-like states.

Erika Gebel Berg, Ph.D.

■ FINDING THE SOLUTION: THE STRUCTURE OF SOLUBLE AMYLOID OLIGOMERS

Alzheimer's disease is a rising health problem, and effective treatments for the disease remain elusive. One challenge in developing novel therapeutics is that β -amyloid peptide, the molecule that clumps together to form plaques in the diseased brain, forms oligomers of various sizes in solution before aggregating into the large fibrils that make up plaques. Such variation makes studying the molecules' structures nearly impossible, hindering the development of medications that target harmful oligomers.

One workaround is to probe β -amyloid peptide in a solid state, which should limit structural heterogeneity. However, it is unclear whether these structures are physiologically relevant. To better study oligomers in the solution state, a team of researchers led by James Nowick has developed a chemical model system by incorporating a nine-residue stretch of the β -amyloid peptide into a macrocyclic β -sheet peptide framework that blocks fibril formation (DOI: 10.1021/ja500996d).

The researchers use NMR to analyze the interactions between β -amyloid peptides in a four-member complex in solution. Individual peptides are found to be only partially

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folded, while the tetramer exhibits well-defined structure, reminiscent of proteins, according to the authors. Compared to the structure of the same tetramer in a solid state, which shows the peptide residues aligned, the solution structure demonstrates an out-of-register organization. These significant differences suggest that researchers should be cautious about drawing conclusions based on structures solved in a solid state. The chemical model system may prove useful for additional studies of amyloidogenic peptides.

Erika Gebel Berg, Ph.D.

■ A HIGH-SPIN MANGANESE–MAGNESIUM(0) COMPLEX, VIA A BULKY LIGAND

The utility of compounds that contain a metal–metal bond in catalysis and other applications has given rise to considerable research into this class of materials. Most of the effort in this subfield has centered on the second- and third-row d-block metals. Recently, interest in the first-row d-block metals has grown, with scientists creating highly reactive open-shell complexes. Significant advances in this chemistry involve stabilizing the low-coordinate metal dimers with very bulky or highly dentate ligands.

Extending beyond this foundation, Cameron Jones and colleagues have used a remarkably bulky monodentate amide ligand to synthesize a metal–metal bonded system with a high spin two-coordinate manganese in the zero oxidation state, the first known species of this type (DOI: 10.1021/ja5021348). The researchers find that the manganese–magnesium compound can act as an “inorganic Grignard reagent”. Traditional organomagnesium Grignard reagents form a new carbon–carbon bond by transferring an organic group from magnesium to another organic molecule. Correspondingly, an inorganic Grignard reagent forms a new bimetallic compound by transferring a metal and its ligand from magnesium to another metal complex.

The ability to synthesize these types of heterobimetallic compounds in a controlled fashion may positively impact catalysis research and applications using these materials. The authors also suggest that their compound may have use as a strong reductant in organic synthesis.

Leigh Krietsch Boerner, Ph.D.