

Atomistic Simulation of Pathways for Mg²⁺-Water Dissociation with Rigorous Kinetics

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Metal cations and especially Mg²⁺ play a very important role in many biological processes such as RNA folding and catalysis. In order for Mg²⁺ to interact with RNA, a water molecule must first dissociate from its water hydration shell: this process is very slow and a rare event due to the shell's rigidity. The accurate simulation of Mg²⁺-water dissociation is necessary for future simulations of processes that involve Mg²⁺ interaction, but the length of the process makes it unfeasible to simulate using regular brute force methods. The overall purpose of this study is to find a working methodology to effectively simulate Mg²⁺-water dissociation. Previous simulations of the Mg²⁺-water system using umbrella sampling and TST approximations have been unable to obtain accurate results for the dissociation rate constant of the system. Instead, this study utilizes the weighted ensemble (WE) path sampling approach along with a two-dimensional progress coordinate that tracks the distance and orientation of the dissociating water molecule. These methods were tested on the faster but similar Ca²⁺-water system with the TIP3P water model and AMBER99SB-ILDN all-atom force field parameters. The results proved successful for the methodology since dissociation events were captured and the simulation results reached convergence. The achieved stability concludes that the methods used (the progress coordinate with weighted ensemble) result in sampling efficiency that will allow for the simulation of Mg²⁺-water. In addition, the accurate estimate of the rate constant of dissociation provides evidence to consider the water model and force field used in this simulation as reasonably accurate in describing ion-water interactions and as utile for the simulation of Mg²⁺-water dissociation.