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Spotlights on Recent *JACS* Publications

PINPOINTING THE SOURCE OF SUPEROXIDE

A molecular machine—the bc_1 protein complex—helps generate the fuel of life, ATP, but at the same time is suspected of producing a superoxide, a reactive and mobile radical that is toxic and may accelerate aging. The bc_1 protein complex pumps protons across the mitochondrial membrane using a series of redox reactions, moving electrons from quinol substrates to downstream proteins. An intermediate radical is created at each step, offering multiple opportunities for stray reactions to make a superoxide. However, because of the experimental challenges in detecting oxygen species, researchers are not sure where or how the protein complex produces a superoxide.

To identify superoxide's origin, Peter Husen and Ilia Solov'yov perform molecular dynamics simulations, charting the interactions between oxygen and bc_1 in a water lipid/membrane system (DOI: 10.1021/jacs.6b04849). In the simulation, the researchers track oxygen as it diffuses into the protein, looking for conditions that could produce a superoxide: close proximity to an electron donor and a noticeable binding time at a reaction site. The simulation shows that oxygen intermingles at several reaction sites in the bc_1 protein complex, but that one site, named Q_o, is particularly accessible to oxygen. The site is a likely candidate for superoxide production, though future studies with quantum chemical calculations will be needed for confirmation.

Erika Gebel Berg, Ph.D.

ONE-SHOT HAT TRICK ON ARYNES

Arynes, rings with strained formal triple bonds, are highly reactive intermediates that can undergo a variety of transformations to generate functionalized aromatic rings quickly. Aryne chemistry involves nucleophilic additions, cycloadditions, bond insertions, among others, all of which are 1,2-difunctionalization reactions. Yang Li and co-workers report a 1,2,3-trifunctionalization strategy for arynes, where *in situ* generated arynes can couple with aryl allyl sulfoxides to build vicinal C—S, C—O, and C—C bonds in a single step under mild conditions (DOI: 10.1021/jacs.6b06981).

The reaction likely proceeds with a formal [2 + 2] cycloaddition between the aryne and S═O double bond, followed by an allyl S → O migration and a final Claisen rearrangement to complete the C—H functionalization. This development represents a creative advance in aryne chemistry, as it enables the simultaneous construction of three vicinal bonds of different types, overcoming the limitations of conventional difunctionalization. The new approach provides facile access to tetra- and penta-substituted arenes that are widely found in pharmaceuticals and natural products, and it also establishes an excellent precedent for multifunctionalization of arynes.

Xin Su, Ph.D.

γ-AMINO ACIDS PROMOTE STRUCTURAL RIGIDITY FOR PEPTIDIC FOLDAMERS

When designing synthetic oligomers to mimic biopolymers, one must take several factors into consideration, including whether the molecule will retain the intended secondary structure under all conditions. Maintaining a folding pattern can be particularly challenging in aqueous media, because water tends to disrupt intramolecular hydrogen bonds that define particular secondary structures. Samuel Gellman and Brian Fisher demonstrate that ring-constrained γ-amino acid residues can help overcome these disruptive solvation forces to yield stable foldamer helices in aqueous solution (DOI: 10.1021/jacs.6b06177).

The team uses 2-D NMR to compare the ability of different peptide sequences to form helices in methanol and in water, depending on whether the peptides contain linear, flexible γ-amino acid residues or ring-constrained counterparts. The researchers find that although both γ-residue types support the desired folding in methanol, only the cyclically constrained γ-residues promote helicity in water. The findings should encourage continued research into new foldamer building blocks that can favor diverse conformations in biologically relevant media.

Christine Herman, Ph.D.

A SWEET ROUTE TO SUGARS IN STEREO

Fine-tuning the stereochemistry and regiochemistry of glycosylation reactions is challenging but critical in synthesizing complex sugar molecules. Recently, there has been considerable interest in using external reagents or catalysts to influence this selectivity, as it may offer new ways to approach the formation of challenging classes of linkages. Borinic acid catalysts show great promise toward the goal, but readily available glycosyl donors that are compatible with these catalysts remain to be identified. Kyan D'Angelo and Mark Taylor describe a method that employs glycosyl sulfonate donors in borinic acid-catalyzed glycosylations of diol-containing acceptors to create a variety of regio- and stereodefined linkages (DOI: 10.1021/jacs.6b06943).

The glycosyl sulfonates are generated in situ under mild conditions and their reactions with glycosyl acceptors occur at room temperature. This method represents a facile protocol for generating 1,2-*trans*-configured linkages. When the catalyst is not applied in some reactions, the stereoselectivity is reversed in comparison to results of the reaction in the presence of catalyst; yet despite these different outcomes, kinetic studies suggest that both mechanisms are associative (S_N2-type).

The work elucidates the reactivity of glycosyl sulfonates, and could help spur the development of similar catalytic methods for controlling the stereoselectivity of other glycosylation reactions.

Deirdre Lockwood, Ph.D.

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MOLECULAR REACTIONS UNDER THE MICROSCOPE YIELD NEW INSIGHTS

Scanning probe microscopy (STM), a technique widely used to observe the atomic structure on surfaces of materials, is proven to be a powerful tool to elucidate chemical reaction mechanisms by directly observing molecular structures before and after reactions taking place on surfaces. Several recent studies have yielded STM images of such reactions, but because of their complexity and large number of reaction products, reaction mechanisms remained difficult to study.

Dimas G. de Oteyza and co-workers, using STM techniques combined with computer simulations, investigate a relatively simple yet important reaction, enediyne cyclization on a gold surface (DOI: 10.1021/jacs.6b05203). They deposit a sub-monolayer of a simple enediyne, 1,2-bis(2-phenylethynyl)-benzene, onto the Au(111) surface, and induce cyclization by heating, thereby transforming virtually all molecules into one distinct product. The large majority of the product monomers self-assemble into noncovalent dimer complexes. Both the monomers and dimers are clearly visible on STM images, which match density functional theory computations on the reaction products. This work provides insights of the microscopic mechanisms of enediyne cyclization reactions and subsequent self-assembly, which is of great interest in medicine, biochemistry, and nanotechnology.

Alexander Hellemans

ELUCIDATING MECHANISTIC VARIANTS OF METHANE ACTIVATION

Methane, the major component of natural gas, is an important feedstock for the production of value-added chemicals. However, conversion of methane poses a serious challenge in catalysis, as selective cleavage of the inert C−H bond under ambient conditions is difficult. Methane activation by metal oxide in the gas phase serves as an ideal model for studying the reaction mechanism, which may help researchers understand and address the problem. Using an interplay of gas phase mass spectrometry and quantum mechanical calculations, Helmut Schwarz, Sason Shaik, and colleagues elucidate how a heteronuclear metal-oxide cluster, $[Al_2Mg_2O_5]^{\bullet+}$, activates methane (DOI: 10.1021/jacs.6b07246).

The authors demonstrate that the activation of methane occurs by two competing mechanisms: proton-coupled electron transfer and conventional hydrogen-atom transfer. Differences between the reactivity of $Al_2O_3^{\bullet+}$ and the $[Al_2Mg_2O_5]^{\bullet+}$ show that "doping" a free cluster in a designed way not only allows control over its chemistry but also systematically changes mechanistic details. The work uncovers mechanistic variants in metal-oxide mediated C−H bond activation and may inspire future rational catalyst design.

Hui Jin, Ph.D.

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