

Role of Mg^{2+} and Local Solvation in Hammerhead Ribozyme Self-Cleavage Reaction

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Ions play a central role in ribozyme self-cleavage reactions, with Mg^{2+} exhibiting a particularly strong catalytic effect compared to other divalent (e.g., Ca^{2+}) or monovalent cations. Here, we investigate the mechanistic role of Mg^{2+} by exploring multiple reaction pathways originating from distinct hammerhead ribozyme conformations using QM/MM simulations combined with the adaptive string method. Our results show that, beyond activating catalytically competent conformations, Mg^{2+} influences the reaction by shaping the local solvation environment, which in turn modulates the free energy barrier. These observations suggest that local solvation effects contribute to catalytic activity in an unexpected way, which merits further consideration.