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Higher order structures involving post transcriptionally modified nucleobases in RNA

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Post transcriptionally modified nucleotides play an important structural role in RNA by providing additional chemical diversity to the architecture of the constituent nucleotides. To understand the contribution of these modified nucleotides in tertiary interactions that help in RNA folding, we present a systematic investigation of higher order hydrogen bonded structures involving modified nucleotides using bioinformatics based crystal structural database analysis and quantum chemical calculations. Our analysis reveals that 29% of the modified bases that participate in hydrogen-bonding interactions form higher order motifs, which points towards their importance as RNA building blocks. Although greater geometric variations in such motifs are observed in tRNA, they occur most commonly in rRNA, where they may play a role in RNA folding. Characterization of the optimum geometries and binding strengths of the modified motifs reveals that structures that involve either a positively charged modified nucleobase (m^7G^+), or a protonated nucleobase (A^{H^+}) paired with a modified base (Ψ), possess stronger binding compared to uncharged (neutral) motifs. Thus, they seem to play an important role in stabilizing complex RNA structures, possibly through enhanced electrostatic interactions. Overall, our combined statistical, geometric, energetic and contextual analysis of these modified motifs reveals their importance as stable RNA building blocks, and highlights the need for further investigations related to their functional roles.

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