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# How Does $Mg^{2+}$ Modulate the RNA Folding Mechanism: A Case Study of the G:C W:W Trans Basepair

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Reverse Watson-Crick G:C basepairs (G:C W:W Trans) occur frequently in different functional RNAs. This is one of the few basepairs whose gas-phase-optimized isolated geometry is inconsistent with the corresponding experimental geometry. Several earlier studies indicate that through post-transcriptional modification, direct protonation, or coordination with  $Mg^{2+}$ , accumulation of positive charge near N7 of guanine can stabilize the experimental geometry. Interestingly, recent studies reveal significant variation in the position of putatively bound  $Mg^{2+}$ . This, in conjunction with recently raised doubts regarding some of the  $Mg^{2+}$  assignments near the imino nitrogen of guanine, is suggestive of the existence of multiple  $Mg^{2+}$  binding modes for this basepair. Our detailed investigation of  $Mg^{2+}$ -bound G:C W:W Trans pairs occurring in high-resolution RNA crystal structures shows that they are found in 14 different contexts, eight of which display  $Mg^{2+}$  binding at the Hoogsteen edge of guanine. Further examination of occurrences in these eight contexts led to the characterization of three different  $Mg^{2+}$  binding modes: 1) direct binding via N7 coordination, 2) direct binding via O6 coordination, and 3) binding via hydrogen-bonding interaction with the first-shell water molecules. In the crystal structures, the latter two modes are associated with a buckled and propeller-twisted geometry of the basepair. Interestingly, respective optimized geometries of these different  $Mg^{2+}$  binding modes (optimized using six different DFT functionals) are consistent with their corresponding experimental geometries. Subsequent interaction energy calculations at the MP2 level, and decomposition of its components, suggest that for G:C W:W Trans,  $Mg^{2+}$  binding can fine tune the basepair geometries without compromising with their stability. Our results, therefore, underline the importance of the mode of binding of  $Mg^{2+}$  ions in shaping RNA structure, folding and function.

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