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Calculating the shift in pKa of the position 66 for an Staphylococcal nuclease mutant with the Replica Exchange Free Energy Perturbation method DANIAL SABRI DASHTI, Physics Department and Quantum Theory Project at University of Florida, ADRIAN ROITBERG, Quantum Theory Project at University of Florida — The Experimental pKa value of Glutamate66 in a hyperstable mutant of Staph Nuclease, which has been measured by Moreno et al., shows a large shift of around 5 pKa units with respect to a glutamate in solution. In order to reproduce the large experimental shift by single structure continuum solvent computational methods, it is required that the dielectric constant of the interior of the protein be set to around ten in the simulations. The physical reason behind this is not understood as of yet and hypotheses have been produced by the Moreno group regarding solvent penetration, protein reorganization etc. We tried to resolve this inconsistency between experimental and continuum methods by introducing a four-state thermodynamic cycle that has couples conformational states with protonation state of the side chain of E66. We propose that what the experimental methods, (which are mostly sensitive to configurational changes) are measuring is actually the equilibrium constant between the two configurational states rather than between the two protonation states. In this regard we applied our recently developed Replica Exchange method Free Energy Perturbation (REFEP) in implicit solvent to calculate the pKa value of E66 for each of the configurational states as well as the mixed configuration, and our results are in almost perfect agreement with the experiments of Moreno.

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