JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Spotlights on Recent *JACS* Publications

A PROTEIN'S EVOLUTION FROM FLEXIBLE TO FIRM

The evolution of a new species begins at the molecular level. The magic happens when a protein with one function undergoes mutations until it adopts a new function. Kenneth Prehoda, Brian Volkman, and colleagues study the previously mysterious role protein flexibility plays in protein evolution (DOI: 10.1021/jacs.6b05954).

The researchers focus on the mutations that allow enzyme guanylate kinase to evolve into the GK protein interaction domain (GKPID). Guanylate kinase is a flexible protein that undergoes a large conformational change from an open shape that binds the nucleotide to a closed shape that facilitates catalysis. Perhoda's team analyzes a series of historical mutations in guanylate kinase using a combination of nuclear magnetic resonance spectroscopy and molecular dynamics simulations to assess the protein's flexibility residue by residue at each step of the evolutionary trajectory. They find that one particular evolutionary mutation, s36P, greatly reduces this flexibility, keeping the enzyme from adopting the closed conformation. The closed shape would make it impossible for GKPID to engage its binding partner. By reducing guanylate kinase's flexibility, the mutation opens the possibility for the evolution of GKPID. The findings highlight the importance of flexibility as a key parameter in protein function and rigidifying mutations in preventing the adoption of non-functional conformations.

Erika Gebel Berg

POLYPEPTIDE SYNTHESIS: CHALLENGES AND PROMISE

Is complex peptide synthesis a solved problem, or is there immense untapped potential for advances in the field? That is the question that Kenneth Schwieter and Jeffrey Johnston tackle in a recent Perspective that highlights the challenges and promise of polypeptide synthesis for advances in peptide-based drugs (DOI: 10.1021/jacs.6b08663).

The authors present several analyses of peptide syntheses, with a focus on complex peptides containing unnatural α-amino amides. Among these analyses are two case studies of highly complex biologically active peptides that incorporate multiple rare amino acids. The chosen examples highlight how state-of-the-art synthetic efforts have led to advances in the field of "biotherapeutics", and also illustrate the challenges currently facing this field, such as stereochemical control and synthetic conciseness. At the center of the article is the question of whether the development of straightforward general synthetic approaches—such as "on-demand" peptide synthesis—is truly attainable. Although the gap between peptide drugs and small molecule drugs persists, the authors are optimistic that innovation in α-amino amide synthesis can, and will bridge that gap. "As peptidic molecules find increasing value in therapeutic development, especially in clinical applications," the authors write, "their impact will ultimately be determined by efficient preparative methods."

Christine Herman

PSEUDO-MIRROR ON THE WALL, MAKE ME THE FAIREST QUASI-RACEMIC CRYSTAL

To solve the structures of challenging biomolecules, chemists sometimes mix a chiral molecule with its mirror image, or enantiomer. These racemic mixtures tend to form co-crystals that are especially amenable to structure solution. But to use this approach, known as racemic crystallography, researchers must synthesize the D-enantiomer, which is not found in nature. In an effort to circumvent this costly step, some chemists have shown that co-crystals form almost as readily when a molecule is combined with its almost-but-not-quite mirror image.

Now Jiawei Wang, Lei Liu, and colleagues have expanded this strategy of quasi-racemic crystallography to solve several polyubiquitin crystal structures for the first time, including linear tri- and tetra-ubiquitin chains (DOI: 10.1021/jacs.6b09545). The team combines each of the oligomers with an easily synthesized monomeric D-ubiquitin. They find that several of the monomeric ubiquitins align to form a pseudo-mirror image of the oligomers, leading to co-crystallization and structure solution.

This work will help elucidate the biochemistry of these molecules, which play a role in the tumor necrosis factor pathway, among other physiological processes. Further, the new monomer/oligomer quasi-racemic crystallography method could potentially be used to help solve the structures of other recalcitrant biomolecules.

Deirdre Lockwood

ISOSTERISM CREATES NEW CATALYTIC REACTIVITY

Organic isosterism refers to the replacement of a molecular fragment or a functional group with a structural and/or electronic equivalent, often leading to new chemical properties and reactivity. One notable example is BN/CC isosterism, that is, replacing a C−C bond unit with the isoelectronic and isosteric B−N bond unit, which has expanded the structural diversity of organic compounds for various applications.

Recently, Shih-Yuan Liu and co-workers report a series of monobenzofused 1,4-azaborine phosphine ligands that can form palladium(0) complexes for *trans*-hydroboration of both terminal and internal 1,3-enynes to dienylboronates with high site- and diastereoselectivity, a previously unattained feat with carbonaceous phosphine ligands (DOI: 10.1021/jacs.6b09759). The researchers find that the azaborine ligands coordinate to palladium(0) in a different mode compared to their monodentate all-carbon skeletal isosteres, which may explain their distinct catalytic performance.

This study represents an interesting and valuable demonstration of BN/CC isosterism applied in ligand-supported metal-catalyzed organic transformations, enriching current ligand design with emerging reactivity. It also provides new pathways as well as inspirations for accessing new chemical functions through expanding chemical space.

Xin Su

Published: November 16, 2016

DOI: 10.1021/jacs.6b11713
J. Am. Chem. Soc. 2016, 138, 15097−15097