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Spotlights on Recent *JACS* Publications

SAM ENZYMES KEEP RADICALS CLOSE FOR EFFICIENT CATALYSIS

Joan B. Broderick, Brian M. Hoffman, and colleagues uncover the mechanism of radical *S*-adenosylmethionine (SAM) enzymes, finding that their efficient catalysis results from the active site's tight control over a radical intermediate (DOI: 10.1021/jacs.5b00498). These enzymes catalyze a wide variety of biochemical reactions, including peptide modification and cofactor biosynthesis. They use an iron−sulfur cluster to cleave SAM, producing a highly reactive radical intermediate. But because of its reactivity, researchers have not been able to directly observe the radical, precluding a clear understanding of the enzymes' mechanism.

By using electron nuclear double resonance spectroscopy to examine a SAM analogue that produces a more stable radical, the researchers find that the active site of the enzyme allows the SAM substrate target to bind within 3 Å of the position where the radical is formed. This configuration keeps the radical on a tight leash. Rather than undergoing side reactions, it reacts via various slight movements mediated by van der Waals contacts with a range of partner molecules.

The resulting effective and broad catalysis may explain why SAM enzymes are so widespread in radical reactions in Nature. By contrast, the less common B12 radical enzymes generate the same radical, but its binding configuration makes it less accessible to reaction partners.

Deirdre Lockwood, Ph.D.

OXYGENASE REACTION SPECIFICITY PROBED

The iron- and 2-(oxo)glutarate-dependent oxygenases conduct a range of enzymatic reactions, and members of this family of enzymes play important roles in the biochemistry of organisms ranging from microbes to humans. One particular bacterial enzyme, *Pseudomonas syringae* SyrB2, chlorinates the amino acid threonine on its C4 position but hydroxylates norvaline on C5, and the enzyme can both chlorinate and hydroxylate aminobutyric acid.

One proposed explanation for these differing activities invokes the positioning of the different substrates with respect to the enzyme iron center, but previously no structural data existed to support or refute that idea. Now, Alexey Silakov and colleagues have used an electron paramagnetic resonance-active form of SyrB2 and various deuterated substrates to measure the relative distances and angles of different substrate atoms with respect to the enzyme active site (DOI: 10.1021/jacs.5b03370).

The team finds that the geometries of these substrates within the active site explain the enzyme's activities. For instance, the threonine C4 methyl group, which reacts most slowly, is located farthest from the iron center, while the norvaline C5, which reacts fastest, is closest. "These data do not rule out the possibility that coordination isomerism also contributes to selectivity, but the magnitude of the differences in positioning observed in this study strongly suggests that substrate positioning exerts a major influence," they write.

Jeffrey M. Perkel

NEW COMPOUND EASES CHEMICAL SYNTHESIS OF PEPTIDES AND PROTEINS

Chemical ligation—an approach often used by researchers to build artificial peptides and proteins—allows short segments of peptides, which are synthesized in a laboratory, to be joined together to make longer proteins. Native chemical ligation is one type, and this method is useful for making proteins with natural amide backbone bonds. A peptide's N-terminal's cysteine residue reacts with a C-terminal thioester group on a second peptide, but a complication is that the thioester group can be labile during solid-phase peptide synthesis.

Philip Dawson and colleagues previously created *N*-acylbenzimidazolinones, better known as *N*-acylureas, to address the labile-thioester issue, but these *N*-acylureas sometimes cause glycine-rich residues to undergo undesirable acylation reactions. Now the same group describes a second-generation *N*-acylurea that sidesteps undesirable reactions (DOI: 10.1021/jacs.5b03504). The compound, containing an *o*-amino(methyl)aniline moiety, is less prone to unwanted acylation reactions during peptide synthesis and is compatible with fast peptide synthesis technologies performed at high temperatures.

With the second-generation *N*-acylurea, the investigators demonstrate that they can easily generate glycine-rich peptide sequences as well as quickly synthesize cysteine-rich proteins. They suggest that this new *N*-acylurea will offer an important way to speed up the chemical synthesis of proteins in order to incorporate non-natural amino acids and specific post-translational modifications.

Rajendrani Mukhopadhyay, Ph.D.

PHOTOACID RELEASED AFTER LIGHT-TRIGGERED CYCLIZATION

Molecules that generate protons when excited by light have been known for more than 30 years. They are commonly used to trigger polymerization during curing, etching, and 3-D printing of materials. Photoacid generators, like triaryl iodonium and sulfonium salts, typically form radicals when exposed to light, and these radicals generate acid by snatching hydrogen atoms from other molecules.

Now Takuya Nakashima, Tsuyoshi Kawai, and their colleagues have developed a photoacid generator that releases one of its own protons during a light-induced molecular cyclization (DOI: 10.1021/jacs.5b02826). The net photochemical quantum yield of this new molecule is about 0.5, among the highest of uncharged photoacid generators. The researchers also use this new molecule to initiate the cationic polymerization of cyclohexene oxide.

Acid generation through light-induced molecular cyclization, as seen in this new molecule, offers an alternative to existing methods of photoacid generation. Modifying the molecule's structure could help further increase the quantum yield and expand its applications to 3-D lithography, the researchers write.

Melissae Fellet, Ph.D.

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QUANTUM ANALYSES REVEAL SECRETS OF SWEET ENZYMES

Carbohydrates are critical macromolecules in biochemistry and cell biology, notably in immunity and intercellular communication. Enzymes that help build, degrade, and modify these sugars are attractive targets for drug development and also find major use in industrial biotechnology. But carbohydrates are often highly complex and flexible structures, ones that are synthetically challenging, and studying their intimate chemistry has proved difficult. To harness their potential as drug targets, better tools for the study of their interactions with enzymes are required.

In this Perspective, Albert Ardèvol and Carme Rovira look at new molecular dynamics simulations using quantum mechanics and molecular mechanics (QM/MM) techniques that have fostered understanding of the mechanisms and conformational dynamics of two important classes of carbohydrate-active enzymes in the past decade (DOI: 10.1021/jacs.5b01156). The two classes, glycoside hydrolases and glycosyltransferases, catalyze the hydrolysis and synthesis, respectively, of glycosidic bonds between carbohydrates and their partner molecules.

Simulations have revealed the conformational dynamics of distinct reaction pathways taken by different families of glycoside hydrolase and characterized their transition states, findings that will aid inhibitor design. The results have also fueled ongoing debate over which of two proposed mechanisms certain classes of glycosyltransferases follow. The authors show that QM/MM techniques are now at the forefront of carbohydrate enzymology, providing insights not accessible by other techniques.

Deirdre Lockwood, Ph.D.

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