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Spotlights on Recent *JACS* Publications

LONG LIVE THE TYROSINE RADICAL: A PCET STUDY

The amino acid tyrosine serves as a high-potential redox cofactor in enzyme biocatalysis and thus plays an important role in biology. Tyrosine, the side chain of which contains a phenol, undergoes oxidation−reduction to form a reactive radical in a reaction known as proton-coupled electron transfer (PCET). Several studies performed to date have involved small-molecule tyrosine/phenol model systems, aiming to form an experimental and theoretical framework for PCET in chemistry and biology. However, the understanding gained from these systems cannot readily translate to reactions that occur in proteins. Consequently, radical reactions involving tyrosine in proteins remain poorly understood. Now, a new report from Cecilia Tommos, Leif Hammarström, and co-workers sheds light on PCET reactions within proteins (DOI: 10.1021/ja503348d).

The team uses a model protein system, α_3Y, which contains a deeply buried tyrosine whose environment is characterized by solution NMR. They generate a tyrosine radical using light and perform spectroscopic analyses to study its remarkably slow decay ($t_{1/2}$ = 2−10 s at both pH 5.5 and 8.5), which they attribute to its hydrophobic environment that prevents common modes of rapid decay. Instead the radical is proposed to react via structural fluctuations in the protein matrix. The findings offer insights into the mechanisms underlying protein radical formation, stabilization, and decay.

Christine Herman, Ph.D.

PHOSPHORUS DUO TRACKED DOWN

Unlike its lighter congener nitrogen, phosphorus under ordinary conditions does not persist as a stable diatomic molecule. Instead, elemental phosphorus mainly exists in two forms, the tetrahedral white phosphorus and the amorphous polymeric red phosphorus, both of which are much more reactive than dinitrogen.

Some evidence has shown that diphosphorus (P_2) might be a reactive intermediate, especially as a dienophile in Diels−Alder reactions. Now, Christopher C. Cummins and co-workers synthesize a novel diphosphorus bisanthracene adduct that can thermally transfer P_2 to various 1,3-dienes in solution with high efficiency (DOI: 10.1021/ja507922x). Importantly, using molecular beam mass spectroscopy, the authors directly detect the molecular fragment of P_2 from the thermolysis of this adduct.

Their results, while establishing a firm link between P_2 transfer in solution and P_2 generation in the gas phase by mild heating of a solid, provide the most convincing evidence so far for the generation of P_2 using a molecular precursor. Moreover, the method used in this study may facilitate further research on other similar reactive intermediates.

Xin Su, Ph.D.

A GAS-PHASE SOLUTION FOR PROBING PEPTIDE HELICES

Lindsay J. Morrison and Vicki H. Wysocki explore the intrinsic molecular properties that influence the structure of peptide helices (DOI: 10.1021/ja507298e). Helical regions of proteins participate in many key biological interactions, including the binding of drugs to their biomolecular targets and histones to DNA.

The authors use gas-phase and computational experiments, specifically ion mobility mass spectrometry and molecular dynamics simulations, respectively, to probe peptide helix structure. Examination of the peptides in the gas phase eliminates potential confounding factors associated with solution-phase studies, giving a unique perspective into how N-terminal capping interactions contribute to helix stability.

The investigators find that the identity of the first amino acid and the length of the helix have a strong influence on helix stability in the gas phase. Their findings are consistent with observations in solution, indicating that gas-phase studies can yield information on helix formation and stability that is relevant to proteins in their native environment. Their studies also examine helix abundance in the fragment ions generated from the helical peptides and find that helical fragments preferentially form from helical peptides, suggesting that elements of secondary structure may persist through the fragmentation process.

Eva J. Gordon, Ph.D.

MODELING THE MAMMALIAN MEMBRANE

Cells are defined by their membranes. Membranes determine which signals a cell can send and receive, its mobility and interactions with other cells and pathogens, and more. But how membranes work at a molecular level has so far proved difficult to study. Now Siewert-Jan Marrink and colleagues have figured out a way to crack the problem using "computational microscopy" (DOI: 10.1021/ja507832e).

The team simulates "an average idealized mammalian plasma membrane" measuring 71 × 71 × 11 nm and containing some 20,000 lipids over 40 μs. The simulation comprises 63 lipid classes including cholesterol, saturated and polyunsaturated lipids, gangliosides, and others—but not protein. Previous simulations comprised just a handful of molecular types, a constraint imposed by computational power. Here, the authors simplify the matter by making a "coarse-grained" model in which groups of atoms are treated as single entities.

The simulation illuminates the unequal distribution of cholesterol on either leaflet of the membrane bilayer, the spatiotemporal dynamics of lipid domains, and the formation and composition of ganglioside nanoclusters. Now the authors plan to extend their model to incorporate proteins. "Our study enables a large variety of new computational studies on realistic cellular membranes," they conclude.

Jeffrey M. Perkel

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