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A Stability Concept for Metal Ion Coordination to Single-Stranded Nucleic Acids and Affinities of Individual Sites

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The three-dimensional architecture and function of nucleic acids strongly depend on the presence of metal ions, among other factors. Given the negative charge of the phosphate−sugar backbone, positively charged species, mostly metal ions, are necessary for compensation. However, these ions also allow and induce folding of complicated RNA structures. Furthermore, metal ions bind to specific sites, stabilizing local motifs and positioning themselves correctly to aid (or even enable) a catalytic mechanism, as, for example, in ribozymes. Many nucleic acids thereby exhibit large differences in folding and activity depending not only on the concentration but also on the kind of metal ion involved. As a consequence, understanding the role of metal ions in nucleic acids requires knowing not only the exact positioning and coordination sphere of each specifically bound metal ion but also its intrinsic site affinity. However, the quantification of metal ion affinities toward certain sites in a single-stranded (though folded) nucleic acid is a demanding task, and few experimental data exist.

In this Account, we present a new tool for estimating the binding affinity of a given metal ion, based on its ligating sites within the nucleic acid. To this end, we have summarized the available affinity constants of Mg^{2+}, Ca^{2+}, Mn^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} for binding to nucleobase residues, as well as to mono- and dinucleotides. We have also estimated for these ions the stability constants for coordinating the phosphodiester bridge. In this way, stability increments for each ligand site are obtained, and a clear selectivity of the ligating atoms, as well as their discrimination by different metal ions, can thus be recognized.

On the basis of these data, we propose a concept that allows one to estimate the intrinsic stabilities of nucleic acid-binding pockets for these metal ions. For example, the presence of a phosphate group has a much larger influence on the overall affinity of Mg^{2+}, Ca^{2+}, or Mn^{2+} compared with, for example, that of Cd^{2+} or Zn^{2+}. In the case of Cd^{2+} and Zn^{2+}, the guanine N7 position is the strongest intrinsic binding site. By adding up the individual increments like building blocks, one derives an estimate not only for the overall stability of a given coordination sphere but also for the most stable complex if an excess of ligating atoms is available in a binding pocket saturating the coordination sphere of the metal ion. Hence, this empirical concept of adding up known intrinsic stabilities, like building blocks, to an estimated overall stability will help in understanding the accelerating or inhibiting effects of different metal ions in ribozymes and DNAzymes.

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