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## Nonadiabatic Dynamics of Photoinduced Proton-Coupled Electron Transfer Processes

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Final Report

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<b>14. ABSTRACT</b> <p>The design of efficient and economical devices for the conversion of solar energy to chemical fuel and electrical power is important for national security and therefore is critical to the mission of the Air Force. Photoinduced proton-coupled electron transfer (PCET) is essential for a wide range of energy conversion processes in chemical and biological systems. Understanding the underlying principles of photoinduced PCET at a level that allows tuning and control of the ultrafast dynamics is crucial for designing renewable and sustainable energy sources, such as artificial photosynthesis devices and photoelectrochemical cells. Theoretical methodology for simulating the nonadiabatic dynamics of photoinduced PCET reactions in solution has been developed. The electronic potential energy surfaces are generated on-the-fly with a hybrid quantum mechanical/molecular mechanical approach that describes the solute with a multiconfigurational method in a bath of explicit solvent molecules. The transferring hydrogen nucleus is represented as a quantum mechanical wavefunction calculated with grid-based methods, and surface hopping trajectories are propagated on the adiabatic electron-proton vibronic surfaces. This approach was applied to an experimentally studied phenol-amine complex in 1,2-dichloroethane. Using this system as a prototype, these calculations provided insights into fundamental aspects of photoinduced PCET, including</p>					
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## **Final Progress Report**

Nonadiabatic Dynamics of Photoinduced Proton-Coupled Electron Transfer Processes

Grant #: FA9550-14-1-0295

Sharon Hammes-Schiffer, Yale University

### **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.<sup>1-5</sup> 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.<sup>6-11</sup> 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.

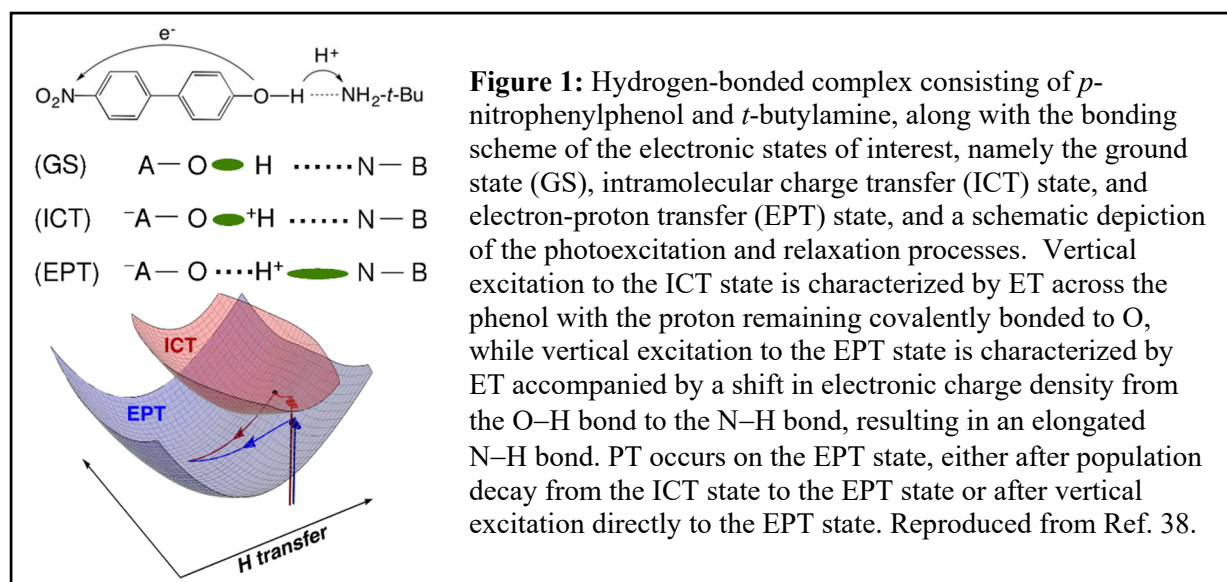
In addition, we started a new direction focused on photoinduced PCET in photoreceptor proteins, which allow the control of biological processes by light absorption. Photoreceptor proteins play a central role in the field of optogenetics, which is of interest to the Air Force because of the potential 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.<sup>12-15</sup> 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.<sup>16-17</sup> 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.<sup>18</sup> 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.<sup>19-21</sup>

## II. Overview of Accomplishments

### II.A. Photoinduced PCET in Solvated Molecular Systems

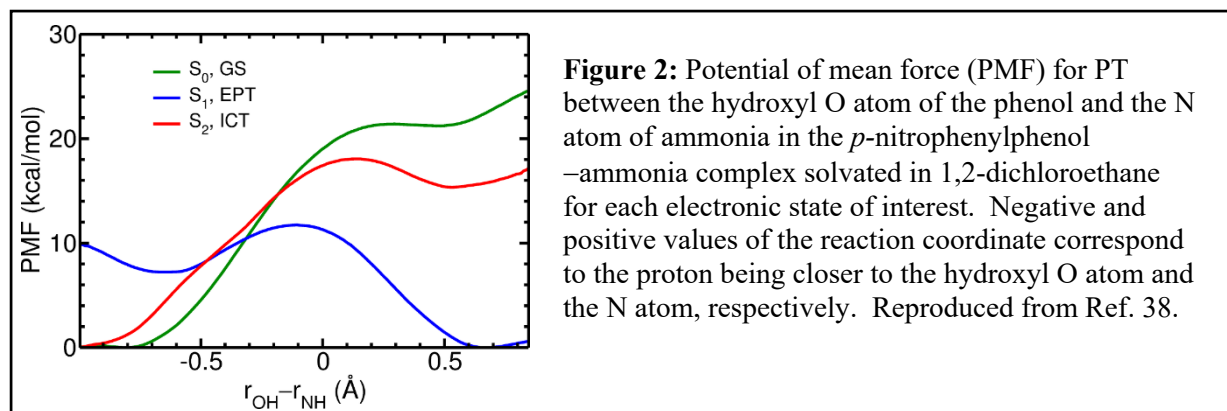
Over the past grant period, we developed a general theoretical approach to study photoinduced PCET processes and applied this approach to the *p*-nitrophenylphenol–ammonia complex solvated in 1,2-dichloroethane.<sup>22-24</sup> This application was motivated by experimental studies<sup>10-11</sup> on 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,<sup>11</sup> 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.

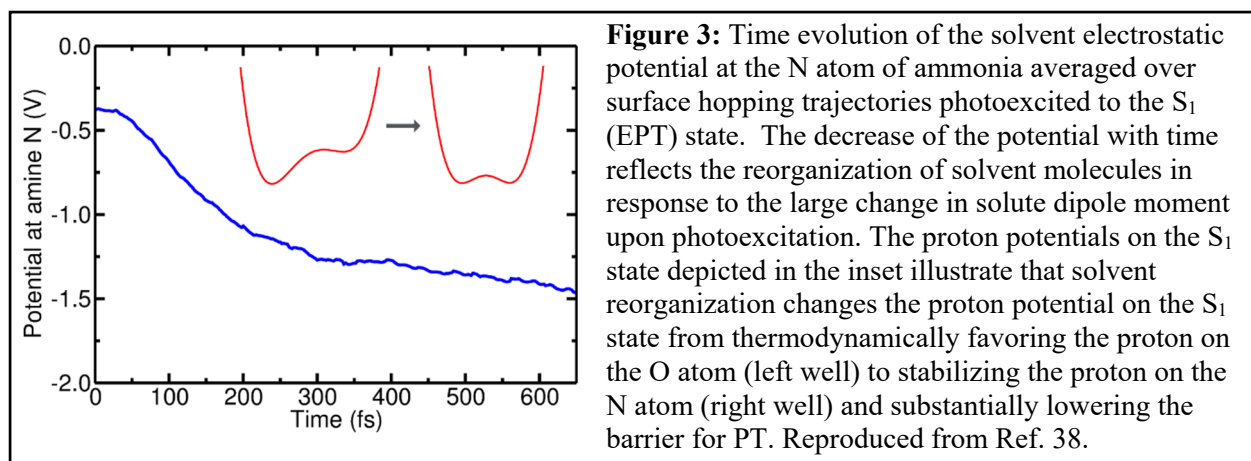
We performed theoretical calculations on the *p*-nitrophenylphenol–ammonia complex solvated in 1,2-dichloroethane to determine whether the proton actually transfers on the EPT state and the timescale of this PT if it occurs.<sup>22</sup> The calculations also provided insight into the roles of solute and solvent dynamics and vibrational relaxation, as well as a prediction of the isotope effect for this system.<sup>23-24</sup> 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.<sup>25-27</sup> 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,<sup>28</sup> 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  $\sim 4$  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 method<sup>29-30</sup> 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  $\sim 0.9$  ps, which is in qualitative agreement with the transient absorption timescale of  $\sim 4.5$  ps. The decay from the  $S_2$  to the  $S_1$  state occurs in  $\sim 100$  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.

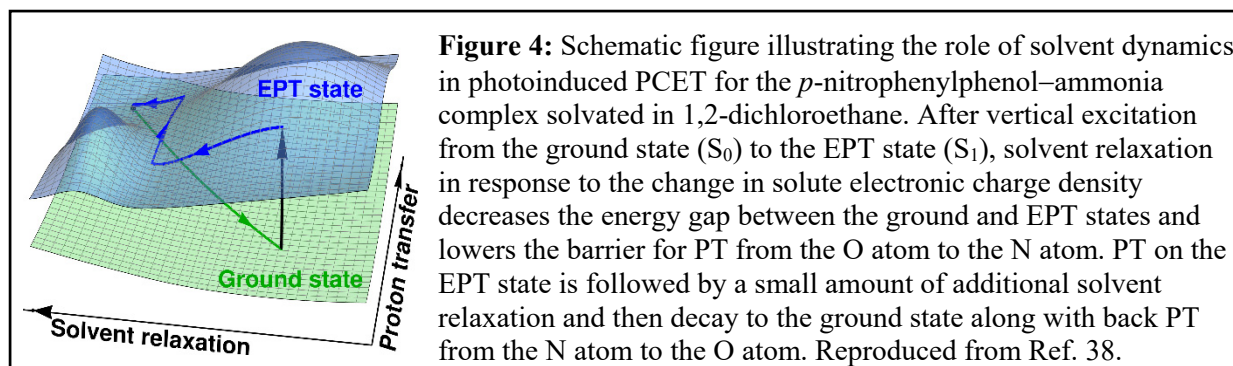
Because photoexcitation to the  $S_1$  state alters the dipole moment of the solute molecule by  $\sim 13$  D, solvent dynamics is expected to play a significant role. The solvent is out of equilibrium immediately following photoexcitation and subsequently relaxes as it equilibrates to the new electronic 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.<sup>23</sup> As shown in Figure 3, the solvent relaxation occurs on the  $\sim 250$  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.<sup>31-32</sup> These previous studies identified two relaxation timescales in response to electronic charge redistribution in a solute: the slower timescale is related



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 nanocage<sup>33-34</sup> 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.

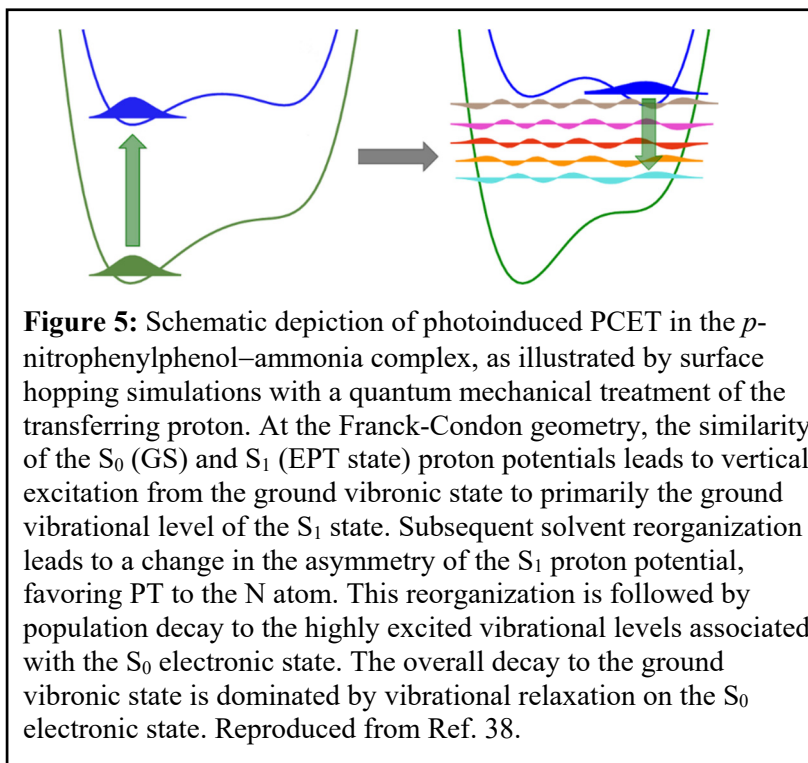
Moreover, the solvent dynamics was found to impact the PCET process in two distinct ways. First, it decreases the energy gap between the  $S_0$  and  $S_1$  states, facilitating decay to the ground state. Second, it generates an electrostatic environment conducive to PT on the  $S_1$  state, as depicted 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  $\sim 250$  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.<sup>24</sup> 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.<sup>35–37</sup> 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.

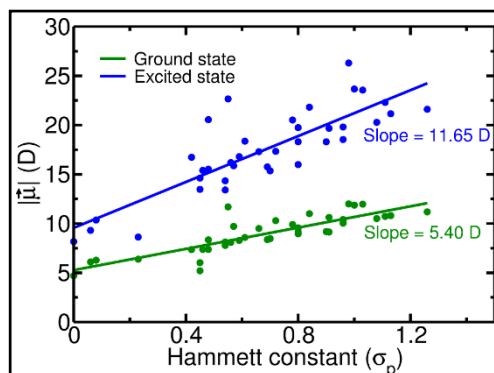
Photoexcitation to the  $S_1$  state was distributed among the vibronic states according to the Franck-Condon overlaps but mainly populated the ground proton vibrational state of the  $S_1$  electronic state, as depicted in Figure 5. After photoexcitation, the surface hopping trajectories evolved and 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



analyzed by defining PT in terms of the expectation value of the proton coordinate. One type of PT was found to occur on the  $S_1$  state according to the same mechanism as described above, namely by solvent reorganization flipping the asymmetry of the proton potential and reducing the PT barrier. Another type of PT was found to occur on the  $S_0$  state in the highly excited, delocalized vibrational states

when a small solute or solvent fluctuation shifted the delocalized proton vibrational wavefunction toward the acceptor. The sum of both types of PT was similar to the percentage of trajectories exhibiting PT with the classically treated proton.

The hydrogen/deuterium isotope effect was predicted by repeating all of the simulations with deuterium rather than hydrogen. Interestingly, no isotope effect was observed for relaxation to the ground vibronic state. This observation was explained in terms of the two mechanisms for PT. On the  $S_1$  state, the solvent dynamics altering the proton potentials is not isotopically sensitive. On the  $S_0$  state, the highly excited vibrational states are delocalized for both hydrogen and deuterium and therefore do not distinguish between the two isotopes. Because the process is governed by solvent dynamics and vibrational relaxation and does not involve tunneling between localized states, an isotope effect is not observed, in contrast to many thermal PCET reactions. Note that an isotope effect could be observed for some photoinduced PCET systems, depending on the specific characteristics of the potential energy surfaces, but the isotope effects are expected to be relatively moderate. An important conclusion of this work is that the absence of an isotope effect does not imply the absence of PT in photoinduced PCET processes.



**Figure 6:** Variation of the magnitudes of the ground state and  $S_1$  (EPT) excited state dipole moments with the Hammett constant ( $\sigma_p$ ) of the substituent replacing  $\text{NO}_2$  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.

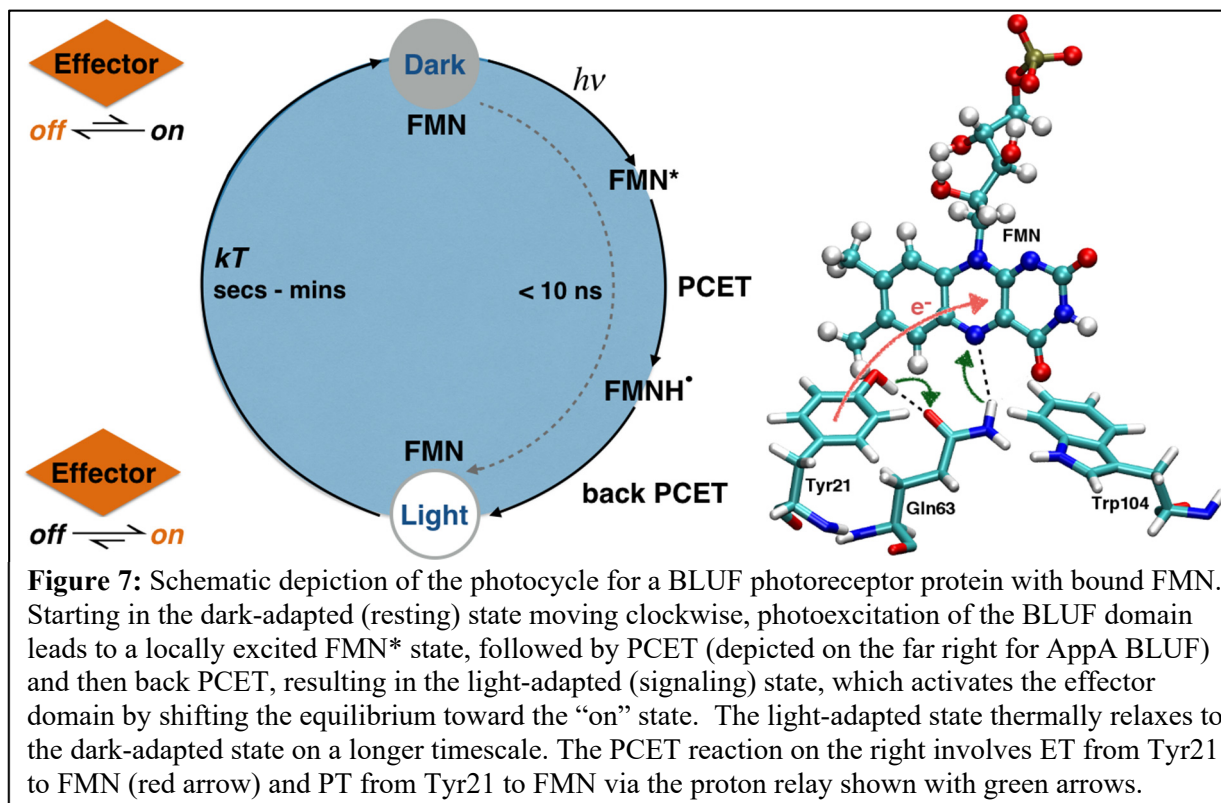
We also explored the ability to tune the ultrafast dynamics of photoinduced PCET processes.<sup>38</sup> Figure 6 depicts the calculated dipole moments as a function of the Hammett constant,<sup>39</sup> which reflects the electron-withdrawing or electron-donating nature of a given substituent, for a series of substituents replacing the  $\text{NO}_2$  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,<sup>40</sup> 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  $\text{p}K_a$  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.<sup>16-17</sup> 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.<sup>16-17</sup> Figure 7 depicts the basic mechanism for signal transmission

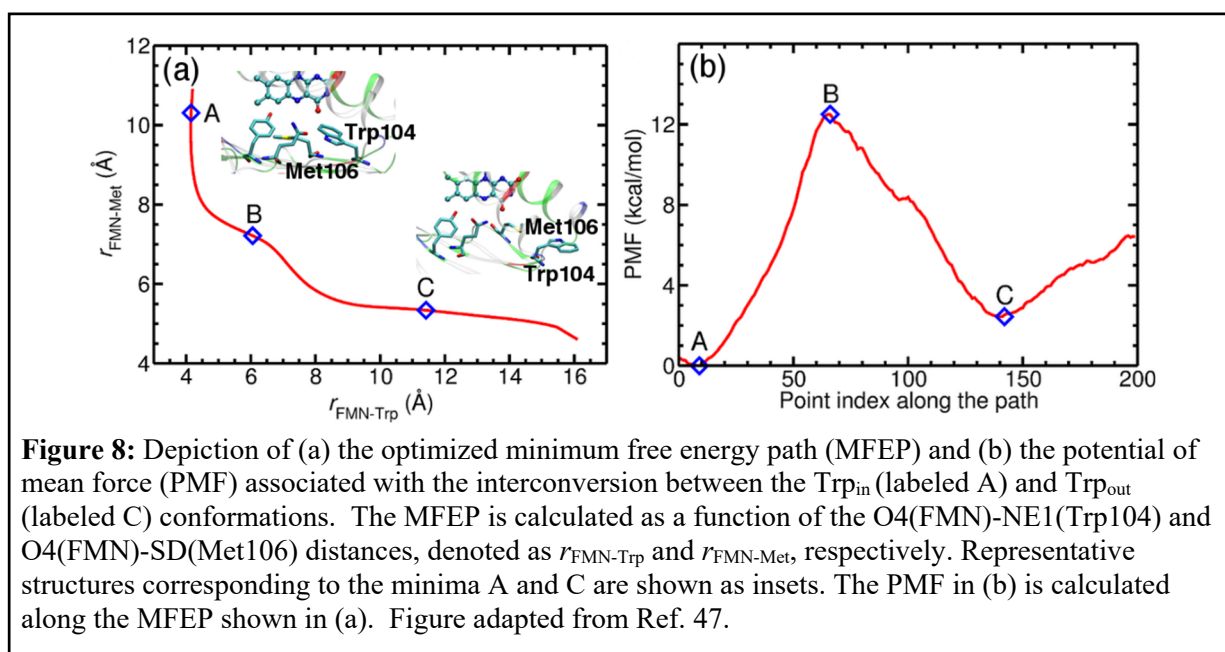
from light absorption by the BLUF domain to activation of the effector domain, which subsequently impacts various physiological processes. The activation of the effector domain can be viewed as shifting the equilibrium from the *off* state toward the *on* state. In the resting state, also denoted the 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,<sup>16-17,41-46</sup> 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



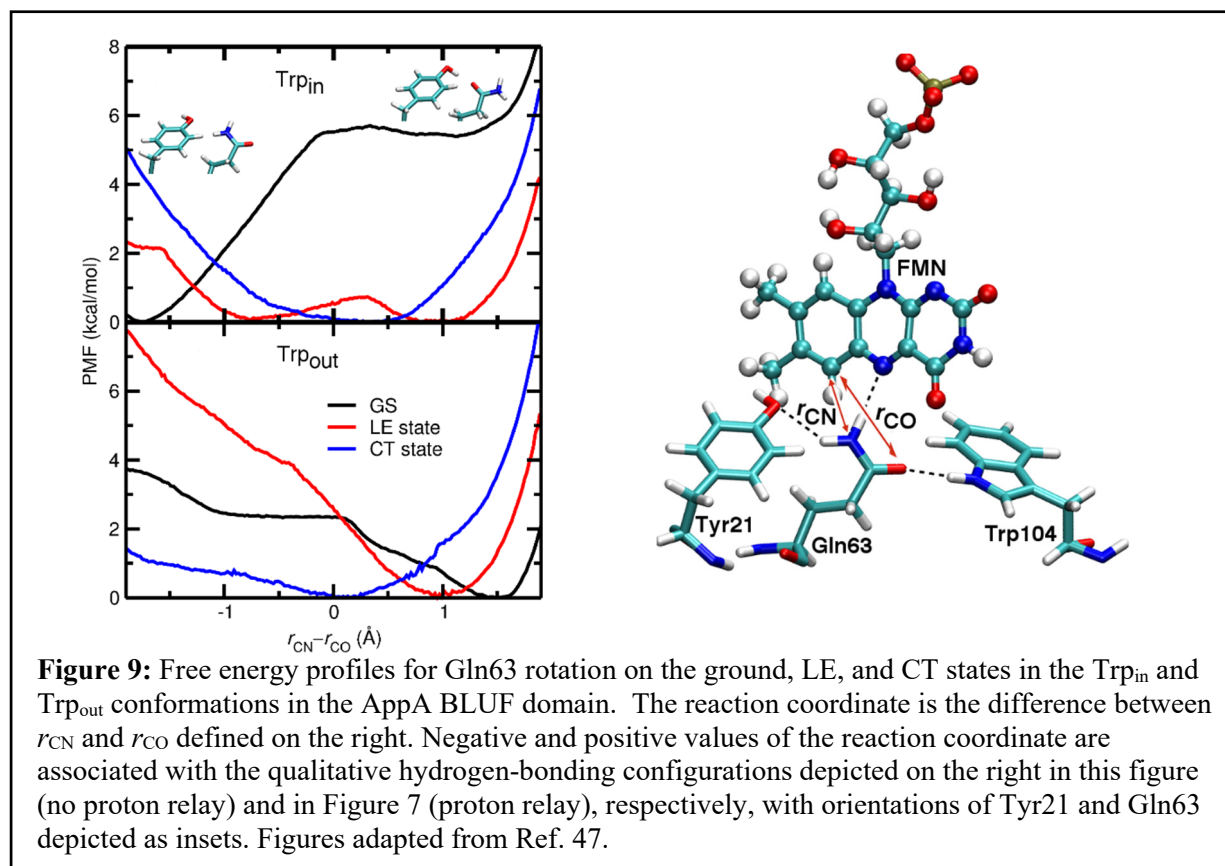
eventually thermally relaxes back to the resting state on a timescale of several seconds to tens of minutes, depending on the specific BLUF photoreceptor.

We performed free energy simulations of the AppA BLUF domain prior to and following photoexcitation.<sup>47</sup> Specifically, we used the adaptively biased path optimization method<sup>48</sup> 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<sub>in</sub> and Trp<sub>out</sub>, respectively. As shown in Figure 8, our calculations revealed that both conformations are sampled on the ground state, with the Trp<sub>in</sub> conformation thermodynamically favorable by ~3 kcal/mol. Moreover, at equilibrium at room temperature, the ground state BLUF domain can undergo interconversion between the Trp<sub>in</sub> and Trp<sub>out</sub> conformations on a ~100  $\mu$ s timescale. These results are consistent with the observation of both conformations in different X-ray crystallography and solution NMR structures of AppA BLUF.<sup>49-52</sup>



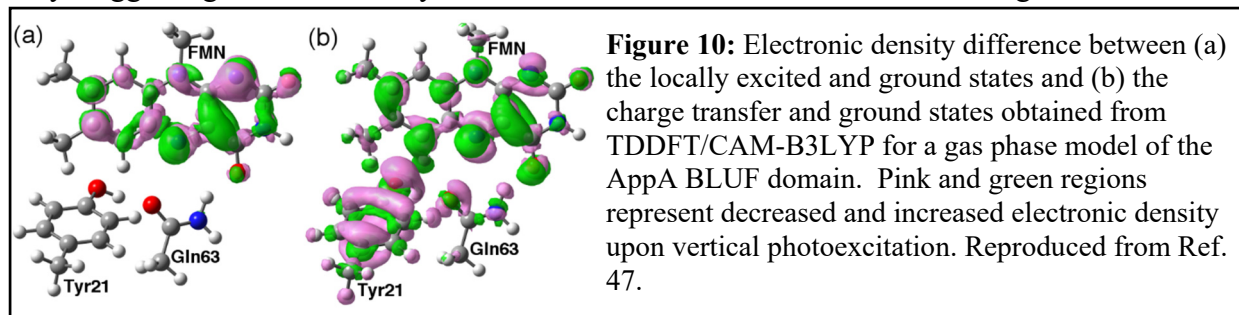
Moreover, to analyze the proton relay from Tyr21 to the flavin via Gln63, we calculated the free energy profiles for Gln63 rotation on the ground state, the locally excited state of the flavin, and the charge transfer state associated with ET from Tyr21 to the flavin. These results are depicted in Figure 9. For the Trp<sub>in</sub> 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  $\sim 0.5$  kcal/mol (red curve). On the other hand, for the Trp<sub>out</sub> 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)<sup>53-54</sup> 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<sub>in</sub> conformation is predicted to hamper the signaling efficiency, which requires ET from Tyr21. The significant population of the Trp<sub>in</sub> 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 photocycle<sup>55</sup> and the Trp fluorescence experiments indicating that Trp104 remains buried in the AppA BLUF domain active site throughout the photocycle.<sup>56</sup> 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.<sup>55,57</sup> 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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Nonadiabatic Dynamics of Photoinduced Proton-Coupled Electron Transfer Processes

**Grant/Contract Number**

AFOSR assigned control number. It must begin with "FA9550" or "F49620" or "FA2386".

FA9550-14-1-0295

**Principal Investigator Name**

The full name of the principal investigator on the grant or contract.

Sharon Hammes-Schiffer

**Program Officer**

The AFOSR Program Officer currently assigned to the award

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**Abstract**

The design of efficient and economical devices for the conversion of solar energy to chemical fuel and electrical power is important for national security and therefore is critical to the mission of the Air Force. Photoinduced proton-coupled electron transfer (PCET) is essential for a wide range of energy conversion processes in chemical and biological systems. Understanding the underlying principles of photoinduced PCET at a level that allows tuning and control of the ultrafast dynamics is crucial for designing renewable and sustainable energy sources, such as artificial photosynthesis devices and photoelectrochemical cells. Theoretical methodology for simulating the nonadiabatic dynamics of photoinduced PCET reactions in solution has been developed. The electronic potential energy surfaces are generated on-the-fly with a hybrid quantum mechanical/molecular mechanical approach that describes the solute with a multiconfigurational method in a bath of explicit solvent molecules. The transferring hydrogen nucleus is represented as a quantum mechanical wavefunction calculated with grid-based methods, and surface hopping trajectories are propagated on the adiabatic electron-proton vibronic surfaces. This approach was applied to an experimentally studied phenol-amine complex in 1,2-dichloroethane. Using this system as a prototype, these calculations provided insights into fundamental aspects of photoinduced PCET, including

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the characterization of different types of excited electronic states, as well as the roles of solute and solvent dynamics, nonadiabatic transitions, proton delocalization, and vibrational relaxation. Furthermore, general strategies were developed for tuning and controlling the charge transfer dynamics and relaxation processes by altering the nature and positions of molecular substituents, the distance associated with electron transfer, the proton transfer interface, and the solvent properties. These insights, as well as the computational methods developed, will play an important role in guiding the design of more effective catalysts for energy production and storage.

Photoreceptor proteins play a critical role in the light regulation of physiologically essential processes and are particularly important in the field of optogenetics, which is of interest to the Air Force because of the potential impact on human performance. In these systems, photoexcitation of a chromophore bound to the photoreceptor protein leads to local conformational changes that propagate to distal regions of the protein and thereby drive vital chemical and physical changes. Understanding the fundamental mechanisms of these proteins is important for engineering systems that use light to control biological processes with high spatiotemporal resolution. Theoretical methods were used to study the AppA blue light using flavin (BLUF) protein, which is essential for the light regulation of a variety of physiologically important processes and serves as a prototype for photoinduced PCET in proteins. Free energy simulations elucidated the active site conformations in the BLUF domain prior to and following photoexcitation. The free energy profile for interconversion between conformations with either Trp104 or Met106 closer to the flavin, denoted Trpin and Trpout, respectively, revealed that both conformations are sampled on the ground state, with the former thermodynamically favorable by ~3 kcal/mol. These results are consistent with the experimental observation of both conformations, with the Trpin conformation determined to be the active form. To analyze the proton relay from Tyr21 to the flavin via Gln63, the free energy profiles for Gln63 rotation were calculated on the ground state, the locally excited state of the flavin, and the charge transfer state associated with electron transfer from Tyr21 to the flavin. For the Trpin conformation, the hydrogen-bonding pattern conducive to the proton relay was found to be thermodynamically unfavorable on the ground state but was observed to become more favorable, corresponding to approximately half of the configurations sampled, on the locally excited state. The calculated energy gap between the locally excited and charge transfer states suggests that electron transfer from Tyr21 to the flavin is more facile for configurations conducive to proton transfer. When the active site conformation is not conducive to PCET from Tyr21, Trp104 can directly compete with Tyr21 for electron transfer to the flavin through a non-productive pathway, impeding the signaling efficiency. These insights will facilitate the design of novel photoreceptor proteins with long-range signaling capabilities relevant to optogenetics.

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#### **Archival Publications (published) during reporting period:**

- (1) Sirjoosingh, A.; Pak, M. V.; Brorsen, K. R.; Hammes-Schiffer, S. Quantum Treatment of Protons with the Reduced Explicitly Correlated Hartree-Fock Approach. J. Chem. Phys. 2015, 142, 214107.
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Photoinduced Proton-Coupled Electron Transfer in a Solvated Phenol-Amine Complex. J. Phys. Chem. B 2015, 119, 2758-2768.

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**New discoveries, inventions, or patent disclosures:**

**Do you have any discoveries, inventions, or patent disclosures to report for this period?**

No

**Please describe and include any notable dates**

**Do you plan to pursue a claim for personal or organizational intellectual property?**

**Changes in research objectives (if any):**

None

**Change in AFOSR Program Officer, if any:**

None

**Extensions granted or milestones slipped, if any:**

None

**AFOSR LRIR Number**

**LRIR Title**

**Reporting Period**

**Laboratory Task Manager**

**Program Officer**

**Research Objectives**

**Technical Summary**

**Funding Summary by Cost Category (by FY, \$K)**

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Equipment/Facilities			
Supplies			
Total			

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## Appendix Documents

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