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Spotlights on Recent *JACS* Publications

ADVANCING CHEMICAL COMPLEXITY

Self-replicating chemical systems are prerequisite to the emergence of molecular evolution and complex function. In order to self-replicate, the molecular building blocks that make up a system must be equipped with complementary recognition and reactive sites. These sites enable the building blocks to come together to produce a template that catalyzes the binding of two additional building blocks to form yet another template, setting off a cascade.

Much remains unknown about how to create mechanically interlocked architectures that are capable of both self-assembly and self-replication. In a new report, researchers led by Douglas Philp propose a kinetic model for doing just that (DOI: 10.1021/jacs.5b09738). The team has previously described a kinetic framework for a self-replicating rotaxane, which is composed of a dumbbell-shaped molecule threaded through a macrocyclic molecule. However, in practice, the proposed design has not yet led to the creation of a functional self-replicating rotaxane.

In the new model, the researchers incorporate two orthogonal molecular recognition processes that help drive the assembly and replication processes. There are still a few kinks in the current system—such as the formation of undesirable pseudorotaxane complexes—but the results nevertheless represent a significant step toward the design of molecular assemblies with complex functions.

Christine Herman, Ph.D.

STRUCTURE OF NITROXIDE RADICALS PREDICTS THEIR ELECTROCHEMICAL ACTIVITY

Shelley Minteer, Matthew Sigman, and their co-workers have determined how the structure of some nitroxide radicals relates to their electrochemical activity. This relationship enables the researchers to predict which molecules would be best for synthesis, fuel cells, radical trapping, or *in vivo* imaging (DOI: 10.1021/jacs.5b11252).

More than 100 structural analogues of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) have been previously synthesized and characterized. However, structure–function studies have only looked at relatively small sets of these molecules, and they cannot explain trends observed with other nitroxyl radical catalysts. Now, Minteer, Sigman, and colleagues have synthesized and electrochemically characterized 29 water-soluble TEMPO derivatives, identifying a correlation between the electrocatalytic activity of a compound and its electrochemical properties. A newly developed computer model helps the researchers identify structural features that correlate with electrochemical properties, and those relationships enable the authors to predict which TEMPO derivatives will be most useful in various applications.

The researchers want to use nitroxyl radical catalysts in fuel cells and batteries. Structure–function correlations make it easier for them, and other researchers, to design a catalyst for a particular application, rather than synthesizing a large library and testing the properties of each molecule.

Melissae Fellet, Ph.D.

NEW STRATEGY REGULATES GENE EXPRESSION USING RNA POLYMERASES

In synthetic biology, researchers are drawn to RNA as a tool that can be programmed to manipulate biological systems. Thanks to specific nucleotide binding, RNA can be encoded with information that causes it to interact in a defined fashion with other nucleotide-based targets. But there is a shortage of tools available for linking the production of RNA to protein-based biomolecules in such a way that protein-based biochemical inputs can "switch on" the activity or presence of the RNA to yield a measurable output.

Now, researchers led by Bryan Dickinson describe a new strategy for doing just that (DOI: 10.1021/jacs.5b10290). The team fuses RNA polymerase (RNAP) enzymes to a protein, which puts the enzyme into an inactive state. Upon activation of proteases that target the linkage between the RNAP and the inactivating protein, the RNAP is released to transcribe RNA from a specific DNA promoter. The researchers demonstrate that these bioconjugates can function in live mammalian cells, responding to specific protease activities and driving programmed gene expression outputs. The findings demonstrate the potential of this new method for regulating gene expression for applications in mammalian synthetic biology.

Christine Herman, Ph.D.

RECONSTRUCTED ANTIBIOTIC BIOSYNTHESIS TO COMBAT DRUG-RESISTANT BACTERIA

Thiopeptides are a class of antibiotics with promising activity against multi-drug-resistant bacteria. Because of their suboptimal pharmacological properties, however, they have so far been used only to treat animals. Chemists want to modify these natural products so that they could be exploited to treat problematic infections like methicillin-resistant *Staphylococcus aureus* (MRSA). But synthesizing these natural products is challenging: they are naturally made in ribosomes followed by a complex series of post-translational modifications that transform a linear peptide into a macrocyclic structure.

Now Douglas Mitchell, Wilfred van der Donk, and their colleagues have completed the in vitro biosynthesis of the core scaffold of one thiopeptide, thiomuracin (DOI: 10.1021/jacs.5b10194). To achieve this goal, the researchers first screen for biosynthetic bacterial genes using bioinformatics, express the genes in *Escherichia coli*, and then purify six enzymes that catalyze the peptide transformation. In reconstructing the biosynthesis, they elucidate the complex catalytic mechanism involved, which includes 22 chemical transformations.

The resulting peptide shows potent activity against MRSA and another drug-resistant bacterium. Despite the fact that it is not fully post-translationally modified, its antibacterial activity is comparable with that of native thiomuracin. This biosynthetic approach could be used to derive synthetic thiopeptide variants for potential development as new antibiotics.

Deirdre Lockwood, Ph.D.

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