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Spotlights on Recent *JACS* Publications

OBSERVATION OF UV-INDUCED PROTON TRANSFER BETWEEN DNA STRANDS

UV radiation excites DNA, causing DNA damage and mutation. Most excitations in single DNA bases decay on a sub-picosecond time scale, with minimal likelihood of lasting damage; however, longer-lived excited states are detected in single- and double-stranded DNA. The mechanism behind the slower energy relaxation in double-stranded DNA remains intensely debated, and understanding this mechanism is fundamental to further unraveling complex mutagenic events.

Bern Kohler, Roberto Improta, and colleagues use femtosecond vibrational spectroscopy combined with quantum mechanical calculations to observe the photoinduced transfer of a proton between strands of the DNA double helix (DOI: 10.1021/jacs.5b03914). Interstrand proton transfer, which occurs in response to intrastrand electron transfer, is sensitive to the DNA base sequence and results in tautomeric base pairs with picosecond lifetimes.

Further experimental and theoretical work will establish whether any of the observed radicals persist long enough to initiate DNA damage. The photoinduced proton-coupled electron transfer observed in this study provides a new framework for understanding and possibly manipulating charge carrier formation and transport in DNA and other nanoscale systems.

Hui Jin, Ph.D.

RECIPE FOR QUICK AND EASY DNA PARTICLES

Just as a basic brick can be used to build an intricate cathedral or a much simpler backyard barbeque pit, DNA can be the building block of life or a tool for human invention. Not surprisingly, researchers have exploited DNA's base-pairing interactions to create precisely controlled molecular structures, from complex DNA origami to high-dimensional structures such as rings, tubes, and boxes. Small molecule-DNA hybrids (SMDHs), which contain organic cores with multiple attached DNA strands, have become popular as starting materials for nanotechnology applications. Frustratingly, SMDHs bearing more than three DNA strands have a tendency to clump, forming ill-defined products.

SonBinh Nguyen and colleagues have capitalized upon this clumping tendency by forming spherical nanoparticles out of four-stranded SMDHs (DOI: 10.1021/jacs.5b03485). The size of these small particles can be easily tuned by varying assembly time and salt and nucleic acid concentrations. In experiments, these particles are more resistant to enzymes that cleave DNA, and cells internalize them more quickly than the individual synthetic nucleic acid components. Moreover, the particle surfaces can be further functionalized for applications including sensing, tracing, or capture−release.

These attributes make the nanoparticles attractive new molecular vehicles to deliver therapeutic molecules, flag cancer cells or other diseases, follow tracer species through the body, and much more.

Jenny Morber, Ph.D.

NEW PROBE CAPTURES REACTIVE CYSTEINES IN LIVE CELLS

Many of the post-translational modifications that tweak protein activity act on cysteine residues. Researchers have probes for cysteine reactivity, but many are broadly cytotoxic and afford neither spatial nor temporal control. Now, Masahiro Abo and Eranthie Weerapana describe a caged electrophilic probe that overcomes these issues (DOI: 10.1021/jacs.5b04350).

The researchers synthesize a ketone-containing electrophile that is caged with a photoreactive protecting group. Brief UV irradiation activates the probe, promoting conjugation to cysteine thiol groups. An alkyne moiety provides a handle for click-chemistry addition of fluorophores or biotin, the latter of which enables mass spectrometric identification. The caged reagent is nontoxic at concentrations up to 250 μM in eukaryotic cells, compared with 3 μM for an alternative iodoacetamide-alkyne reagent, and uncaging is complete within 5 min. Researchers can induce uncaging where and when they desire, the authors note.

When applied to A431 skin cancer cells, the reagent identifies several hundred cysteines whose reactivity changes under oxidative conditions that result from growth factor stimulation, including several previously identified as participating in disulfide bonding. "The versatility of this platform enables quantification of cysteine modification in living cells upon treatment with various oxidative insults, cysteine-reactive small molecules, or thiophilic metal ions," the authors write.

Jeffrey M. Perkel

LITHIUM ENOLATE SOLVATION MYSTERY SOLVED

Organic lithium compounds, especially lithium enolates, are a classic type of reagent used extensively in carbonyl functionalization. While it is well established that auxiliary ligands can alter the thermodynamics and kinetics of reactions involving lithium enolates, too little is known about these species' solvation states to establish a similar correlation with their structures or their reactivity.

This complication has led Paul G. Williard and co-workers to investigate the influence of hexamethylphosphoramide (HMPA), a common additive used to "activate" lithium salts, on the aggregation behavior of lithium pinacolone enolate in both the solid and the solution states (DOI: 10.1021/jacs.5b01906). Combining crystal structure analysis and 1-D/2-D NMR titrations, the researchers examine the structures of a number of HMPA-solvated lithium enoloates and find that steric interaction within enolate aggregates dominates their solvation states.

"Crystal structures of HMPA-solvated lithium simple ketone enolates are reported for the first time," the authors note in this study, which enables structural correlation with their aggregates in solution. More importantly, by identifying the key factor that controls enolate solvation, the results shed light on how to tune the reactivity of lithium enolates.

Xin Su, Ph.D.

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