Quantum dynamical studies on Soybean Lipoxygenase-1

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$$i\hbar\frac{\partial}{\partial t}\Psi = H\Psi$$

Abstract

We discuss the hydrogen tunneling problem in the active site of the biological enzyme, soybean lipoxygenase-1. Toward this, we utilize quantum wavepacket dynamics [1, 2, 3, 4] performed on potential surfaces obtained by using hybrid density functional theory under the influence of a dynamical active site. By computing the hydrogen nuclear orbitals (eigenstates) along the reaction coordinate, we note that tunneling for both hydrogen and deuterium occurs through the existence of distorted, spherical s-type proton wave functions and p-type polarized proton wave functions for transfer along the donor-acceptor axis. In addition, there is also a significant population transfer through distorted p-type proton wave functions directed perpendicular to the donor-acceptor axis (via intervening pi-type proton eigenstate interactions) which underlines the three-dimensional nature of the tunneling process. The quantum dynamical evolution indicates a significant contribution from tunneling processes both along the donor-acceptor axis and along directions perpendicular to the donor-acceptor axis. Furthermore, the tunneling process is facilitated by the occurrence of curve crossings and avoided crossings along the proton eigenstate adiabats [5]. In addition we investigate the role of hydrogen bonding interactions on the proton transfer process in the active site. We will also discuss the tunneling process from the perspective of a new, complementary, analysis tool that utilizes concepts from von Neumann quantum measurement theory. In this case, the problem is reduced to that of a control problem, where the active site is interpreted as a control device so as to reproduce several qualitative features of the hydrogen transfer from this tool[6]

Introduction

- Experimental studies have indicated that hydrogen tunneling plays a crucial role in enzyme catalysis for example in case of Soybean Lipoxygenase-1 (SLO-1) as suggested by unexpectedly large primary kinetic isotope effect (KIE) and weak temperature dependence of KIE.

- SLO-1 is an oxygen-dependent non-heme iron enzyme and catalyses the oxidation of linoleic acid (LA). Experimental studies have indicated that in SLO-1, the room-temperature rate constant for proton transfer catalyzed by SLO-1 is $\sim$80 larger than that for deuteron transfer (k_D) and thus understanding effect of hydrogen tunneling in SLO-1 is challenging.

- The rate-limiting step in the catalytic cycle is the abstraction of a hydrogen atom from the linoleic acid chain by the octahedral Fe^{3+}-OH complex present in the active site.

- The reaction is then followed by a radical attack by O_2 that results in a final peroxide complex.

- In our study, the transferring hydrogen nucleus is treated as a three-dimensional quantum wavepacket.

- We simulate the rate-limiting hydrogen abstraction step by using quantum wavepacket dynamics of the hydrogen undergoing transfer[1, 2, 3, 4], facilitated by *ab initio* molecular dynamics (AIMD).

Langevin type *ab initio* Molecular Dynamics (AIMD)

- To sample rare events, we couple the fictious particles with coordinates $\tilde{R}$, momenta $\tilde{P}$, and mass tensors $\tilde{M}$ directly to the nuclear degrees of freedom via a harmonic potential. Each fictious particle is assigned a mass that allows us to define kinetic energy. The Hamiltonian for the nuclear-electronic-fictious particle system is then,
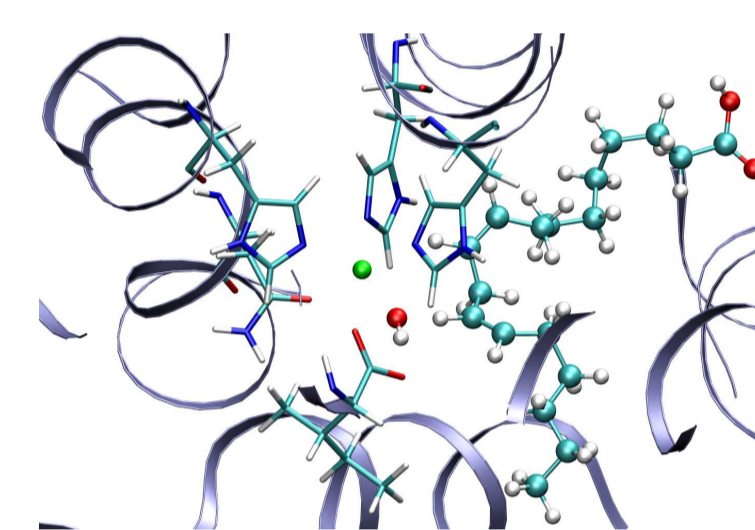
$$\tilde{H}(R, P, \tilde{R}, \tilde{P}) = \frac{1}{2}Tr[P^T M^{-1} P] + \frac{1}{2}Tr[\tilde{P}^T \tilde{M}^{-1} \tilde{P}] + V(R) + \frac{1}{2}Tr[(R - \tilde{R})^T K(R - \tilde{R})]$$

- For Quantum dynamics, the fictious particles are all included in the classical subsystem and the Hamiltonian is written as,

$$\tilde{H} = \frac{1}{2}Tr[P^T \mathbf{M}^{-1} P] + \frac{1}{2}Tr[\tilde{P}^T \tilde{M}^{-1} \tilde{P}] + \frac{\tilde{P}_{QM}^2}{2\tilde{M}_{QM}}$$
$$+ \langle \chi | V(R_C, R_{QM}) + \frac{1}{2}K_{QM}\left(R_{QM} - \tilde{R}_{QM}\right)^2 | \chi \rangle$$
$$+ \frac{1}{2}Tr\left[\left(R_C - \tilde{R}_C\right)^T K \left(R_C - \tilde{R}_C\right)\right]$$

- As a model of SLO-1, we used pruned representation of the active site amino acid ligands binding to the central iron atom in addition to a portion of the substrate that contains the π-bonded atoms on either side of the donor carbon atom.

- The variation of the reaction coordinate ($R_{CH} - R_{OH}/R_{CO}$) as a function of the number of steps is displayed in the figure below with the active site geometries in right panel (reactant state: (a), shared proton state: (b), and product state: (c)).
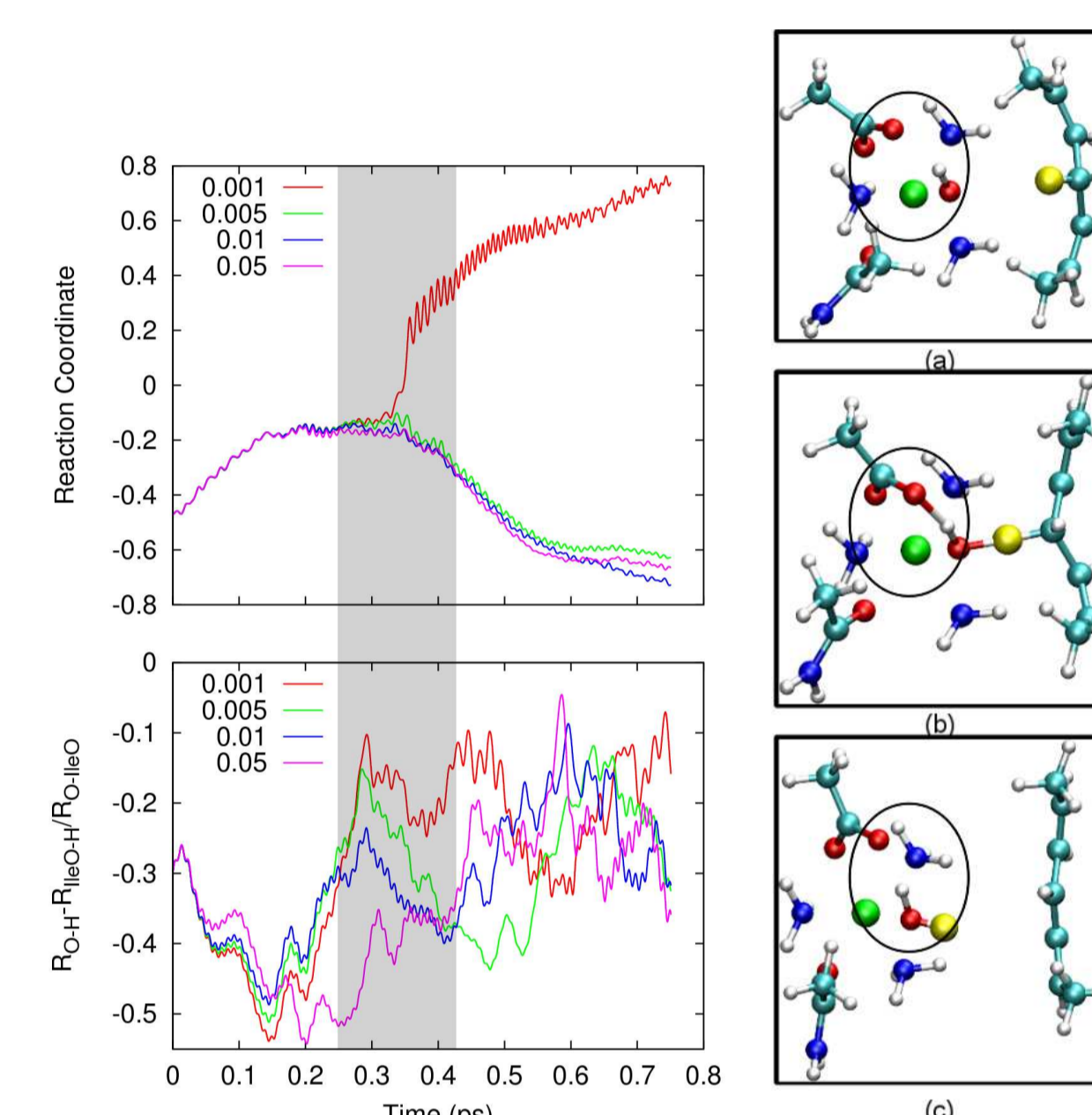

- The simulations thus indicate importance of hydrogen-bonding interaction of Ile839 with acceptor group is neccessary for the proton transfer.

- The minimum-energy reaction profile for the rate-limiting hydrogen abstraction step, and the critical tunneling region is highlighted within a box (see figure below). Note that the horizontal axis represents a reduced reaction coordinate computed from donor, acceptor and the shared proton, and the vertical axis represents the corresponding electronic-structure energy.
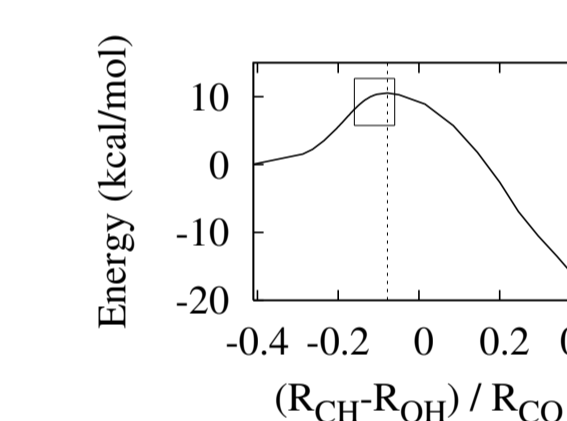
Nuclear quantum effects

- To account for nuclear quantization, we compute proton potential surfaces as a function of three-dimensional Cartesian proton coordinates for a large number of geometries along the classical reaction profile[5].

- For constructing proton potential surface, the electronic-structure calculations at each model geometry were performed using the B3LYP density functional and lanl2dz Gaussian-type basis set.
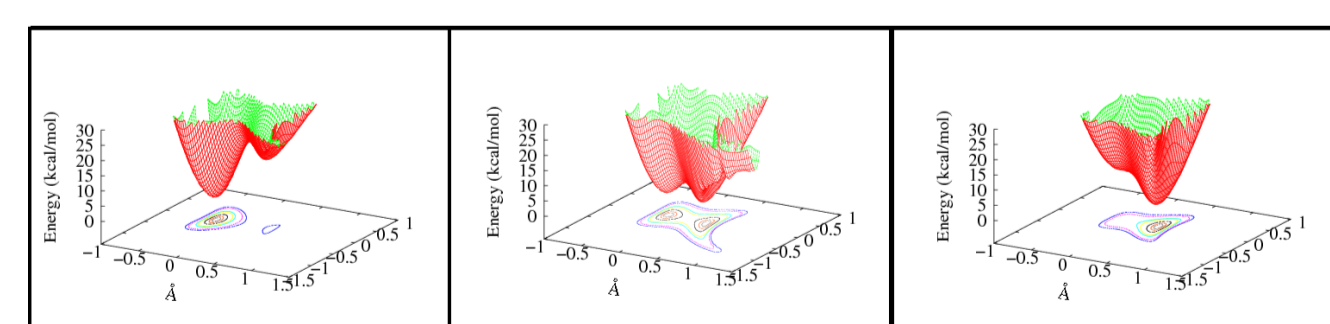
- Level surfaces as a function of two Cartesian dimensions and contour lines of the full proton potential-energy surface is illustrated above. The left panel is the surface on the reaction coordinate situated on the reactant side of the tunneling region, the central panel displays the surface in the tunneling region, and the right panel displays the surface at the classical transitions state.

- The classical transition-state localize the lower-energy proton eigenstates to the acceptor side (right panel in above figure), and intermediate-state surfaces enforce a double-well character that retains the proton to be partially bound to both donor and acceptor.

- In the figure below, the evolution of first three proton (left panel) and deuterium (right panel) eigenstates are displayed. The classical transition state is shown by using a vertical dashed line.
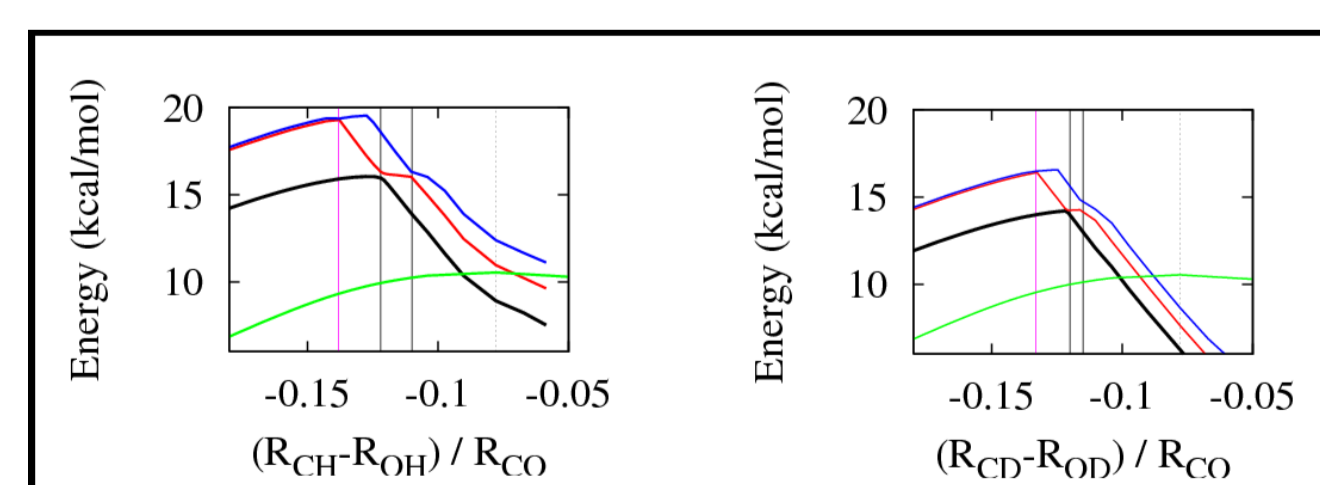
- The quantum nuclear eigenstate energies peak before the classical transition state and drop down as one approaches the classical barrier. In the figure below, evolution of the proton ground eigenstates (a-c) and deuteron ground eigenstates (d-f) are displayed.

(a) RC=-0.143   (b) RC=-0.133   (c) RC=-0.121
(d) RC=-0.133   (e) RC=-0.122   (f) RC=-0.121
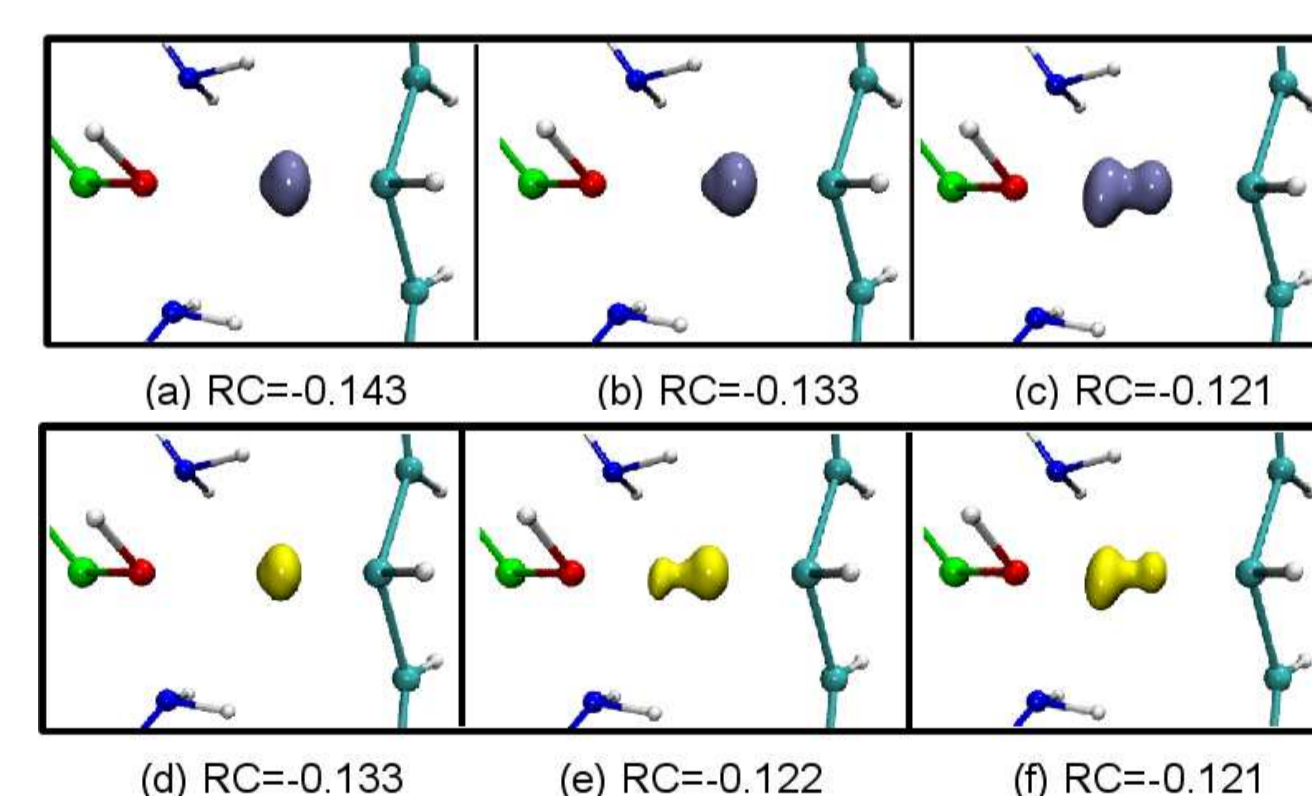
- It should be noted that if an effective reaction profile were to be constructed that included contributions from the quantum mechanical ground state of the tunneling nucleus, the new profile would display a maximum closer to the reactant. This effect is completely caused by the quantum mechanical nature of the hydrogen nucleus and the associated potential-energy surface.

von Neumann Measurements

- We treat the enzyme active site as a device that performs a measurement on the quantum proton at each step in dynamics [6] and employ the ideas of von Neumann measurement theory.

- The figure below is an illustration of filtered (top panel) and unfiltered (bottom panel) measurements: The initial density matrix population is shown using a red, horizontal arrow. The measurements are represented by the horizontal, dotted arrows and the eigenstates of the measurement operators are shown using dark green, dashed lines above these arrows.
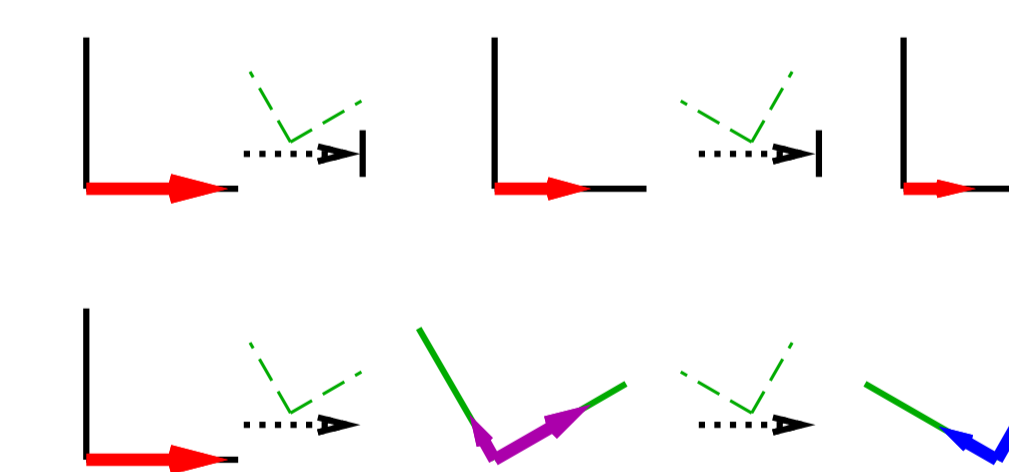
- For example, the eigenstates of the first measurement are oriented at $30°$ and $120°$, while those for the second are oriented at $60°$ and $150°$. The vertical line after the arrow in (top panel) is the $\{|D\rangle; |A_m\rangle\}$ filter, which removes the vertical, $|A\rangle\langle A|$ component and repopulates the $|D\rangle\langle D|$ dyad. In the unfiltered case, the measurements populate the measurement eigenstates as can be seen from the purple and blue arrows in Fig. (bottom panel). The population driven to the $|A\rangle\langle A|$ dyad after both measurements is 0.61 for (top panel) and 0.56 for (bottom panel).

- We find that such a measurement can accelerate the hydrogen nuclear transfer process as compared to the deuterium transfer process[6].

References

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Conclusions

- The hydrogen bonding interactions of the active-site residues is essential for the hydrogen transfer reaction.

- The calculations indicate that a quantum dynamically corrected transition state may be shifted toward the reactants relative to the classical transition state and depends on the temperature.

- The shift in the corrected transition state is obtained purely from quantizing the transferred proton and thus emphasize the importance of nuclear quantum effects in enzyme catalysis.

Acknowledgments