Combining quantum wavepacket *ab initio* molecular dynamics with QM/MM and QM/QM techniques: Implementation blending ONIOM and empirical valence bond theory

Isaiah Sumner and Srinivasan S. Iyengar^{a)}

Department of Chemistry and Department of Physics, Indiana University, 800 E. Kirkwood Ave., Bloomington, Indiana 47405, USA

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We discuss hybrid quantum-mechanics/molecular-mechanics (QM/MM) and quantum mechanics/ quantum mechanics (QM/QM) generalizations to our recently developed quantum wavepacket ab *initio* molecular dynamics methodology for simultaneous dynamics of electrons and nuclei. The approach is a synergy between a quantum wavepacket dynamics, *ab initio* molecular dynamics, and the ONIOM scheme. We utilize this method to include nuclear quantum effects arising from a portion of the system along with a simultaneous description of the electronic structure. The generalizations provided here make the approach a potentially viable alternative for large systems. The quantum wavepacket dynamics is performed on a grid using a banded, sparse, and Toeplitz representation of the discrete free propagator, known as the "distributed approximating functional." Grid-based potential surfaces for wavepacket dynamics are constructed using an empirical valence bond generalization of ONIOM and further computational gains are achieved through the use of our recently introduced time-dependent deterministic sampling technique. The ab initio molecular dynamics is achieved using Born–Oppenheimer dynamics. All components of the methodology, namely, quantum dynamics and ONIOM molecular dynamics, are harnessed together using a time-dependent Hartree-like procedure. We benchmark the approach through the study of structural and vibrational properties of molecular, hydrogen bonded clusters inclusive of electronic, dynamical, temperature, and critical quantum nuclear effects. The vibrational properties are constructed through a velocity/flux correlation function formalism introduced by us in an earlier publication. © 2008 American Institute of Physics. [DOI: 10.1063/1.2956496]

I. INTRODUCTION

In a recent series of publications, $^{1-6}$ we introduced a methodology that accurately computes nuclear quantum effects in a subsystem while simultaneously treating the dynamics of the surrounding atoms and changes in the electronic structure. Our approach is quantum-classical⁷⁻¹⁴ and involves the synergy between a time-dependent quantum wavepacket treatment and ab initio molecular dynamics. As a result, the approach is called quantum wavepacket *ab initio* molecular dynamics (QWAIMD). Since the quantum dynamics is performed on a grid, the predominant bottleneck is the computation of the grid-based, time-dependent potential and gradients generated by the motion of the classical atoms and change in electronic structure.¹⁻⁴ We overcome this limitation through the introduction of a time-dependent deterministic sampling (TDDS) technique,^{3,4} which when combined with numerical methods such as an efficient wavelet compression scheme and low-pass filtered Lagrange interpolation⁴ provides computational gains of many orders of magnitude. We have utilized QWAIMD to compute vibrational properties of hydrogen-bonded clusters inclusive of quantum nuclear effects⁴ and have also adopted the method to study hydrogen tunneling in enzyme active sites.⁵ The

approach has been generalized to treat extended systems,⁶ which may be useful for condensed phase simulations.

In this paper we aim to combine the QWAIMD methodology with the ONIOM (Refs. 15-27) approach to facilitate hybrid quantum-mechanics/molecular-mechanics (QM/MM) and QM/QM (Refs. 15, 26, and 28-44) studies in conjunction with quantum wavepacket dynamics for the study of larger systems. An ONIOM-QWAIMD combination will allow us to tackle large problems⁵ inclusive of dynamical, quantum nuclear, and electronic effects. This kind of a generalization is potentially useful for the treatment of many biological enzyme active sites and proteins where nuclear quantization, electronic polarization, and anharmonic effects from low-barrier hydrogen $bonds^{5,45-59}$ are thought to play an important role. The unification with the ONIOM scheme is described in Sec. II B. Specifically, a complication arises in computing the grid potential and gradients if QM/MM techniques are used. The source of the complication is that using the ONIOM approximation leads to discontinuities at the MM level on account of changing bond topologies. We view this problem within a diabatic approximation and construct smooth potential surfaces by invoking an empirical valence bond (EVB)-type approximation $^{60-65}$ over ONIOM. These aspects are also discussed in Sec. II B. In Sec. II A, we also discuss our TDDS technique that greatly reduces the computational expense of the method.³ In Sec. III, we benchmark

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^{a)}Electronic mail: iyengar@indiana.edu.

the approach by studying two hydrogen bonded clusters: phenol-trimethylamine, represented as PhOH-N(CH₃)₃, and the protonated dimethyl ether cation, represented as $[(Me_2O)-H-(OMe_2)]^+$. These systems differ due to the type of hydrogen bonding interactions involved. While the former test problem involves a single-well, weak hydrogen bond with asymmetric anharmonic contributions, the latter is an example of a short, strong hydrogen bond where both lowbarrier effects as well as true double well characteristics can play a role depending on the temperature of the system.⁶⁶ In fact, the latter is very much reminiscent of the Zundel cation⁶⁶⁻⁸⁰ that is characterized by a symmetric, strong hydrogen bond. To benchmark the QWAIMD-ONIOM generalization, results obtained from hybrid QM/MM and QM/QM treatments are compared with those obtained by treating all electrons in the system at the same level of electronic structure theory (i.e., without using hybrid methods). We use a unified velocity-flux autocorrelation function technique⁴ to obtain quantum dynamical effects on vibrational spectral properties and we also compute the distribution of key structural features to evaluate the effects of the hybrid QM/MM and QM/QM approximation on dynamics. Our studies rigorously examine the limits of utility for hybrid techniques in computing spectral and structural properties for strongly hydrogen bonded systems, inclusive of quantum nuclear effects, which are very sensitive to the accuracy of the potential energy surface calculations.

II. A HYBRID QM/MM AND QM/QM GENERALIZATION FOR QWAIMD

A. A brief description of QWAIMD

We first outline QWAIMD before discussing generalizations to QM/MM and QM/QM hybrid schemes. The main features of QWAIMD are as follows: The quantum dynamical evolution is described through a third-order Trotter factorization of the quantum propagator,^{1,81–83} where the freepropagator is approximated in the coordinate representation using a formally exact expression known as the "distributed approximation functional" (DAF),^{1,2,84–86}

Here, $\{\sigma(\Delta t_{\rm QM})\}^2 = \sigma(0)^2 + i\Delta t_{\rm QM}\hbar/M_{\rm QM}$, $\{H_{2n}(x)\}$ are even order Hermite polynomials (note that the arguments for the Hermite polynomials and the Gaussian function, $(R_{\rm QM} - R'_{\rm QM}/\sqrt{2}\sigma(\Delta t_{\rm QM}))$, are complex in general), $R_{\rm QM}$ represents the quantum mechanical degrees of freedom, and the parameters $M_{\rm DAF}$ and σ are chosen as in previous studies^{1,85} for a best compromise between accuracy and efficiency. Specifically, in all calculations performed here $M_{\rm DAF}$ =20 (that is,



FIG. 1. (Color online) Depicted here is the timing for QM and QM/MM calculations with and without TDDS. Note that the vertical axis is the logarithm of CPU time. TDDS provides enormous reduction in computational time for both hybrid QM/MM and regular calculations.

all even Hermite polynomials up to order 20 are used) and $\sigma/\Delta=1.5744$, where Δ is the grid spacing. The freepropagation of a wavepacket is thus given in the discrete representation as

$$\chi(x_i, \Delta t) = \sum_j \langle x_i | \exp\{-\iota K \Delta t/\hbar\} | x_j \rangle \chi(x_j, 0)$$
$$= \sum_j \tilde{K}(x_i - x_j, M_{\text{DAF}}, \sigma, \Delta t) \chi(x_j, 0).$$
(2)

The evolution of the classical nuclei involves the wavepacket averaged Hellmann–Feynman forces obtained from electronic structure calculations carried out on the discrete wavepacket grid. To minimize the number of electronic structure calculations carried out on the grid while directing their placement for maximum effect, we introduced the adaptive, time-dependent deterministic sampling (TDDS) function

$$\omega(R_{QM}) \propto \frac{\left[\tilde{\rho} + 1/I_{\chi}\right] \times \left[\tilde{V}' + 1/I_{V'}\right]}{\tilde{V} + 1/I_{V}},\tag{3}$$

which is proportional to the wavepacket density $\tilde{\rho}$ and the potential gradients \tilde{V}' and inversely proportional to the grid potential \tilde{V} . The parameters I_{χ} , $I_{V'}$, and I_V are chosen to yield an equal distribution of calculations in the classically allowed (minimum energy regions) and classically forbidden (classical turning point) regions.³ The TDDS function is evaluated at every instant in time to determine the grid points where the potential and gradients will be evaluated at the next time step. Details on the TDDS algorithm as well as its connections to Bohmian mechanics and the Wentzel Kramers Brillouin (WKB) approximation are discussed in Refs. 3 and 4. This technique allows large scale reductions in accuracy.

B. Unification of QWAIMD with the ONIOM approach

In the current contribution, we introduce an EVB QM/MM generalization to QWAIMD. QM/MM hybrid models have a long history^{15,26,28–41,43} and have been used for dynamics on the Born–Oppenheimer surface.^{25–27,36,39,40,87,88} QM/MM techniques divide a calculation into a relatively small QM region where the important chemistry takes place and an MM region for other areas of the system. (Note that

this level of partitioning in the electronic degrees of freedom should not be confused with the quantum-classical partitioning of nuclei in QWAIMD.) Hybrid methods differ mainly in how the two regions interact.^{32,43} Additionally, if the boundary between the two regions intersects a chemical bond, there are different methods to saturate the dangling valencies. Real atoms,^{15,30,89} parametrized pseudoatoms,^{34,90,91} and localized boundary orbitals^{31,33,92} are employed for this purpose.

We employ the ONIOM (Refs. 15–27) (QM/MM and QM/QM) scheme to facilitate QWAIMD in large systems. ONIOM is an extrapolation technique that combines high-level calculations on a portion of a (large) system with lower level calculations on the full system. The full system is divided into n layers, called the *model* and *real* systems for two-layer ONIOM. The calculation at the highest level of theory is performed on the chemically reactive part of the system. Following the notation used in Ref. 24, we write the n-layer ONIOM energy expression as

$$E_{n-\text{layer}}^{\text{ONIOM}}(\mathbf{R}) = \sum_{i=2}^{n,(n\geq2)} S_{(i);(i-1)}^{i}(\mathbf{R}) + E_{\text{system},1}^{\text{level},1}(\mathbf{R}),$$
(4)

where $S_{(i);(i-1)}^{i}(\mathbf{R}) = (E_{\text{system},i}^{\text{level},i}(\mathbf{R}) - E_{\text{system},i-1}^{\text{level},i}(\mathbf{R}))$, the ONIOM extrapolation term. The system size increases and the calculation level decreases from *i* to *i*+1. Each layer is treated at two levels (*i* and *i*-1), while the entire system is only considered at the lowest level (*n*). If chemical bonds intersect the boundary between two layers, link atoms are used to saturate the dangling valencies of the smaller system.⁸⁹ The positions of link atoms are uniquely determined based on the connectivity of the system, which makes conservative dynamics possible.²⁵ Thus, the selected atoms and additional link atoms of each system are influenced by the properties of the atoms in the larger systems.

There are two main techniques available to couple the within ONIOM: Mechanical and electronic lavers embedding.²⁴ In mechanical embedding, the smaller system calculations are performed in the absence of the larger system atoms. Here, only the link atoms are directly influenced by the larger system and their placement is constrained by the positions of the substituted atoms in the larger system. In electronic embedding, the influence of the larger layer on the smaller layer is accounted for not only through the link atoms but also through point charges on those atoms that are only present in the larger layer. Thus, the smaller system wave function is polarized by the charge distribution of the larger system. The choice of point charges is clearly important and is an active area of study.^{24,43,44,89,93–95} Furthermore, the charges for atoms within a few bonds of the link atoms are scaled down to avoid overpolarization.

Although the above discussion is general for any partitioning scheme (*n*-layer ONIOM), the present work focuses on a quantum wavepacket generalization of two-layer implementations, ONIOM(MO:MM) [SCF (MO) and MM] and ONIOM(MO:MO) [SCF (MO) and SCF(MO)]. We first examine the properties of the quantum wavepacket interaction potential energy when QM and MM techniques are combined. We assume that all QM methods are on the set of smaller systems, now called the *model* system, and the MM



FIG. 2. (Color online) (a) represents the potential energy surface obtained when the shared proton is incrementally scanned along the O–O axis in $[(Me_2O)-H-(OMe_2)]^+$ using an ONIOM(MO:MM) treatment. The atoms in the *real* and *model* (spheres) partition are shown in (b). The central (scanned) shared proton is enlarged. The singularities in (a) represent the changing bonding topology during the scan and this aspect is addressed in Sec. II B

methods are utilized for the remaining larger systems, now called the *real* system. We present a sample potential surface in Fig. 2(a), which is obtained with the partitioning scheme shown in Fig. 2(b). Specifically, the shared proton in $[(Me_2O)-H-(OMe_2)]^+$ is scanned on a one-dimensional grid and the ONIOM energies are evaluated at each grid point. The singularities in Fig. 2(a) represent the fact that the bonding topologies change during the scan process and the MM portion of the calculation suffers as a result.

In two-layer ONIOM(MO:MM), the $S_{(i);(i-1)}^{l}$ term in Eq. (4) becomes $S_{(real);(model)}^{MM}$ and $E_{system,1}^{level,1}(\mathbf{R})$ becomes $E_{model}^{QM}(\mathbf{R})$. The S^{MM} term contains information about the interaction between *real* and *model* systems (systems 2 and 1) at the MM level as well as the energy contributions of the portion of *real* system that is only calculated at the MM level. Unless all MM functions in the E_{real}^{MM} and E_{model}^{MM} terms that change upon bond breaking/formation exactly cancel out, the S^{MM} term will yield discontinuities in the wave-packet potential as seen in Fig. 2(a). If the *model* system size were increased to include all atoms at least three bonds away from the site of the changing bond topology, all such terms (stretching, bending, and torsional) would cancel out in the $S_{(real);(model)}^{MM}$ especially sensitive to the system size (due to the interaction potential calculations), we suggest a solution to this problem in this section by employing a di-

abatic surface treatment, as allowed by EVB theory, in conjunction with ONIOM. Alternatively, an ONIOM(MO:MO) approach will also solve the problem since MO energy expressions do not explicitly depend on bond connectivity, an aspect that is also considered in later sections.

In our scheme, we calculate the E^{MM} portions of the potential surface twice, once when the shared quantum proton is designated to be donor-bound and once when it is acceptor bound. These calculations provide approximate diabatic potentials. We then smoothly interpolate between these surfaces to produce one low energy adiabatic surface that describes bond breaking and formation without discontinuities. (In principle we could include all adiabats in our quantum dynamics scheme to perform non-adiabatic quantum dynamics and this aspect will be considered in future publications. This is especially important to note since the quantum wavepacket treatment employed here allows an accurate description of non-adiabatic vibrational dynamics.^{1,5,86}) The two diabatic states are coupled by diagonalizing 2×2 а diabatic Hamiltonian,

$$\begin{bmatrix} E_{\text{donor}}^{\text{MM}}(\mathbf{R}) & E_{\text{DA}}(R_{\text{QM}}) \\ E_{\text{AD}}(R_{\text{QM}}) & E_{\text{acceptor}}^{\text{MM}}(\mathbf{R}) \end{bmatrix},$$
(5)

as is done in non-adiabatic dynamics^{96–98} and also within the EVB formalism.^{60–65} Here, $E_{donor}^{MM}(\mathbf{R})$ is the MM potential when the proton is designated to be bound to the donor atom, $E_{acceptor}^{MM}(\mathbf{R})$ is the acceptor-bound MM potential, and $E_{DA}(R_{QM}) = E_{AD}(R_{QM})$ is the coupling or off-diagonal matrix element. Note that while $E_{donor}^{MM}(\mathbf{R})$ and $E_{acceptor}^{MM}(\mathbf{R})$ depend on the geometry of the entire nuclear framework, the coupling element, $E_{DA}(R_{QM})$ is chosen to only depend on the quantum dynamical particle grid coordinate R_{QM} . We utilize the ground state for both the MM, *real* and MM, *model* surfaces,

$$E^{\text{MM}}(\mathbf{R}) = \frac{1}{2} \{ E_{\text{donor}}^{\text{MM}}(\mathbf{R}) + E_{\text{acceptor}}^{\text{MM}}(\mathbf{R}) - \sqrt{\{ E_{\text{donor}}^{\text{MM}}(\mathbf{R}) - E_{\text{acceptor}}^{\text{MM}}(\mathbf{R}) \}^2 + 4E_{\text{DA}}(R_{\text{QM}})^2 } \},$$
(6)

in the ONIOM energy expression [Eq. (4)] and the corresponding gradients are obtained from the appropriate derivatives of the above expression.

There are many choices for $E_{\text{DA}}(R_{\text{QM}})^2$ with varying degrees of parametrization.^{60,61,63,96,98–100} In this publication, we benchmark two coupling schemes. The first coupling element is a simple Gaussian, as proposed by Tully⁹⁶ within the context of non-adiabatic dynamics and by Chang and Miller⁶¹ for EVB calculations^{61,63}

$$E_{\rm DA}^{\rm CM}(R_{\rm QM})^2 = A \, \exp\{-\,\alpha(R_{\rm QM} - R_{\rm QM_0})^2\}.$$
(7)

The quantity R_{QM_0} is chosen dynamically, at every time step, to be at the lowest diabatic curve crossing. The constants, A and α , are time-independent and are chosen to preserve the structure of the original diabatic surfaces close to their respective local minima. In general, the associated ground state surface obtained from Eq. (6) is in qualitative agreement with the diabatic surfaces in the respective bonding regions.

The second off-diagonal coupling element studied here is

$$E_{\rm DA}^{\Delta}(R_{\rm QM})^2 = (E_{\rm donor-acceptor}^{\rm MM}(R_{\rm QM}) - E_{\rm donor}^{\rm MM}(R_{\rm QM})) \times (E_{\rm donor-acceptor}^{\rm MM}(R_{\rm QM}) - E_{\rm acceptor}^{\rm MM}(R_{\rm QM})).$$
(8)

With this coupling element, the natural bonding topology of the molecule is altered so that the $E^{\rm MM}$ portions of the ONIOM quantum proton potential energy surface are calculated as if the proton were simultaneously bound to both donor and acceptor, represented as $E^{\rm MM}_{\rm donor-acceptor}$ in Eq. (8). Thus, there are no distinct donor and acceptor complexes at the MM level. A potential with these properties may be preferable if the electrons on the hydrogen are shared equally between the donor and acceptor, as might be the case for systems involved in short, strong hydrogen bonds. One such example is treated in this publication.

We further note the relation between the coupling term $E_{\text{DA}}(R_{\text{QM}})^2$ and the switching function $W(\mathbf{R})$ employed in the ONIOM-XS methodology,⁸⁷ which allows a dynamical exchange of particles between two layers. The ONIOM-XS energy expression is

$$E^{\text{ONIOM-XS}}(\mathbf{R}) = (1 - W(\mathbf{R}))E_1^{\text{ONIOM}}(\mathbf{R}) + W(\mathbf{R})E_2^{\text{ONIOM}}(\mathbf{R}),$$
(9)

where $E_1^{\text{ONIOM}}(\mathbf{R})$ is the energy with the new ONIOM boundaries (the energy after the particle is exchanged between layers), $E_2^{\text{ONIOM}}(\mathbf{R})$ is the energy for the original ONIOM boundaries, and $W(\mathbf{R})$ is a smooth approximation to the step function defined between 0 and 1 that depends on the distance of the exchanged particle from the zone boundary. The switching term is related to $E_{\text{DA}}(R_{\text{OM}})^2$ by

$$E_{\rm DA}^{\rm XS}(R_{\rm QM})^2 = W(R_{\rm QM})(W(R_{\rm QM}) - 1)(E_{\rm donor}^{\rm MM}(R_{\rm QM}) - E_{\rm acceptor}^{\rm MM}(R_{\rm QM}))^2.$$
(10)

From this perspective, QM grid points (or virtual particles) exchange bond topologies within a given MM layer in our scheme. It is also of interest to note that Heyden *et al.*¹⁰¹ generalized the ONIOM-XS scheme to allow for *N* atoms to smoothly exchange between layers. In the current paper, we have tested only a single particle using quantum wavepacket dynamics and, hence, this complication does not arise. However, Eq. (10) generalizes readily to multiple quantum particles and these connections will be explored further in future publications.

Finally, we emphasize that the approach discussed here is not constrained to dual bonding topologies.⁶⁰ We may diagonalize an $N \times N$ EVB Hamiltonian in general, as is the case within the multistate EVB theory,⁶² but one may anticipate that three different bonding types, donor bound, acceptor bound, and unbound [see Fig. 2(a)], will be most common. The associated 3×3 Hamiltonian can be diagonalized exactly and the ground state energy *E* is found by solving for the smallest real root of the following cubic equation:

$$(E_{\text{donor}}^{\text{MM}} - E)(E_{\text{unbound}}^{\text{MM}} - E)(E_{\text{acceptor}}^{\text{MM}} - E) - E_{\text{AU}}^2(E_{\text{donor}}^{\text{MM}} - E) - E_{\text{DU}}^2(E_{\text{acceptor}}^{\text{MM}} - E) = 0.$$
(11)

Additional coupling elements between $E_{\rm DU}$ and $E_{\rm AU}$ can also

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FIG. 3. (Color online) The (a) PhOH–N(CH₃)₃ and (b) $[(Me_2O)-H-(OMe_2)]^+$ systems. The shared proton (enlarged and highlighted in yellow) in each system is studied using wavepacket dynamics and the rest of the system is treated using Born–Oppenheimer dynamics. The *model* system atoms are shown with large, colored spheres (dark) while the *real* systems are shown with both lines and spheres. The link atoms are small, pink (light) spheres. The link atom on the oxygen side of phenol trimethylamine is bromine and those on the nitrogen side are hydrogens. All link atoms for $[(Me_2O)-H-(OMe_2)]^+$ are hydrogens.

be added if necessary.⁶⁰ In indicating these connections as well as noting possible expansions of our EVB-ONIOM method, we show that the scheme is general and its applications move beyond the uses benchmarked in this paper.

III. NUMERICAL RESULTS

Figure 3 displays the systems under study. In Fig. 3(a)we present the PhOH $-N(CH_3)_3$ system, while in Fig. 3(b) [also Fig. 2(b)] we present $[(Me_2O)-H-(OMe_2)]^+$. Both systems are characterized by a proton shared between donoracceptor-type hydrogen bonding moieties. Such systems are common in biological, ^{102–106} condensed phase, ^{107–110} and gas phase^{66,67,69,74–76,79,80,111–114} chemistries, and the vibrational properties in such systems are of experimental and theoretical interest. For both systems, three different calculations were performed. In one case, all electrons were treated with B3LYP/6-31+G(d, p), i.e., no hybrid techniques were used and this is referred to as full QM in later discussions. In the other two cases, only the highlighted atoms and link atoms in Figs. 3(a) and 3(b) were treated with B3LYP/6-31 +G(d,p) and the rest of the atoms were treated using either the semiempirical method AM1,¹¹⁵ designated as QM/QM, or the Dreiding/M (Ref. 116) force field, designated as QM/MM. In all cases, the shared proton was treated as a one-dimensional quantum wavepacket for simplicity and to probe the accuracy of the QM/MM and QM/QM calculations efficiently. (We have recently demonstrated^{4,5} that the threedimensional nature of the shared proton may be critical in some hydrogen bonding systems while computing vibrational properties and reaction tunneling rates. In this publication we only gauge the accuracy of the QM/MM generalization of QWAIMD and hence restrict ourselves to a computationally simpler one-dimensional treatment.) The rest of the atoms obeyed classical Born–Oppenheimer molecular dynamics. The full dynamics of the systems was computed using the QWAIMD methodology.^{1–4} A comparison between the spectral properties and the distributions of structural features of these systems using both ONIOM and full QM QWAIMD allowed us to determine the effect of QM/MM and QM/QM treatments.

To demonstrate the ONIOM implementation of OWAIMD, we first consider the dynamics in PhOH $-N(CH_3)_3$. This system is considered prototypical for condensed phase proton transfer in solution^{14,100,117} and has been studied with several approaches including surface hopping,^{14,118} centroid molecular dynamics,¹⁰⁰ quantum Kramers methods,^{117,119} Landau–Zener-type methods,¹⁰⁰ variational transition state theory,¹²⁰ and *ab initio* calculations.^{121,122} Gas-phase phenol-amine studies have also been utilized to explore hydrogen bond induced red-shifts of the OH stretch in infrared spectroscopy.^{121,123}

The effects from the ONIOM partitioning of PhOH $-N(CH_3)_3$ could have a drastic effect since the phenyl ring is treated as a single link atom in the model ONIOM calculation. The position of the link atom is determined based on the primary phenyl carbon. The choice of this link atom is crucial since the delocalization of electrons in the phenyl ring may be expected to affect the proton transfer process. In our studies we have chosen a bromine link atom to represent the phenyl side instead of the standard hydrogen link atom used in most ONIOM studies.^{25,89} This choice is based on the similarities between the pK_a of phenol (9.95) and HOBr (8.5). This should be compared to the fact that choosing the default hydrogen link atom would lead to the inappropriate substitution of phenol by water in the model calculation. Choosing the correct boundary atom is a general concern and there have been several attempts to overcome this problem; ${}^{30-32,34,38,90-92}$ we do not explore this problem further in this publication. For the MM calculations we use the Dreiding/M force field that represents bond stretches as Morse oscillators. Since it provides a description of the dissociation portion of the diabatic interaction potentials, this choice of force field obviates the need for a 3×3 EVB description of the shared proton. Finally, we represent the shared hydrogen with the H_HB atom type, which includes a CHARMM-like hydrogen bonding potential.¹¹⁶ The QM/QM studies of this system combine B3LYP/6-31+G(d,p) with AM1.

We also examine the proton-bound dimethyl-ether system, $[(Me_2O)-H-(OMe_2)]^+$, which has recently been studied using experimental single-photon⁷⁵ and multiple-photon^{74,124} action spectroscopy. In addition, computational techniques including AIMD along with a study of the quantum nature of the shared proton,⁶⁶ have been utilized to understand the differences between the spectral features arising from multiple-photon and single-photon processes.

TABLE I. Energy conservation summary.

	Level of theory	Time (ps)	Temp. (K) ^a	$\Delta E(\text{kcal/mol})^{\text{b}}$
PhOH-N(CH ₃) ₃	ONIOM(MO:MM) ^c	1.7	64.5 ± 5.5	0.027
	ONIOM(MO:MO) ^d	2.5	63.9 ± 5.9	0.022
	full QM ^e	1.9	64.4 ± 5.7	0.060
$[(Me_2O) - H - (OMe_2)]^+$	ONIOM(MO:MM) ^c	2.8	78.4 ± 9.5	0.098
	ONIOM(MO:MM) ^f	2.4	65.3 ± 7.8	0.043
	ONIOM(MO:MO) ^d	3.5	62.4 ± 8.6	0.047
	full QM ^e	2.2	66.1 ± 8.1	0.028

^aThe temperature is calculated from the kinetic energy of the system and the standard deviation is also reported. ^b ΔE represents the standard deviation of the total (kinetic plus potential) energy of the system during the simulation.

^cONIOM(B3LYP/6-31+G(d,p):Dreiding/M) is used for all QM/MM calculations and, unless noted, $E_{DA}^{CM}(R_{QM})$ is the EVB coupling element.

dONIOM(B3LYP/6-31+G(d,p):AM1) is used for all QM/QM calculations.

^eB3LYP/6-31+G(d,p) is used for all full QM calculations.

 ${}^{t}E_{DA}^{\Delta}(R_{QM})$ is the EVB coupling element.

The effect of cluster temperature is critical and the high temperature AIMD results in Ref. 66 are in good agreement with experimental multiple-photon results, whereas the lowtemperature results agree with the single-photon spectrum. In AIMD and QWAIMD, cluster temperature is determined using nuclear velocities and the wavepacket kinetic energy. This provides a measure of the amount of energy in the system, which helps "randomize" motion and thus affects the The extent potential sampling. of energy $[(Me_2O)-H-(OMe_2)]^+$ system is also a prototypical protonbound organic system similar to that found in many biological systems. The most basic form of such systems is the well-known Zundel cation, $H_5O_2^+$, which has been the subject of much experimental and theoretical debate.^{67–73} (This type of system is also common in water clusters.^{67,69,76,79,80,112–114}) Here, $[(Me_2O)-H-(OMe_2)]^+$ is also treated using B3LYP/6-31+G(d,p) for the *model* system and both Dreiding/M and AM1 for the *real* system [the *model* system] is described in Fig. 3(b)]. We also computed the interaction potential using the H HB atom type for the shared proton. All the link atoms in this case are hydrogen atoms. The dynamics of both systems was calculated with the QWAIMD formalism.

We provide simulation data in Table I. The simulations in this table all use the TDDS procedure described in Secs. I and II A. In particular, the size of the grid used to discretize the quantum wavepacket and potential surface is comprised of 101 evenly spaced points. The overhead involved in the computation of the ONIOM potential and gradients is reduced by the TDDS scheme to only 11 evaluations based on Eq. (3). (In higher dimensional quantum dynamical calculations, TDDS has been demonstrated⁴ to provide a much greater reduction in computing time, as seen from Fig. 1. Here, the use of a one-dimensional wavepacket treatment provides one order of magnitude reduction in computational cost as a result of TDDS.) The potential and gradient values on the remaining grid points are interpolated,³ using Hermite-curve interpolation.^{3,4,125-127} Since each grid point calculation is independent from the others, the overall computation runs in parallel over a large number of processors (see Fig. 4). The QM/MM simulations use the EVB- E_{DA}^{CM} and

EVB- E_{DA}^{Δ} methods described in Sec. II B. All AIMD simulations conducted here are microcanonical (*NVE*), with acceptable fluctuations (noted in Table I) in the internal temperature. Since time-correlation functions involving nuclear velocities and wavepacket flux are utilized here to obtain vibrational properties, a constant energy simulation with an associated conserved Hamiltonian is critical.

Table I displays good energy conservation (measured by the standard deviation of the total energy over the simulation time) over picosecond time scales, which indicates that the EVB-ONIOM/QWAIMD generalization performs well in smoothing the discontinuities in the potential. The accuracy of the resultant dynamics is evaluated further in this section. We also note the good conservation for the QM/QM and full QM simulations, where there is no need for an EVB interpolation.

A. Structural and vibrational properties of PhOH–N(CH₃)₃ from ONIOM-QWAIMD simulations 1. Structural and dynamical properties

In this section, we first compare structural parameters obtained from QWAIMD simulations. Following this, an analysis of the dynamically averaged, vibrational properties is undertaken. In Fig. 5, the evolution of the donor, acceptor, and wavepacket centroid in relation to the quantum mechanical grid center is presented. In Fig. 6 the distribution of



FIG. 4. Computational scaling of QWAIMD with number of processors on a Xeon cluster with gigabit Ethernet.





FIG. 5. An evolution of the distance of the donor oxygen, acceptor nitrogen, and proton wavepacket centroid from the center of the quantum mechanical grid (Gr₀) for (a) the QM/MM, (b) QM/QM, and (c) full QM PhOH–N(CH₃)₃ simulations. The negative oxygen-grid center distance ($-R_{OGr_0}$) is the left vertical axis and the nitrogen-grid center (R_{NGr_0}) distance is the right vertical axis on all three figures. The scales are the same for both axes and the oxygen is on the negative side of the grid and the nitrogen is on the positive side). Finally, the centroid-grid center ($R_{\chi Gr_0}$) distance is also on the right vertical axis, but it is shifted so that it is plotted between the other two measures. Again, a more negative value means that it is closer to the phenol side of the grid and a less negative distance is toward the amine side of the grid.

donor-acceptor distances are displayed. In Fig. 7 the angular distributions encountered during the QWAIMD simulations are analyzed. The time-averaged shared proton potential energy surface is presented in Fig. 8, and in Table II we analyze their eigenstates. These structural parameters were chosen for the following reasons: The C–O–N angle and the N–O–C–C dihedral are of interest since they penetrate through the *model-real* boundary and reflect the accuracy of the low-level calculations as well as the coupling of the two layers. The distribution of the oxygen-nitrogen (donor-acceptor) distances ($R_{\rm DA}$), the wavepacket centroid evolution, and the shared proton potential energy surfaces and associated eigenstates show the effect of the level of theory on the shared proton quantum dynamics.



FIG. 6. The distribution of donor-acceptor distances for the $PhOH-N(CH_3)_3$ system.

Figure 6 indicates that the O–N distance is slightly elongated in the QM/QM simulation as compared to the full QM and QM/MM simulations. Specifically, the QM/QM distribution is shifted by about 0.05 Å. It is particularly relevant to compare these dynamical distribution functions in Fig. 6 with their respective optimized O-N distances, which are 2.79 Å for the full QM structure, 2.82 Å for QM/QM, and 2.78 Å for QM/MM. All three distributions show a shift toward lower O-N distances as a result of the quantum proton dynamics. This effect is most pronounced for the full QM case, which shifts by about 0.05 Å. The explanation is evident upon inspection of Fig. 8. Since the shared proton potential is highly anharmonic (more so for the full QM, see Fig. 8), the proton is not completely localized in the attractive well on the oxygen side. (The zero-point energies and $1 \leftarrow 0$ transition energies are provided in Table II.) The pres-



FIG. 7. Angular distribution for the PhOH-N(CH₃)₃ system.



FIG. 8. The time-averaged proton potential energy surface, $(1/T)\int_0^T dT' E(R_{QM};T')$, is presented for PhOH–N(CH₃)₃. The origin for the horizontal axis is the position of the classical shared hydrogen atom at the minimum energy (optimized) geometry. Note that the average potentials are slightly shifted toward the phenol side (left side of plot) as a result of dynamical and anharmonic effects.

ence of positive charge density more delocalized toward the amine as a result of anharmonicity creates an attractive force and thus shortens the O–N distance. Note that the wave-packet centroid and phenol oxygen are highly correlated, as seen in Figs. 5(a)-5(c), due to the moderate strength hydrogen bond interaction.

The C–O–N angle in Fig. 7(a) displays a 6° shift for the QM/MM simulation with respect to the full QM, whereas the QM/QM simulation is approximately in agreement with the full QM QWAIMD result in the lower angle region but lacks density in the higher angle regions. A similar shift, however, is also seen in the optimized geometries at each level, where this angle is 116° for QM/MM, 119° for QM/QM, and 121° for full QM. This trend is exaggerated in the N-O-C-C dihedral distribution in Fig. 7(b) where the distributions for each method are centered about their minimum energy positions (0° for full QM and QM/QM and -25° for QM/MM). In this respect, the *real* system dynamics of AM1 is closer to the full QM dynamics than that of the Dreiding/M force field, although both angular distributions of the hybrid simulations are tighter than the full QM distribution and the QM/MM distributions both have long tails. These angles, however, are correlated. When the N–O–C–C dihedral angle is 0° , one of the lone pairs on the phenol oxygen can participate in the delocalization of the benzene ring electrons if the oxygen is sp^2 hybridized. With this hybridization, the

TABLE II. PhOH–N(CH $_3)_3$ shared proton eigenstate and wavepacket characteristics.

Level of theory	$E^0_{\langle E \rangle}$ a	$1_{\langle E \rangle} \leftarrow 0_{\langle E \rangle}^{\ b}$	$\Delta_{R_{ m QM}}^{\langle E angle \ \ m c}$	$\langle H_{\rm nuc} \rangle \ ^{\rm d}$
ONIOM(MO:MM) ^e	4.19	2702.4	0.078	4.25
ONIOM(MO:MO) ^e	4.14	2660.6	0.078	4.14
QM ^e	4.06	2585.5	0.079	4.21

^aThe zero-point energy of the time-averaged proton potential, $(1/T)\int_0^T dT' E(R_{OM};T')$, in kcal/mol.

^bThe $1 \leftarrow 0$ vibrational energy transition of the time-averaged proton potential in cm⁻¹.

 $^c\sqrt{\langle R^2_{QM}\rangle-\langle R_{QM}\rangle^2}$ of the ground state of the time-averaged proton potential in Å.

^dThe time-averaged energy of the dynamical proton. wavepacket, $(1/T)\int_0^T dT' \langle \psi(T')|H_{T'}|\psi(T')\rangle$, in kcal/mol.

^eThe level of theory used is as described in Table I.

N–O–C angle is expected to be close to 120° . In the QM/MM case, such an electron delocalization is not possible and deviations from an sp^3 oxygen (the atom type chosen in this case) are purely based on electrostatic and steric effects.

A comparison of the time-averaged proton potential energy surfaces in Fig. 8 indicates that the quantum dynamical nature of the shared proton is, on average, similar for all three cases. However, the effects of confinement enforced by each potential is a little different, as is clear from the more careful analysis presented in Table II. The time-averaged potential is less confining for the higher-level calculations and this is noted from the lower zero-point energy and $1 \leftarrow 0$ vibrational eigenstate transition energy for the full QM calculation as compared to the QM/MM and QM/QM calculations. This aspect is also apparent upon inspection of Fig. 8. In fact, this trend goes beyond just the lower eigenstates of the potential since the proton affinity of NH3 (the trimethylamine model system in the ONIOM calculations) is 20 kcal/mol less than the affinity of $N(CH_3)_3$ (the system in the full QM simulation).¹²¹ The eigenstates are calculated with an iterative Arnoldi diagonalization $^{128-130}$ and the kinetic energy operator we utilize is the second derivative, zero-time limit of the DAF propagator.^{2,85,86} A more detailed discussion of the proton stretch frequency is undertaken later in this section.

We further analyze the eigenstructure and wavepacket spread in Table II. The position uncertainties of the eigenstates in the third column are similar. However, these measures derived from the time-averaged potential do not capture all the dynamical aspects and fluctuations in the potential are lost. The time-averaged energy of the dynamical wavepacket in column 4, however, seems to indicate a higher contribution from excited vibrational states in the case of the QM/MM and full QM calculations as compared to the QM/QM calculations.

It is clear from the above discussion that both QM/QM and QM/MM simulations are able to recover many of the structural features seen in the QWAIMD trajectories constructed without hybrid electronic structure methods. The differences essentially arise where a potential π -bond character can be assigned to a QM/MM or QM/QM boundary bond, which the latter captures more effectively. In addition, for hybrid methods, it is necessary to choose the substituted link atoms carefully since the accuracy of the results depends on the relative agreement of the shared proton potential in Fig. 8.

2. Vibrational properties

Next, we analyze the spectroscopic properties of the molecular cluster. Generally, hybrid QM/MM and QM/QM methods are not utilized for the study of spectral properties of hydrogen bonded systems because of the relatively low accuracy of MM methods in describing such interactions. A few exceptions include Refs. 27, 131, and 132 where the errors seen are noted to be due to the coupling of the two regions, the placement of the boundary, and the accuracy of the low-level calculation. However, these studies did not include strong hydrogen bonds of the kind studied in this publication. We perform the spectroscopic analysis to gauge the

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effectiveness and accuracy of our QWAIMD method in facilitating qualitatively accurate spectral predictions when combined with hybrid methods.

To obtain spectroscopic data from these dynamics calculations, we construct the Fourier transform of the unified velocity-flux autocorrelation function as introduced in Refs. 3 and 4,

$$C(\omega) = \int_{-\infty}^{+\infty} dt \, \exp[-\iota \omega t] \{ \langle v(t)v(0) \rangle_c + \langle \mathbf{J}(t)\mathbf{J}(0) \rangle_Q \},$$
(12)

where the average flux $\mathbf{J}(t)$ of the quantum wavepacket is

$$\mathbf{J}(t) = \langle \mathcal{J} \rangle = \mathcal{R}\left[\left\langle \psi(t) \left| \frac{-\iota \hbar}{m} \nabla \right| \psi(t) \right\rangle \right].$$
(13)

 $\mathcal{R}[A]$ represents the real part of the complex number A. Symbols $\langle \cdots \rangle_C$ and $\langle \cdots \rangle_Q$ represent the classical and quantum variables ensemble averages. In Eq. (12), we have exploited the connection between the probability flux and the semiclassical velocity operator. We have shown that the flux autocorrelation function of a time-independent Hamiltonian produces spectral features corresponding to eigenenergy differences, i.e., vibrational excitation energies.⁴ In the studies considered in this section, we compare results obtained from Eq. (13) and also the vibrational properties of the proton wavepacket flux,

$$C_{J}(\omega) = \int_{-\infty}^{+\infty} dt \exp[-\iota \omega t] \{ \langle \mathbf{J}(t) \mathbf{J}(0) \rangle_{Q} \}.$$
(14)

Our results from the construction of the Fourier transform of the unified velocity-flux autocorrelation function for the full QM and ONIOM PhOH– $N(CH_3)_3$ calculations are presented in Fig. 9(a). In Fig. 9(b) the proton wavepacket flux spectrum is displayed for each level of electronic structure theory. The harmonic frequencies from the optimized geometries are displayed in Fig. 9(c). It must be noted that the vertical axes in Figs. 9(a) and 9(b) represent intensities derived from Eqs. (13) and (14). As a result, the harmonic spectral peaks in Fig. 9(c) are also plotted as vibrational density of states (without IR intensities) for consistency. A comparison of intensities between the harmonic and QWAIMD spectra is beyond the scope of the current publication and will be considered in future.

From Figs. 9(a) and 9(b) we note that there is general qualitative agreement between the QWAIMD/ONIOM and the QWAIMD/QM simulations. The dominant ideas from these figures are as follows: The proton stretch spectrum in Fig. 9(b) is reasonably consistent between the full QM and QM/QM treatments, whereas the QM/MM feature is only slightly blue-shifted. A similar blue-shift is seen in the 1 \leftarrow 0 transition of the average proton potential surfaces in Table III and can be understood based on the differences in potential surfaces in Fig. 8. Additional insight into the shared proton spectra may be obtained from an analysis of the harmonic frequencies provided in Fig. 9(c) and Table III. An aspect that is consistent among all simulations is the fact that there is a relative red-shift noted in the dynamics simula-



FIG. 9. A comparison of (a) the QM/MM, QM/QM, and full QM vibrational density of states [Eq. (12)], (b) the proton flux spectra [Eq. (14)], and (c) the harmonic spectrum at the optimized geometry for PhOH–N(CH₃)₃.

tions, which is also expected based on the potential surfaces in Fig. 8, which are anharmonic toward the amine. The difference between the $1 \leftarrow 0$ transitions in Table III and the corresponding dynamical values indicates the effect of donor-acceptor coupled motion on the shared proton. This has an effect of about 100–150 cm⁻¹ in all three cases. (The first column is blue-shifted by about 100–150 cm⁻¹ with

TABLE III. PhOH-N(CH₃)₃ ν_{OH} (cm⁻¹).

Level of theory	Flux modes	$1_{\langle E \rangle} \leftarrow 0_{\langle E \rangle}^{a}$	Harmonic modes
ONIOM(MO:MM) ^b	2817	2702.4	3209.7
ONIOM(MO:MO)	2753	2660.6	3113.7
QM	2708	2585.5	3190.0/3196.7 ^c

^aThe $1 \leftarrow 0$ vibrational energy transition of the time-averaged proton potential.

^bThe level of theory used is as described in Table I.

^cThe mode containing the OH stretch is a doublet since it is symmetrically and antisymmetrically coupled to phenyl hydrogen stretching modes.



FIG. 10. An evolution of the distance of the donor oxygen, acceptor oxygen, and proton wavepacket centroid from the center of the quantum mechanical grid (Gr₀) for the QM/MM EVB- E_{DA}^{Δ} in (a), $EVB-E_{DA}^{CM}$ in (b), QM/QMin (c), and full QM in (d) $[(Me_2O)-H-(OMe_2)]^+$ simulations. The negative oxygen1-grid center distance $(-R_{O1Gr_0})$ is the left vertical axis and the oxygen2-grid center (R_{O2Gro}) distance is the right vertical axis on all three figures. The scales are the same for both axes and the oxygen1-grid distance is negative since it accounts for directionality (i.e., this oxygen is on the negative side of the grid and the other is on the positive side). Finally, the centroid-grid center $(R_{\chi Gr_0})$ distance is also on the right vertical axis, but it is shifted so that it is plotted between the other two measures. Again, a more negative value means that it is closer to the oxygen1 side of the grid and a less negative distance is toward the oxygen2 side of the grid.

respect to the second column.) The reason behind the blueshift can be understood upon inspection of Figs. 5(a) and 5(c), where the shared proton centroid motion is strongly coupled to the oxygen motion and both have a time period of about 200 fs or 167 cm⁻¹. Thus, the effect of the centroid motion causes a blue-shift that is absent in the $1 \leftarrow 0$ transition of the time-averaged potential.

Other important differences arise from the motion of the phenyl and amino groups due to the differences between the QM/MM and QM/QM treatments. We also note that the peaks at 1500 and 2000 cm⁻¹ in the QM/MM harmonic spectrum, 1600-1800 cm⁻¹ in the QM/QM harmonic spectrum, and 1600 cm⁻¹ in the full QM harmonic spectrum correspond to proton vibrations perpendicular to the O–N axis. Since our wavepacket is one-dimensional, we do not capture these modes and they are absent in Fig. 9(b). However, these results are encouraging and show that despite the differences between the QM and hybrid simulations, important chemical (classical and quantum) features for moderate strength hydrogen bonds can be captured within the framework presented here.

B. Structural and vibrational properties of $[(Me_2O)-H-(OMe_2)]^+$ from ONIOM-QWAIMD simulations

1. Structural and dynamical properties

For the $[(Me_2O)-H-(OMe_2)]^+$ simulations, we also provide a structural analysis followed by a comparison of vibrational properties. The geometric parameters shown in Figs. 10 and 11 were picked for the same reasons discussed in Sec. III A. We show the evolution of the donor, acceptor, and wavepacket centroid relative to the quantum mechanical grid in Fig. 10. We also plot the O–O (R_{DA}) distance distribution in Fig. 11(a), the C–O–O–C dihedral angle distribution in Fig. 11(b), and the time-averaged proton potential surfaces in Fig. 12, and in Table IV we analyze their eigenstates.

Upon examination of Fig. 10, it becomes evident that the nature of the shared proton quantum dynamics of $[(Me_2O)-H-(OMe_2)]^+$ is different from that in PhOH-N(CH₃)₃. These figures indicate that the wavepacket



FIG. 11. A comparison of important structural parameters of the $[(Me_2O)-H-(OMe_2)]^+$ cluster. We compare the distribution of (a) the donor-acceptor distances and (b) the C-donor-acceptor-C dihedral.



FIG. 12. We compare the time-averaged proton potential energy surface, $(1/T)\int_0^T dT' E(R_{QM};T')$, of $[(Me_2O)-H-(OMe_2)]^+$ at each level of theory. The *x*-axis corresponds to the placement of the potential grid. The origin, and grid center, is the position of a classical hydrogen at the minimum energy (optimized) geometry. The full grid extends from -0.5 to 0.5 Å.

centroid remains centrally located and has no preference for either oxygen, consistent with a short, strong hydrogen bond. This is the opposite for PhOH–N(CH₃)₃ in Fig. 5, where the centroid is strongly correlated with the donor motion. Finally, it is apparent that the EVB- E_{DA}^{CM} dynamics differ substantially from the other levels of theory. The oscillatory nature of this trajectory as compared to the other plots is because the wavepacket oscillates about the grid resulting in some amount of probability density leaking outside the grid. A consequence of this effect was recorded in Table I where the energy conservation is slightly worse for EVB- E_{DA}^{CM} and the average temperature is higher for this calculation. We are currently implementing an adaptive, moving quantum dynamical grid¹ algorithm that will be discussed in detail in future publications.

The O–O distances have a similar range for the full QM and both QM/MM trajectories (2.38–2.49 Å). This range is shifted by 0.05 Å for the QM/QM simulation. When the R_{DA} distribution is compared with the optimized values, 2.39 Å for full QM and EVB- E_{DA}^{CM} , 2.41 Å for EVB- E_{DA}^{Δ} , and 2.44 Å for QM/QM, a trend becomes evident. The equilibrium values of the O–O distributions are not the optimized values but define the low end of the distribution. The opposite is seen for the PhOH–N(CH₃)₃ simulations, where the optimized R_{DA} values are on the higher end of the distance in

TABLE IV. [(Me₂O)-H-(OMe₂)]⁺ proton wavepacket.

Level of theory	$E^0_{\langle E angle}$ a	$1_{\langle E \rangle} \leftarrow 0_{\langle E \rangle}^{b}$	$\Delta^{\langle E angle \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$	$\langle H_{\rm nuc} \rangle^{\rm d}$
ONIOM(MO:MM) ^e	1.89	1497.3	0.098	2.13
ONIOM(MO:MM) ^f	1.66	1353.6	0.10	1.78
ONIOM(MO:MO) ^g	1.35	1175.4	0.11	1.54
QM ^g	1.62	1352.1	0.10	1.85

^aThe zero-point energy of the time-averaged proton potential, $(1/T)\int_0^T dT' E(R_{QM};T')$, in kcal/mol.

^eSee Table I, $E_{\text{pA}}^{\text{CM}}$.

^fSee Table I, $E_{\rm DA}^{\Delta}$

Fig. 6 (see associated discussion in Sec. III A 1). This switch in trends is explained by comparing the average potential surfaces in Figs. 12 and 8. The shared proton potential in $[(Me_2O)-H-(OMe_2)]^+$ is much more symmetric and is characterized by a flatter potential at the bottom of the well, which is noted by the lower zero-point energies and $1 \leftarrow 0$ transition energies in Table IV as compared to Table II. This results in a greater wavepacket spread for $[(Me_2O)-H-(OMe_2)]^+$, as noted in Table IV. (Compare $\Delta_{R_{\text{OM}}}^{\langle E \rangle} \approx 0.1$ in Table IV as compared to $\Delta_{R_{\text{OM}}}^{\langle E \rangle} \approx 0.08$ in Table II, for the ground state.) In addition, the proton potential becomes strongly repulsive at both ends. The repulsive wall is caused in part by the fact that the oxygens are participating in a short, strong hydrogen bond. Compare the equilibrium R_{DA} of 2.43–2.48 Å for $[(Me_2O)-H-(OMe_2)]^+$ with 2.75–2.8 Å for PhOH–N(CH₃)₃. Steric interactions involving the methyl groups also play a role in constructing the repulsive wall. The larger delocalization of the shared proton coupled with the strong repulsive wall in the shared proton potential contributes to the positive shift in R_{DA} distribution as compared to the respective optimized geometry values. As noted earlier, this effect is markedly different from that in the case of PhOH $-N(CH_3)_3$. Finally, we can understand the shift in $R_{\rm DA}$ seen for QM/QM when we consider the fact that AM1 uses a minimal basis set and thus has difficulty accurately calculating the weaker, nonbonding interactions (like hydrogen bonding).¹³³ In the MM calculations, we use an H HB atom-type for the shared proton, which includes an explicit hydrogen bonding potential.

The nature of the shared proton potential discussed above, i.e., symmetric, flat at the bottom of the well and repulsive at the ends, is a characteristic of quartic anharmonicity. In this sense, the potential for $[(Me_2O)-H-(OMe_2)]^+$ is similar to that in $[Cl-H-Cl]^-$ previously studied by us⁴ but differs through the R_{DA} distribution described here. In $[Cl-H-Cl]^-$, the dynamical R_{DA} oscillates about the optimized value since the distance is larger (3.15–3.2 Å).

In Fig. 11(b), we compare dihedral angles sampled during the trajectories. The general features gleaned from these plots are as follows: The spreads are comparable, although QM/QM and EVB- E_{DA}^{CM} are 10° broader and EVB- E_{DA}^{Δ} is 5° narrower. Also, all distributions except EVB- E_{DA}^{CM} center around the optimized values. The EVB- E_{DA}^{CM} equilibrium is 10° larger than the optimized C-O-O-C dihedral. Furthermore, the QM dihedral distribution is bimodal. Only the QM/QM calculation approaches this structure. Reasons for these trends can be understood by examining the different ways each level of theory treats the methyl interactions. Since this is a weak van der Waals-type interaction, only a full QM simulation can properly account for it. The fact that the full QM distribution is bimodal implies that this interaction is harmonic-like. The QM/MM techniques account for this interaction with a combination of explicit angle bend, torsion, and van der Waals potential functions. The bend potentials are a bonded interaction that affects the C-O-shared proton angles. In the EVB- E_{DA}^{CM} calculations, this interaction is an EVB average of the shared proton bound to either oxygen, whereas in the EVB- E_{DA}^{Δ} simulation, this interaction is the sum of both C-O-shared proton angles. In addition

^bThe $1 \leftarrow 0$ vibrational energy transition of the time-averaged proton potential in cm⁻¹.

 $[^]c\sqrt{\langle R^2_{QM}\rangle-\langle R_{QM}\rangle^2}$ of the ground state of the time-averaged proton potential in Å.

^dThe time-averaged energy of the dynamical proton wavepacket, $(1/T)\int_0^T dT' \langle \psi(T') | H_{T'} | \psi(T') \rangle$, in kcal/mol.

^gSee Table I.



FIG. 13. A comparison between the (a) QM, QM/QM, and QM/MM (EVB- E_{DA}^{CM} and EVB- E_{DA}^{Δ}) full vibrational density of states, only the (b) proton flux spectra, (c) the harmonic spectra of the optimized geometries for each level of theory, and (d) the harmonic proton stretch modes.

 $\text{EVB-}E_{\text{DA}}^{\Delta}$ also contains an explicit angle term involving the donor oxygen, shared proton, and acceptor oxygen. These subtle differences are important since the oxygen atom type chosen for the MM calculations is sp^3 hybridized, so the equilibrium C-O-shared proton angle used for the potential function is 109.5°, if the proton is explicitly bound to the oxygen. Since the proton is explicitly bound to both oxygens using the EVB- E_{DA}^{Δ} scheme, both C–O-proton angles attempt to approach a tetrahedral structure, which indirectly affects the methyl-methyl distances and hence the C–O–O–C dihedral. However, this interaction is only present in EVB $-E_{DA}^{CM}$ through EVB averaging. The QM and QM/QM calculations are not constricted by a preset atom type and these hybridizations, and thus dihedral angles, can change fluidly. Also, the torsion (dihedral) potential, which is also a bonded interaction, is only present in the EVB- E_{DA}^{Δ} calculations and accounts for the C-O-H-O dihedral. The only direct interaction between the methyl groups is a van der Waals interaction potential, which occurs in both schemes. The combination of these explicit potential energy functions is responsible for the differences between QM/MM, QM/QM, and full QM distributions in Fig. 11(b).

We now inspect the time-averaged proton potential surfaces in Fig. 12. The QM/QM potential is much broader and the EVB- E_{DA}^{CM} is much more confining than the QM potential, whereas EVB- E_{DA}^{Δ} is similar to the full QM potential. These trends are reflected in Table IV. The zero-point energy and the 1 \leftarrow 0 transition of the time-averaged potential surface are higher for EVB- E_{DA}^{CM} compared to full QM. However, for QM/QM, they are lower than the full QM simulations, which is explained by the larger O–O distances seen in Fig. 11(a) and the flatter QM/QM potential in Fig. 12. The EVB- E_{DA}^{Δ} potential shows good agreement the with full QM potential. Agreement between these two levels of theory is also seen in column 4, the time-averaged wavepacket energy. Again, the differences between the QM/MM methods are understood by the way the EVB schemes treat the potential functions as discussed in the previous paragraph. Like in the PhOH–N(CH₃)₃ trajectories, the dynamics sample excited nuclear vibrational states for all levels of theory. Additionally, the better agreement between the EVB- E_{DA}^{Δ} and the full QM simulation for the quantum parameters (potential surface and wavepacket properties) indicate that EVB- E_{DA}^{Δ} performs better in the potential calculation than the EVB- E_{DA}^{CM} since the electrons on the hydrogen are shared equally between the donor and acceptor oxygens.

In summary, the molecular geometries sampled during the dynamics are similar across the different levels of theory. Subtle differences arise since the interactions between the various portions of the $[(Me_2O)-H-(OMe_2)]^+$ cluster are treated differently for each scheme. These differences are especially important with regard to the different EVB calculations. From these comparisons, it seems that care is needed when choosing a hybrid electronic structure method for short, strong hydrogen bonded systems. However, the EVB- E_{DA}^{Δ} potential seems to possess some of the qualitative features required to describe the structural features in short, strong hydrogen bonded systems.

2. Vibrational properties

We also present a spectral comparison of the $[(Me_2O)-H-(OMe_2)]^+$ cluster using the full QM, QM/QM, and both QM/MM schemes (see Sec. II B) in Fig. 13(a), a comparison of the wavepacket flux spectrum in Fig. 13(b), and a comparison of the harmonic spectra for all levels of theory in Figs. 13(c) and 13(d). Before we embark into a detailed analysis of the differences among the spectra, we

state the following general factors at the outset. The published experimental and theoretical results for this system are in the 600-1800 cm⁻¹ region.^{66,74,75,124} There are three main features in the published experimental and theoretical results: The 800 cm⁻¹ region corresponds to the shared proton stretch and the 1100-1200 cm⁻¹ region corresponds to the shared proton stretch coupled to the motion of heavier atoms such as CO stretch and methyl wag and also to the motion of the shared proton orthogonal to the O-O axis. The 1300–1500 cm⁻¹ region corresponds primarily to the motion of the shared proton orthogonal to the O-O axis and its coupled motion with heavier atom modes. In Ref. 66 a detailed discussion on the temperature dependence of this spectrum, along with an analysis of the differences between experimental single-photon and multiple-photon action spectroscopy results for this system, has been provided. Furthermore, the intensities discussed in Ref. 66 are dipole intensities that are in close agreement with experimental IR intensities. The intensities for the classical atoms here are based on classical velocities and the treatment generally involves a vibrational density of states for classical atom motion in Figs. 13(a) and 13(b). Hence, like in Sec. III A, all harmonic modes are plotted without IR intensities in Figs. 13(c) and 13(d) to facilitate comparison. In addition, due to the occurrence of proton motion orthogonal to the donor-acceptor axis and its coupling to the proton stretch mode,⁶⁶ we do not expect our one-dimensional treatment here to provide a quantitative description of the vibrational spectral problem in $[(Me_2O)-H-(OMe_2)]^+$. We, instead, focus on whether qualitatively consistent results can be obtained using the full QM, QM/QM, and QM/MM spectral analyses.

Unlike in the PhOH $-N(CH_3)_3$ cluster, there is significant coupling between the proton motion and the rest of the system since $[(Me_2O)-H-(OMe_2)]^+$ contains a short, strong hydrogen bond. One of the most striking features from Figs. 13(c) and 13(d) is the fact that the harmonic frequencies are not in good agreement using the various levels of theory. The dynamical simulations only partially overcome this intrinsic deficiency in the underlying hybrid methods for the system considered here. This is in contrast to the case of $PhOH-N(CH_3)_3$ and again the reason is due to the short, strong nature of the hydrogen bond involved. The proton flux for all simulations has two or three peak clusters in the range of 800–1700 cm⁻¹. Note again that the intensities in these spectra correspond to classical nuclear velocity and wavepacket flux. A careful comparison of the dynamical spectra and the harmonic frequencies reveal several interesting features. The harmonic spectra for both QM/MM methods in Fig. 13(c) are in close agreement. (We note that the normal modes labeled as EVB- E_{DA}^{CM} were actually calculated as if the proton were not bound to either oxygen. This approximation is justified since the position of the proton on this point on the EVB potential is midway the donor and acceptor wells.) In both spectra, the modes dominated by methyl motions are between 1600 and 1700 cm⁻¹. The proton vibrations, shown in Fig. 13(d), display modes with motion perpendicular to the O–O axis at 1500 and 1200 cm^{-1} , and the parallel modes are also at 1200 and 1050 cm^{-1} for EVB- E_{DA}^{Δ} and 1200 and 980 cm⁻¹ for EVB- E_{DA}^{CM} . The remaining low-frequency vibrations are also dominated by the methyl motion. A similar pattern is seen in the velocity/flux spectra in Figs. 13(a) and 13(b). There are methyl modes at 1600–1800 cm⁻¹ and the parallel proton modes are blue-shifted to 1500 cm⁻¹ for EVB- E_{DA}^{Δ} and 1550 cm⁻¹ for EVB- E_{DA}^{CM} . The difference in shift is due to the more confining nature of the EVB- E_{DA}^{CM} potential. As a result the dynamical proton flux spectrum for EVB- E_{DA}^{CM} is very different from that indicated by the harmonic frequency calculations. The low-frequency parallel modes are at 1150 cm⁻¹ for EVB- E_{DA}^{Δ} and 950 cm⁻¹ for EVB- E_{DA}^{Δ} .

The QM/QM harmonic spectrum has three sets of peaks corresponding to parallel proton vibrations at 1550, 1200, and 700 cm⁻¹. The perpendicular vibrations are present at 1600, 1500, and 1300 cm⁻¹. The remaining modes are methyl dominated. The parallel modes are shifted in the velocity/flux spectra to 900, 1300, and 1600 cm⁻¹ and the remaining peaks are the methyl modes. Finally, in the full QM harmonic spectrum, the parallel modes are at 1550, 1300, and 850 cm⁻¹. The remaining peaks correspond to the coupled motion between the perpendicular proton motion and the methyl modes. Only the major perpendicular modes are shown in Fig. 13(d). On the velocity/flux spectrum, we have parallel modes at 1650, 1350, and 850 cm⁻¹. The remaining peak is comprised of methyl motion.

Patterns are also discernable when the spectra are compared among the methods. For instance, the full QM and QM/MM methods have doublets corresponding to methyl motion in the dynamical spectra, with relative shifts comparable to those seen in the harmonic spectra. The QM/QM methyl modes are well separated in the dynamic and harmonic spectra. Another interesting trend is seen in the harmonic proton spectra with respect to the perpendicular proton vibrations. All modes in the 1500 cm⁻¹ region have two peaks except the EVB- E_{DA}^{CM} spectrum, which is a singlet. When the C-O-O-C dihedral deviates from 90°, there are two distinguishable perpendicular modes: One bisects the major C-O-O-C angle and the other bisects the minor dihedral. Since the EVB- E_{DA}^{CM} optimized geometry has a 90° C-O-O-C dihedral, all directions are the same. The reasons behind these differences have been discussed in the previous paragraphs. These modes cannot be captured with our onedimensional wavepacket, so they do not appear in Fig. 13(b). Also, due to anharmonicity, the parallel proton vibrations with the highest intensity in the dynamic spectra are blueshifted by 300-400 cm⁻¹ compared to the highest harmonic frequencies. This shift direction is opposite for this system than is seen for the proton modes in PhOH $-N(CH_3)_3$ since the anharmonicity here comes from quartic terms because the potential is symmetrically bound. A similar blue-shift in proton vibrations is seen in [Cl-H-Cl]⁻ when the harmonic spectra are compared to the vibrational eigenstate transitions of the full potential.⁴ In PhOH $-N(CH_3)_3$, the anharmonicity comes from cubic terms as the potential is completely bound only on one side of the quantum grid. Overall, these spectra show that hybrid methods and the low-level calculation utilized have a large effect on the calculated vibrational properties. This is in stark contrast to PhOH-N(CH₃)₃ since the types of hydrogen bonds in these systems are different. The structural properties for both systems, on the contrary, are in good qualitative agreement between simulations.

IV. CONCLUSION

In this paper we present a hybrid QM/MM and QM/QM generalization of our recently developed approach¹⁻⁴ to perform simultaneous dynamics of electrons and nuclei. The generalization combines the ONIOM scheme for both QM/MM and QM/QM treatments with the QWAIMD method for simultaneous ab initio and quantum wavepacket dynamics. Our ONIOM/QWAIMD scheme enhanced with TDDS has the potential to be useful for simulations of large systems, like biological enzymes. This combination requires special care when calculating the quantum interaction potential since MM methods are unable to properly describe a potential that smoothly changes from a proton donor-bound complex to a proton acceptor-bound complex. The potential is only problematic if the model system is calculated at the MM level and does not contain all atoms three bonds away from the site of the changing bond. In order to overcome this problem, we have shown that an adiabatic EVB potential energy surface constructed from donor-bound and acceptorbound diabatic potentials is adequate to remove discontinuities originating from a changing bond topology. In this contribution, we introduce two schemes to calculate EVB surfaces. The first method, $EVB-E_{DA}^{CM}$, averages proton donor- and acceptor-bound complexes by including an offdiagonal Gaussian coupling between the diabatic donor and acceptor bound states. The other scheme, EVB- E_{DA}^{Δ} , simultaneously binds the proton to both donor and acceptor. The first scheme is seen to be a more appropriate description if the donor and acceptor complexes are well separated, as in hydrogen bonding systems of moderate strength, whereas the second EVB surface better describes a proton equally shared between its donor and acceptor, i.e., a short-strong hydrogen bond.

We have also analyzed the vibrational spectral properties using a novel unified velocity-flux autocorrelation function.^{3,4} This provides us with a vibrational density of states, inclusive of quantum dynamical effects. The vibrational properties depend on several variables, including the accuracy of the low-level calculation and how the vibrational modes in the *model* system couple with those in the *real* system. In the case of PhOH– $N(CH_3)_3$, we find that as the low-level calculation is improved from MM to semiempirical, an important effect is seen. Since the model system vibrations are mostly decoupled from the *real* system vibrations, the proton flux peaks converge to the full QM calculation. $[(Me_2O)-H-(OMe_2)]^+$, on the other hand, has a strong coupling between the *real* and the *model* system motion. This coupling is reflected in the proton flux spectra by the fact that the spectra show large variations across the different electronic structure methods. These observations suggest that if quantitative vibrational spectra were required, the real and the model systems should be chosen such that the coupling of their vibrational modes is small. This generalization can be extended to state that for strongly hydrogen bound clusters, the *model* system size should be extended beyond what we have benchmarked here for $[(Me_2O)-H-(OMe_2)]^+$ for qualitatively accurate spectra. If the hydrogen bond is weak, as is the case for PhOH-N(CH₃)₃, the partitioning scheme we present (only the donor, hydrogen, acceptor, and associated link atoms are included in the high-level system) is still capable of qualitative agreement with full QM simulations.

The analysis of the dynamical structure of both systems shows good agreement among all simulation levels. From these differences, we can see the effects of the system partitioning, low-level calculation, and the EVB method. In the $PhOH-N(CH_3)_3$ simulations, for instance, we see the effect of substituting $N(CH_3)_3$ with ammonia in the *model* system. It increases the dissociation energy of the average potential surface, resulting in a blue-shifted peak for the ONIOM calculations. The accuracy of the low-level calculation makes a difference in the C–O–N angle of PhOH– $N(CH_3)_3$ since this parameter depends more directly on the real system via the oxygen atomic orbital hybridization. Thus, this distribution agrees more with the full QM calculation when QM/QM is used. The same can be said for the N-O-C-C dihedral angle. The R_{DA} distribution is affected more by the QM/QM calculation since AM1 generally predicts incorrect geometries for hydrogen bonded clusters.¹³³ These inaccuracies, however, have an effect on the calculated potential surfaces. Finally, although the effects of the different EVB methods are difficult to discern from the vibrational spectra, they are more obvious when the structural parameters are compared. The choice of EVB coupling element shows an effect on the R_{DA} distribution, as well as the overall donor, acceptor, and wavepacket centroid dynamics in the $[(Me_2O)-H-(OMe_2)]^+$ system. For these parameters, $EVB-E_{DA}^{CM}$ differs from the QM calculations the most. However, the wavepacket and potential properties are better predicted by this EVB method. This is likely due to the nature of the shared hydrogen electrons between the two ether oxygens. The dynamical behavior of the C–O–O–C dihedral is better predicted in the EVB- E_{DA}^{Δ} distribution (it oscillates about its optimized value), although the overall spread is better represented by the EVB- E_{DA}^{CM} scheme. It is difficult to generalize when one EVB method is preferable over the other unless a specific property is desired.

Finally, our results indicate that our new QWAIMD/ ONIOM formalism can be used to calculate accurate dynamics of large problems. We achieve good energy conservation over picosecond time scales, Furthermore, the OWAIMD methodology introduces no new errors into the ONIOM scheme. We find that the embedding model, the link atom choice, the system partitioning, and the degree of coupling between the model and real systems could impact the accuracy of a simulation. The latter consideration is more significant when calculating vibrational spectra than when calculating structural properties. Our results are also dependent on the quality of the force field for a QM/MM calculation and on the lower level of theory in a QM/QM calculation. A systematic improvement of these parameters will result in more accurate simulations. Also, depending on the properties one wishes to examine from a particular simulation, different hybrid QM/MM and QM/QM methods as well as different EVB schemes are available.

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