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Spotlights on Recent *JACS* Publications

ELUSIVE FOUR-MEMBERED NITROGEN RING UNVEILED

Tetrazetidines are four-membered rings containing only nitrogen atoms. While they may be easy to draw on paper, their synthesis has proven much harder to achieve in the laboratory. Calculations from 1989 suggested that the parent tetrazetidine, which has the formula N_4H_4, could exist as a short-lived intermediate. Since that time, chemists have tried to build many tetrazetidines (of the general formula N_4R_4), but they have never been successful.

Now the group of David Camp, Marc Campitelli, Graeme Hanson, and Ian Jenkins have identified and characterized this elusive ring system (DOI: 10.1021/ja303019y). They discovered a tetrazetidine during an unrelated study involving triphenylphosphine and azodicarboxylates. Spectral analysis of a solution containing these two reagents revealed a mysterious radical species. Using computational chemistry and computer simulation, they were able to demonstrate that the observed spectrum matched that expected for a tetrazetidine.

Finding the ring system itself solves only part of the mystery of this molecule. The proposed pathway for the formation of the tetrazetidine is a new and unexpected variant of known reactions in organic chemistry, the researchers said. **Melissae Fellet, Ph.D.**

TOOLBOX FOR SWITCHABLE MOLECULAR SYSTEMS EXPANDS

Researchers are interested in molecular machines—microscopic analogues of macroscopic objects such as rotors, tweezers, and grippers—for applications in nanorobotics, drug delivery, and fundamental physical organic chemistry studies. Many types of molecular machines have been reported in the literature, including molecular grippers that can grab and release a guest molecule in response to external stimuli such as pH, temperature, light, or metal ion concentration.

Francois Diederich and co-workers have developed a new class of redox-switchable molecular grippers that expands the repertoire of molecular machines (DOI: 10.1021/ja306473x). The research team set out to develop a new class of molecular grippers that responds to changes in redox state, which would allow the compounds to be addressable on electroactive metal interfaces. The team synthesized and characterized redox-active variants of the resorcin[4]arene cavitand scaffold, which respond to changes in redox state to switch between a closed and an open conformation, causing guest molecules to be trapped or released, respectively. This new class of switchable molecular machines expands the toolbox available to researchers for the design of molecular systems that can be manipulated on the nanoscale. **Christine Herman, Ph.D.**

LEAD WEIGHS IN ON PROTEIN STRUCTURE

It is not always possible to solve the structure of a protein by crystallography or nuclear magnetic resonance (NMR) spectroscopy. Proteins with multiple components or subunits pose a particular challenge. Small-angle X-ray scattering (SAXS) can determine the overall shape and size of a biological molecule but does not typically provide atomic detail. Researchers led by Marius Clore of the National Institutes of Health have developed a new structure-solving method that relies on SAXS to determine distances between lead atoms in a protein, providing critical and unique structural information (DOI: 10.1021/ja306359z).

The researchers tested their approach on peptide-bound calmodulin, a protein with two domains. First, they replaced the protein's four calcium atoms with atoms of lead. The lead does not significantly perturb the protein structure and generates a SAXS pattern that reveals lead-to-lead distances. However, scattered X-rays from the other atoms in the protein can get in the way, so before collecting SAXS data, the researchers bathed the protein in a 65% sucrose solution that renders signals from non-lead atoms effectively invisible. When they attempted to figure out how calmodulin's domains orient with respect to one another using NMR and regular SAXS measurements alone, the researchers ended up with three different structures, all consistent with the data. Adding in the lead SAXS data narrowed it down to a single structure. **Erika Gebel, Ph.D.**

LANTHANIDE BIOLOGICAL PROBE ON A ZRO_2 NANOPARTICLE HOST

Lanthanide ions are well known for their luminescent properties and have been utilized for decades in television sets and fluorescent lights. More recently, scientists have become interested in utilizing the strong, long-lasting luminescence to create biological probes. When a lanthanide probe is tuned to bind to biological targets of interest, the luminescence can be used to track the location of the probe at low concentrations due to its strong emission properties.

Xueyuan Chen and co-workers have synthesized small ZrO_2 nanoparticles doped with either europium or terbium ions (DOI: 10.1021/ja306066a). These nanoparticles are coated with a hydrophilic amine ligand, a characteristic that helps with water solubility in biological applications, and functionalized with a tumor-targeting peptide. The nanoparticle materials were tested in cancer cells overexpressed with a protein marker of tumor biology and metastasis; the probes demonstrated specific recognition capability, and provided very low detection limits as well as low cytotoxicity.

There are many varieties of oxide materials and ligand possibilities to combine in the development of these new types of materials, which have potential to become state-of-the-art bioassay or imaging probes for cancer screening tests. **Polly Berseth, Ph.D.**

ONE-POT HISTONE DEACETYLASE PROBE

Histone deacetylases (HDACs) are key regulators of the so-called epigenome. They play an important role in gene expression by regulating the coiling of DNA around proteins called histones, and, in so doing, they tweak gene expression.

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Until now, the only way to monitor removal of acetyl groups from histone lysine residues was to use radioisotopes or antibodies, or fluoregenic probes that required post-reaction processing. Now Kazuya Kikuchi and colleagues describe a one-pot fluorogenic HDAC probe that simplifies the process (DOI: 10.1021/ja306045j).

The probe, K4(Ac)-CCB, is a nine-residue piece of the histone H3 N-terminus that is acetylated on the fourth amino acid and bears an acylated coumarin at the C-terminus. That acyl group prevents the dye from fluorescing under normal conditions, meaning the reaction is dark in the absence of HDAC. When HDAC is around to deacetylate the lysine group, a transesterification reaction transfers the acyl group from the dye to the lysine, unquenching the fluorophore.

When the team tested their probe with the HDAC enzyme Sirt1, it worked as expected: chromatographic traces track the transition first from the probe to its deacetylated form and then more slowly, to the transesterified, fluorescent state. Once optimized, "this probe should be a useful tool for epigenetic research and the development of HDAC-targeted drugs", the authors conclude. **Jeffrey M. Perkel**