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Spotlights on Recent *JACS* Publications

STRUCTURE-BASED EVOLUTION YIELDS HIGHLY DISCRIMINATING MOLECULAR RECEPTORS

Chemists have taken inspiration from biopolymers in the design of "foldamers"—modular strands that fold into well-defined structures and can perform sophisticated functions, such as bind specific molecules. One of the greatest challenges in this field is creating molecular receptors that are capable of discriminating between structurally similar molecules.

In a new proof-of-principle study, researchers led by Ivan Huc and Yann Ferrand use a technique known as structure-based evolution to create foldamers that can accomplish this task (DOI: 10.1021/jacs.6b05913). The team begins with a synthetic oligoamide foldamer that binds tightly and specifically to tartaric acid. They subject the starting foldamer to a series of iterative structural mutations, additions, and deletions to create new modified sequences. After seven iterations, a sequence is obtained that binds with high specificity to malic acid, which differs from tartaric acid by only a single oxygen atom. To the researchers' surprise, the modified sequences have greater affinity for malic acid than the original foldamer has for tartaric acid, despite having fewer recognition features for binding. The new report demonstrates the potential of foldamers to be rationally designed in such a way that they can discriminate between molecules with extremely high structural similarity.

Christine Herman, Ph.D.

RHODIUM(I)-MEDIATED BENZENE PHOTOCARBONYLATION USING CARBON DIOXIDE

As an abundant one-carbon synthon, carbon dioxide holds great promise for a variety of synthetic applications with high atom economy and at low cost. However, because it is a thermodynamically inert molecule, carbon dioxide is very difficult to activate, especially through a reductive pathway.

Recently, David Milstein and colleagues have demonstrated the reductive cleavage of carbon dioxide to carbon monoxide under mild conditions by a rhodium(I) pincer complex, yielding a photoactive species that can couple with benzene to eventually afford benzaldehyde (DOI: 10.1021/jacs.6b05128). The entire process is a stepwise stoichiometric cycle involving four steps, in which metal–ligand cooperation plays a crucial role.

Although in the current system each individual step requires different reaction conditions, these results provide the mechanistic basis for developing a fully catalytic transformation. Such an advance may replace the carbon monoxide-based aromatic carbonylation with the abundant, nontoxic, and cheap carbon dioxide. In the meantime, the benzoyl intermediate, when intercepted by suitable coupling partners, could also enable facile functionalization leading to benzaldehyde-based complex products.

Xin Su, Ph.D.

GETTING THE LONG VIEW ON PROTEIN FOLDING

Damage to proteins can trigger the molecules to unfold or misfold, inactivating them and, in some cases, causing cell death and disease. Under physiological conditions, these unfolding or misfolding events are rare, which means they can be masked in experiments that include many molecules. Studying single molecules provides direct access to folding events, but scientists must then watch a protein for a long time—days to weeks—to catch it in the rare act of unraveling. Generally, standard single-molecule techniques are not stable enough to monitor proteins for hours or weeks on end, but now Ionel Popa, Julio Fernández, and colleagues have developed a magnetic tweezers-based approach that facilitates week-long studies of protein behavior (DOI: 10.1021/jacs.6b05429).

The key to the new method is a super-stable protein "ruler" that very accurately measures changes in a protein's length, a proxy for the extent of protein folding/unfolding, over a long time scale. The technology involves tethering a protein to a glass surface and tagging the protein with a paramagnetic bead. The researchers can then apply an adjustable force to the protein, via the paramagnetic bead, with a magnet positioned above the protein. The distance between the magnet and paramagnetic bead is correlated with folding and unfolding steps of a protein.

Erika Gebel Berg, Ph.D.

GROWING THE TOOLKIT FOR SYNTHETIC TRANSPORT SYSTEMS

Biological transporters that move ions and molecules across lipid bilayer membranes are central to many important biological systems that may inform the design of useful drugs and antimicrobial agents, and so on. Such synthetic molecules or transport systems may have improved stability or activity if they incorporate less common molecular interactions in their design.

A group of organic chemists led by Stefan Matile has now added chalcogen bonds to the synthetic toolkit that can transport anions across membrane bilayers (DOI: 10.1021/jacs.6b05779). Chalcogen bonds are non-covalent interactions involving group 16 elements including sulfur, selenium, or tellurium, but not oxygen. The orbital alignment of frequently used endocyclic chalcogens has previously limited chalcogen bonds to control of intramolecular conformation.

With experimental and theoretical work, the team demonstrates that dithienothiophenes are particularly well-suited to bind to and transport anions across lipid bilayers. The authors conclude that the new chalcogen-bond transporters do not disrupt membranes and may therefore have potential applications in sensing, medicine, and catalysis.

Dalia Yablon, Ph.D.

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