Metal Interactions with Structured and Catalytic RNA Molecules

Victoria J. DeRose, Shannon Burns, Matthew Vogt, Edith M. Osborne,[1] Janell E. Schaak, Nak-Kyoon Kim, Murali Ayaluru

Department of Chemistry, Texas A&M University, [1]Department of Biochemistry and Biophysics, Texas A&M University

RNA (ribonucleic acid) is a unique biopolymer whose complexity of structure and function is an ever-growing topic. The bioinorganic chemistry of RNA is of significant interest because cations, both monovalent and divalent, control RNA folding as well as catalysis in those RNAs that perform chemical reactions (ribozymes). RNA folds into compact structures, requiring energetic compensation for the close proximity of multiple charged phosphodiester linkages. Both monovalent (Na^+, K^+) and divalent (Mg^{2+}) ions promote RNA folding, but structure and catalysis are more sensitively influenced by divalent ions. Based on biochemical studies and models derived from X-ray crystallography, cations have been invoked as specific cofactors in some reactions catalyzed by ribozymes. Presumably, cofactors that are critical to a reaction would have defined binding sites, but the properties of such sites in RNA may differ substantially from expectations that are based on studies of metalloproteins.

We have applied spectroscopic and other techniques in an effort to understand the properties of metal 'sites' in RNA. A combination of EPR spectroscopy, used both for monitoring surrogate Mn^{2+} binding and nitroxide spin labels, ^{31}P NMR, and activity and other biochemical measurements, allows correlation of metal association with RNA folding and activity. In the case of the self-cleaving hammerhead ribozyme (HHRz), a high-affinity metal site that has a specific coordination environment is found to control a key folding step. HHRz catalytic activity is sensitive to the ligands of this metal ion. Similarly, in the P5abc subdomain of the Group I intron, a metal ion cluster is formed whose properties depend specifically on the ligands available to coordinate the ions. In both of these cases, metal ion sites can be characterized that have relatively high affinities and distinct RNA ligands. These results indicate that even in a background of electrostatic screening, population of distinct metal sites can sensitively control RNA function.