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Spotlights on Recent *JACS* Publications

MECHANICALLY INTERLOCKED MOLECULES: ITERATIVE SYNTHESIS OF OLIGO-ROTAXANES

The development of iterative syntheses of biological polymers—such as DNA, peptides, and oligosaccharides—has unfolded seemingly endless possibilities for research applications of those macromolecules. The same could be the case for mechanically interlocked molecules like rotaxanes, which are composed of a linear axle that threads any number of ring-shaped molecules, "locking" them in place with bulky end groups. Being able to iteratively synthesize oligo-rotaxanes could open up the information-rich scaffolds to more extensive studies on the structure–function relationships and molecular interactions that occur within precision-engineered oligomeric interlocked molecules.

Stephen Goldup and colleagues describe a general, high-yielding approach to the synthesis of oligo-rotaxanes composed of a single linear axle and multiple different rings arranged in a precise order (DOI: 10.1021/jacs.6b08958). While previous methods have been developed to create poly[*n*]rotaxanes, most of these result in homocircuit units—composed of a single axle threading multiple rings of the same composition. Methods for more synthetically challenging heterocircuit systems have lagged behind. The new approach is a step in the direction of discovering poly[*n*]rotaxanes for potential applications in drug delivery, electronic and stimuli-responsive materials, and sensors.

Christine Herman, Ph.D.

SMALL MOLECULES PLAY A BIG ROLE IN CELLULAR REGULATION

Uncoupling proteins (UCPs) are a class of fatty acid-activated protein transporters that induce proton leakage across the mitochondrial inner membrane, helping to regulate energy expenditure in living cells. In a new report, Philp Gale and his team describe the first synthetic small molecules that are able to mimic UCPs (DOI: 10.1021/jacs.6b10615).

The researchers find that the proton transport capabilities of the tripodal thiourea molecules are "switched on" by the presence of long-chain fatty acids, even with only a trace amount. These small-molecule UCP mimics demonstrate proton transport capabilities that are close to those of a commonly used protonophore. The team also explores various questions pertaining to the transport of protons across the phospholipid bilayers. Evidence supports a fatty acid cycling mechanism, in which the anion transporters induce proton permeability by catalyzing the "flip-flop" transition of anionic forms of fatty acids. These findings open up a potential new route for the use of anion receptor chemistry. Additionally, the knowledge gained regarding the biological activities of synthetic anion transporters may shed light on the uncoupling mechanism of naturally occurring membrane proteins.

Christine Herman, Ph.D.

UNRAVELING THE MECHANISM OF A DNA CLEAVER

The bacterial metabolite lomaiviticin A creates double-strand breaks in DNA, and researchers are investigating it as a potential treatment for tumors deficient in repairing such breaks. Though the exact mechanism by which this natural product potently cleaves DNA has not been fully determined, scientists have hypothesized that vinyl radicals act as intermediates in the formation of single- and double-strand nicks in DNA. Now Mengzhao Xue and Seth Herzon shed more light on that mechanism (DOI: 10.1021/jacs.6b09657).

In this experimental study, they show that the vinyl radicals are produced through 1,7-conjugate addition of thiol-based nucleophiles to the natural product's two diazofluorene functional groups. The radicals can cleave relatively strong C–H bonds in methanol and acetone. The resulting hydrogen atom abstraction has been proposed to initiate DNA cleavage. This overall cleavage mechanism resembles that of enediyne antitumor antibiotics, and its elucidation may help scientists design new anticancer agents.

Deirdre Lockwood, Ph.D.

EXPLORING THE ORIGINS OF ELECTRON SPIN SELECTIVITY IN DUPLEX DNA

Although it is well-established that electrons travel through chiral molecules in a spin-selective manner, much remains unknown about the origins of this behavior. Now, Jacqueline Barton and co-workers describe the use of electrochemistry on DNA-modified magnetized electrodes to explore differences in the yield of charge transport through hydrated duplex DNA (DOI: 10.1021/jacs.6b10538).

The team observes spin filtering and establishes the source and critical characteristics needed for it to occur, ultimately finding that the chirality of a DNA duplex determines the spin selectivity. The researchers also demonstrate that shifting the same duplex DNA between two different forms (right-handed B- and left-handed Z-) leads to a "diode-like switch" in spin selectivity. Interestingly, it is not the chirality of individual monomers that matters but rather the supramolecular organization of those chiral moieties that determines the selectivity in spin. Understanding the factors that affect the flow of electrons through DNA has important implications for future applications of DNA-based materials in electronic devices and biosensors.

Christine Herman, Ph.D.

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