

NON-BORN-OPPENHEIMER EFFECTS BETWEEN ELECTRONS AND PROTONS

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EXECUTIVE SUMMARY

The quantum mechanical behavior of nuclei plays an important role in a wide range of chemical and biological processes. The inclusion of nuclear quantum effects and non-Born–Oppenheimer effects between nuclei and electrons in computer simulations is challenging. Our group has developed the nuclear-electronic orbital (NEO) method for treating electrons and select nuclei quantum mechanically on the same level using an orbital-based formalism. We have used Blue Waters to perform NEO calculations on systems in which all electrons and one proton or positron are treated quantum mechanically. In addition, we have studied the active site conformations of a blue light using flavin adenine dinucleotide (BLUF) photoreceptor protein and their relation to photocycle activation. This work serves as groundwork for subsequent nonadiabatic dynamics studies of photoinduced proton-coupled electron transfer (PCET) reactions that have been proposed to be involved in biological signaling by BLUF proteins [1].

RESEARCH CHALLENGE

The inclusion of nuclear quantum effects such as zero-point energy and tunneling in electronic structure calculations is important in a variety of chemical systems, particularly those involving hydrogen transfer or hydrogen-bonding interactions. Moreover, nonadiabatic effects—also called non-Born–Oppenheimer effects—between electrons and certain nuclei are significant for many of these systems. In this case, the electrons cannot be assumed to respond instantaneously to the nuclear motions, and the concept of the nuclei moving on a single electronic potential energy surface is no longer valid. This type of nonadiabaticity has been shown to play a critical role in PCET reactions, which are essential for a wide range of chemical and biological processes, including phototaxis, photosynthesis, respiration, enzyme reactions, and energy devices such as solar cells. The development of non-Born–Oppenheimer methods to enable accurate and efficient calculations of PCET reactions will impact many scientific endeavors, from the design of novel materials for optogenetics to the design of more effective catalysts for solar energy devices.

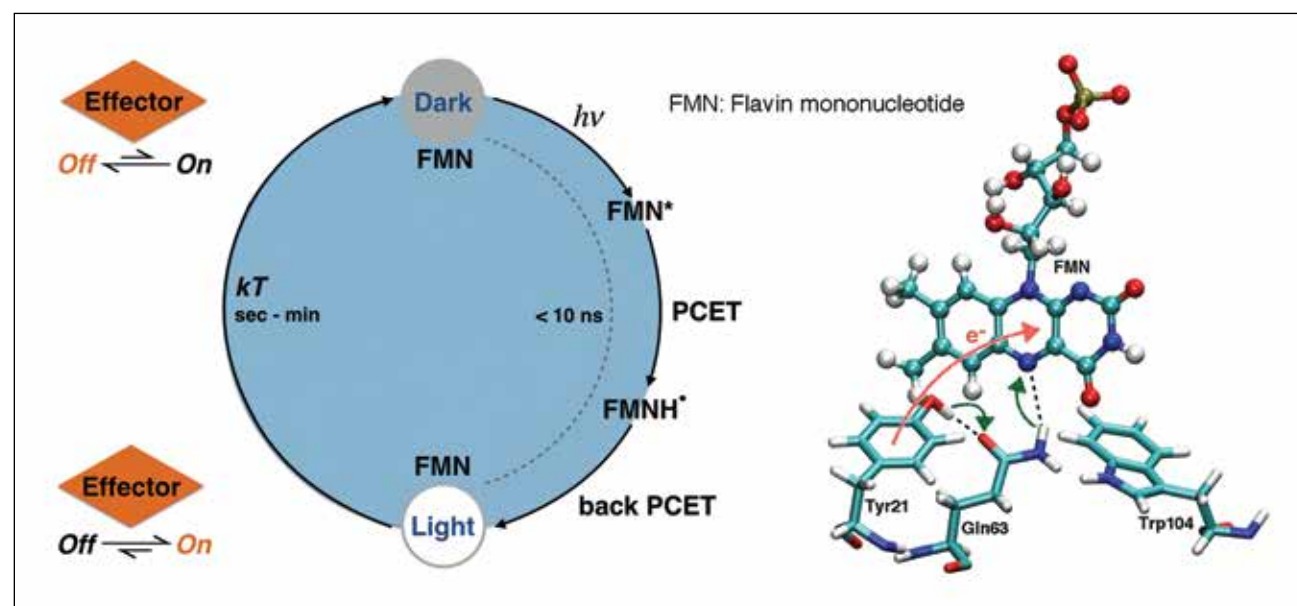


Figure 1: (Left) A schematic diagram of the photocycle in BLUF photoreceptor proteins. The dark state to light state conversion is believed to involve photoinduced PCET and shifts the equilibrium between the “off” and “on” states of the effector domain. (Right) Our studies indicate that the proton relay conformation of the active site Tyr and Gln residues is important for electronic charge transfer from Tyr to the flavin.

METHODS & CODES

Typically, in the NEO approach, all electrons and one proton or positron are treated quantum mechanically, and a mixed nuclear-electronic time-independent Schrödinger equation is solved [2]. We have recently proposed an ansatz with the primary goal of improving computational tractability to enable the study of larger systems of chemical interest within the NEO framework [3]. In this approach, denoted NEO-RXCHF, only select electronic orbitals are explicitly correlated to the nuclear or positronic orbital, and certain exchange terms are approximated. We recently incorporated an improved integral package into the NEO code. The new and fully optimized integral code enables the use of a direct algorithm for the NEO-RXCHF method and provides a multiple order of magnitude speed-up compared to the old integral code while significantly reducing the memory overhead.

The study of photoinduced PCET in the BLUF photoreceptor proteins requires resolution of the debate over the conformations of key active site residues arising from inconsistent X-ray crystallographic and solution nuclear magnetic resonance structures. Unlike most computational studies reported in the literature, we carried out comprehensive free energy calculations to elucidate the dominant conformations of key residues on different electronic states and studied the effects of active site conformations on the photocycle activation mechanism. The free energy calculations were carried out using the adaptively biased path optimization (ABPO) [4] and umbrella sampling [5] techniques implemented in the CHARMM [6] software package, while excited electronic states were calculated using the time-dependent density functional theory [7] method implemented in Gaussian 09 [8].

RESULTS & IMPACT

The NEO-RXCHF method was used to compute the binding energies of a positron to neutral atoms. The NEO-RXCHF results agreed well with highly accurate stochastic variational method (SVM) calculations. The inclusion of explicit electron-positron correlation was found to be essential for even qualitative accuracy, as NEO methods that neglect explicit electron-positron correlation did not predict the positron to bind to the atomic systems. The NEO-RXCHF method has better computational scaling characteristics than SVM, and SVM calculations have never been performed on a system with more than five quantum particles. Because of this limitation, the SVM method cannot be used for larger molecular systems. No *ab initio* or first principles method has ever predicted that a positron will bind to an alkane, which has been observed experimentally. The accuracy of the NEO-RXCHF calculations combined with this method’s computational tractable scaling characteristics demonstrate that NEO-RXCHF is a promising method for computing the binding energy of positrons to molecules such as alkanes.

Our free energy simulations of the AppA BLUF domain have elucidated the active site conformations before and

following photoexcitation [9]. For the dominant Trp_{in}/Met_{out} conformation, the hydrogen-bonding pattern conducive to the proton relay from Tyr21 to the flavin chromophore is not thermodynamically favorable on the ground electronic state but becomes more favorable, corresponding to approximately half of the configurations sampled, on the locally excited state of the flavin. The calculated energy gaps between the locally excited state and the charge-transfer state associated with electron transfer from Tyr21 to the flavin suggest 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 compete directly with Tyr21 for electron transfer to the flavin through a nonproductive pathway, impeding the signaling efficiency. These insights have contributed to the resolution of a long-standing debate in the field of BLUF protein research and pave the way for nonadiabatic dynamics studies that will be crucial in understanding the signaling mechanism of the AppA BLUF domain.

WHY BLUE WATERS

The NEO-RXCHF method requires the calculation of trillions of integrals. Our in-house NEO code has been parallelized using the MPI (Message Passing Interface) protocol and requires a large number of processors. Additionally, with the implementation of a direct algorithm for the NEO-RXCHF method, the fast calculation of the integrals is even more important, as the integrals must be computed many times during the calculation instead of a single time at the start. The speed and scalability of Blue Waters is crucial in enabling large NEO-RXCHF calculations.

To investigate the conformations of the active site tryptophan and methionine residues in the AppA BLUF domain, we used the ABPO method implemented in CHARMM. The calculations employed 21 images of the system and were carried out on a total of 1344 processors. Blue Waters provided a large number of simultaneously available nodes and efficient inter-node communication important for these calculations. Assistance from the project staff was crucial in successful building and testing of the locally modified CHARMM code on Blue Waters.

PUBLICATIONS AND DATA SETS

Borsen, K. R., M. V. Pak, and S. Hammes-Schiffer, Calculation of Positron Binding Energies and Electron-Positron Annihilation Rates for Atomic Systems with the Reduced Explicitly Correlated Hartree-Fock Method in the Nuclear-Electronic Orbital Framework. *J. Phys. Chem. A*, 122:2 (2017), pp. 515–522.

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Goyal, P., and S. Hammes-Schiffer, Role of active site conformational changes in photocycle activation of the AppA BLUF photoreceptor. *Proc. Natl. Acad. Sci. USA*, 114:7 (2017), pp. 1480–1485.