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Spotlights on Recent *JACS* Publications

QM/MM MODELING DECIPHERS HPPD REACTION MECHANISM

4-Hydroxyphenylpyruvate dioxygenase (HPPD) is a key enzyme in tyrosine catabolism and the biosynthesis of photosynthetic cofactors. It has been implicated in various genetic diseases, and inhibitors of this enzyme act in plants as herbicides. How HPPD works, though, is unclear, as few structural and computational studies have been completed. Here, Tomasz Borowski and colleagues use molecular simulations to work out important elements of the enzyme's reaction mechanism (DOI: 10.1021/ja506378u).

Borowski's team applies a quantum mechanics/molecular mechanics method called ONIOM(B3LYP:AMBER) to model 6634 atoms comprising the active site of HPPD covalently bound to a reaction intermediate, hydroxyphenylacetate. They probe various possible reaction mechanisms, as well as the molecular specificity that differentiates HPPD from a related bacterial enzyme, hydroxymandelate synthase.

The results resolve previous conflicting "kinetic isotope effect" data suggesting alternative reaction mechanisms for HPPD. "From the computed reaction free energy profiles it follows that the most likely mechanism of 4-hydroxyphenylpyruvate dioxygenase involves electrophilic attack on the C1 carbon of the ring and subsequent single-step heterolytic migration of the [carboxymethyl] substituent," they conclude.
Jeffrey M. Perkel

BLOCK COPOLYMERS COME TOGETHER AS SEGMENTED CYLINDRICAL MICELLES

Owing to their ability to self-assemble in solution, block copolymers—macromolecules made of two or more covalently linked homopolymer units—are the ideal building blocks for nanoscale objects. Cylindrical micelles are one of the many possible shapes that block copolymers can take, and several examples of block copolymer micelles have emerged in the recent literature, with applications ranging from drug delivery to etch resists for surface patterning.

In this study, researchers led by George Whittell, Mitchell Winnik, and Ian Manners report a method for the synthesis of a new class of block copolymer micelles that have a uniform crystalline core surrounded by a complex surface topography (DOI: 10.1021/ja507121h). The micelle structures have a crystalline poly(ferrocenyldimethylsilane) core and are composed of both linear and brush block copolymers that assemble through a process known as crystallization-driven self-assembly. The monodisperse nanostructures exhibit "patchy" coronal domains, the outer layers of the micelles whose size and frequency can be varied by adjusting the type and amount of brush block copolymer used.

This report provides new insights into the process of crystallization-driven self-assembly and sets the stage for future investigations into the usefulness of these and other unique micelle nanostructures based on block copolymers.
Christine Herman, Ph.D.

IT'S ALL ABOUT ORIENTATION

Enzymatic reactions depend on delicate substrate recognition mechanisms to achieve high chemo-, regio-, and stereoselectivity. For metalloproteins, this recognition usually involves specific spatial arrangements in terms of the position and the orientation of substrates relative to metal centers, which coincides with what inorganic chemists try to accomplish with transition metal-based catalysts.

Recently, a multinational research team headed by David Goldberg, Sam de Visser, and Guy Jameson has designed a nonheme iron(IV)−oxo complex capable of mediating intramolecular arene C−F hydroxylation (DOI: 10.1021/ja507346t). The team successfully traps and characterizes the complex at low temperature and further confirms the participation of the $Fe^{IV}(O)$ species in fluoroaryl hydroxylation.

This study represents the first example of this type of a reaction mediated by a nonheme iron complex. More importantly, it identifies the proper orientation of the substrate as a crucial prerequisite, providing valuable insights into understanding ligand structural factors that regulate the reactivity of transition metal complexes.
Xin Su, Ph.D.

CALCULATING DNA REPAIR

Sason Shaik and co-workers uncover that a previously proposed DNA repair mechanism is not correct (DOI: 10.1021/ja507934g). DNA damage is fundamentally linked to the development of cancer, and understanding how the cell repairs DNA lesions can illuminate the processes that drive carcinogenesis and may inform the design of novel anticancer agents.

The authors use quantum mechanical/molecular mechanical simulations, a computational approach that enables the investigation of chemical reactions at an atomistic level, to explore the mechanism of the DNA repair enzyme AlkB. They determine that AlkB repairs an etheno-bridged version of the DNA base adenine via formation of a zwitterionic species, not an epoxide as previously hypothesized. Their simulations further reveal the identity of the reaction intermediates and byproducts, outlining a revised mechanism.

This study highlights the capacity of computational chemistry to reveal aspects of reaction mechanisms not easily identified with experimental methods. This powerful complementary approach facilitates exploration of key aspects of biological processes, with potentially broad academic and therapeutic applications.
Eva J. Gordon, Ph.D.

COMPUTATIONAL MODEL PREDICTS TRANSMEMBRANE PROTEIN INTERACTIONS

Transmembrane (TM) proteins typically contain helical domains that span the membrane. Weak hydrogen bonds formed by carbon donors may cause such helices to interact, forming a so-called GAS_{right} motif. Previously, Alessandro Senes

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and colleagues developed an algorithm called CATM to predict the structure of TM proteins capable of interacting via GAS_{right} motifs (*Proc. Natl. Acad. Sci. U.S.A.* **2014**, DOI: 10.1073/pnas.1319944111). Now, Senes, David Pagliarini, and coworkers experimentally test those predictions for a mitochondrial protein of unknown structure, called ADCK3 (DOI: 10.1021/ja505017f).

The researchers use CATM to develop five possible models for ADCK3 homodimerization. Then, after demonstrating that the protein actually can self-associate in bacterial membranes, they systematically mutate every residue along the TM domain to test their impact, from which they identify the most likely of the CATM models for ADCK3 dimerization.

The results implicate a "glycine zipper" motif in ADCK3 protein−protein interaction, while at the same time arguing against other potential interacting residues. "The work provides a first practical demonstration of the applicability of [CATM] to the characterization of a TM dimer of unknown structure," the authors note, "and it reveals a number of leads that may be important for the biological role of ADCK3, a mitochondrial kinase required for coenzyme Q biosynthesis."

Jeffrey M. Perkel