

Final Progress Report

Nonadiabatic Dynamics of Photoinduced Proton-Coupled Electron Transfer Processes

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I. Introduction

The development of sustainable energy sources is critical to the mission of the Air Force. In particular, the design of efficient and economical devices for the conversion of solar energy to chemical fuel and electrical power is important for national security. To ensure sustainability, these devices should utilize renewable resources and be environmentally benign. The coupling of electron and proton transfer reactions is central to the energy conversion processes in many biological and chemical systems, including solar energy devices.¹⁻⁵ Thus, understanding the fundamental physical principles underlying proton-coupled electron transfer (PCET) processes, which involve coupled electron and proton transfer reactions, is important for the design of more effective solar cells and other energy conversion devices.

Our research over the past grant period focused on the development of theoretical and computational methods for the investigation of photoinduced PCET processes. The overall objective was to provide fundamental conceptual insights that will guide the design of more effective catalysts for energy production and storage. Many theoretical and experimental methods have been used to study photoinduced electron transfer (ET) and photoinduced proton transfer (PT), but much less effort has been directed toward the study of photoinduced PCET.⁶⁻¹¹ In general, photoinduced PCET may exhibit ET and PT in the same or in different directions and may occur via either a concerted or a sequential mechanism. We developed general theoretical methods to simulate these processes and applied these approaches to experimentally studied systems in order to elucidate the fundamental principles governing such processes.

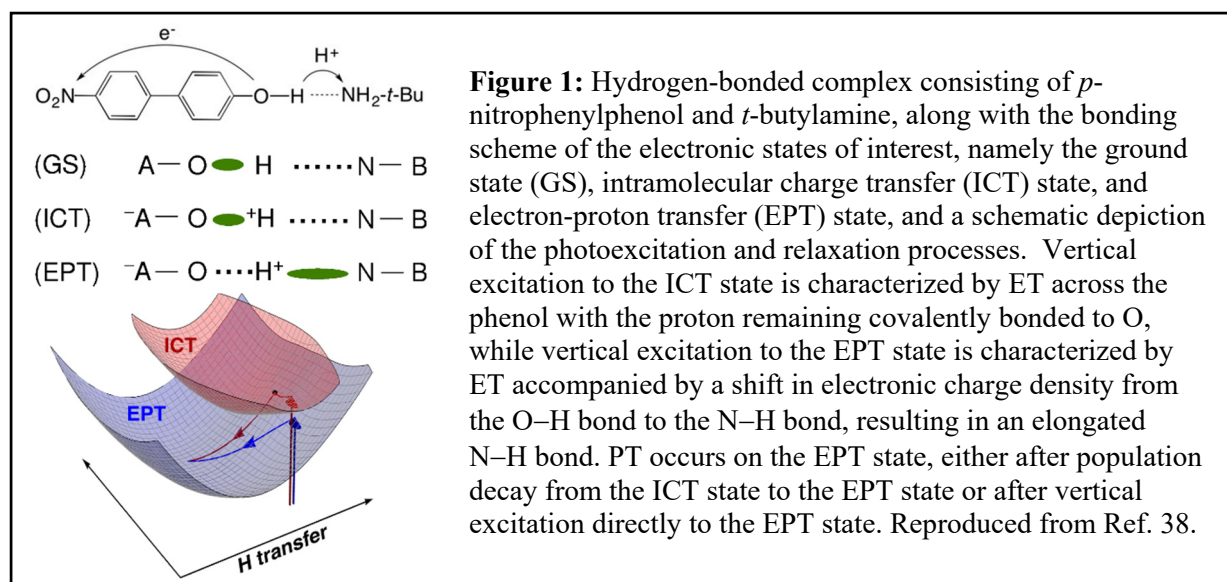
In addition, we started a new direction focused on photoinduced PCET in photoreceptor proteins, which allow the control of biological processes by light absorption. Photoreceptor proteins play a central role in the field of optogenetics, which is of interest to the Air Force because of the potential impact on human performance. In optogenetics, light is used to manipulate cells in living tissue, such as neurons, with high spatial and temporal resolution. Photoreceptor proteins may be introduced into a wide range of cell types and hence are useful for a variety of purposes, including the stimulation of neurons and the regulation of gene expression.¹²⁻¹⁵ In particular, blue light using flavin adenine dinucleotide (BLUF) photoreceptor proteins have been shown to be

critical for physiologically important processes such as the light regulation of photosynthetic gene expression and phototaxis.¹⁶⁻¹⁷ Due to the modular architecture of BLUF proteins, the N-terminal flavin-binding domain, often referred to as the BLUF domain, may be fused to the C-terminal effector domains of various other proteins, leading to photocontrol of a variety of processes.¹⁸ Thus, understanding the fundamental principles underlying BLUF photoreceptors is important for engineering novel systems that use light as a tool to achieve noninvasive control of biological processes with high spatiotemporal resolution.¹⁹⁻²¹

II. Overview of Accomplishments

II.A. Photoinduced PCET in Solvated Molecular Systems

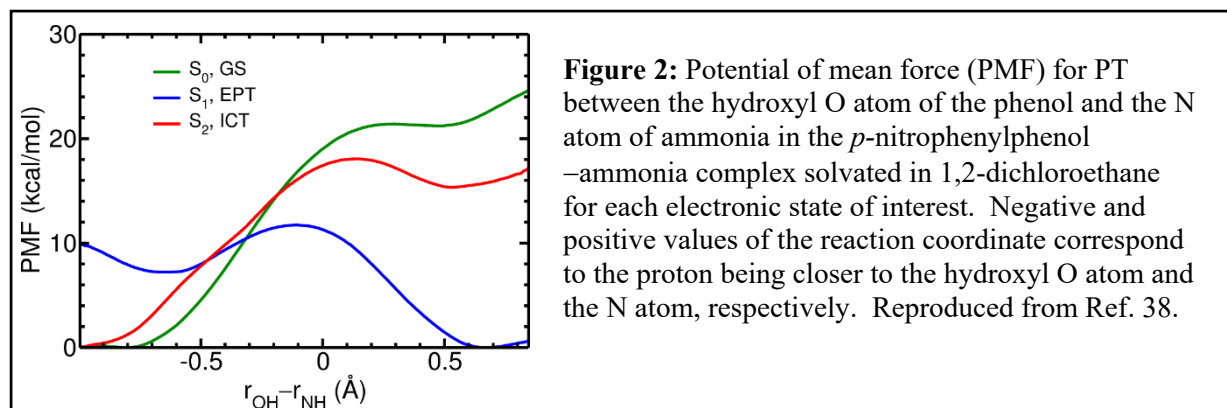
Over the past grant period, we developed a general theoretical approach to study photoinduced PCET processes and applied this approach to the *p*-nitrophenylphenol–ammonia complex solvated in 1,2-dichloroethane.²²⁻²⁴ This application was motivated by experimental studies¹⁰⁻¹¹ on the *p*-nitrophenylphenol–*t*-butylamine complex depicted in Figure 1. The transient absorption experiments implicated two different mechanisms, which were qualitatively designated sequential and concerted by interpretation in terms of the states shown in Figure 1. The intramolecular charge transfer (ICT) state corresponds to ET across the phenol molecule, while the electron-proton transfer (EPT) state corresponds to this ET as well as a shift of the electronic density from the O–H to the N–H covalent bond, thereby describing PT as well as ET. According to the initial interpretation,¹¹ photoexcitation to the EPT state corresponds to a concerted PCET



process in which the proton effectively transfers instantaneously upon photoexcitation through covalent bond rearrangement at the PT interface, although the hydrogen nucleus itself does not move instantaneously because of the Franck-Condon principle. The evidence for this concerted PCET process was an elongated N–H bond observed upon photoexcitation to the EPT state in coherent Raman experiments. However, the actual PT process involving movement of the proton from the oxygen to the nitrogen was not observed experimentally.

We performed theoretical calculations on the *p*-nitrophenylphenol–ammonia complex solvated in 1,2-dichloroethane to determine whether the proton actually transfers on the EPT state and the timescale of this PT if it occurs.²² The calculations also provided insight into the roles of solute and solvent dynamics and vibrational relaxation, as well as a prediction of the isotope effect for this system.²³⁻²⁴ In these calculations, the excited state electronic potential energy surfaces were generated on-the-fly with a semiempirical implementation of the floating occupation molecular orbital complete active space configuration interaction (FOMO-CASCI) method.²⁵⁻²⁷ This method includes the required multireference character as well as dynamical correlation through the reparameterized semiempirical Hamiltonian, where the semiempirical parameters were modified to reproduce key aspects of the potential energy surfaces for this system. Our simulations utilized a mixed quantum mechanical/molecular mechanical (QM/MM) approach,²⁸ in which the solute was treated quantum mechanically with the FOMO-CASCI method and was immersed in a sphere of explicit 1,2-dichloroethane solvent molecules that were treated with a molecular mechanical force field.

The three electronic states of interest were characterized in both the gas phase and in solution. The S_1 and S_2 states both correspond to $\pi\pi^*$ transitions but differ in the extent of charge transfer. In the gas phase, the proton transfer potential energy curves along the O–N axis exhibit a deep minimum on the O side for the S_0 (ground), S_1 (EPT), and S_2 (ICT) states, indicating that PT is highly unfavorable on all of these states. The free energy profiles in solution were obtained by calculating the potential of mean force along the proton transfer coordinate with QM/MM umbrella sampling simulations. As illustrated in Figure 2, the S_0 and S_2 states still exhibit a deep minimum on the O side, but the S_1 state has a lower minimum on the N side, with a small barrier of ~ 4 kcal/mol for PT from the O to the N. These free energy profiles suggest that the solvent significantly influences the nature of the S_1 state and that PT to the N atom is thermodynamically favorable on this state.



Connecting directly to the transient absorption experiments requires nonequilibrium dynamical simulations. For this purpose, the system was equilibrated on the ground state (GS) and photoexcited to either the EPT or the ICT state, as depicted schematically in Figure 1. We used the molecular dynamics with quantum transitions (MDQT) surface hopping method²⁹⁻³⁰ to describe the nonadiabatic dynamics. Several hundred surface hopping trajectories were propagated on the electronic surfaces to simulate the relaxation to the ground state. The timescale of the decay from the S_1 to the S_0 state is ~ 0.9 ps, which is in qualitative agreement with the transient absorption timescale of ~ 4.5 ps. The decay from the S_2 to the S_1 state occurs in ~ 100 fs, which is consistent with the transient absorption timescale of < 1 ps, although a more specific experimental timescale is not available due to limited resolution. Analysis of the surface hopping trajectories indicated that proton transfer from the O to the N occurred on the S_1 state in $\sim 54\%$ of the trajectories. Thus, the simulated timescales are in qualitative agreement with the experimental data, and the simulations provided evidence of PT on the EPT state.

Because photoexcitation to the S_1 state alters the dipole moment of the solute molecule by ~ 13 D, solvent dynamics is expected to play a significant role. The solvent is out of equilibrium immediately following photoexcitation and subsequently relaxes as it equilibrates to the new electronic charge distribution associated with the S_1 state. This solvent relaxation was monitored by calculating the electrostatic potential at the amine nitrogen due to the solvent molecules as a function of time, averaging over hundreds of trajectories.²³ As shown in Figure 3, the solvent relaxation occurs on the ~ 250 fs timescale, and further analysis revealed that this relaxation involves predominantly the first solvation shell. This timescale is consistent with previous experimental and computational studies of the ultrafast solvation response to changes in the electronic charge distribution of the solute.³¹⁻³² These previous studies identified two relaxation timescales in response to electronic charge redistribution in a solute: the slower timescale is related

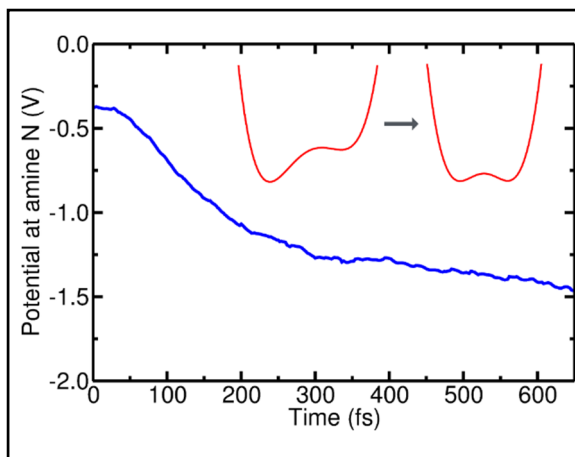
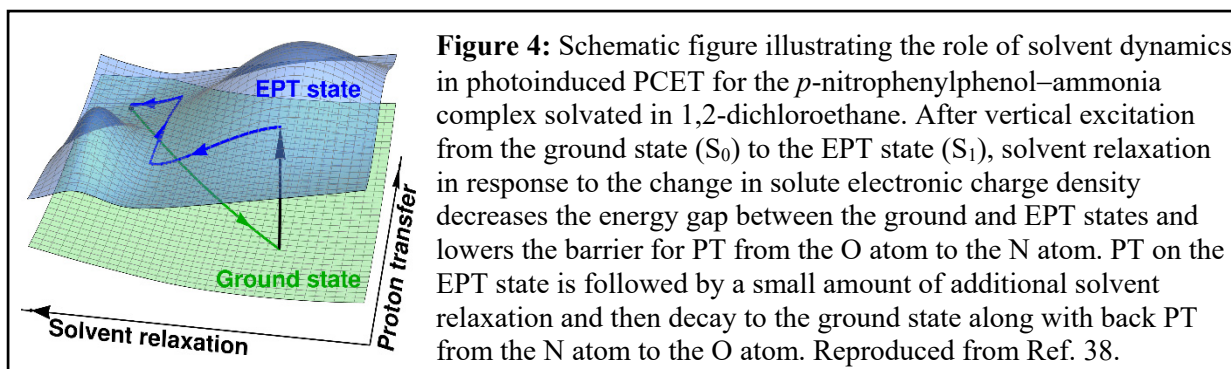


Figure 3: Time evolution of the solvent electrostatic potential at the N atom of ammonia averaged over surface hopping trajectories photoexcited to the S_1 (EPT) state. The decrease of the potential with time reflects the reorganization of solvent molecules in response to the large change in solute dipole moment upon photoexcitation. The proton potentials on the S_1 state depicted in the inset illustrate that solvent reorganization changes the proton potential on the S_1 state from thermodynamically favoring the proton on the O atom (left well) to stabilizing the proton on the N atom (right well) and substantially lowering the barrier for PT. Reproduced from Ref. 38.

to the Debye timescale of the solvent (i.e., the dielectric response of bulk solvent), and the faster timescale was interpreted as the predominantly librational motions associated with the first solvation shell response. A more recent experimental study on a photoinduced PCET system in a nanocage³³⁻³⁴ implied that the dominant reaction coordinate for PT corresponds to reorganization of the first coordination shell of water around the nanocage on a timescale of 120 fs and therefore is also consistent with our simulations.

Moreover, the solvent dynamics was found to impact the PCET process in two distinct ways. First, it decreases the energy gap between the S_0 and S_1 states, facilitating decay to the ground state. Second, it generates an electrostatic environment conducive to PT on the S_1 state, as depicted by the change in the proton potentials shown in the inset of Figure 3. Immediately upon photoexcitation to the S_1 state, the proton potential exhibits a deep minimum on the O side because the solvent is equilibrated to the ground state. Relaxation of the solvent on the S_1 state following photoexcitation decreases the relative energy of the minimum on the N side and lowers the PT barrier. The PT reaction cannot occur immediately upon photoexcitation because of the large barrier and can only occur after the solvent relaxation significantly decreases this barrier. Thus, PT is not instantaneous upon photoexcitation to the EPT state, but rather requires solvent reorganization on a timescale of ~ 250 fs. In addition to solvent relaxation, the solute geometry, specifically the O–H---N hydrogen-bonding interface, must also be conducive to PT. As depicted for a typical trajectory in Figure 4, photoexcitation to the S_1 state is followed by solvent relaxation and a decrease in the energy gap, followed by PT and a little more solvent relaxation before the system decays to the ground state.



To investigate the role of vibrational relaxation, we developed an approach that treats the transferring hydrogen nucleus quantum mechanically and includes electron-proton nonadiabatic effects.²⁴ In this treatment, the transferring proton was represented by a one-dimensional wavefunction along a grid spanning the O–N axis. At each time step, the proton potential energy curves and associated hydrogen vibrational wavefunctions were calculated for the S_0 , S_1 , and S_2 states. The double adiabatic vibronic states, which are products of an electronic state and an associated proton vibrational state, were used as basis functions to calculate the adiabatic electron-proton vibronic surfaces. In this case, we performed surface hopping dynamics on electron-proton vibronic surfaces rather than electronic surfaces.³⁵⁻³⁷ Because there were 20 proton vibrational states for each of the three electronic states, the surface hopping dynamics was propagated on 60 vibronic states. In this case, the interpretation of the relaxation process was more complicated, and the analysis was simplified by focusing on the double adiabatic states, which are each associated with a single electronic state.

Photoexcitation to the S_1 state was distributed among the vibronic states according to the Franck-Condon overlaps but mainly populated the ground proton vibrational state of the S_1 electronic state, as depicted in Figure 5. After photoexcitation, the surface hopping trajectories evolved and switched to an excited proton vibrational state of the S_0 electronic state, followed by relaxation to the ground state. The population decay from the S_1 to the S_0 state was found to be significantly faster with the quantum proton than was observed experimentally. However, the population rise of the ground vibronic state was of similar timescale as the experimental value. This analysis resulted in a slightly modified interpretation of the transient absorption experiments. The calculations suggest that the experimental timescale for decay from the S_1 to the S_0 state includes a relatively fast decay from S_1 to an excited vibrational state of S_0 , followed by vibrational relaxation within the S_0 state (Figure 5). In addition, the degree of PT for each trajectory was

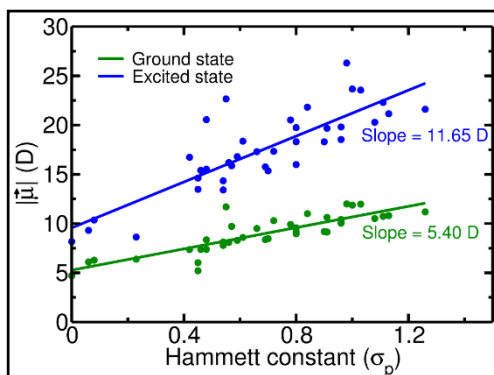


Figure 6: Variation of the magnitudes of the ground state and S_1 (EPT) excited state dipole moments with the Hammett constant (σ_p) of the substituent replacing NO_2 in the *p*-nitrophenylphenol–ammonia complex in the gas phase (Figure 1). The dipole moments were determined from TDDFT/CAM-B3LYP/6-31+G** calculations, and each set of points was fit to a line. The dipole moment varies with the Hammett constant more steeply for the excited state than for the ground state. Reproduced from Ref. 38.

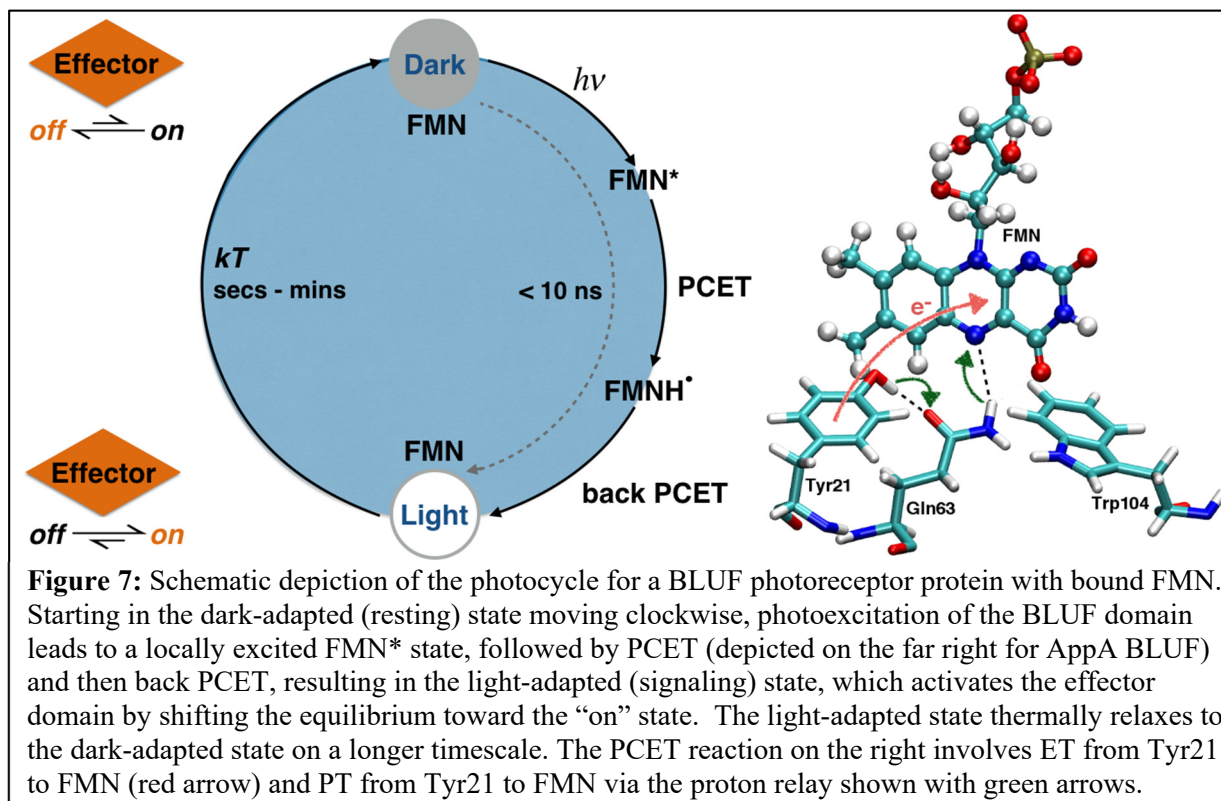
We also explored the ability to tune the ultrafast dynamics of photoinduced PCET processes.³⁸ Figure 6 depicts the calculated dipole moments as a function of the Hammett constant,³⁹ which reflects the electron-withdrawing or electron-donating nature of a given substituent, for a series of substituents replacing the NO_2 group for the system in Figure 1. The dipole moment increases with the Hammett constant for both the ground state and the excited state because of the enhanced electron-withdrawing character, but the slope is greater for the excited state,⁴⁰ mainly because the excited state has greater electronic density than the ground state near the substitution site. Thus, as the Hammett constant of the substituent increases, the change in dipole moment upon photoexcitation increases, thereby inducing a greater degree of solvent reorganization. Altering the change in dipole moment upon photoexcitation is expected to impact the timescale and probability of PT, as well as the timescale of relaxation to the ground state. We also examined the effects of moving the substituent to different positions, increasing the number of substituents, and increasing the number of phenyl rings that serve as a bridge for ET across the molecule. In addition, we explored the effects of replacing the amine with a different base to modify the pK_a or altering the polarizability, dielectric properties, molecular size, and hydrogen-bonding capabilities of the solvent. All of these calculations have provided insights that will assist in the tuning of catalysts that undergo photoinduced PCET in energy conversion processes.

II.B. Initial Simulations of BLUF Photoreceptor Protein

BLUF proteins are essential for the light regulation of a variety of physiologically important processes and serve as a prototype for photoinduced PCET in proteins.¹⁶⁻¹⁷ In BLUF proteins, photoexcitation of a flavin chromophore induces PCET, followed by local conformational changes that subsequently propagate to distal parts of the protein and drive other chemical and physical changes.¹⁶⁻¹⁷ Figure 7 depicts the basic mechanism for signal transmission

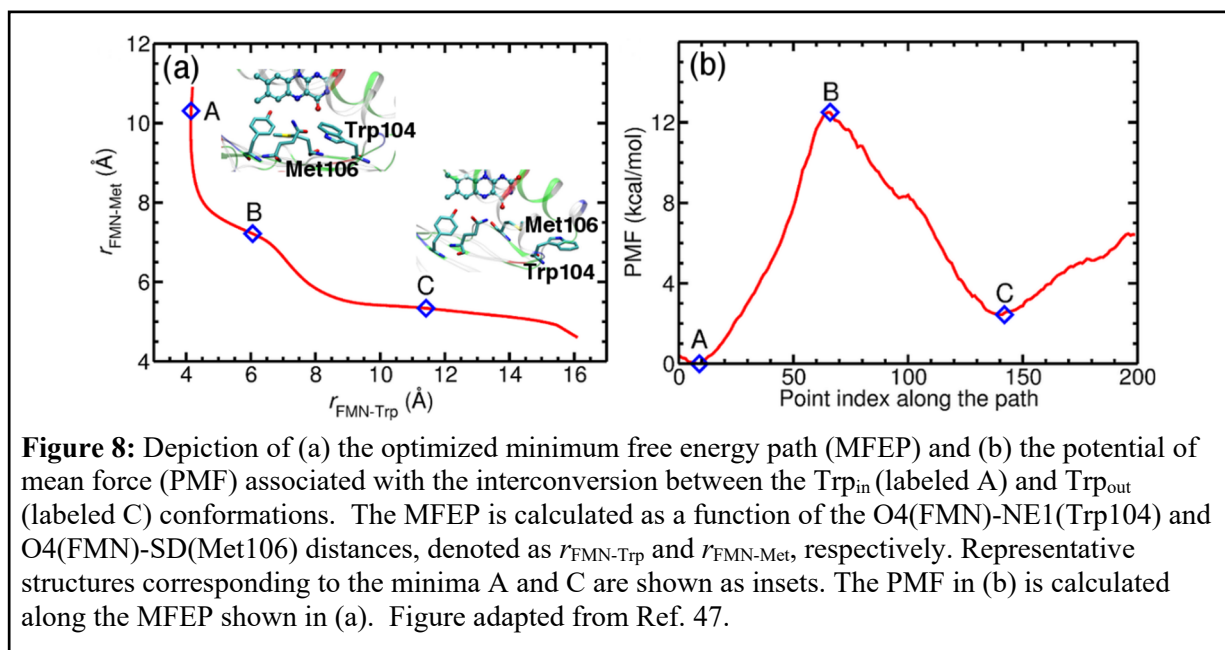
from light absorption by the BLUF domain to activation of the effector domain, which subsequently impacts various physiological processes. The activation of the effector domain can be viewed as shifting the equilibrium from the *off* state toward the *on* state. In the resting state, also denoted the dark-adapted state, the effector is predominantly in the *off* state.

Our simulations of BLUF proteins over the past grant period focused on the *Rhodobacter sphaeroides* AppA (activation of photopigment and *puc* expression) BLUF domain. In this system, application of blue light photoexcites the flavin chromophore, which is FMN (flavin mononucleotide) in Figure 7, to a locally excited state, denoted FMN*. Subsequently, a PCET reaction involving electron transfer from Tyr21 to FMN, followed by proton transfer from Tyr21 to FMN via a proton relay through Gln63, leads to the neutral radical FMNH*. In less than 10 ns after the initial photoexcitation, another PCET reaction, which involves electron transfer back to Tyr21 and relaxation to the ground electronic state with FMN in its original form, leads to the signaling state, also denoted the light-adapted state. Despite extensive experimental and theoretical studies,^{16-17,41-46} the nature of the signaling state and signaling mechanism are not fully understood. The signaling state is proposed to be characterized by hydrogen-bonding conformations that activate the effector domain, shifting its equilibrium toward the *on* state. It

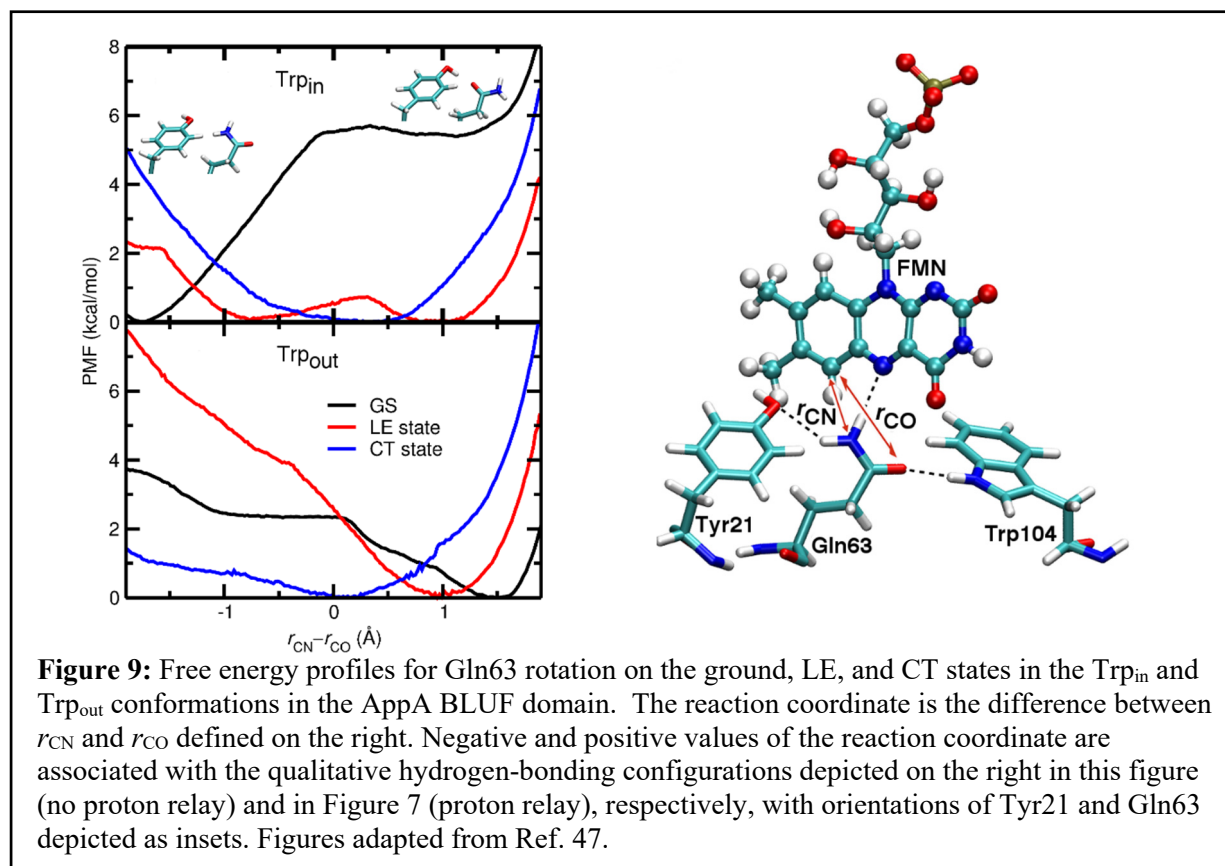


eventually thermally relaxes back to the resting state on a timescale of several seconds to tens of minutes, depending on the specific BLUF photoreceptor.

We performed free energy simulations of the AppA BLUF domain prior to and following photoexcitation.⁴⁷ Specifically, we used the adaptively biased path optimization method⁴⁸ to calculate the minimum free energy path and the associated free energy profile for interconversion between conformations with either Trp104 or Met106 closer to the flavin, denoted Trp_{in} and Trp_{out}, respectively. As shown in Figure 8, our calculations revealed that both conformations are sampled on the ground state, with the Trp_{in} conformation thermodynamically favorable by ~ 3 kcal/mol. Moreover, at equilibrium at room temperature, the ground state BLUF domain can undergo interconversion between the Trp_{in} and Trp_{out} conformations on a ~ 100 μ s timescale. These results are consistent with the observation of both conformations in different X-ray crystallography and solution NMR structures of AppA BLUF.⁴⁹⁻⁵²

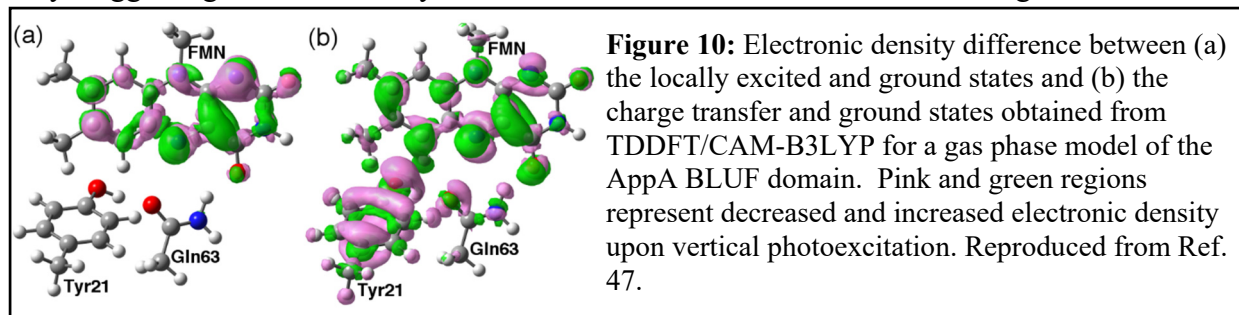


Moreover, to analyze the proton relay from Tyr21 to the flavin via Gln63, we calculated the free energy profiles for Gln63 rotation on the ground state, the locally excited state of the flavin, and the charge transfer state associated with ET from Tyr21 to the flavin. These results are depicted in Figure 9. For the Trp_{in} conformation, Gln63 and Tyr21 are not properly oriented for the proton relay from Tyr21 to FMN via Gln63 on the ground state (black curve). After photoexcitation to the locally excited state, the conformations with and without the hydrogen-



bonding pattern conducive to the proton relay become approximately equally probable, separated by a free energy barrier of only ~ 0.5 kcal/mol (red curve). On the other hand, for the Trp_{out} conformation, the hydrogen-bonding pattern conducive to the proton relay is thermodynamically favorable on both the ground state and locally excited state.

In addition, we performed time-dependent density functional theory (TDDFT)⁵³⁻⁵⁴ calculations to understand the effect of the active site hydrogen-bonding pattern on the feasibility of ET to the flavin. The locally excited and charge transfer states calculated with TDDFT/CAM-B3LYP/6-31+G** are depicted in Figure 10. The calculated energy gap between the locally excited and charge transfer states is significantly smaller for configurations conducive to the proton relay, suggesting that ET from Tyr21 to the flavin is more facile for these configurations.



Thus, these simulations indicate that photoexcitation to the locally excited state leads to a conformational change corresponding to the formation of the proton relay (Figure 7, right side), which in turn facilitates ET from Tyr21 to FMN. This charge transfer reaction is required for long-range signaling in the photocycle. Furthermore, our calculations indicate that when Trp104 is sufficiently close to FMN, it can compete directly with Tyr21 for ET to FMN, especially if ET from Tyr21 is hindered by the absence of the conducive hydrogen-bonding network. Thus, occupation of the Trp_{in} conformation is predicted to hamper the signaling efficiency, which requires ET from Tyr21. The significant population of the Trp_{in} conformation found in our simulations, as well as the possibility of competition from Trp104, is consistent with experimental studies that detected formation of a Trp104 radical during the photocycle⁵⁵ and the Trp fluorescence experiments indicating that Trp104 remains buried in the AppA BLUF domain active site throughout the photocycle.⁵⁶ As further experimental evidence, the mutation of Trp104 to Phe was observed to enhance the quantum yield of the signaling state, indicating that Trp104 provides a non-productive competing decay pathway.^{55,57} Our simulations have assisted in the interpretation of these experimental data and have provided fundamental insights into the key active site conformational changes influencing the BLUF photocycle.

III. Summary

We have developed nonadiabatic molecular dynamics methods for simulating photoinduced PCET reactions in solution and protein environments. These methods were applied to photoinduced PCET within a hydrogen-bonded phenol-amine complex in solution. Our calculations provided fundamental insights into the roles of solute and solvent dynamics, as well as proton delocalization and vibrational relaxation, in photoinduced PCET reactions. We also explored strategies to tune these types of molecular systems through chemical modifications, such as the attachment of electron-withdrawing or electron-donating substituents. Our simulations of the BLUF photoreceptor protein elucidated the active site conformational changes that are essential to the photocycle leading to long-range signaling. The computational methods developed during the past grant period will assist in the theoretical design of more effective catalysts for energy production and storage. They will also facilitate the design of novel photoreceptor proteins with long-range signaling capabilities relevant to optogenetics.

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