

Studying Catalysis of *Escherichia coli* Prolyl-tRNA Synthetase using Quantum Mechanical/Molecular Mechanical Simulations

Tiffany Huynh, Clorice Reinhardt, Sanchita Hati, Sudeep Bhattacharyya

Prolyl-tRNA synthetase is a multi-domain enzyme belonging to the family of aminoacyl-tRNA synthetases. It catalyzes the attachment of proline to its cognate tRNA in a two-step reaction. In the first step, the proline is activated forming prolyl-adenylate. Next, the proline is attached to the cognate tRNA. The various domains of the enzyme are known to be dynamically coupled, however, the precise role of the domain motions on the catalytic steps are poorly understood. Using quantum mechanical/molecular mechanical simulations, the adenylate formation (the first step) was modeled in the enzyme as well as enzyme-free (aqueous) systems. In both simulated models, the proline and triphosphate group of the ATP has been treated with self-consistent charge density functional tight-binding (SCC-DFTB) method, while the protein and/or solvent atoms are treated with classical mechanics. Similar simulations are being extended to mutant enzymes, which were generated by in-silico mutagenesis of residues pertaining to hinge and active site regions. Herein, we present the preliminary results, which include the free-energy of activation of prolyl-adenylate formation in water, the wildtype enzyme, and mutant enzymes.