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Spotlights on Recent *JACS* Publications

ORGANIZING ORGANOCATALYSTS WITH A METAL SCAFFOLD

Some organocatalysts speed up a reaction between two substrates by just forming weak connections to each substrate, pulling the molecules close enough together to react. But these weak connections are easily disrupted and can form in ways that do not lead to a reaction, which means such reactions typically need large amounts of organocatalyst for maximum efficiency.

Lei Gong, Eric Meggers, and their colleagues wanted to improve the efficiency of such noncovalent organocatalysts by creating a molecule with a rigid structure that would hold each substrate in the optimum position. To this end, the researchers build an inert iridium-based metal catalyst scaffold that is decorated with ligands that carry the functionality of an organocatalyst used to hydrogenate a nitroalkene (DOI: 10.1021/ja403777k). Even using 0.1 mol % of catalyst, the researchers form a reduced nitroalkene in a yield and enantiomeric selectivity that meets or surpasses the best metal, bio-, or organocatalysts for such a reaction.

Blending these two forms of catalysis—organocatalysis and transitional metal complex catalysis—could be a new strategy for designing asymmetric catalysts, according to the researchers. Asymmetric catalysis is important in the synthesis of pharmaceuticals, agriculture chemicals, flavors, fragrances, and other products. **Melissae Fellet, Ph.D.**

EXPECT THE UNEXPECTED: A PERSPECTIVE ON DYNAMIC COMBINATORIAL CHEMISTRY

Combinatorial chemistry is a key tool in drug development and compound screening laboratories. Most often, combinatorial libraries are static. Recently, though, researchers have explored a dynamic alternative in which library members can interact and react with one another to produce unexpected combinations. Now, Sijbren Otto and colleagues offer a comprehensive Perspective on the methods, applications, and future directions of so-called "dynamic combinatorial chemistry (DCC)" (DOI: 10.1021/ja402586c).

DCC's applications include everything from receptor ligand discovery and catalyst design to origin-of-life modeling and information processing. The authors describe DCC-enabled screens, explain how the technique can identify molecules able to ferry compounds from one phase to another, and demonstrate the application of DCC to identify self-replicating compounds as well as bipedal molecules that can "walk" across a "floor" of alternating reactive groups. They discuss new DCC variants, for instance, using solid-phase reactants, as well as such limitations as library size.

In nearly two decades, the authors conclude, DCC has continually surprised. "Predicting exactly where the field will go from here is beyond us, as one of the most exciting features of DCC, proven time and again, is its ability to deliver the unexpected". **Jeffrey M. Perkel**

VIRAL MUTANT MEETS ITS MATCH

Flu viruses mutate prolifically, sometimes outsmarting antiviral medications. In recent years, resistant strains of H1N1, H5N1, and H3N2 have emerged with a serine to asparagine mutation in a specific proton channel. This membrane protein is critical for the virus' survival, allowing the pathogens to unwrap their viral DNA inside a cell. The mutant strains are resistant to antiviral agent amantadine, a drug that blocks the proton channel in wild-type viruses.

Recently, scientists discovered a class of compounds containing an isoxazole moiety that potently inhibits the mutant channels and cuts the replication of mutant viruses, though questions remain as to how the drugs work. To better understand how the isoxazole compounds shut down the mutant proton channel, Mei Hong and colleagues have studied the complex within a lipid membrane using solid-state nuclear magnetic resonance (NMR) spectroscopy (DOI: 10.1021/ja4041412).

The NMR data show that the isoxazole compound binds inside the proton channel, altering the structure of the helices that form the pore and creating a less ideal conformation for proton passage. Furthermore, the drug binding causes key residues to convert to their closed-state chemical shifts, suggesting that the drug twists the pore into its closed conformation. The new information provides valuable mechanistic insight that may aid in the development of new antiviral medications. **Erika Gebel, Ph.D.**

ENZYMES IN TIGHT SPACES GET AN ACTIVITY BOOST

In the crowded spaces inside a cell, proteins, enzymes, and other biomolecules constantly bump up against each other in a way that can significantly affect their behaviors. Researchers have sought to understand crowding effects by studying proteins in crowded molecular environments in vitro. But to date, the structural effects of the most popular crowding agent, poly(ethylene glycol), or PEG, have remained unexplored.

Now, researchers led by Gerhard Wagner show that introducing a protein into a crowded PEG solution brings about both structural changes and a boost in enzyme activity (DOI: 10.1021/ja404404h). Using NMR and SAXS, they observe the crowding effects in both single- and multidomain proteins and find the most significant effects in multidomain proteins with flexible linkers. The team studies the multidomain human translation factor, known as eIF4A, which contains an enzyme domain that plays a crucial role in initiating the translation of RNA into proteins inside cells.

The studies highlight the importance of evaluating enzyme activity and structure in the context of macromolecular crowding, rather than only incomparably dilute solutions, especially for multidomain and flexible proteins and macromolecular complexes. **Christine Herman, Ph.D.**

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