Quantum Hydride Transfer in Formate Dehydrogenase: Environment Reorganization, Coupled Primary and Secondary Hydrogen Motions, and Kinetic Isotope Effects

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We present a new theoretical and computational framework for the simulation of enzymatic hydrogen-transfer reactions, here applied to the study of the hydride transfer step in Formate Dehydrogenase. The main features of our approach are the combination of a collective environmental coordinate adapted to QM/MM calculations, and an explicit quantization for the motion of the key light particles involved in the process. We find that in Formate Dehydrogenase the hydride transfer motion is coupled to the rearrangement of a secondary hydrogen atom. Depending on the donor-acceptor distance attained at the Transition State, the rearrangement of the primary and secondary hydrogen atoms can take place via tunneling through a potential energy barrier (nonadiabatic regime) or without an effective potential energy barrier (adiabatic regime). To calculate the reaction rate constant, we used a general theoretical framework that considers both adiabatic and nonadiabatic contributions. The calculated primary and secondary Kinetic Isotope Effects compare well with experimental determinations, supporting our simulations and approach. Our results show that the Kinetic Isotope Effect value strongly depends on the Transition-State donor-acceptor distance, and can thus be used as a sensitive probe of Transition State geometry changes. The approach and method presented here can be generalized to study other enzymatic proton- and hydride-transfer reactions. The combination of an adequate collective environment coordinate and the quantization of participating light particles, together with an appropriate theoretical framework, improve the understanding of quantum effects in these enzymatic reactions, and show how they are modulated by the protein structure through the selection of the donor-acceptor distances attained at the TS.