Nuclear-Electronic Orbital Quantum Mechanical/Molecular Mechanical Real-Time Dynamics

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Abstract

Simulating the nuclear-electronic quantum dynamics of large-scale molecular systems in the condensed phase is key for studying biologically and chemically important processes such as proton transfer and proton-coupled electron transfer reactions. Herein, the real-time nuclear-electronic orbital time-dependent density functional theory (RT-NEO-TDDFT) approach is combined with a hybrid quantum mechanical/molecular mechanical (QM/MM) strategy to enable the accurate description of coupled nuclear-electronic quantum dynamics in the presence of heterogeneous environments such as solvent or proteins. The densities of the electrons and quantum protons are propagated in real time, while the other nuclei are propagated classically on the instantaneous electron-proton vibronic surface. This approach is applied to phenol bound to lysozyme, intramolecular proton transfer in malonaldehyde, and nonequilibrium excited-state intramolecular proton transfer in *o*-hydroxybenzaldehyde. These examples illustrate that the RT-NEO-TDDFT framework, coupled with an atomistic representation of the environment, allows the simulation of condensed phase systems that exhibit significant nuclear quantum effects.

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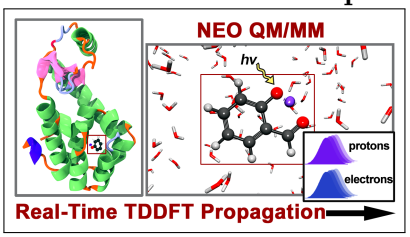

The nuclear-electronic orbital (NEO) approach treats electrons and specified nuclei, usually protons, quantum mechanically on the same level.[1–3] In this approach, nuclear quantum effects such as zero-point energy, proton delocalization, and vibrational anharmonicity are conveniently included into quantum chemistry calculations and molecular dynamics simulations. Many of the conventional electronic wave function and density functional theory (DFT)[4–6] techniques for both ground and excited states have been extended to the NEO framework.[7–12] Various strategies for performing direct dynamics within the NEO framework have also been developed, such as adiabatic ground state NEO-DFT dynamics[13] and real-time NEO time-dependent density functional theory (RT-NEO-TDDFT or for brevity RT-NEO) dynamics.[14] The RT-NEO approach has been combined with Ehrenfest dynamics[15] to enable the simulation of nonequilibrium nuclear-electronic dynamics beyond the BO approximation.[16] Furthermore, the constrained NEO method presents another elegant approach for performing NEO ground state dynamics.[17,18] Although other approaches such as path-integral molecular dynamics have been successful,[19–21] the NEO approach is straightforward to use for propagating nonequilibrium, real-time dynamics while capturing the non-Born-Oppenheimer effects between the electrons and the protons as well as the nuclear quantum effects. As a result, NEO is an especially attractive platform for performing adiabatic and nonadiabatic dynamics simulations.

Many important processes in biology and chemistry occur in the condensed phase, such as solution or proteins. Therefore, understanding how these condensed phase environments affect chemical reactions and molecular properties is valuable. All of the dynamics approaches mentioned above could in principle be extended to the condensed phase using an implicit solvation scheme such as the polarizable continuum model (PCM) or various other formulations.[22,23] For instance, the RT-NEO PCM approach has been developed and used to investigate the nonequilibrium, real-time dynamics of a photoinduced proton transfer reaction.[24] Implicit solvation models are appealing for many reasons, but they usually assume a structureless, homogeneous solvent, and a time-dependent treatment of the solvent

response requires additional assumptions.[25–27] Hybrid quantum mechanical/molecular mechanical (QM/MM) methodologies provide an alternative multiscale approach that allows explicit solvent and heterogeneous environments such as proteins to be described using a classical force field while simultaneously allowing key components to be treated using quantum mechanical methods.[28,29] Previously, we developed the adiabatic ground state NEO-DFT QM/MM approach to describe the dynamics of a phenol molecule in explicit solvent with the phenolic proton treated quantum mechanically on the same level as the electrons.[30] A disadvantage of this approach is that the proton responds instantaneously to the other nuclei, and therefore the proton vibrational mode is quenched.

In this Letter, we develop the RT-NEO Ehrenfest QM/MM approach. In this approach, the nonequilibrium electronic and protonic densities in the QM region are propagated in real time, incorporating the MM environment using electrostatic embedding.[31,32] The classical nuclei in both the QM and MM regions move according to Ehrenfest dynamics on the time-dependent, instantaneous electron-proton vibronic surface. For processes occurring on the ground electronic state, the electronic BO approximation can be invoked to enable the use of a significantly larger time step, leading to substantial computational savings.[33] In the resulting BO-RT-NEO approach, the electronic density is quenched using the NEO-DFT self-consistent-field (SCF) procedure at each time step, but the nonequilibrium protonic densities are still propagated according to the RT-NEO equations. In the BO-RT-NEO Ehrenfest dynamics approach, the classical nuclei still move on the instantaneous electron-proton vibronic surface, but this surface corresponds to the electronic ground state for the classical nuclear configuration and nonequilibrium proton density at each time step. Herein, we use the BO-RT-NEO Ehrenfest QM/MM approach to investigate a phenol bound to an enzyme active site and proton transfer in malonaldehyde in explicit water. We use the RT-NEO Ehrenfest QM/MM approach without the electronic BO approximation to investigate excited-state intramolecular proton transfer (ESIPT) in explicit water. These developments enable the inclusion of nuclear quantum effects and, when warranted, non-BO effects directly

into molecular dynamics trajectories in the condensed phase to simulate coupled nuclear-electronic quantum dynamics in solution and enzymes.

Here we provide a brief overview of the key equations for the RT-NEO QM/MM approach. More detailed expressions for the RT-NEO method[14] and the NEO QM/MM strategy[30] can be found in our earlier work. We assume that the form of the NEO wave function (or reference system for NEO-DFT) can be written as a single Slater determinant product that is represented as

$$\Psi_{\mathrm{NEO}}\left(\mathbf{x}^{\mathrm{e}}\ ,\ \mathbf{x}^{\mathrm{p}}\ ;\ t\right)=\Phi^{\mathrm{e}}\left(\mathbf{x}^{\mathrm{e}}\ ;\ t\right)\Phi^{\mathrm{p}}\left(\mathbf{x}^{\mathrm{p}}\ ;\ t\right) \tag{1}$$

where $\mathbf{x}^{\mathrm{e}}$ ($\mathbf{x}^{\mathrm{p}}$) are the collective spatial and spin electron (proton) coordinates, Φ^{e} (Φ^{p}) is the electronic (protonic) Slater determinant, and t is the time. Analogous to conventional electronic real-time TDDFT methods,[34] substitution of this wave function into the time-dependent Schrödinger equation yields the following set of multicomponent von Neumann equations:

$$i\hbar\frac{\partial}{\partial t}\mathbf{P}^{\mathrm{e}}\left(t\right)=\left[\mathbf{F}^{\mathrm{e}}\left(t\right),\mathbf{P}^{\mathrm{e}}\left(t\right)\right] \tag{2}$$

$$i\hbar\frac{\partial}{\partial t}\mathbf{P}^{\mathrm{p}}\left(t\right)=\left[\mathbf{F}^{\mathrm{p}}\left(t\right),\mathbf{P}^{\mathrm{p}}\left(t\right)\right] \tag{3}$$

In these equations, $\mathbf{P}^{\mathrm{e}}$ (or $\mathbf{P}^{\mathrm{p}}$) is the single particle density matrix and $\mathbf{F}^{\mathrm{e}}$ (or $\mathbf{F}^{\mathrm{p}}$) is the Kohn-Sham matrix for the electrons (or protons) in the orthonormal atomic orbital basis.

In a straightforward manner, we can extend this theoretical framework to incorporate an external field of MM charges through the electrostatic QM/MM embedding approach:

$$\begin{aligned}\mathbf{F}^{\mathrm{e}}\left(t\right)&=\mathbf{H}^{\mathrm{e}}_{\mathrm{elst}}+\mathbf{H}^{\mathrm{e}}_{\mathrm{core}}+\mathbf{J}^{\mathrm{ee}}\left(\mathbf{P}^{\mathrm{e}}\left(t\right)\right)+\mathbf{V}^{\mathrm{e}}_{\mathrm{xc}}\left(\mathbf{P}^{\mathrm{e}}\left(t\right)\right)-\mathbf{J}^{\mathrm{ep}}\left(\mathbf{P}^{\mathrm{p}}\left(t\right)\right)+\mathbf{V}^{\mathrm{ep}}_{\mathrm{c}}\left(\mathbf{P}^{\mathrm{e}}\left(t\right),\mathbf{P}^{\mathrm{p}}\left(t\right)\right)\\ \mathbf{F}^{\mathrm{p}}\left(t\right)&=\mathbf{H}^{\mathrm{p}}_{\mathrm{elst}}+\mathbf{H}^{\mathrm{p}}_{\mathrm{core}}+\mathbf{J}^{\mathrm{pp}}\left(\mathbf{P}^{\mathrm{p}}\left(t\right)\right)+\mathbf{V}^{\mathrm{p}}_{\mathrm{xc}}\left(\mathbf{P}^{\mathrm{p}}\left(t\right)\right)-\mathbf{J}^{\mathrm{pe}}\left(\mathbf{P}^{\mathrm{e}}\left(t\right)\right)+\mathbf{V}^{\mathrm{pe}}_{\mathrm{c}}\left(\mathbf{P}^{\mathrm{p}}\left(t\right),\mathbf{P}^{\mathrm{e}}\left(t\right)\right)\end{aligned} \tag{4}$$

In these equations, $\mathbf{H}^{\mathrm{e}}_{\mathrm{elst}}$ (or $\mathbf{H}^{\mathrm{p}}_{\mathrm{elst}}$) is the additional one-particle electrostatic embedding term corresponding to the Coulomb interactions between the MM charges and the electrons (or protons). The remaining terms are the same as in the NEO-DFT vacuum case: $\mathbf{H}^{\mathrm{e}}_{\mathrm{core}}$

is the core electronic Hamiltonian, which includes the kinetic energy of the electrons and the Coulomb interaction of the electrons with the classical nuclei of the QM region; $\mathbf{J}^{\mathrm{ee}}$ represents the Coulomb interactions between the electrons; $\mathbf{V}_{\mathrm{xc}}^{\mathrm{e}}$ is the electron exchange-correlation potential; $\mathbf{J}^{\mathrm{ep}}$ represents the Coulomb interactions between the electrons and the quantum protons; and $\mathbf{V}_{\mathrm{c}}^{\mathrm{ep}}$ is the correlation potential between the electrons and the quantum protons. All of these terms are defined analogously for protons p except that the proton-proton correlation in $\mathbf{V}_{\mathrm{xc}}^{\mathrm{p}}$ has been shown to be negligible and therefore is typically omitted.

The time-dependent Eqs. 2 and 3 are strongly coupled through the $\mathbf{J}^{\mathrm{ep}}$ ($\mathbf{J}^{\mathrm{pe}}$) Coulomb interaction terms and $\mathbf{V}_{\mathrm{c}}^{\mathrm{ep}}$ ($\mathbf{V}_{\mathrm{c}}^{\mathrm{pe}}$) electron-proton correlation terms in the electronic (protonic) Kohn-Sham matrix, and thus they are propagated simultaneously in real time. In practice, integrating these equations of motion for the quantum subsystem typically requires a very small time step due to the fast motion of the electrons. This time step is often several orders of magnitude smaller than that required for evolving the dynamics of the classical nuclei, rendering longer simulation times computationally intractable. Recently, we have shown that for electronically adiabatic systems, the electronic BO approximation can be invoked within the RT-NEO framework.[33] In this BO-RT-NEO approach, evaluation of the time-dependent Schrödinger equation for the electrons is avoided by quenching the electrons to the ground state at every time step using the standard SCF procedure,

$$\mathbf{P}^{\mathrm{e}}\left(t\right) = \mathrm{SCF}\left[\mathbf{P}^{\mathrm{p}}\left(t\right), \left\{\mathbf{R}_A\left(t\right)\right\}\right] \tag{5}$$

where $\mathbf{R}_A$ represents the classical nuclear coordinates. In this case, the electronic density is solved variationally for each classical nuclear geometry and nonequilibrium proton density sampled along the trajectory. Invoking the electronic BO approximation in conjunction with the RT-NEO method is advantageous because a larger time step for the quantum subsystem can be used, as the electronic density is no longer being propagated. We have shown that

this approach recovers nearly identical proton density dynamics for electronically adiabatic systems compared to the original RT-NEO implementation at a fraction of the cost.[33]

The RT-NEO approach has been formulated to describe the motion of the classical nuclei on the instantaneous electron-proton vibronic surface through RT-NEO Ehrenfest dynamics.[16] In this treatment, the motion of the classical nuclei in the QM and MM regions follow Newtonian dynamics. In our implementation, the positions and velocities of the classical nuclei are evolved via the velocity Verlet algorithm. The dynamics of the quantum subsystem can be propagated either in the original RT-NEO framework by integrating Eqs. 2 and 3 or in the BO-RT-NEO framework by integrating Eqs. 3 and 5 if the electronic BO approximation is invoked. A different time step can be used to propagate the classical and quantum subsystems, but for convenience we use the same time step for the calculations performed herein (see Supporting Information, SI).

We applied the RT-NEO QM/MM approach to a phenol ligand interacting with an enzyme, proton transfer in malonaldehyde in explicit water, and ESIPT in the *o*-hydroxybenzaldehyde (oHBA) molecule in explicit water (Fig. 1). The MM regions were described with the OPLS-AA force field[35–37] and the rigid TIP3P water model[38] for the explicit solvent. The QM/MM calculations were carried out using a modified version of INAQS,[39] which interfaces GROMACS 4.6.5[40] with a developer branch of Q-Chem 5.4[41] containing the RT-NEO implementation. For the ligand-enzyme system, we used the 6-31G(d,p) electronic basis set.[42] Consistent with earlier studies, we used the cc-pVDZ electronic basis set[43] for the malonaldehyde and oHBA systems. In all cases, electron correlation and exchange were treated with the B3LYP functional,[44,45] the electron-proton correlation was treated with the epc17-2 functional,[11,46] and the PB4-F2 protonic basis set[47] was used for the quantum proton. The same electronic basis set and functional were used for the corresponding conventional DFT and TDDFT simulations. The initial configurations for malonaldehyde and oHBA were obtained by equilibrating the aqueous solvent around a fixed solute geometry. The enzyme-ligand complex was surrounded with explicit water molecules, and the entire

system was prepared following the protocol outlined in the SI.

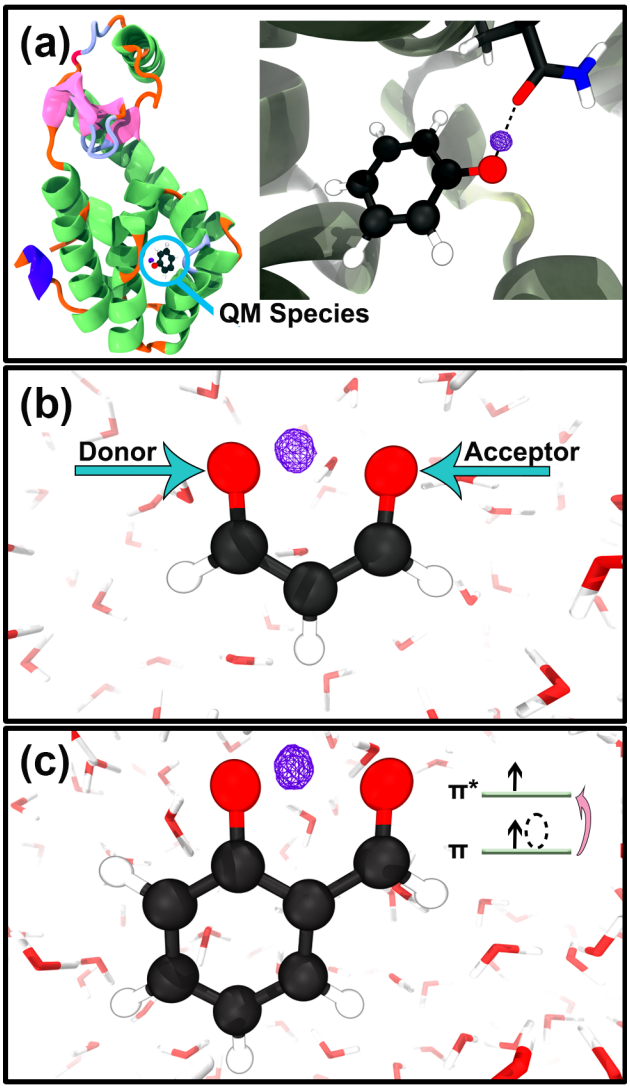

Figure 1: Illustrations of the three systems simulated with the RT-NEO QM/MM approach: (a) phenol bound to the active site of the enzyme lysozyme, (b) malonaldehyde in explicit water, and (c) oHBA in explicit water. The purple mesh depicts the proton densities at the initial configuration of the RT-NEO QM/MM trajectory.

For NEO calculations, the protonic basis set must be flexible enough to properly describe the motion of the protons during the entire trajectory. Two viable approaches are the fixed proton basis (FPB) or the traveling proton basis (TPB).[16,48] The TPB approach has the benefit of being more general without requiring knowledge of how the proton will move during the trajectory. The FPB and TPB approaches have been shown to produce similar

results for proton transfer in oHBA when four fixed proton basis function centers are used.[48] To be consistent throughout, we utilized the TPB approach for all the RT-NEO QM/MM simulations.

For comparison, we also performed conventional BOMD simulations, where the nuclei move on the adiabatic electronic ground state, and conventional RT-TDDFT Ehrenfest simulations, where the electronic density is propagated in time and the nuclei move on the instantaneous electronic surface. For electronically adiabatic systems, conventional BOMD and conventional RT-TDDFT Ehrenfest calculations yield similar results, as shown previously.[15,33] Moreover, the conventional RT-TDDFT Ehrenfest simulations are significantly more computationally expensive than the analogous BOMD simulations because of the small time step required to integrate the electronic density. For these reasons, we performed conventional RT-TDDFT Ehrenfest simulations for malonaldehyde and oHBA but not for the enzyme system.

The first application focuses on a QM phenol bound to the active site of the L99A/M102Q double mutant of T4 lysozyme (PDB ID: 1LI2).[49] This bound phenol is hydrogen bonded to the oxygen atom of an MM glutamine residue (Fig. 1a). The solvated enzyme-ligand system was partially equilibrated to provide initial coordinates and velocities for a representative trajectory (see SI). Fig. 2 shows the intramolecular H−O distance of the phenol hydroxyl group, and the other key distances at the hydrogen-bonding interface are shown in Fig. S1. For the conventional electronic BO molecular dynamics (BOMD) trajectory, the nuclei moved on the electronic ground state generated on-the-fly with DFT. For the NEO BOMD trajectory, the classical nuclei moved on the electron-proton vibronic ground state generated on-the-fly with NEO-DFT, where the phenol hydroxyl proton was treated quantum mechanically. For the BO-RT-NEO Ehrenfest dynamics trajectory, the protonic density was propagated with RT-NEO-TDDFT, quenching the electronic density at each time step, and the classical nuclei moved on the instantaneous NEO vibronic surface corresponding to the classical nuclear configuration and the nonequilibrium proton density.

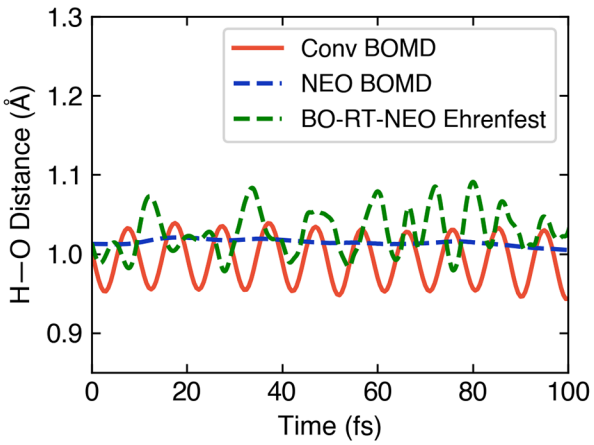

Figure 2: Time evolution of the H−O distance between the phenol hydroxyl hydrogen atom and its covalently bonded oxygen atom for the lysozyme-phenol system shown in Fig. 1a. The initial coordinates and velocities are the same for all three types of trajectories: conventional electronic BO molecular dynamics (Conv BOMD); NEO-DFT dynamics on the electron-proton vibronic ground state (NEO BOMD); and BO-RT-NEO-TDDFT Ehrenfest dynamics, invoking the electronic BO approximation but propagating the protonic density in real time. The H−O distance is calculated using the classical proton position for the conventional BOMD trajectory and using the quantum proton position operator expectation value for the NEO trajectories. Moreover, the quantum proton basis function center position is determined through variational optimization at each time step (including time $t = 0$) for the NEO BOMD method but is propagated using the semiclassical TPB approach for the BO-RT-NEO Ehrenfest method. The NEO BOMD trajectory quenches the oscillations of the quantum proton, whereas the BO-RT-NEO-TDDFT Ehrenfest dynamics trajectory fully describes these oscillations.

The time evolution of the H−O distance is qualitatively different in the NEO-BOMD trajectory compared to the conventional BOMD and BO-RT-NEO Ehrenfest trajectories. In the NEO BOMD trajectory, the proton responds instantaneously to the motion of the classical nuclei, in the same manner as the electrons, thereby relaxing to the vibronic ground state during each time step. As a result, the proton motion is quenched at each time step (solid blue line in Fig. 2), rather than oscillating as it does in the conventional BOMD trajectory (solid orange line in Fig. 2). In contrast, the dynamics of the quantum proton is propagated in real time in the BO-RT-NEO Ehrenfest dynamics trajectory, recovering the H−O oscillations (dashed green line in Fig. 2) absent in the NEO BOMD result. As pointed out in our earlier work simulating phenol in explicit water,[30] the real-time propagation of

the proton density is important for an accurate description of nuclear-electronic dynamics within the NEO framework. For completeness, the results from this previous study are compared to the results obtained using the BO-RT-NEO Ehrenfest method in the SI (Fig. S2). Although the BO-RT-NEO Ehrenfest and conventional BOMD trajectories appear to display qualitatively similar behavior in terms of the oscillations in the H−O bond distances, the BO-RT-NEO Ehrenfest approach is different from conventional BOMD because of the quantum mechanical treatment of the proton, which introduces proton delocalization, zero-point energy effects, and greater anharmonicity.

To further probe the impact of explicit solvent on chemical reactions within the NEO framework, we also used the RT-NEO method to simulate intramolecular proton transfer in malonaldehyde. Previously we showed that the BO-RT-NEO Ehrenfest and RT-NEO Ehrenfest methods produce nearly identical trajectories for the same initial conditions,[33] indicating that the electronic BO approximation is valid for this process (i.e., the proton transfer reaction is occurring on the electronic ground state). Moreover, our analysis provided evidence of delocalization of the proton density between the two oxygen atoms along the trajectory, characteristic of hydrogen tunneling. These previous simulations were performed in the gas phase. Here we use the BO-RT-NEO QM/MM method to examine the influence of explicit solvation on this proton transfer reaction. All of the trajectories were started from the same initial conditions for malonaldehyde as in the previous study,[33] namely the same initial classical nuclear geometry and proton basis function center position, as well as initial velocities of zero. Explicit water was introduced around this structure, followed by a partial equilibration of the solvent with malonaldehyde kept fixed. Although a QM/MM equilibration step would allow further relaxation prior to the start of the trajectory, our protocol enabled a direct comparison of different approaches with the same initial conditions. More details about the system preparation are provided in the SI.

BO-RT-NEO QM/MM trajectories were propagated for three different initial configurations of the explicit water environment around malonaldehyde. Fig. 3 shows that the proton

transfer dynamics is sensitive to the initial water configuration. For simplicity, proton transfer is designated to occur when the expectation value of the transferring proton position operator is equidistant from the donor and acceptor oxygen atoms, although a more rigorous definition would account for the formation of a covalent bond with the acceptor oxygen. In some cases, the rate of proton transfer is accelerated (Fig. 3c), while in other cases the rate of proton transfer is decelerated (Fig. 3b). We also observed instances in which proton transfer does not occur at all within the time scale of the simulation performed (Fig. 3a). Analogous simulations performed with conventional RT-TDDFT Ehrenfest dynamics, where all nuclei are treated classically, do not exhibit proton transfer in the gas phase for this initial geometry or in solution for any of these three initial solvent configurations (Figure S3). This observation highlights the importance of treating the transferring proton quantum mechanically for proton transfer reactions, particularly those involving hydrogen tunneling. A thorough sampling of the initial conditions would be required to comprehensively investigate the impact of explicit water on this reaction and to relate these calculations to experimental studies. However, these three representative trajectories illustrate that the BO-RT-NEO QM/MM approach is a viable method for studying solvation effects on chemical reactivity within the NEO framework.

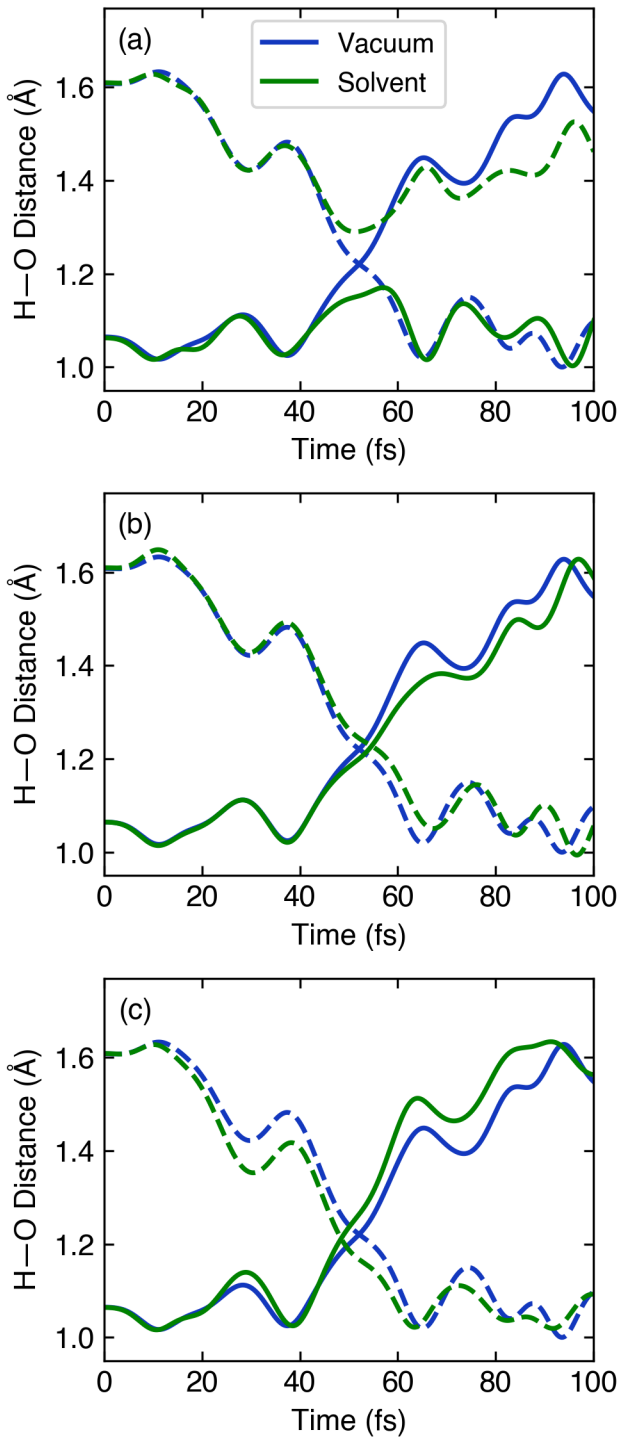

Figure 3: Intramolecular proton transfer dynamics on the electronic ground state in malonaldehyde solvated in explicit water for three different initial solvent configurations but the same initial malonaldehyde geometry. These simulations were performed with the BO-RT-NEO-TDDFT Ehrenfest dynamics method, invoking the electronic BO approximation but propagating the protonic density in real time. The H−O distance is calculated using the proton position operator expectation value. Proton transfer occurs when the distance between the expectation value of the transferring proton position operator and the donor oxygen (solid lines) and acceptor oxygen (dashed lines) is the same. Comparing the solvated reaction (green) to the gas phase reaction (blue, the same in all three panels), these three trajectories show examples of explicit solvation (a) suppressing proton transfer, (b) decelerating proton transfer, and (c) accelerating proton transfer.

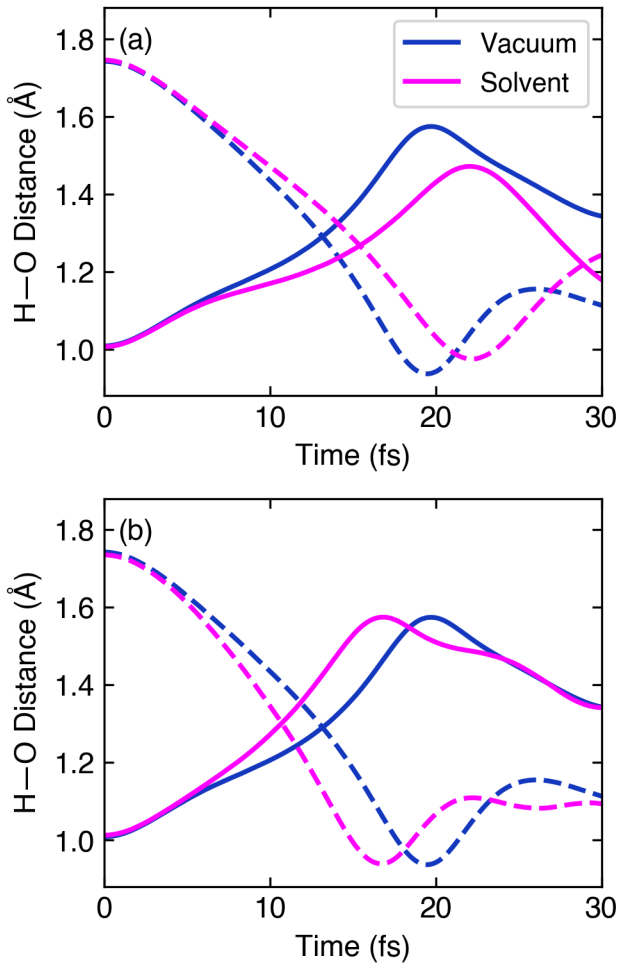

Figure 4: ESIPT dynamics in oHBA solvated in explicit water for two different initial solvent configurations but the same initial oHBA geometry. These simulations were performed with the RT-NEO-TDDFT Ehrenfest dynamics method, propagating both the electronic and protonic densities in real time. The H−O distance is calculated using the proton position operator expectation value. Proton transfer occurs when the distance between the expectation value of the transferring proton position operator and the donor oxygen (solid lines) and the acceptor oxygen (dashed lines) is the same. Comparing the solvated reaction (magenta) to the gas phase reaction (blue), these two trajectories show examples of solvation (a) decelerating proton transfer and (b) accelerating proton transfer.

More generally, we also combined the original RT-NEO Ehrenfest approach, which does not invoke the BO separation between the electrons and quantum protons, with this QM/MM scheme to allow the investigation of processes occurring on excited electronic states. In this approach, the nonequilibrium electron and proton densities are propagated in real time, and the classical nuclei move on the instantaneous vibronic surface. We applied this approach to

ESIPT in oHBA, which has been investigated with various conventional electronic structure methods.[50,51] Previously we studied this photoinduced reaction with RT-NEO Ehrenfest dynamics in the gas phase[48] and with RT-NEO for a fixed nuclear geometry in implicit solvent using the PCM approach.[24] Here, we investigate this photoinduced reaction in explicit solvent, treating all classical and quantum degrees of freedom, including those in oHBA and the explicit water molecules, dynamically.

The initial coordinates of oHBA were chosen to be those corresponding to the ground state geometry obtained from Aquino et al.[50] As in our earlier work,[48] photoexcitation corresponding to an $S_0 \rightarrow S_1$ transition was modeled by moving one electron from the highest occupied molecular orbital to the lowest unoccupied molecular orbital. Similar to the malonaldehyde example above, explicit water was introduced around this structure, followed by a partial equilibration of the solvent with the oHBA molecule fixed. As shown in Fig. 4, excited-state intramolecular proton transfer in oHBA is also sensitive to the initial water configuration. We show a case where proton transfer is decelerated (Fig. 4a) and another case where it is accelerated (Fig. 4b). Analogous simulations performed with conventional RT-TDDFT Ehrenfest dynamics, where all nuclei are treated classically, exhibit slower proton transfer dynamics for the classical proton but qualitatively similar effects of the explicit solvent environment (Figure S4). As for the other systems studied, these trajectories illustrate the utility of the RT-NEO QM/MM approach, but direct connection to experimental measurements would require a more comprehensive investigation with sampling of initial conditions.

In this Letter, we present the RT-NEO QM/MM approach for simulating coupled nuclear-electronic quantum dynamics in solution and enzymes. In this approach, the electronic and protonic densities are propagated in real time, and the classical nuclei are propagated on the instantaneous vibronic surface. Although this approach is designed to avoid the BO separation between the electrons and quantum protons, the electronic BO approximation can be invoked to significantly speed up the computation if the process is known to occur on

the electronic ground state. Our application to an enzyme-ligand system demonstrates the ability to simulate large biomolecules using this approach and highlights the importance of propagating the proton density dynamically within the NEO framework. Our applications to ground and excited electronic state proton transfer reactions shows that these processes can be influenced by explicit solvation. In the future, the generalized NEO multistate DFT (NEO-MSDFT) method[52–54] can also be integrated with a QM/MM strategy to describe proton transfer and tunneling in heterogeneous environments. The combination of NEO methods with QM/MM strategies will provide the capacity for probing underlying quantum dynamical phenomena of many essential chemical and biological processes.

Supporting Information

System preparation procedure; production simulation details; comparison of BO-RT-NEO Ehrenfest and NEO-BOMD result for phenol in explicit water; analagous conventional RT-TDDFT Ehrenfest simulations for malonaldehyde and oHBA systems; additional results utilizing different protonic basis sets for BO-RT-NEO Ehrenfest simulations on malonaldehyde.

Acknowledgments

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