Investigating the effects of molecular charges and water desolvation on the complex formation of Neuraminidase and its inhibitors.

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The highly mutative influenza virus causes seasonal epidemics and the occasional pandemic. Several drugs have been developed in order to combat this virus, many of which inhibit the active site of the viral enzyme neuraminidase. Neuraminidase's function is to catalyze the cleavage of terminal sialic acid moieties from host cell surface receptors, enabling nascent viral shedding and subsequent infection. In this work, we have used Brownian dynamics (BD) simulations to study the binding kinetics of the competitive neuraminidase inhibitors oseltamivir, peramivir, and zanamivir, along with the natural substrate, sialic acid. Surprisingly, even though all four molecules are similar in chemical structure, oseltamivir has a much higher association rate constant to the active site of neuraminidase than any of the other ligands. Upon analyzing the BD simulations, it was found that oseltamivir and sialic acid approached the active site differently, with oseltamivir approaching the active site from many directions whereas sialic acid only approached from one primary direction. Additionally, oseltamivir approached with many orientations, while sialic acid only arrived with its carboxylate moiety facing up. As such, we investigated whether peramivir and zanamivir followed the same complex forming patterns as oseltamivir, as well as whether molecular charges or water desolvation was the main determinant of the ligand orientations.