Spotlights on Recent JACS Publications

G-QUADRUPLEXES FLEX SLOWLY INTO THEIR DIFFERENT FORMS

G-Quadplexes are four-stranded helical structures that form in sections of nucleic acids with high guanine content. Because they are instrumental in the transcription and replication of oncogenes, they are promising targets for new cancer therapies. Researchers have found that these motifs dynamically shift conformation, with important biological implications. But they still do not understand exactly how this happens or how fast.

Harald Schwalbe and co-workers investigate these questions in two G-quadruplex structures from the promoter regions of the cMYC oncogene and the human telomerase-reverse-transcriptase (hTERT) gene (DOI: 10.1021/jacs.9b10367). They prevented conformational changes in the G-quadruplexes by using protective groups to block hydrogen bonding and then released the block and traced the kinetics of refolding with time-resolved NMR. They compared these results with thermal hysteresis kinetics experiments.

The team finds that shifts in conformation in these structures take place slowly, over hours. In the case of hTERT, the kinetics are consistent with unfolding of one form before refolding into a new one. Further exploration of these “long-lived folding intermediates” could help expand our understanding of how G-quadruplexes function.

Deirdre Lockwood Ph.D.

EPITRANSCRIPTOMICS AND THE SHAPE OF RNA

N^6-Methyladenosine (m^6A) is a prevalent post-transcriptional modification on mRNA; its presence on transcripts guides numerous cellular functions and has been implicated in various disease processes. Aside from recruiting reader proteins to RNA, how the m^6A modification specifically impacts RNA function, including effects on the kinetics of conformational changes, is not well understood. Now, Al-Hashimi and co-workers present an NMR-based approach to site-specifically examine the kinetics of RNA duplex hybridization in the context of m^6A (DOI: 10.1021/jacs.9b10939).

Using NMR spin relaxation dispersion and chemical exchange saturation transfer, the authors show that while m^6A has little effect on the melting rate of an RNA duplex, it meaningfully decreases the annealing rate. They propose that the decrease stems from energetic differences between the unpaired and paired states. In the unpaired state, the N^6-methyl group exists in the syn conformation, but it must rotate to the energetically unfavorable anti conformation in the duplex. The resulting altered kinetics could impact various aspects of RNA activity, including tRNA selection, interaction with microRNAs, proteins, and other biomolecules, and RNA folding. These findings provide valuable insight into how epitranscriptomic alterations shape RNA structure and function.

Eva J. Gordon Ph.D.

OPENING THE DOOR TO CONTROLLABLE DEGRADATION WITH LOCKABLE POLYMERS

Developing degradable polymers is an important step in reducing the environmental impact caused by humanity’s ubiquitous use of plastics. Typically accomplished by introducing cleavable groups into the polymer backbone, this often has the unfortunate side effect of reducing the material’s durability and chemical resistance, since degradation can be unintentionally triggered. Tze-Gang Hsu and co-authors have developed a unique method of “locking” these cleavable portions of the polymer, preventing breakdown until the locks are broken through mechanical force (DOI: 10.1021/jacs.9b12482).

While ester groups have previously been used as a cleavable component in degradable polymers, the authors iterate upon this with the addition of cyclobutane, resulting in a cyclobutane group in the polymer backbone fused to a lactone ring. Under conditions that cleave the lactone, the cyclobutane remains intact in the backbone, keeping the polymer together. The lactone can then be re-formed, leading to recovery of the polymer’s undegraded structure. Only when the cyclobutane group is first broken via sonication does subsequent cleavage of the ester lead to degradation of the polymer backbone, as verified with ^1H NMR spectroscopy and gel permeation chromatography. Looking forward, the authors see their work as an introduction to a broad class of polymers that can be controllably degraded.

Charlie Crowe

HIGH-TEMPERATURE FERROELECTRICS WITH TUNABLE PHOTOLUMINESCENCE

Perovskites have garnered much interest over the past decade for their remarkable ferroelectric properties. The ability to design synthetic ferroelectrics via organic—inorganic, two-dimensional (2D) hybrid double perovskites over the past decades even led to the enthusiastic exploration of hybrid 3D double perovskites. However, the complicated design and
symmetry requirements that have to be met toward the synthesis of both ferroelectric 3D and 2D perovskites are currently limiting factors in the design of high-temperature perovskites.

Working on the premise that 2D hybrid double perovskites with rare-earth nitrates can circumvent many of the known limitations of hybrid perovskites and thus create high-temperature ferroelectrics, Chao Shi and co-workers have synthesized perovskite ferroelectrics by incorporating trivalent rare-earth ions and chiral organic cations within the network (DOI: 10.1021/jacs.9b11697). Currently, high-temperature ferroelectric perovskites that can operate under ambient conditions are rare, and therefore, these perovskites pave the way for highly efficient sensors and multifunctional devices which can be operated under a wider range of temperatures. Additionally, the ability to simultaneously tailor the photoluminescence by varying the relative concentrations of the rare-earth ions and the cations within the perovskite indicates that the material can be tuned to elicit a wide range of responses. This aspect of the perovskites can potentially open up new applications, especially in the fields of high-performance photovoltaics and optoelectronics.

Devatha P. Nair Ph.D.

INVERTING OUR UNDERSTANDING OF ENZYMATIC EPOXIDE FORMATION

Epoxide-containing molecules represent an important class of enzyme-inhibiting drugs due to their ability to attach to active site residues upon nucleophilic ring-opening. The enzyme (S)-2-hydroxypropylphosphonate epoxidase (HppE) catalyzes the installation of the epoxide moiety on the naturally occurring antibiotic fosfomycin, which is commonly used to treat urinary tract infections. HppE has been shown to invert the stereochennical cofigureation of the molecule at one carbon center, yielding the more active cis-epoxide compound with remarkable selectivity.

While this reaction step has been proposed to proceed through a cation at the inverted carbon center, Shengbin Zhou and colleagues now challenge the notion of chemically enforced stereoselectivity (DOI: 10.1021/jacs.9b10974). The researchers first found that HppE can epoxidize analogs of the substrate that were halogenated to destabilize organic cations, thereby providing evidence against a carbocation intermediate. They then introduced various active site mutations into the enzyme and discovered a correlation between the steric bulk of the amino acid side chains and the stereochemistry of the epoxidation product. Collectively, these results support a radicaloid coupling mechanism that is guided by specific steric interactions between the enzyme and substrate. This work reveals a unique biological strategy to control epoxide stereochemistry that could be harnessed to develop new, highly potent synthetic antibiotics.

Sarah Anderson