Fast Dynamics Associated with Barrier Crossing in Born-Oppenheimer Enzyme Purine Nucleoside Phosphorylase

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Abstract

The role of dynamic motions in enzyme catalysis on different time scales has been investigated for decades and remains an active debate. The connection between enzyme dynamics and transition state formation in human purine nucleoside phosphorylase (PNP) has been explored through our computational studies in collaboration with the Schramm group. Experimental isotope labeling of human PNP (heavy PNP) probed the mechanism of chemical barrier crossing by perturbing the single-turnover rate constant while not altering the kinetic isotope effect and steady-state kinetic parameters. To further elucidate the underlying mechanism of barrier crossing in this enzymatic reaction, theoretical models were constructed for both light and heavy PNPs. QM/MM transition path sampling (TPS) was applied to study the fast (femtosecond) dynamics during barrier crossing in explicit solvent. Vibrational motions were analyzed to find Fourier components at specific frequencies on degrees of freedom associated with the reaction coordinates at the transition path ensemble. The present study confirms the previously proposed reaction mechanism in PNP catalysis, and provides insight into how the vibrational motions are coupled to the chemical barrier crossing, and how they effect the catalytic efficiency.