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Interfacing ab initio Quantum Mechanical Method with Classical Drude Oscillator Polarizable Model for Molecular Dynamics Simulation of Chemical Reactions

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Abstract

In order to further improve the accuracy and applicability of combined quantum mechanical/molecular mechanical (QM/MM) methods, we have interfaced the ab initio QM method with the classical Drude oscillator polarizable MM force field (ai-QM/MM-Drude). Different coupling approaches have been employed and compared: 1. the conventional dual self-consistent-field (SCF) procedure; 2. the direct SCF scheme, in which QM densities and MM Drude positions are converged simultaneously; 3. the micro-iterative SCF scheme, in which the Drude positions of the polarizable model are fully converged during each self-consistent field (SCF) step of QM calculations; 4. the one-step-Drude-update scheme, in which the MM Drude positions are updated only once instead of fully converged during each molecular dynamics (MD) step. The last three coupling approaches are found to be efficient and can achieve the desired convergence in a similar number of QM SCF steps comparing with the corresponding QM method coupled to a non-polarizable force field. The feasibility and applicability of the implemented ai-QM/MM-Drude approach have been demonstrated by carrying out Born-Oppenheimer molecular dynamics simulations with the umbrella sampling method to determine potentials of mean force for both the methyl transfer reaction of the methyl chlorine-chlorine ion system and the glycine intra-molecular proton transfer reaction in aqueous solution. Our results indicate that the ai-QM/MM-Drude approach is very promising, which provides a better description of QM/MM interactions while can achieve quite similar computational efficiency in comparison with the corresponding conventional ab initio QM/MM method.

I. Introduction

The combined quantum mechanical/molecular mechanical (QM/MM) approaches^{1, 2} have been widely used in modeling chemical reactions in complex systems, from the solid and surface catalysis to solution and enzyme reactions³⁻¹². With the increase of computer power and the development of more efficient algorithms which make high level electronic structure calculations more affordable, there is a great deal of interest in developing and applying QM/MM approaches based on ab initio quantum mechanical methods to achieve better accuracy and wider applicability. Over the last few years, this field is expanding rapidly, and molecular dynamics simulations with ab initio QM/MM methods have become increasingly feasible¹³⁻¹⁹. Meanwhile, it has been recognized that in order for ab initio QM/MM approaches to become an equal partner of experimental methods, significant development efforts are still needed.

In most QM/MM methods and applications, the conventional non-polarizable molecular mechanical force fields have been employed, and QM/MM electrostatic interactions are

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calculated through a Coulombic term in an effective Hamiltonian with MM atoms as fixed point charges. In such a formulation, the electronic-configuration of the QM sub-system changes in response to the presence of MM electrostatic environment while MM charges are always kept fixed. Thus it only takes into account the polarization effect of the MM charges on the QM sub-system, but does not include the polarization effect of the QM subsystem on MM atoms or the polarization interactions among MM atoms. It is clear that the origin of this limitation comes from conventional pair-wise additive force fields which use fixed atomic charges to model electrostatics. An intuitive and well-known step to make progress is to couple QM methods with polarizable MM force fields to achieve a consistent treatment of QM and MM electrostatic polarization interactions²⁰⁻⁴¹.

The available polarizable MM force fields can be mainly divided into three categories^{42, 43}: the induced point dipole model^{1, 44-47}, the fluctuating point charge model (also known as electronegativity equalization model)⁴⁸⁻⁵¹, and the classical Drude oscillator model⁵²⁻⁶⁵ (also known as the shell model or charge-on-spring model). In the first two approaches, either atomic point dipoles or atomic charges are allowed to fluctuate in response to the environmental electric field changes. In the Drude oscillator model, an induced dipole is represented as a pair of point charges connected with a harmonic spring.

Among polarizable force fields, the induced dipole model was the first employed to interface with QM methods, which was presented when the QM/MM approach was introduced by Warshel and Levitt¹. Later, the QM/induced-point-dipole method was further developed and implemented by a number of groups, and had been employed to investigate the molecular properties in ground state and excited states and study the spectroscopy of organic molecules and biological systems²⁰⁻³². Instead of using the induced point dipole model, Bryce et al. and Field et al. used the fluctuating charge models in their QM/MM-pol calculations^{33, 34}. Zhang et al. also made use of the fluctuating charge model to treat the polarizability of MM boundary atoms and they demonstrated that including the mutual polarization of the QM and MM subsystems can yield more accurate results when modeling proton affinities³⁷. Compared to the other two categories of polarizable models, the applications of the oscillator Drude model to the QM/MM calculations are seldom seen. Until very recently Geerke et al. combined semi-empirical QM method with their charge-on-spring polarizable model (also known as the classical Drude oscillator model or shell model) to perform potential of mean force (PMF) simulations for a S_N2 reaction in the solvent dimethyl ether³⁵. Besides the polarizable force field approaches, the importance of the mutual polarization between the QM and MM subsystems is also realized in QM/MM studies treating the environment with the reaction field approach³⁸⁻⁴¹.

Most of the above QM/MM-pol calculations so far employed a semi-empirical Hamiltonian and a dual SCF procedure: at each iteration cycle, the MM induced dipoles/fluctuating charges were optimized in the presence of a frozen QM wavefunction, followed by the regular QM self-consistent field (SCF) calculation in the presence of external charges/dipoles. Generally, depending on the convergence criterion, two to five iterative cycles are usually needed to achieve the self-consistencies of both QM wavefunction and MM induced dipoles/fluctuating charges^{20, 23, 35}. Therefore, the dual SCF scheme makes the QM/MM-pol calculation significantly slower than the corresponding conventional QM/MM calculation. This is especially problematic for the ab initio QM/MM-pol approach, in which the QM SCF calculation is much more expensive than the one in semi-empirical QM methods. To circumvent the dual SCF scheme and improve the computational efficiency, Dupuis et al. presented a direct SCF approach²⁶, in which QM wavefunctions and MM induced dipoles are converged simultaneously instead of iteratively. With this direct SCF algorithm, they studied the structure and energy of the formaldehyde and water complex in the ground state and excited state with ai-QM/MM-pol calculations²⁶.

From the above account, it is very clear that to couple QM methods with polarizable force fields is both desirable and feasible. However, the QM/MM-pol approaches have been rarely adopted in QM/MM studies of chemical reactions so far, even with the recent renewed enthusiasm in the development of polarizable force fields. Besides the availability of polarizable force field parameters, the lack of popularity of the QM/MM-pol approaches may also be due to the following two concerns: one is the computational cost of such calculations, and the other is the effect of such consistent treatment of polarization on the final results. It can be easily envisioned that the QM/MM-pol approaches would meet much less resistance if they can be demonstrated to have a similar efficiency while better accuracy than the corresponding conventional QM/MM methods. Thus in this paper, we have interfaced *ab initio* QM methods with the classical Drude oscillator polarizable MM force field (ai-QM/MM-Drude) for Born-Oppenheimer molecular dynamics simulations of chemical reactions. In order to improve the efficiency and stability of such simulations, we have explored several schemes of optimizing/updating the Drude particles during MD simulations. The resulted ai-QM/MM-Drude methods have been tested on the water dimer, and applied to calculate the potentials of mean force for both the methyl transfer reaction of the methyl chlorine-chlorine ion system and the glycine intra-molecular proton transfer reaction in aqueous phase. The results and computational efficiency have been compared with the corresponding conventional ai-QM/MM methods. Our work indicates that the ai-QM/MM-Drude approach is very promising, which provides a more realistic description of QM/MM interactions while can achieve quite similar computational efficiency in comparison with the corresponding conventional ai-QM/MM method. We also found that the inclusion of polarization effects can have a significant effect on the calculated free energy profile for the glycine intra-molecular proton transfer reaction in aqueous solution.

The outline of the paper is as follows: In Sec. II we give a brief introduction to the Drude oscillator model and the conventional QM/MM approach, followed by the description about the coupling between the QM Hamiltonian and the Drude oscillator model, and the one-step-Drude-update scheme for QM/MM-Drude MD simulations. In Sec. III we present the computational details. Results and discussion are given in Sec. IV.

II. Methodology

A. Classical Drude oscillator model

In the classical Drude oscillator model, the induced dipole is represented by a pair of point charges separated by a variable distance. One point charge q_α is fixed to the charge center site while the other point charge (called Drude particle) $q_{\alpha'}$ is bounded to the charge center site via a harmonic spring of force constant $k_{\alpha'}$. The net charge and dipole moment on this charge center site are $q_\alpha + q_{\alpha'}$ and $\mu_{\alpha'} = q_{\alpha'} \mathbf{d}_{\alpha'}$, where $\mathbf{d}_{\alpha'} = |\mathbf{r}_{\alpha'} - \mathbf{r}_\alpha|$. The total electrostatic energy of the system for a Drude oscillator system is

$$\begin{aligned}
 E_{ele} &= E_{static-ele} + E_{Drude-ele} + E_{self} \\
 &= \sum_{\alpha} \sum_{\beta > \alpha} \frac{q_\alpha q_\beta}{r_{\alpha\beta}} + \left(\sum_{\alpha} \sum_{\beta'} \frac{q_\alpha q_{\beta'}}{r_{\alpha\beta'}} + \sum_{\alpha'} \sum_{\beta' > \alpha'} \frac{q_{\alpha'} q_{\beta'}}{r_{\alpha'\beta'}} \right) + \frac{1}{2} \sum_{\alpha'} k_{\alpha'} d_{\alpha'}^2
 \end{aligned} \quad (2.1)$$

where the prime denotes the Drude particle site. Comparing the self-energy term in the above equation with the one from the induced dipole model, $E_{self} = \frac{1}{2} \sum_{\alpha'} \frac{\mu_{\alpha'}^2}{\alpha_{\alpha'}}$, it leads to the following expression for the isotropic atomic polarizability

$$\alpha_{\alpha'} = \frac{q_{\alpha'}^2}{k_{\alpha'}}. \quad (2.2)$$

B. QM/MM approach

The total energy of a QM/MM system can be written as

$$E_{tot} = E_{qm} + E_{qm/mm} + E_{mm}. \quad (2.3)$$

For the Hatree-Fock theory or Kohn-Sham density functional theory, E_{qm} can be written as

$$E_{qm} = \sum_{\mu\nu}^{AO} D_{\mu\nu} H_{\mu\nu}^{core} + \frac{1}{2} \sum_{\mu\nu\lambda\sigma}^{AO} D_{\mu\nu} D_{\lambda\sigma} (\mu\nu|\lambda\sigma) + E^{XC}[\rho], \quad (2.4)$$

where μ, ν denote the atomic basis set, $D_{\mu\nu}$ is the density matrix element, and $E^{XC}[\rho]$ is the exchange-correlation functional of electron density whose form depends on the theory used. $E_{qm/mm}$ is the coupling term between the QM and MM subsystem, and can be decomposed into

$$E_{qm/mm} = E_{qm/mm}^{ele} + E_{qm/mm}^{vdw} + E_{qm/mm}^{MM-bonded}, \quad (2.5)$$

where $E_{qm/mm}^{MM-bonded}$ refers to the bond, angle and dihedral energy terms at the QM/MM interface. In the actual implementation, the QM/MM electrostatic coupling enters into the QM SCF calculation by adding the following one-electron core Hamiltonian into the Fock matrix $F_{\mu\nu}$

$$H_{\mu\nu}^{core,qm/mm} = \langle \mu | - \sum_i^{electron} \sum_{\alpha}^{MM} \frac{q_{\alpha}}{r_{i\alpha}} | \nu \rangle, \quad (2.6)$$

where q_{α} is MM atomic charge, and i is the index for electron. Then

$$E_{qm/mm}^{ele} = \sum_{\mu,\nu}^{AO} D_{\mu\nu} H_{\mu\nu}^{core,qm/mm} + \sum_A^{QM} \sum_{\alpha}^{MM} \frac{Q_A q_{\alpha}}{r_{A\alpha}}, \quad (2.7)$$

where Q_A is the QM nuclei charge. Now combining Eq. (2.4) and (2.7), the final electronic energy can be obtained after determining $D_{\mu\nu}$ with the SCF approach according to the variational principle.

C. QM/MM-Drude oscillator model

In the QM/MM-Drude approach, the total energy of the system can be written as

$$E_{tot} = E_{qm} + E_{qm/mm} + E_{mm} + E_{Drude-ele} + E_{self} \quad (2.8)$$

where $E_{Drude-ele}$ is the electrostatic energy term involving the Drude particles

$$\begin{aligned}
 E_{\text{Drude-ele}} &= \sum_{\alpha} \sum_{\beta'} \frac{q_{\alpha} q_{\beta'}}{r_{\alpha\beta'}} + \sum_{\alpha'} \sum_{\beta' > \alpha'} \frac{q_{\alpha'} q_{\beta'}}{r_{\alpha'\beta'}} + \sum_A \sum_{\alpha} \frac{Q_A q_{\alpha'}}{r_{A\alpha'}} + \sum_{\mu, \nu}^{AO} D_{\mu\nu} \langle \mu | - \sum_i \sum_{\alpha'} \frac{q_{\alpha'}}{r_{i\alpha'}} | \nu \rangle, \\
 &= \sum_{\alpha'}^{MM'} q_{\alpha'} \left(\phi_{\alpha'}^{MM} + \frac{1}{2} \phi_{\alpha'}^{MM'} + \phi_{\alpha'}^{Nuc} + \phi_{\alpha'}^{electron} \right)
 \end{aligned} \quad (2.9)$$

and

$$E_{\text{self}} = \frac{1}{2} \sum_{\alpha'}^{MM'} k_{\alpha'} d_{\alpha'}^2. \quad (2.10)$$

Here $\phi_{\alpha'}^{MM}$, $\phi_{\alpha'}^{MM'}$, $\phi_{\alpha'}^{Nuc}$, $\phi_{\alpha'}^{electron}$, are the electrostatic potentials at the Drude site α' generated by the classical point charges (whose positions are immobile during the energy evaluation), the charges of Drude particles, the QM nuclei charge and QM wave-function respectively. Again the prime indicates the Drude particle site.

It is clear from Eqs. (2.4), (2.7), (2.9) and (2.10) that now the total energy of the system should be minimized with respect to both $D_{\mu\nu}$ and the Drude particle position $\mathbf{r}_{\alpha'}$. Typically, a dual SCF coupling procedure can be employed:

1. With a frozen QM density, according to Eqs. (2.9) and (2.10) the Drude particle positions are updated to satisfy

$$\begin{aligned}
 \nabla_{\mathbf{r}_{\alpha'}} (E_{\text{Drude-ele}} + E_{\text{self}}) &= - \sum_{\alpha'}^{MM'} q_{\alpha'} \left(\mathbf{E}_{\alpha'}^{MM} + \frac{1}{2} \mathbf{E}_{\alpha'}^{MM'} + \mathbf{E}_{\alpha'}^{Nuc} + \mathbf{E}_{\alpha'}^{electron} \right) + k_{\alpha'} \mathbf{d}_{\alpha'}, \\
 &= 0
 \end{aligned} \quad (2.11)$$

or rearranged as

$$\mathbf{d}_{\alpha'} = \frac{1}{k_{\alpha'}} \sum_{\alpha'}^{MM'} q_{\alpha'} \left(\mathbf{E}_{\alpha'}^{MM} + \frac{1}{2} \mathbf{E}_{\alpha'}^{MM'} + \mathbf{E}_{\alpha'}^{Nuc} + \mathbf{E}_{\alpha'}^{electron} \right). \quad (2.12)$$

Either a SCF approach based on Eq. (2.12) (since the electric field $\mathbf{E}_{\alpha'}$ depends on $\mathbf{d}_{\alpha'}$) or a minimization method based on Eq. (2.11) can be applied to obtain $\mathbf{d}_{\alpha'}$ or equivalently $\mathbf{r}_{\alpha'}$.

2. With the updated Drude particle positions determined from step (1), regular QM SCF calculations as implemented in QM software packages are performed to obtain a converged $D_{\mu\nu}$. If the total energy is converged, exit; otherwise, go back to step (1).

For clarity, the above dual SCF coupling procedure is illustrated in Scheme 2, which has been employed in most QM/MM-pol methods.

D. Direct SCF and micro-iterative SCF coupling schemes

Although the dual SCF coupling is very straightforward to implement, it increases QM SCF steps and makes QM/MM-pol calculations significantly slower than the corresponding conventional QM/MM calculations. The alternative is the direct SCF coupling scheme presented by Dupuis et al.²⁶, in which step (1) and step (2) are combined so that the QM wavefunction and the MM induced dipoles can be converged simultaneously. In our current

work, we extend the direct SCF algorithm to treat the coupling between the Drude oscillators and the QM wavefunction and the details are described as follows:

- A. At each QM SCF step, the current density matrix is used to update the Drude particle positions only once according to Eq. (2.12).
- B. The one-electron integral $\langle \mu | -\sum_i^{electron} \sum_{\alpha'}^{MM'} \frac{q_{\alpha'}}{r_{i\alpha'}} | v \rangle$ is calculated and added to the core Hamiltonian;
- C. The updated Fock matrix is diagonalized to obtain a new density matrix. If the density matrix and the total energy are converged, exit; otherwise start another QM SCF step.

If we replace the step (A) with a fully optimization step (A'):

- A. At each QM SCF step, the current density matrix is used to fully optimize the Drude particle positions according to Eq. (2.12).

We obtain a micro-iterative SCF coupling scheme. From the above description, we can see that step (1) in the dual SCF algorithm corresponds to step (A'), a micro-iteration step as part of the QM SCF step. In the direct SCF and micro-iterative coupling schemes, due to the re-

evaluations of the one-electron integral $\langle \mu | -\sum_i^{electron} \sum_{\alpha'}^{MM'} \frac{q_{\alpha'}}{r_{i\alpha'}} | v \rangle$ at each QM SCF step, the core Hamiltonian keeps changing until convergence. For clarity, the direct SCF and micro-iterative SCF coupling schemes are illustrated in Scheme 3.

Compared to the conventional QM/MM approach, the increase of computational time in the QM/MM-Drude calculation using the direct SCF algorithm or the micro-iterative SCF coupling scheme may also come from the following two aspects:

1. Computing $\mathbf{E}_{\alpha'}$ according to Eq. (2.12) for updating the Drude particle positions at step (A) or (A') and evaluating $\langle \mu | -\sum_i^{electron} \sum_{\alpha'}^{MM'} \frac{q_{\alpha'}}{r_{i\alpha'}} | v \rangle$ at step (B).
2. The possible increase of QM SCF steps in comparison to the conventional QM/MM calculation.

For the second concern, as demonstrated later from our tests, there is almost no increase of QM SCF steps in our ai-QM/MM-Drude MD simulations. The cost due to (1) needs some comments. Although the two-electron coulomb integral and exchange-correlation integral calculations are computationally much more expensive than the one-electron integral and MM calculations, the cost of computing $\mathbf{E}_{\alpha'}$ and one-electron integrals repetitively involving the Drude particles is still not ignorable, especially when the size of MM-Drude system is large. If $d_{\alpha'}$ remains small enough (which means the current Drude oscillator model is a good approximation to the induced point dipole model), then $\mathbf{E}_{\alpha'}$ can be well approximated by $\mathbf{E}_{\alpha}$, the electric field at the fixed charge center site. Unlike $\mathbf{E}_{\alpha'}$ which is dependent on the position of the mobile Drude particles, $\mathbf{E}_{\alpha}$ needs to be computed only once at each QM SCF step. The work from Thompson²¹ indicates that for $d_{\alpha'} < 0.1 \text{ \AA}$, the error in energy caused by such an approximation is small. This approximation was taken by Geerke et al in their semi-empirical QM/MM-Drude MD simulations³⁵. However, it has been very recently found that the resulted error can be quite significant unless the charges of Drude particles are very large⁶⁶. Here we did not take such an approximation, and evaluated $\mathbf{E}_{\alpha'}^{electron}$ whenever the Drude particles move. Therefore, the micro-iterative SCF coupling scheme is more computationally demanding than the direct SCF scheme, because of the repetitive $\mathbf{E}_{\alpha'}$ calculations at each QM step in the former approach.

E. One-step-Drude-update scheme

In MD simulations with polarizable force fields, instead of obtaining the converged $\mathbf{d}_{\alpha'}$ with either an optimizer or a SCF approach, there are two more efficient ways for updating the Drude particle positions at each MD step. One is called the extended Lagrangian method⁶⁷, in which the Drude particles are assigned with a fictitious mass and treated as dynamic variables and their positions are propagated according to the extended Lagrangian function. By coupling the motions of the Drude particles with a low-temperature thermostat, the system can remain close to the SCF regime⁶⁸. Another method to avoid the SCF calculations in MD polarizable force field simulations is called the always stable predictor-corrector (ASPC) method^{69, 70}. In this method, the induced dipoles (or $\mathbf{d}_{\alpha'}$ for Drude oscillator model) at time $t + h$ is:

$$\boldsymbol{\mu}(t+h) = \omega M(\boldsymbol{\mu}^p(t+h)) + (1 - \omega)\boldsymbol{\mu}^p(t+h), \quad (2.13)$$

where h denotes the time step, ω is the relaxation parameter to ensure the stability, which prevents the error in $\boldsymbol{\mu}(t+h)$ accumulating along the trajectory, and M represents the right-hand side (RHS) equation for $\boldsymbol{\mu}$ in the SCF procedure. From Eq. (2.12) we can see that the RHS equation of $\mathbf{d}_{\alpha'}$ in the Drude oscillator model is just

$$M \equiv \frac{1}{k_{\alpha'}} \sum_{\alpha'}^{MM'} q_{\alpha'} \left(\mathbf{E}_{\alpha'}^{MM} + \frac{1}{2} \mathbf{E}_{\alpha'}^{MM'} + \mathbf{E}_{\alpha'}^{Nuc} + \mathbf{E}_{\alpha'}^{electron} \right). \quad (2.14)$$

In Eq. (2.13), $\boldsymbol{\mu}^p(t+h)$ is the guess of the induced dipole based on the historical information from previous MD steps. While the simplest form is just a linear extrapolation, $\boldsymbol{\mu}^p(t+h) = 2\boldsymbol{\mu}(t) - \boldsymbol{\mu}(t-h)$, Kolafa gave more elaborate forms to improve the accuracy and time reversibility^{69, 70}.

Recently Niklasson et al. proposed a lossless time-reversible ab initio QM MD scheme^{71, 72}, which allows stable Hatree-Fock MD simulations with only one single QM SCF cycle per time step. In our current work, we extend their method to update the positions of Drude particles in a similar manner as they update the density matrix along the MD simulations. Specifically:

$$\mathbf{d}_{\alpha'}^p(t+h) = 2\mathbf{d}_{\alpha'}^p(t) - \mathbf{d}_{\alpha'}^p(t-h), \quad (2.15)$$

$$\mathbf{d}_{\alpha'}(t+h) = M(\mathbf{d}_{\alpha'}^p(t+h)), \quad (2.16)$$

where M is defined in Eq. (2.14). In Eq. (2.15) a simple linear extrapolation form is used and the time reversibility is reserved by using $\mathbf{d}_{\alpha'}^p(t-h)$ instead of $\mathbf{d}_{\alpha'}(t-h)$. As tested, the resulted lossless time-reversible MD with one-step-Drude-update scheme allows a stable MM Drude oscillator MD simulation by updating the positions of Drude particles only once at each time step. The details of integrating this lossless time-reversible MD scheme into QM/MM-Drude MD simulations are described in Scheme 4.

III. Computational Details

In the QM/MM-Drude oscillator approach, for the water solvent, we employed a SWM4-NDP model, a Drude oscillator model from Lamoureux et al.^{64, 65}, which is calibrated to reproduce important bulk properties of the water at room temperature and pressure. The parameters of

the SWM4-NDP water model are shown in Scheme 1. In conventional QM/MM calculations, we use the TIP3P water model⁷³. The QM/MM and QM/MM-Drude schemes were implemented by modifying Gaussian03⁷⁴ and the TINKER program⁷⁵. The correctness of the implementation has been carefully checked by comparing the analytical and numerical gradients, and the energy conservation from short NVE MD runs.

For the PMF calculation of glycine intra-molecular proton transfer reaction, the solutes were solvated with a 20 Å sphere of waters. Only the waters within 15 Å of the sphere center were allowed to move during the MD simulations. For the methyl-transfer reaction, the solute was solvated with a 18 Å sphere of waters and only 13 Å of the sphere center were allowed to move during MD simulations. The bonds in water molecules were constraint using the RATTLE algorithm^{76, 77}. A time step of 1 fs was employed for the MD simulations and the mass of deuterium was used for the hydrogen atoms in the glycine molecule. No cutoff was used for the non-bonded interactions. The velocity verlet integrator implemented in the TINKER program was used and the temperatures of the systems were controlled at 300 K with the Berendsen velocity scaling method⁷⁸. The PMF calculations were performed with the umbrella sampling and the Weighted Histogram Analysis method^{79, 80}.

For the methyl transfer reaction of the methyl chlorine-chlorine ion system, the reaction coordinate (rc) is chosen as $rc = d_{c-cl1} - d_{c-cl2}$ and 22 windows centering from reaction coordinate of -3.8 to 0.0 Å were used. The symmetry was used to obtain a full PMF curve. For each window, 10 ps equilibration was performed, followed by a 20 ps data collection. HF/6-31G(d) was employed for the QM calculations. The convergence criterion in the micro-iterative SCF algorithm was set to RMS gradient $0.001 \text{ kcal mol}^{-1} \text{ Å}^{-2}$ per Drude.

For the glycine intra-molecular proton transfer reaction, the reaction coordinate is defined as $rc = d_{H10-N1} - d_{H10-O5}$ (see Fig. 1), and 17 windows were employed. For each window, 12 ps equilibration were performed, followed by 24 ps data collection. B3LYP/6-31G(d) was employed for the QM calculations. The convergence criterion in the micro-iterative SCF algorithm was set to RMS gradient $0.01 \text{ kcal mol}^{-1} \text{ Å}^{-2}$ per Drude. The Lennard-Jones parameters from the Amber94 force field⁸¹ were used for the QM subsystems in both ai-QM/MM-Drude and ai-QM/MM calculations. It should be noted that ideally different QM van der Waals parameters should be used to further improve the description of QM/MM interactions. Some work were already done in parameterizing the QM van der Waals parameters for the QM/MM models⁸²⁻⁸⁴, but the influence of the QM van der Waals parameters on the ai-QM/MM-Drude calculations has not been addressed. The work along this direction is currently in progress, and will be presented in future publications.

IV. Results and Discussion

A. Comparison between the SWM4-NDP water and the QM water

As illustrated in Scheme 1, the SWM4-NDP water model^{64, 65} uses the point charges for electrostatic interactions and the 12-6 Lennard-Jones potentials for the repulsive and dispersion interactions. The molecular polarizability is modeled by a Drude particle attached to the oxygen atom. According to Eq. (2.2), the molecular polarizability given by this model is 0.97825 Å^3 , much smaller than the experimental value 1.44 Å^3 . The reduced molecular polarizability was found to be essential in reproducing the liquid properties⁶⁴, which may be due to the simplicity of this model.

Before applying this water model in our ai-QM/MM-Drude simulations, it will be informative to learn how accurate this simple polarizable water model is in modeling the electrostatic interactions. To avoid the complexity caused by choosing Lennard-Jones parameters, we studied the interactions between a water and a point charge. As shown in the insets of Fig. 2,

we moved either a +1e or -1e point charge in four different directions and calculated the interaction energies along the charge-oxygen distance for the SWM4-NDP water, the TIP3P water and the QM water in the MP2/aug-cc-pvtz description. From Fig. 2 we can see that in general the SWM4-NDP water model yields a better agreement with the QM description than the TIP3P water, although the electrostatic interactions are underestimated in the SWM4-NDP water, which is not a surprise considering that the molecular polarizability given by SWM4-NDP is significantly lower than the values from experiments or the MP2/aug-cc-pvtz calculation.

Another test we performed is to calculate the water dimer interaction energies. The QM calculations were done at B3LYP/6-31G(d,p) level. Two cases were considered for the QM/MM-Drude and QM/MM calculations. One corresponds to the QM water as the hydrogen bond donor, while in the other case the QM water is the hydrogen bond acceptor. For the QM/MM-Drude calculations, the Lennard-Jones parameters of the QM water are taken from those of the SWM4-NDP water model, while in the QM/MM calculations, the Lennard-Jones parameters of the QM water are taken from those of the TIP3P water model. As illustrated in Fig. 3, in contrary to those from the QM/MM calculations, the QM/MM-Drude calculations for the two cases considered yield the consistent binding energies and binding distances, and have close agreement with those from pure QM calculations, which suggest that the SWM4-NDP water has a better performance in terms of “mimicking” the QM water than the TIP3P water does. These results are encouraging, which indicate that the ai-QM/MM-Drude method can provide a better description of QM/MM interactions than the corresponding conventional ai-QM/MM method.

B. Computational efficiency of ai-QM/MM-Drude MD simulations

To evaluate the feasibility of ai-QM/MM-Drude calculations, we performed short-time MD simulations for several systems with both conventional ai-QM/MM and ai-QM/MM-Drude simulations. The computational efficiency of the dual SCF, direct SCF and micro-iterative SCF schemes, as well as the one-step-Drude-update scheme have been tested. The results of these short MD simulations (0.1 ps ~ 1.0 ps) are summarized in Table 1. Firstly we observe that in comparison with conventional QM/MM calculations, except the dual SCF scheme, coupling the QM subsystem with the MM-Drude subsystem will not increase the QM SCF steps for all the other three Drude optimization/updating schemes. Secondly, among the different Drude optimization/updating schemes, the one-step-Drude-update scheme is the most efficient one. This is fully expected because comparing with other schemes, there is no increase in QM SCF steps and no repetitive one-electron integrals calculation involved in this scheme. Thirdly, the increase in the size of the QM subsystem leads to the decrease of the time ratio between ai-QM/MM MD and ai-QM/MM-Drude MD, which becomes more close to the unity. We can see that for a medium QM subsystem of ~300 basis functions, the increase of computational time due to employing the Drude oscillator polarizable force field becomes insignificant for the direct SCF, micro-iterative SCF and one-step-Drude-update schemes.

C. Potential of mean force calculations of the chemical reactions in solution

The chemical reactions often involve the charge transfer steps, which cause significant changes of the electrostatic properties around the reaction center. The polarizable waters should be able to adapt to the change of electronic configurations of the reaction center by adjusting its dipole moments, which in turn has an impact on the charge distributions of the reaction center. Therefore, the polarizable water model may have a strong influence on the calculated energetics of chemical reactions. In this work, we have investigated two chemical reactions in solution, one is a S_N2 reaction, the methyl transfer of the methyl-chlorine-chlorine ion system, and the other is the glycine intra-molecular proton transfer reaction (see Fig. 1).

The potential of mean force curves for the S_N2 reaction are shown in Fig. 4. We obtained a barrier of 26.2 kcal/mol from the HF(6-31G(d))/TIP3P simulation and 27.5 kcal/mol from the HF(6-31G(d))/SWM4-NDP simulation. There have been extensive studies on the self-exchange of the $Cl^- + CH_3Cl$ reaction by different groups⁸⁵⁻⁸⁹ and the reported free energy barriers are in range of 26~27 kcal/mol. Our results are in good agreement with those from the literature. The inclusion of the explicit water polarizability increases the barrier by ~1.3 kcal/mol (or ~5%).

The intra-molecular proton transfer reaction of glycine is illustrated in Fig. 1. While the neutral form (NF) of the glycine is energetically more stable than the zwitterion (ZW) form in the gas phase by more than 20 kcal/mol (see Fig. 5), the ZW is the predominant form in water, which indicates that the water solvent plays a critical role in stabilizing the ZW form. The glycine intra-molecular proton transfer reaction has also been widely studied through many different theoretical methods, including the polarizable continuum model (PCM)⁹⁰, the water cluster plus the PCM modeling⁹¹⁻⁹³, the EVB description^{94, 95}, the QM/MM treatment⁹⁶⁻⁹⁸, and the CPMD simulation⁹⁹. While the experimentally measured free energy difference of the form (ZW) and the neutral form (NF) of glycine in aqueous solution is about 7.27 kcal/mol¹⁰⁰, the reported theoretical values of the free energy difference between the ZW conformer and the NF conformer were in a wide range, from about 4.8 kcal/mol to 11.2 kcal/mol. In this work, we used B3LYP/6-31G(d) for the QM calculations and the TIP3P and SWM4-NDP water models. As shown in Fig. 5, by comparing with the results from MP2/aug-cc-pvtz, we find that B3LYP/6-31G(d) is fairly accurate in describing this intra-molecule proton reaction in the gas phase. Fig. 6 demonstrates that the employment of the polarizable force field has a strong effect on the resulted free energy reaction profiles in the aqueous solution. We obtained a 7.4 kcal/mol transition state barrier and a free energy difference of 4.4 kcal/mol between the ZW and the NF from the B3LYP(6-31G(d))/TIP3P simulation. The corresponding B3LYP(6-31G(d))/SWM4-NDP simulation gives a barrier of 8.9 kcal/mol and a free energy difference of 6.4 kcal/mol. By collecting the data from the reactant region (ZW) defined as $-1.5 \text{ \AA} < r_c < -0.8 \text{ \AA}$ and the product region (NF) defined as $0.6 \text{ \AA} < r_c < 1.0 \text{ \AA}$, we find the difference of the averaged glycine-water interaction energy between the ZW and NF is 73 kcal/mol from the QM/MM simulation and 83 kcal/mol from the QM/MM-Drude simulation. Apparently the polarizable water model gives a relatively stronger glycine-water interaction for the ZW. As shown in Fig. 7, there is no significant difference of the radial distribution functions between the TIP3P and SWM4-NDP water model. However, as illustrated in Fig. 8, we observe that the averaged SWM4-NDP water dipoles within the first solvation shell of the N1 atom of glycine in the ZW form are significantly larger than the dipole of TIP3P water (2.35 Deybe). Our results here suggest that the polarizable water model can strongly affect the resulted free energy reaction profiles by influencing the QM/MM interactions without changing the solvation structure.

All the calculations described above have employed the micro-iterative SCF scheme so that the Drude positions are fully converged at each MD step. Such simulations are more expensive than the one-step-Drude-update scheme as presented in section II. E. Since the Drude positions are not fully converged in the one-step-Drude-update scheme, one concern is that the Drude particles may exert systematic drag forces on the physical atoms along the MD simulations, which affects the resulted PMF. As a test, we employed the one-step-Drude-update scheme in our ai-QM/MM-Drude MD simulations for the PMF calculations of the two chemical reactions described above. To make sure the Drude particles stay close to the SCF regime, we switched to the micro-iterative SCF scheme every one hundred MD steps. From Figs. 4 and 6, we can see that the curves obtained with different schemes overlap very well with each other, which suggests the promise of the one-step-Drude-update scheme in the QM/MM-Drude MD simulations.

V. Conclusion

In this work, we have presented a detailed description of the methodologies of coupling the ab initio QM methods with the classical Drude oscillator model and applied the ai-QM/MM-Drude approach to the PMF calculations of two chemical reactions in solution. Besides the dual SCF, direct SCF and micro-iterative SCF schemes, we have presented a one-step-Drude-update scheme, in which the Drude positions of MM sub-system are updated only once instead of fully converged during each molecular dynamics simulation step. The resulted ai-QM/MM-Drude MD simulations are found to be highly efficient, and yield chemical reaction free energy profiles in quantitative agreement with the corresponding fully-converged-Drude-update simulations. In comparison with the corresponding ai-QM/MM calculations, the computational cost overhead for the ai-QM/MM-Drude calculations with efficient implementation schemes is rather insignificant when the QM subsystem consists of tens of atoms, which is typical for most ai-QM/MM applications. The feasibility and applicability of the implemented ai-QM/MM-Drude approach have been demonstrated by performing the potentials of mean force calculations for both the methyl transfer reaction of the methyl chlorine-chlorine ion system and the glycine intra-molecular proton transfer reaction in aqueous solution. Compared with the results from ai-QM/MM, the relative effects on the free energy profiles by switching from TIP3P to a polarizable water model for the MM environment are found to be significant for the glycine intra-molecular transfer reaction. With the continuing development of polarizable MM force fields and the further improvement in describing QM/MM interactions, the ai-QM/MM-Drude approach should become a more robust approach than the conventional QM/MM approach in modeling chemical reactions in solutions and biological systems.

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Scheme 1.
Parameters of the SWM4-NDP water model^{64, 65}.

Scheme 2.
Dual SCF scheme for QM/MM--Drude calculations.

Scheme 3.

Direct and micro-iterative SCF schemes for QM/MM-Drude calculations.

Scheme 4.

One-step-Drude-update scheme for QM/MM-Drude MD simulations.

Figure 1.
Glycine intra-molecular proton transfer reaction.

Figure 2.

Electrostatic interaction energies between a water and a point charge as a function of charge-oxygen distance. The insets illustrate the approaching directions of the point charge (+1 or -1): (a) along the oxygen electron lone pair direction; (b) along the C_2 axis of the symmetry; (c) along the O-H bond direction; (d) along the C_2 axis of the symmetry from the side of the hydrogen atoms.

Figure 3.

water dimer interaction energies as a function of the O-O distance. QM-QM denotes QM treatment for the whole water dimer; QM-SWM4 (TIP3P) denotes QM for the acceptor and SWM4-NDP (TIP3P) for the donor; SWM4 (TIP3P)-QM denotes QM for the donor and SWM4-NDP (TIP3P) for the acceptor.

Figure 4. Potential of mean force for the $\text{Cl}^- + \text{CH}_3\text{Cl}$ reaction in TIP3P and in SWM4-NDP obtained using the micro-iterative SCF scheme and the one-step-Drude-update scheme.

Figure 5.
Energies of the glycine intra-molecular proton transfer reaction in gas.

Figure 6. Potential of mean force for the glycine intra-molecular proton transfer reaction in TIP3P and in SWM4-NDP obtained using the micro-iterative SCF scheme and the one-step-Drude-update scheme.

Figure 7. Radial distribution functions g_{N1-O_w} (top), g_{O5-O_w} (middle) and g_{O4-O_w} (bottom) of the glycine in the ZW form (left panel) and NF form (right panel) solvated in TIP3P and SWM4-NDP waters.

Figure 8. Averaged water dipoles in the ZW form and the NF form of glycine along r_{N1-Ow} , r_{O5-Ow} and r_{O4-Ow} .

Table 1

Comparison of SCF steps and time ratios between ai-QM/MM and ai-QM/MM-Drude with different schemes of optimizing/updating the positions of Drude particles during MD simulations. For calculating the time ratio, we have employed the computational cost of ai-QM/MM calculations as the reference.

		ai-QM/MM				ai-QM/MM-Drude		
		micro-iterative SCF		direct SCF		one-step-Drude-update		dual SCF
Cl ⁻ + CH ₃ Cl (HF 59 basis sets)	SCF steps	6.2		6.1		6.1		10.4
	time ratio	1.0		2.4		1.6		3.4
Glycine (B3LYP 85 basis sets)	SCF steps	7.0		7.0		7.0		11.5
	time ratio	1.0		1.7		1.25		2.0
Adenosine (HF 311 basis sets)	SCF steps	7.0		7.0		7.0		10.7
	time ratio	1.0		1.13		1.05		1.44