Theoretical Perspectives on Non-Born-Oppenheimer Effects in Chemistry

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Abstract

The Born-Oppenheimer approximation, which assumes that the electrons respond instantaneously to the motion of the nuclei, breaks down for a wide range of chemical and biological processes. The rate constants of such nonadiabatic processes can be calculated using analytical theories, and the real-time nonequilibrium dynamics can be described using numerical atomistic simulations. The selection of an approach depends on the desired balance between accuracy and efficiency. The computational expense of generating potential energy surfaces on-the-fly often favors the use of approximate, robust, and efficient methods such as trajectory surface hopping for large, complex systems. The development of formally exact non-Born-Oppenheimer methods and the exploration of well-defined approximations to such methods are critical for providing benchmarks and preparing for the next generation of faster computers. Thus, the parallel development of rigorous but computationally expensive methods and more approximate but computationally efficient methods is optimal. This Perspective briefly summarizes the available theoretical and computational non-Born-Oppenheimer methods and presents examples illustrating how analytical theories and nonadiabatic dynamics simulations can elucidate the fundamental principles of chemical and biological processes. These examples also highlight how theoretical calculations are able to guide the interpretation of experimental data and provide experimentally testable predictions for nonadiabatic processes.

Keywords: nonadiabatic dynamics, non-Born-Oppenheimer, nuclear quantum effects, surface hopping

Introduction

The majority of quantum chemistry and molecular dynamics calculations are predicated on the Born-Oppenheimer separation between the nuclei and the electrons. This approximation is based on the assumption that the electrons respond instantaneously to the motion of the nuclei. However, the Born-Oppenheimer approximation breaks down for a wide range of chemical and biological processes, including numerous molecular reactions at surfaces, photochemical reactions, electron transfer, and proton-coupled electron transfer (PCET). The dynamics of such systems are often described in terms of nuclear motion on multiple adiabatic electronic surfaces that are generated within the Born-Oppenheimer approximation. For simplicity, herein the terms adiabatic and Born-Oppenheimer are used interchangeably, avoiding the distinctions related to the diagonal Born-Oppenheimer corrections [1]. Non-Born-Oppenheimer effects are important when these adiabatic surfaces become close in energy and change character significantly along certain nuclear coordinates, corresponding to large nonadiabatic coupling vector components. When the nuclei are moving fast enough in these regions, they will no longer move on a single adiabatic surface, and the process is considered to be nonadiabatic.

Various analytical theories have been developed to describe nonadiabatic processes. For example, analytical rate constants have been derived using Fermi's golden rule for nonadiabatic electron transfer, proton transfer, and PCET in solution or proteins [2-6]. Typically, such rate constants are valid when the electronic or vibronic coupling is much smaller than the thermal energy and the solvent relaxation is sufficiently fast. In many cases, the application of these analytical theories assumes that the system is in equilibrium, with a Boltzmann distribution of reactant states, although nonequilibrium distributions can also be treated. Extensions beyond the golden rule to span the adiabatic and nonadiabatic regimes and, in some cases, to describe the

solvent-controlled regime have also been developed [7, 8]. These types of analytical theories have provided insight into charge transfer reactions and other chemical processes but are not suitable for simulating the real-time nonequilibrium dynamics.

A variety of non-Born-Oppenheimer methods have been developed to describe the real-time nonequilibrium dynamics of nonadiabatic processes. The following discussion provides examples of nonadiabatic dynamics methods to illustrate the available options but is not meant to be exhaustive. The multiconfiguration time-dependent Hartree (MCTDH) method [9-11] is numerically exact with a sufficient basis set but is computationally expensive and is often used in conjunction with precomputed potential energy surfaces, although recently it has been implemented for potential energy surfaces generated on-the-fly [12]. Alternatively, the exact factorization approach [13-15] describes the nuclear and electronic dynamics in terms of a set of coupled equations of motion that depend on a time-dependent potential energy surface and a time-dependent vector potential. Both of these approaches are formally exact, but approximations must be made for computationally practical implementations.

In addition, a hierarchy of trajectory-based methods have been developed [16-19]. In Ehrenfest dynamics, the nuclei move classically on an average, mean-field potential energy surface that is determined by propagating the time-dependent Schrödinger equation for the electronic wave function, which is typically expanded as a linear combination of adiabatic electronic states. In trajectory surface hopping, the nuclei move classically on a single potential energy surface, incorporating instantaneous transitions between the surfaces according to a stochastic algorithm. The popular fewest switches surface hopping algorithm [20] is designed to ensure that the populations of the adiabatic states are consistent with the quantum amplitudes obtained by propagating the electronic time-dependent Schrödinger equation in parallel with the classical

equations of motion for an ensemble of trajectories. This internal consistency is typically not maintained in practice due to energy-forbidden transitions and divergent independent trajectories [21], but the former feature is essential for achieving Boltzmann populations at equilibrium [22]. An advantage of surface hopping over Ehrenfest dynamics is the capability to describe branching processes involving populations on two potential energy surfaces with distinct forces. In the multiple spawning method [23, 24], the nuclear wave functions are represented by linear combinations of frozen Gaussian functions that are propagated classically and are adaptive through a spawning process. In the limit of a complete basis the full multiple spawning method is exact, but approximations must be made for computationally practical implementations [17]. The details about all of these nonadiabatic dynamics methods, as well as the relationships between them, are discussed elsewhere [17, 18].

All of the methods discussed above require the choice of an electronic structure method for computing the adiabatic electronic potential energy surfaces. In addition to the energies, the nuclear gradients and nonadiabatic coupling vectors are required for most nonadiabatic dynamics methods. The optimal electronic structure method depends on the desired balance of accuracy and computational efficiency. Time-dependent density functional theory (TDDFT) has well-known limitations for the description of conical intersections [25], although spin-flip methods [26, 27] can be used to circumvent some of these limitations. Multireference wave function methods describe conical intersections more accurately but are typically more computationally expensive.

The nuclear-electronic orbital (NEO) approach [28, 29] is another option for non-Born-Oppenheimer dynamics. In this approach, specified nuclei are treated quantum mechanically on the same level as the electrons with molecular orbital techniques. Multicomponent wave function and DFT methods have been developed within the NEO framework. Examples of multicomponent

wave function methods include the coupled-cluster singles and doubles (NEO-CCSD) [30] and complete active space self-consistent-field (NEO-CASSCF) [28] methods, as well as the equation-of-motion (NEO-EOM) [31, 32] methods for describing excited states. The NEO-DFT method in conjunction with recently developed electron-proton correlation functionals [33-35] has been shown to produce accurate densities, energies, and optimized geometries. Moreover, the NEO-TDDFT method [36, 37] provides electronic, vibrational, and vibronic excitation energies, as well as the associated transition densities, oscillator strengths, and intensities. The combination of real-time NEO-TDDFT (RT-NEO-TDDFT) [38] with NEO Ehrenfest dynamics [39, 40] enables the calculation of non-Born-Oppenheimer nuclear-electronic dynamics. This approach includes nonadiabatic effects between the electrons and quantum nuclei via RT-NEO-TDDFT and nonadiabatic effects between the classical nuclei and the quantum subsystem via NEO Ehrenfest dynamics. The combination of linear-response NEO-TDDFT with surface hopping in the basis of the adiabatic vibronic surfaces provides another option for nonadiabatic nuclear-electronic dynamics.

A challenge in this field is to determine which of the many available nonadiabatic dynamics methods is most suitable for a given application. Assuming that the potential energy surface will be generated on-the-fly, computational expense is a serious consideration. For many applications, trajectory surface hopping is the optimal choice because of its simplicity and computational efficiency, as well as its availability in many quantum chemistry packages. Decoherence effects can be included using one of the many proposed strategies [41, 42]. Multiple spawning may be a better choice if nuclear tunneling plays a significant role [43]. Despite the popularity and successes of surface hopping within the chemistry community, it has not been derived rigorously from first principles and has well-known limitations. Thus, the further development of more rigorous and

formally exact methods is critical. The formally exact methods serve as benchmarks for more approximate methods, and well-defined approximations to these formally exact methods may lead to intermediate approaches that could enhance the accuracy and broad applicability of nonadiabatic dynamics simulations. As computers become faster and algorithms are improved, these approximations can be gradually lifted. Overall progress in the field requires the parallel development of rigorous but computationally expensive methods and more approximate but computationally efficient methods.

The remainder of this Perspective will present illustrative examples of theoretical studies of non-Born-Oppenheimer processes. The first section will describe applications of analytical theories to hydrogen tunneling in the enzyme soybean lipoxygenase and electrochemical PCET at a gold electrode. The second section will describe surface hopping calculations of photoinduced PCET in a solvated phenol-amine complex, as well as the application of RT-NEO-TDDFT Ehrenfest dynamics to a photoinduced proton transfer reaction. These examples are from my own research, but many more examples of non-Born-Oppenheimer studies can be found throughout the literature.

Analytical theories

Although numerical, atomistic simulations of chemical and biological systems have become widespread, analytical theories still play an important role. In particular, analytical theories can be used to model complex processes in a manner that explains the experimental data and provides experimentally testable predictions. As an example, the fundamental principles of PCET have been elucidated by analytical theories as well as atomistic simulations. Nonadiabatic PCET theory [5, 44, 45] describes these reactions in terms of nonadiabatic transitions between

reactant and product electron-proton vibronic states. Analytical rate constant expressions have been derived for PCET in solution, proteins, and electrochemical systems [5, 45, 46]. These nonadiabatic rate constant expressions were derived using Fermi's golden rule, which is valid in light of the relatively small vibronic coupling between the reactant and product electron-proton vibronic states. The detailed analytical rate constant expressions, along with the underlying assumptions, are provided elsewhere [5, 45, 46]. This section describes how these analytical theories have provided insights into a biological and an electrochemical system.

The enzyme soybean lipoxygenase catalyzes the PCET reaction shown in Figure 1. The electron transfers from the π-backbone of the linoleic acid substrate to the iron of the cofactor, and the proton transfers from a carbon atom of the substrate to the hydroxyl group coordinated to the iron. This PCET reaction is known to occur by a concerted mechanism because single electron and single proton transfer are highly endoergic, whereas the concerted mechanism is exoergic [47, 48]. Thus, the concerted mechanism is thermodynamically favored and avoids high-energy intermediates. The kinetic isotope effect (KIE), which is the ratio of the rate constants for hydrogen and deuterium transfer, has been measured experimentally to be ~80 at room temperature for the wild-type enzyme [47, 49] and up to ~700 for the L546A/L754A double mutant [50]. These extremely high KIEs are a clear hallmark of hydrogen tunneling.

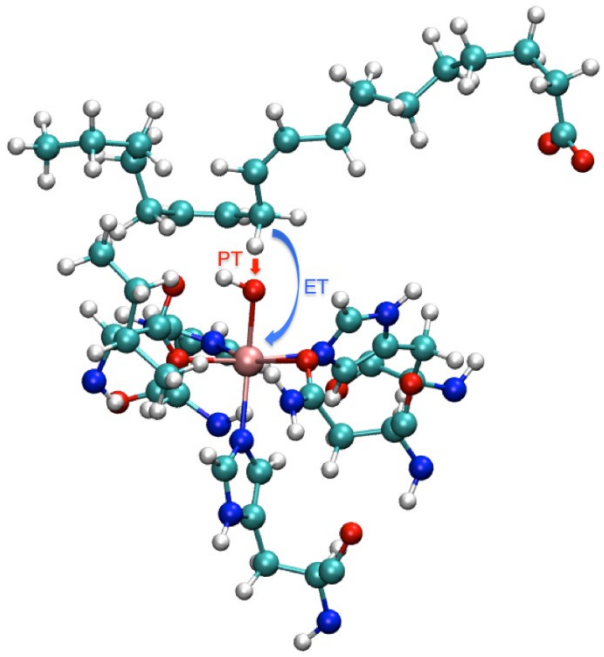

Figure 1. The PCET reaction catalyzed by the enzyme soybean lipoxygenase. This PCET reaction involves electron transfer from the π-backbone of the linoleic acid to the ferric iron, reducing it to the ferrous state, and proton transfer from C11 of the linoleic acid to the iron-coordinated hydroxyl group. Reproduced with permission from Ref. [51].

The application of PCET theory to soybean lipoxygenase has provided an explanation for the origin of the unusually high KIE and the substantial impact of mutations on the KIE [48, 50-52]. According to the analytical PCET rate constant expressions [5, 45, 46], the KIE is approximately proportional to the square of the ratio of the hydrogen and deuterium overlap integrals between the reactant and product proton vibrational wave functions for each pair of reactant and product electron-proton vibronic states. This ratio increases with increasing proton donor-acceptor distance (i.e., the C—O distance in this system), corresponding to a small overlap integral. In soybean lipoxygenase, the dominant contribution to the rate constant arises from the ground reactant and product states. The hydrogen-bonding interaction between the linoleic acid C-H group and the hydroxyl oxygen coordinated to the iron is relatively weak, leading to a relatively

large C—O distance, a small overlap integral, and therefore a high KIE. The double mutation creates a larger cavity for substrate binding [53] that leads to less optimal orientation of the substrate and therefore a smaller overlap integral, resulting in an even larger KIE [51]. These types of enormous KIEs typically occur in constrained environments, such as an enzyme active site, which prevent optimal orientation of the proton transfer interface. This example showcases the insights that can be obtained from theoretical modeling without the necessity of nonadiabatic dynamics simulations. Moreover, nonadiabatic dynamics methods based on classical trajectories cannot adequately describe hydrogen tunneling without quantizing at least some of the nuclei [54].

Another example is electrochemical PCET from triethylammonium acid to a gold electrode in acetonitrile, as depicted in Figure 2. Experimental measurements [55] indicate a potential-dependent KIE for this system, where the transfer coefficient or Tafel slope is different for hydrogen versus deuterium. Specifically, the KIE ranges from 1.5 to 6.3 over the experimentally studied range of applied potentials. This behavior is surprising because different Tafel slopes are usually interpreted as implying different mechanisms in electrochemistry, but in this case the only difference is hydrogen versus deuterium transfer.

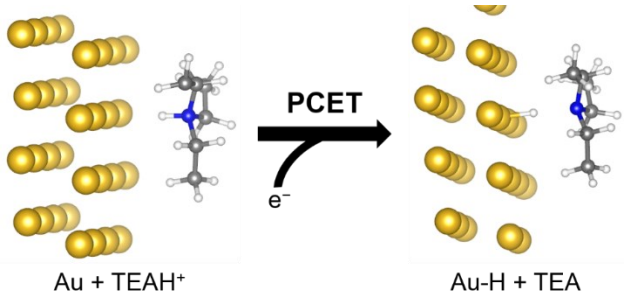

Figure 2. PCET from triethylammonium ($TEAH^+$) to a gold electrode in acetonitrile, producing TEA and a covalent Au-H bond. Reproduced with permission from Ref. [56].

The application of PCET theory to this system [56] has explained the potential-dependent KIE in terms of different pairs of reactant and product vibronic states dominating for hydrogen versus deuterium transfer. The splittings between the vibrational energy levels are smaller for deuterium, leading to greater populations of excited reactant vibrational states. The contributions from different pairs of vibronic states exhibit different dependencies on the applied potential. As a result, the overall dependence of the current density on applied potential differs for hydrogen versus deuterium, leading to a potential-dependent KIE. This type of phenomenon is also observed for PCET from water to a gold electrode in alkaline aqueous solution [8].

These two examples illustrate how analytical theories can be used to interpret experimental data and predict trends that can be tested experimentally. For enzymatic systems, PCET theories have been used to predict the impact of mutations on the rate constant or KIE, as well as the temperature dependence of these two quantities. For electrochemical systems, PCET theories have been used to predict the dependence of the current density on the applied potential and the impact of pH and solvent on this behavior. The advantages of theoretical modeling over atomistic simulations are the simplicity, computational efficiency, and ease of predicting trends as a function of physical properties. On the other hand, nonadiabatic dynamics methods are necessary for simulating the real-time, nonequilibrium dynamics at the atomic level.

Numerical atomistic simulations

Simulation of the real-time dynamics of photoinduced charge transfer reactions can be accomplished with the various nonadiabatic dynamics methods described above. This section presents examples of two different methods applied to two different systems. The first example is surface hopping simulations of photoinduced PCET within a hydrogen-bonded phenol-amine

complex in solution. The second example is RT-NEO-TDDFT Ehrenfest dynamics simulations of photoinduced proton transfer in the *o*-hydroxybenzaldehyde (oHBA) molecule. These examples highlight the insights that can be gained from these types of nonadiabatic dynamics simulations.

Trajectory surface hopping has been used to study photoinduced PCET in the hydrogen-bonded phenol-amine complex depicted in Figure 3 [57-60]. Transient absorption experiments [61] implicate two different mechanisms in this system, corresponding to photoexcitation to the intramolecular charge transfer (ICT) state or to the electron-proton transfer (EPT) state. In the simulations [57-60], the potential energy surfaces were generated using a mixed quantum mechanical/molecular mechanical (QM/MM) method in which the solute is described by a semiempirical implementation of the floating occupation molecular orbital complete active space configuration interaction (FOMO-CASCI) method [62, 63] and the solvent is described with a molecular mechanical force field. According to the QM/MM free energy simulations [57], the minimum free energy corresponds to the proton bound to the oxygen for the ground state and the ICT state and corresponds to the proton bound to the nitrogen for the EPT state. Surface hopping calculations [57] have elucidated the mechanisms of relaxation after photoexcitation to either the ICT or EPT state. After photoexcitation to the ICT state, these calculations indicate fast decay in ~100 fs from the ICT to the EPT state, followed by slower decay on the timescale of ~1 ps to the ground state. Photoexcitation to the EPT state results in similar picosecond decay to the ground state. These timescales are consistent with the experimental measurements [61]. In both cases, proton transfer from the oxygen to the nitrogen occurs on the EPT state prior to relaxation to the ground state, at which time the proton quickly transfers back to the oxygen.

These simulations also elucidate the role of solvent dynamics [58] following photoexcitation, which alters the dipole moment of the solute molecule by ~13 Debye. Analysis

of the time dependence of the electrostatic potential at the amine nitrogen due to the solvent environment implies that solvent dynamics of mainly the first solvation shell occurs on a ~250 fs timescale. This analysis also shows that solvent reorganization decreases the energy gap between the ground state and the EPT state and facilitates proton transfer by lowering the proton transfer barrier significantly and stabilizing the proton on the amine. According to the simulations, proton transfer occurs on the EPT state only after solvent reorganization occurs on a ~250 fs timescale.

The initial surface hopping calculations were conducted on the electronic potential energy surfaces treating all nuclei classically. In subsequent calculations [59], the transferring proton was quantized by representing it as a one-dimensional quantum mechanical wave function computed with the Fourier grid Hamiltonian method [64]. In this case, the surface hopping calculations were conducted on the electron-proton vibronic surfaces. The classical and quantum mechanical treatments of the transferring hydrogen nucleus resulted in similar proton transfer probabilities and timescales for relaxation to the ground state. However, the simulations with the quantized proton showed that photoexcitation to the EPT state induces fast decay to a highly excited proton vibrational state within the ground electronic state followed by slower vibrational relaxation to the ground vibronic state (Figure 3, lower right). No hydrogen/deuterium isotope effect was observed for the relaxation to the ground vibronic state after photoexcitation, mainly because the decay rates were determined by solvent dynamics and vibrational relaxation, which was not isotopically sensitive for this system. This application clearly illustrates that the absence of an isotope effect does not imply the absence of proton transfer. Predictions of the impact of substituents on the dynamics have also been generated by the calculations and await experimental validation [60].

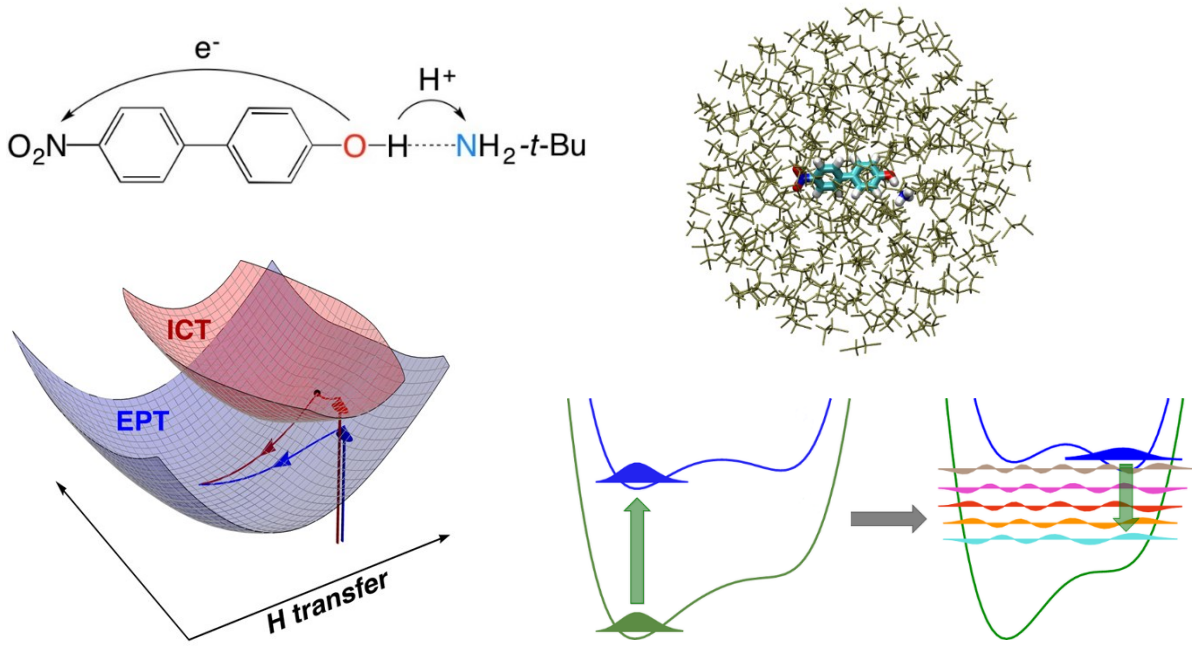

Figure 3. Photoinduced PCET within a hydrogen-bonded complex composed of *p*-nitrophenyl-phenol and *t*-butylamine (upper left). Simplified complex with ammonia as the proton acceptor, solvated in a sphere of 1,2-dichloroethane molecules (upper right). Schematic depiction of the relaxation processes following photoexcitation to the ICT state, characterized by electron transfer across the phenol with the proton remaining covalently bonded to the oxygen, and photoexcitation to the EPT state, characterized by electron transfer accompanied by a shift in electronic charge density from the O—H bond to the N—H bond, resulting in an elongated N—H bond (lower left). Proton transfer occurs on the EPT state, either after population decay from the ICT to the EPT state or after vertical excitation directly to the EPT state. Schematic depiction of this process for simulations with a quantized proton, where vertical excitation from the ground vibronic state to the ground vibrational level of the EPT state is followed by solvent reorganization and population decay to a highly excited vibrational level associated with the ground electronic state (lower right). Adapted with permission from Refs. [60] and [65].

As a final example, the excited state intramolecular proton transfer reaction in oHBA, shown in Figure 4, has been studied with the RT-NEO-TDDFT Ehrenfest dynamics method [40]. The transferring proton and all electrons are treated quantum mechanically on the same level with RT-NEO-TDDFT. In this approach, the electronic and protonic density matrices are propagated numerically via the mixed nuclear-electronic time-dependent Schrödinger equation [38]. The other nuclei are propagated simultaneously via Newton's equations of motion on the average, mean-

field electron-proton vibronic surface [39]. The photoexcitation process is modeled by an electronic transition from the highest occupied molecular orbital to the lowest unoccupied molecular orbital. The calculations reveal that quantization of the proton leads to a faster proton transfer reaction because of proton delocalization, which allows proton transfer to occur at a longer oxygen-oxygen distance. The calculations also indicate that quantization of the proton increases the KIE.

A significant advantage of the NEO approach over the grid-based approach utilized for the phenol-amine system is that the quantized proton is treated in three dimensions, and it is straightforward and computationally efficient to quantize multiple protons [66]. Moreover, the NEO approach inherently includes the non-Born-Oppenheimer effects between the electrons and the transferring proton in the vibronic potential energy surfaces. However, these NEO calculations describe the nonadiabatic effects between the classical nuclei and the electron-proton subsystem with Ehrenfest dynamics rather than trajectory surface hopping, thereby preventing the accurate description of branching processes. Such branching behavior is not expected to be significant for this particular system because of the nature of the excited electronic state.

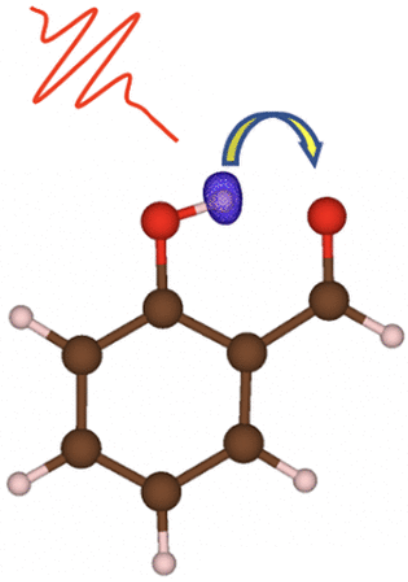

Figure 4: Excited state intramolecular proton transfer in the oHBA molecule, where the transferring proton is treated quantum mechanically on the same level as the electrons within the NEO framework. Adapted with permission from Ref. [38].

Conclusion

This Perspective provides an overview of analytical theories and nonadiabatic dynamics methods available for investigating non-Born-Oppenheimer processes, followed by several chemical and biological examples. This is not meant to be a comprehensive review but rather is intended to enumerate some of the available options and to illustrate what can be learned from these types of calculations and how they can be connected directly to experimental measurements. The computational expense of on-the-fly simulations limits the use of the more rigorous nonadiabatic dynamics methods for relatively large, complex systems and favors the use of approximate yet robust methods such as surface hopping. However, the development of formally exact non-Born-Oppenheimer methods and the exploration of well-defined approximations to such methods are critical to progress within this field. The boundaries of nonadiabatic theories must

continue to be pushed to better understand the fundamental principles controlling the wide range of complex nonadiabatic processes in chemistry and biology.

Data accessibility. This article has no additional data.

Competing interests. The author has no competing interests.

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