Insights into the amazing world of RNA catalysis from hybrid quantum mechanical/molecular mechanical simulations

Darrin M. York

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Department of Chemistry and Chemical Biology and Laboratory for Biomolecular Simulation Research, Rutgers University, 174 Frelinghuysen Road, Piscataway, NJ 08854-8076, USA. Darrin.York@rutgers.edu

In biology, RNA enzymes, or ribozymes, play important roles in gene regulation, RNA processing and peptide synthesis. However, the function of many ribozymes have yet to be unveiled, and new ribozymes continue to be discovered. In industry, synthetic ribozymes have been engineered that have great promise in the design of new biomedical technology and therapeutics.

From a chemical perspective, it is a fascinating question as to how molecules of RNA, with their limited repertoire of building blocks and chemical functionality, are able to fold into three dimensional structures that are able to convey catalytic capability. A detailed understanding of the mechanisms of RNA catalysis, therefore, provides a foundation from which new ribozyme-based technologies or therapeutics can be designed.

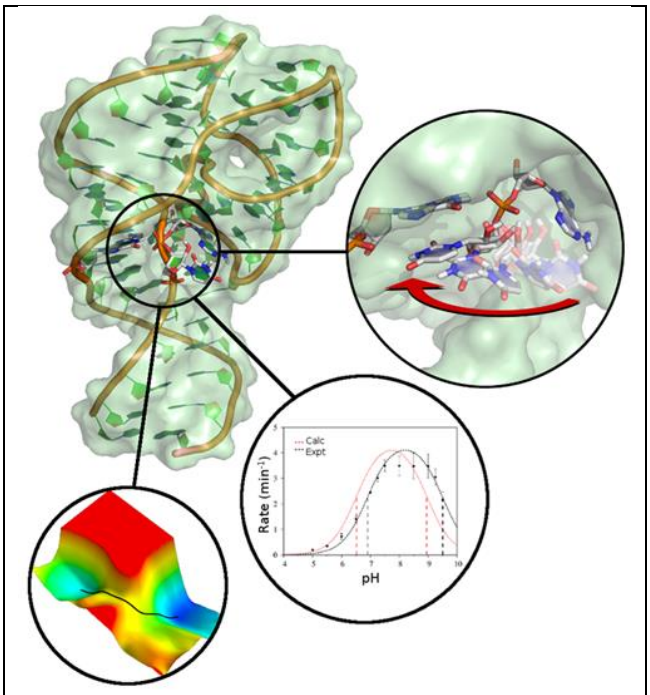

Figure: Mechanism of the twister ribozyme.

Small nucleolytic ribozymes are important model systems in the study of RNA catalysis. Recently, there has been a surge of progress in the identification of new classes of self-cleaving nucleolytic ribozymes that have been revealed by comparative genomics analysis, and characterized structurally by X-ray crystallography. However, crystal structures often are not representative of the active states in solution due to a number of factors, and the mechanistic interpretation of experimental structural and functional data requires detailed molecular simulations and computational modeling.

The present talk will focus on the use of computational enzymology approaches to gain a unified interpretation of experimental data and a detailed, predictive understanding of catalytic mechanism. Molecular simulation models, including from *ab initio* combined quantum mechanical/molecular mechanical (QM/MM) methods as well as fully quantum mechanical force fields (QMFFs), 3D-RISM calculations, and GPU-accelerated free energy methods are used to study the many facets of RNA catalysis for a series of nucleolytic ribozymes including the hammerhead, HDV, twister, and TS ribozymes. These studies reveal common themes and new twists in the diverse array of catalytic strategies employed by RNA enzymes. The talk will conclude with a brief perspective of current challenges and important future directions in the field.