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Spotlights on Recent *JACS* Publications

LARGE-AMPLITUDE MOLECULAR MOTION BY ALLOSTERIC REGULATION

Eiji Yashima and colleagues have synthesized an allosterically regulated, double-stranded, helical structure that undergoes large-scale molecular motion upon binding and release of ions (DOI: 10.1021/jacs.6b00787). Many enzymes are controlled by allosteric regulation, where the binding of a ligand at one site induces conformational changes that facilitate subsequent binding events at other sites. Because this phenomenon is ubiquitous in living systems, it is important for design of artificial receptors.

Researchers are interested in developing synthetic allosteric receptors that undergo conformational changes in response to a chemical stimulus, such as the introduction of a proton or metal ion, and the design of systems that exhibit large-amplitude elastic motions has been particularly challenging. The new structure reported here is composed of one-handed spiroborate pyridine−phenol helicates. The team uses NMR, circular dichroism, X-ray crystallography, and theoretical calculations to define the smaller-scale "*anti*−*syn*" conformational changes that are amplified into what resembles a spring-like motion.

With this allosteric change the molecule contracts to less than half its fully extended length, and the conformational change can be reversed by sequestering the added ions. The results lay the groundwork for the development of a supramolecular asymmetric catalyst whose catalytic activity could be modulated by a unidirectional elastic motion.

Christine Herman, Ph.D.

FOR PROGRESS IN FUNCTIONAL SYSTEMS, THINK OUTSIDE THE BOX

In attempts to discover new ways to create function, researchers have looked to "unorthodox" noncovalent interactions to construct and operate functional molecular systems. These interactions include cation−π and anion−π interactions, as well as halogen bonds and their under-explored homologue chalcogen bonds. In a new Perspective article, Stefan Matile and colleagues summarize the experimental insights gleaned from studies of functional systems comprising noncovalent interactions, with a focus on catalysis (DOI: 10.1021/jacs.5b13006).

The authors cite examples from the literature to demonstrate the principles behind how these unorthodox interactions can be used in various applications. They argue that it is highly likely that the next major milestones in functional systems—including those that can perform catalysis, self-assembly, templating, sensing, and transport—will not be realized without the incorporation of unorthodox interactions. Highlighting ongoing progress toward this end, the authors report on several pioneering examples of research that demonstrate how the clever use of unorthodox interactions can enable scientists to attain what has been previously unattainable for the field of functional systems.

Christine Herman, Ph.D.

IONIC POLYMERS A PLUS FOR DNA-BOUND NANOPARTICLES

Researchers have found that layers of charged polymers can improve the structural rigidity and optical properties of gold nanoparticle superstructures tethered with DNA.

Warren Chan and colleagues have created negatively charged superstructures of gold nanoparticles bound with DNA and then added a positively charged polyamine coating (DOI: 10.1021/jacs.6b00751). The coating compacts the DNA strands holding the nanoparticles together, reducing the space between the nanoparticles and allowing them to cross-link. These compacted superstructures demonstrate enhanced plasmon coupling efficiency and greater structural rigidity than structures without the polymer coating. The researchers then use these structures as templates in a layer-by-layer process, which affords control over the structures' degree of DNA compaction, plasmon coupling efficiency, and response to stimuli.

This work describes a simple method to control the structure and properties of DNA-assembled nanostructures. Previous efforts had explored the use of elemental counterions to control nanoparticle properties, but this polymer-based technique adds stability for solid-state processing and solution-based and biological uses. One clear potential application is sensing, in which researchers can tune the nanoparticle superstructures to respond to subtle changes in environment.

Jenny Morber, Ph.D.

AMPHIPHILIC PHOSPHOLIPIDS "SIT" ON GRAPHITE SURFACES

The ability to tailor the surface chemistry of layered materials has wide-ranging implications for fields including biology and electronics. However, conventional surface assemblies of noncovalent ligands typically involve either standing-up phases, which primarily control interaction with solvent, or lying-down phases, which undergo larger order interactions with the substrate. Now, researchers led by Shelley Claridge report a new route for the functionalization of layered materials that employs "sitting phases" of polymerizable phospholipids, to provide both benefits (DOI: 10.1021/jacs.5b13179).

The team deposits polymerizable amphiphilic lipids on graphite oriented in a sitting geometry in which the two alkyl chains extend along the graphite surface, while two ionizable functional groups, a phosphate and an amine, sit next to the layered material and project into the solvent, respectively. The researchers acquire high-resolution scanning probe measurements and perform other analyses to confirm the precise positioning of the functional groups relative to the layered material surface. Since the headgroup chemistry of the phospholipids can be widely varied, the work opens up the possibility of tuning the functional groups presented at the surface in a highly controlled manner.

Christine Herman, Ph.D.

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POLYKETIDE BIOSYNTHESIS UNRAVELED

Fungal aromatic polyketides exist in two forms. Some, such as anthraquinone, resemble a linear array of fused benzene rings. The second type, called phenalenones, contains a stacked tricyclic core in which one benzene ring is "peri-fused" to naphthalene.

Linear molecules like anthraquinone are created from malonyl-CoA via a linear poly-β-keto-thioester backbone intermediate, through the action of nonreducing polyketide synthases (NR-PKSs). The synthesis of nonlinear aromatic polyketides, though, has remained unclear. Now, Yi Tang, K. N. Houk, and colleagues work out the biosynthesis of herqueinone, a phenalenone from *Penicillium herquei* (DOI: 10.1021/jacs.6b01528).

The team first isolates the herqueinone biosynthetic gene cluster, and using mutagenesis, in vitro assays, and LC-MS they demonstrate that one gene, PhnA, encodes a NR-PKS that catalyzes the initial cyclization steps in the biosynthesis. Unlike with linear aromatic polyketides, though, subsequent steps are carried out by a second enzyme, the FAD-dependent monooxygenase PhnB, and the team describes the mechanism that likely drives these reactions.

These studies "add to the biocatalytic toolbox one can access to rationally control polyketide cyclization toward engineered biosynthesis of new aromatic polyketides," the authors write.
Jeffrey M. Perkel

COMMUNICATION WITHIN POLYKETIDE SYNTHASE COMPLEXES

Polyketides are a general group of complex organic molecules that often have potent biological activity; in fact, many therapeutic drugs are derived from polyketides and their synthetic analogues. In the organisms that produce these secondary metabolites, multidomain enzyme complexes—polyketide synthases (PKSs)—are responsible for the ubiquitous stepwise chain elongation.

A team led by Arnaud Gruez, Benjamin Chagot, and Kira J. Weissman has used structural biology and allied biophysical techniques to characterize docking domains, short protein sequences that contribute to recognition and specificity and are vital for inter-subunit communication during polyketide synthesis (DOI: 10.1021/jacs.5b13372). The researchers identify a new family of docking domains in *trans*-acyl transferase (AT) PKSs and find a mechanism that is different from that of the evolutionarily distinct class of *cis*-AT PKSs. While *cis*-AT PKSs encompass all of the necessary components within a single complex, *trans*-AT PKSs are characterized by one or more free-standing enzyme activities.

The PKS studied here synthesizes the polyketide compound virginiamycin M, whose semi-synthetic derivative dalfopristin is used in combination therapy against multi-drug-resistant bacteria. The authors suggest "that transplantation of docking domains may be sufficient to create novel functional intersubunit interfaces in *trans*-AT PKSs", which could in turn facilitate the synthesis of novel polyketides with unique biological activity.
Sonja Krane, Ph.D.

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