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Spotlights on Recent *JACS* Publications

EXTENDING DIRECTING GROUPS' POWER TO META AROMATIC NITRATION

Nitroarenes, a class of organic compounds containing carbon−nitrogen bonds, are important intermediates in medicinal chemistry and materials science. Traditionally, in the synthesis of nitroarenes, nitration occurs with a regioselectivity that is dictated by the nature of directing groups present in the parent arene; the transformation usually takes place at positions *ortho* and *para* to the directing groups. Now, Ao Zhang and co-workers demonstrate ruthenium-catalyzed C−H nitration of 2-aryl *N*-arenes with exclusive *meta*-selectivity (DOI: 10.1021/jacs.6b03402).

In-depth mechanistic studies reveal a novel octahedral substrate-coordinated ruthenium complex as the key catalytic intermediate in the regioselective electrophilic aromatic substitution step. The new method reduces the number of steps to synthesize Vismodegib and (*R*)-DRF053, two important anti-cancer agents, in which the C−N bonds would otherwise be quite challenging to install.

As the first example of catalytic *meta*-C−H aryl nitration, the reported method is compatible with a broad range of *N*-aromatic substrates, demonstrating its potential in streamlining the synthesis of nitroarenes as pharmaceutical intermediates, among many other applications. The proposed mechanism may also be useful for the rational design and development of new *meta*-selective functionalization reactions.

Xin Su, Ph.D.

SOLID-STATE NMR SETTLES HIV STRUCTURAL DISPUTE

To design drugs that can stop HIV in its tracks, it helps to know the precise structural architecture of key viral proteins, such as the HIV-1 capsid protein, which forms a shell around viral RNA. Capsid protein structures solved previously using X-ray crystallography, solution NMR spectroscopy, and cryo-electron microscopy have not always been in agreement, suggesting that structural disorder may facilitate capsid formation. Alternatively, the protein may behave differently in solution or in a crystal than it does in physiological noncrystalline, yet ordered, capsid assemblies.

To help sort out this discrepancy, Marvin Bayro and Robert Tycko use solid-state NMR to study noncrystalline HIV-1 capsid protein assemblies that mimic the mature HIV capsid structure (DOI: 10.1021/jacs.6b03983). A key step in the formation of HIV capsids is the dimerization of the HIV-1 capsid protein. Context-dependent variations in the dimer interface structure have been reported, so the researchers elucidate the structure specifically at the dimer interface. Instead of finding a disordered interface as suggested by earlier cryo-EM studies, the researchers find order similar to that observed in some previously reported structures. Observation of a structurally ordered dimer interface suggests that formation of closed HIV-1 capsid shells with curved surfaces depends more strongly on variations in intramolecular conformation, rather than intermolecular structure.

Erika Gebel Berg, Ph.D.

STRETCHING TOWARD SIMPLE RELATIVE CONFIGURATION DETERMINATION

Scientists create and screen vast libraries of natural and synthetic compounds in hopes of identifying a new miracle drug or other useful and valuable commodity. However, figuring out the relative stereochemical configuration of small organic molecules, a key characteristic that determines function, is challenging with current methods especially if the compound is only available in minute quantities. Now, researchers led by Armando Navarro-Vázquez, Christian Griesinger, and Yizhou Liu have developed a simple approach for determining relative configuration using an NMR parameter called the residual chemical shift anisotropy that requires only micrograms of sample (DOI: 10.1021/jacs.6b04082).

The anisotropy of the chemical shift provides information on the relative orientations of specific structural moieties, but it averages out in standard NMR experiments as a molecule tumbles in solution. Here, the authors selectively measure residual chemical shift anisotropy within a single sample by either stretching or compressing a gel—an alignment medium, which disrupts random distribution of molecular orientations and reintroduces some of the information-rich anisotropy—in an NMR tube with variable inner diameters or compression levels, in order to obtain different alignment conditions. The researchers successfully demonstrate the method on five structurally distinct molecules, showing that the work has wide applicability.

Erika Gebel Berg, Ph.D.

PROTEIN PHOTOCYCLE COMES INTO FOCUS

When sensing blue light, which is close in wavelength to potentially damaging UV light, the microbe *Halorhodospira halophile* moves to greener pastures. Photoactive yellow protein (PYP), which has long served as a model for protein signaling studies, triggers the locomotion. Yet to date, researchers have been unclear as to precisely how PYP works.

Now Philip Anfinrud and colleagues have used small- and wide-angle X-ray scattering to probe the PYP structure in solution from 100 ps to 1 s following excitation (DOI: 10.1021/jacs.6b03565). They detail a five-step photocycle in which irradiation results in *trans*-to-*cis* isomerization of the *p*-coumaric acid chromophore, protein compaction, and ultimately, unfolding of a 25-residue domain—a dramatic structural elongation into an active signaling form—before returning to ground state.

Three of these intermediate states match previously determined structures, but importantly, the key signaling state is not among them: it could not be captured in earlier experiments due to crystallography constraints. "This mechanistically detailed description...provides a framework for understanding signal transduction in proteins, and for assessing and validating theoretical/computational approaches in protein biophysics," the authors write.

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