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Another Look at the Mechanisms of Hydride Transfer Enzymes from Quantum and Classical Transition Path Sampling[1] MICHAEL DZIERLENGA, DIMITRI ANTONIOU, STEVEN SCHWARTZ, Univ of Arizona — The mechanisms involved in enzymatic hydride transfer have been studies for years but questions remain, due to the difficulty in determining the participation of protein dynamics and quantum effects, especially hydrogen tunneling. In this study, we use transition path sampling (TPS) with normal mode centroid molecular dynamics (CMD) to calculate the barrier to hydride transfer in yeast alcohol dehydrogenase (YADH) and lactate dehydrogenase (LDH). Calculation of the work applied to the hydride during the reaction allows for observation of the change in barrier height due to inclusion of quantum effects. Additionally, the same calculations were performed using deuterium as the transferring particle to validate our methods with experimentally measured kinetic isotope effects. The change in barrier height in YADH upon inclusion of quantum effects is indicative of a zero-point energy contribution, and is evidence that the protein mediates a near-barrierless transfer of the rate-limiting hydride. Calculation of kinetic isotope effects using the average difference in barrier between hydride and deuteride agreed well with experimental results.

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