Mechanistic insight into the catalytic activity of ββα-metallonucleases from computer simulations: *Vibrio vulnificus* periplasmic nuclease as a test case

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Using information from wild-type and mutant *Vibrio vulnificus* nuclease (Vvn) [1-2] and I-Ppol homing endonuclease [3] co-crystallized with different oligodeoxynucleotides, we have built the complex of Vvn with a DNA octamer and carried out a series of simulations to dissect the catalytic mechanism of this metallonuclease in a stepwise fashion. The distinct roles played in the reaction by individual active site residues, the metal cation and water molecules have been clarified by using a combination of classical molecular dynamics simulations and quantum mechanical calculations. Our results strongly support the most parsimonious catalytic mechanism, namely one in which a single water molecule from bulk solvent is used to cleave the phosphodiester bond and protonate the 3'-hydroxylate leaving group [4].