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Quantum Mechanics / Molecular Mechanics Method combined with Hybrid All-Atom and Coarse-Grained Model: Theory and Application on Redox Potential Calculations

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Abstract

We developed a new multi-resolution method that spans three levels of resolution with quantum mechanical, atomistic molecular mechanical and coarse-grained models. The resolution-adapted all-atom and coarse-grained water model, in which an all-atom structural description of the entire system is maintained during the simulations, is combined with the ab initio quantum mechanics and molecular mechanics method. We apply this model to calculate the redox potentials of the aqueous ruthenium and iron complexes by using the fractional number of electrons approach and thermodynamic integration simulations. The redox potentials are recovered in excellent accordance with the experimental data. The speed-up of the hybrid all-atom and coarse-grained water model renders it computationally more attractive. The accuracy depends on the hybrid all-atom and coarse-grained water model used in the combined quantum mechanical and molecular mechanical method. We have used another multi-resolution model, in which an atomic-level layer of water molecules around redox center is solvated in supra-molecular coarse-grained waters for the redox potential calculations. Compared with the experimental data, this alternative multi-layer model leads to less accurate results when used with the coarse-grained polarizable MARTINI water or big multipole water model for the coarse-grained layer.

Graphical Abstract

SUPPORTING INFORMATION

Average restraint energies per TIP3P water molecule (Table S1), external electrostatic potentials at the QM center (Table S2), metal-oxygen radial distribution functions for the aqueous ruthenium and iron in the reduced and oxidized states calculated with QM/TIP3P/PW and QM/TIP3P/BMW methods by varying relative dielectric permittivity between AA and CG (Figures S1 and S2), ensemble average of ϵ_{HOMO} at different fractional numbers of electrons for the aqueous ruthenium and iron (Figure S3), and NVE simulations on aqueous ruthenium with QM/(AA+CG) model (Figure S4). This information is available free of charge via the Internet at <http://pubs.acs.org>

INTRODUCTION

Many fundamental processes in biology and chemistry such as electron transfer reactions usually occur in solution or enzymes rather than in gas phase. Because of the significant change in electronic structure of the molecular system and the complex environment with thousands of degrees of freedom, theoretical simulation of these processes requires an accurate and computationally efficient model. Multi-resolution methods developed in recent years attracted much attention as a very promising approach, in which different levels of resolution of a theoretical or computational model are combined to describe a system at different scales [1, 2, 3, 4, 5, 6]. In practice a multi-resolution method is a compromise between the computational cost and accuracy. Furthermore, a model that spans two or more levels of resolution faces another challenge on how to couple different types of interactions correctly and smoothly.

An example of multi-scale methods is the combined quantum mechanical and molecular mechanical (QM/MM) method first developed by Warshel and Levitt [1], in which the active site of the molecular system is described with highly accurate quantum theory, while the contribution of the rest of the system is described with an approximate, yet efficient molecular mechanical force field. The electrostatic interaction between QM and MM subsystems is the core of this method. In the common “electrostatic-embedding” approach, the contribution of the MM electrostatic potential is involved in the QM self-consistent field (SCF) calculation. The QM/MM method has been widely employed for decades with great success to simulate various types of biological and chemical reactions [2, 7, 8, 9, 10]. For example, it has been shown in our previous work that the “on-the-fly” ab initio QM/MM calculation with molecular dynamics (MD) sampling can be used to calculate the free energy differences for redox reactions in aqueous solution with satisfactory agreement with experimental data [11, 12, 13]. Particularly, it was observed that the MM electrostatic potential does not converge until the cutoff distance reaches 25 Å, indicating that the QM/MM long-range electrostatic interactions are much more significant on the oxidation process than other types of reactions. It was further found that the QM polarization effects become small when the MM atoms are more than 9–14 Å from the QM subsystem. Instead, the MM point charges at a long distance merely contribute by providing a static electrostatic potential [3, 11]. To avoid the technical complication associated with the Ewald-type methods within the QM/MM approach, a long cutoff distance was used in our previous redox free energy calculations. Therefore, the large class of hierarchical techniques, such as the fast-multipole approach [14], the continuum solvent model [15], and the hybrid fine-grained and coarse-grained (CG) method [16], could be useful for the modeling of MM subsystem to improve the accuracy and efficiency of QM/MM calculations.

Another promising multi-resolution method is to combine the all-atom (AA) force field with coarse-grained model, in which the environment part of system is described at the CG level more efficiently by reducing the number of degrees of freedom. The combination of AA and CG is more complicated and the division of the entire system into AA and CG parts is a current research topic. Several schemes have been proposed to couple the interactions at the AA and CG levels in different ways. Following the spirit of QM/MM methods, a straightforward idea so-called “mixed AA/CG model” is to select the resolution of particles

as either coarse-grained or fully atomistic in advance and then fix the identity during the MD simulations [17]. It has been applied into protein simulations with MM force fields, such as the hybrid AA/CG model that combines the GROMOS atomistic force field with the MARTINI coarse-grained force field [18], and the multilayer model in which an atomic-level layer of water molecules around proteins was solvated in supra-molecular coarse-grained waters [19]. The behavior of the proteins was found to be very sensitive to the strength of the electrostatic coupling between AA and CG particles. Moreover, unlike the QM/MM methods where the interactions between the QM and MM subsystems are well-defined, the interactions between the AA and CG particles have been less studied before and must require additional efforts to determine. To overcome these limitations, some advanced models have been proposed. In the adaptive resolution scheme developed by Praprotnik *et al.*, all particles within a small selected region in space are described with AA force fields while the particles within the environment region are described with CG models [20, 21]. A buffer region is set up so that particles within can gradually and smoothly alter their identities between two levels of model. In the mixed resolution interaction method developed by Izvekov *et al.*, the AA and CG forces are coupled based on the distance of inter-particle separations [22]. The all-atom structural description of the entire system is maintained during the simulations. Recently Shen and Hu developed an adaptive AA+CG multi-resolution method [23]. Similar to the mixed resolution interaction method [22], the interactions between two sites automatically adjusted during the simulations according to the distance. However, the energy functions instead of forces are coupled as a general Hamiltonian for the whole system in the AA+CG method, satisfying the conservation of energy and momentum without any constraint or compensation term. The simulations of protein systems have obtained consistent results between the fully atomistic and AA+CG models. Compared with the mixed AA/CG model, the parameters of the existing AA and CG force fields can be used directly without the need to determine new parameters for the interactions between the particles at different resolutions.

In this paper we developed a multi-resolution method that spans three levels of resolution with quantum mechanical, molecular mechanical all-atom, and coarse-grained models. We used the three-scale method to calculate the free energies for redox reactions of metal ions in aqueous solution. The redox center is described as the QM subsystem, and the environmental water molecules are described as the MM subsystem. Furthermore, the MM subsystem is treated at two levels of resolution, i.e., all-atom and coarse-grained levels, rather than just the all-atom force field. Our adaptive AA+CG water model is applied into the MM subsystem in the QM/MM method as a “QM/(AA+CG)” approach, in which the resolution of interactions between all particles is adaptively adjusted in the simulations. In this way, the long-range electrostatic interactions needed for redox potential calculations are more efficiently described than in the usual QM/MM approach. As analyzed by Sokkar *et al.* where the CG water models were introduced into the QM/MM calculations (see below), the savings of computational cost were typically 40–70% compared to the standard QM/MM calculation for a glycine-water system and 11–52% for two enzymes (chorismate mutase and *p*-hydroxybenzoate hydroxylase), strongly depending on the system for analysis, the QM level of theory and the model for MM water layer [16]. Generally speaking, the improvement of efficiency is mainly determined by the component of electrostatic QM/MM

interactions in the QM/MM calculation. Another important aspect of QM/(AA+CG) compared to the periodic QM/MM model using AA representation is the introduction of additional parameters and approximations at the CG level, which may lead to artificial errors on the estimated redox potentials and should be checked carefully during the simulations.

Recently another hybrid quantum mechanics/molecular mechanics/coarse-grained model for solvated biomolecular systems was reported by Sokkar *et al.*, in which the chemically important active site, the biomolecular environment and the solvent were respectively described by the QM theory, the atomistic MM force field and the coarse-grained water model [16]. Here we also use this three-layer model as a “QM/AA/CG” approach to calculate the redox potentials to make a comparison with the present QM/(AA+CG) method. The difference between the QM/(AA+CG) and QM/AA/CG is shown in Figure 1(a). In the QM/AA/CG model the water molecules close to the QM subsystem are described by all-atom TIP3P model, while the waters far away from the redox center are described by the supra-molecular coarse-grained model. Two existing coarse-grained water models, i.e., polarizable MARTINI water (PW) [24] and big multipole water (BMW) models [25], are applied at the CG level, which are named as QM/TIP3P/PW and QM/TIP3P/BMW, respectively.

The rest of this paper is organized as follows. We first review the resolution-adapted AA+CG method and the related water model briefly. The theory of three-level multi-resolution model, i.e., QM/(AA+CG), is then introduced, followed by the simulation details on the calculation on the redox potentials for aqueous metal ions by using the fractional number of electrons (FNE) approach and direct QM/MM MD sampling. Results and discussions with QM/(AA+CG) and QM/AA/CG models are also provided.

THEORY

Review on the AA+CG method

The main motivation of this work is to coarse-grain the charged particles far away from the QM subsystem with a model that spans all-atom and coarse-grained levels of resolution. The mixed resolution interaction method has been successfully applied to several systems such as the bulk water and phospholipid bilayer [22]. But the lack of a Hamiltonian description is a limitation to its application on the electrostatic-embedding QM/MM model. The resolution-adapted AA+CG method formulated in terms of a general Hamiltonian is more suitable for our study [23]. Here we briefly summarize this method and the related multi-resolution water model. In this model the interactions between atoms at a short distance are described at an explicit AA level, while the interactions at a long distance are modeled at a CG level. At the intermediate distance, however, the AA and CG interactions will be mixed together in a distance-dependent fashion. Assume that there is a unique and non-overlapping mapping between a specific set of atoms and a coarse-grained particle. The CG forces are redistributed to the atomic degrees of freedom, and consequently the molecular dynamics sampling is carried out in the atomic space.

The Hamiltonian of a molecular system of N atoms is written as

$$H = \sum_i^N \frac{p_i^2}{2m_i} + V(\mathbf{r}, \mathbf{R}), \quad (1)$$

where m_i and p_i are respectively the mass and momentum of the atom i , $\mathbf{r}$ and $\mathbf{R}$ denote respectively the positions of atoms and CG particles. The first term of Eq (1) is the kinetic energy described solely at the AA level. The second term is the mixed AA+CG potential energy that is subdivided into bonded covalent terms, restraining terms and nonbonded terms as follows

$$V = V^{\text{covalent}} + \sum_{\alpha} V_{\alpha}^{\text{rstr}} + \sum_{\alpha, \beta} V^{\text{nonb}}(R_{\alpha\beta}), \quad (2)$$

where $R_{\alpha\beta}$ is the distance between CG particles α and β . All of the covalent interactions, i.e., bonds, angles, and dihedrals, are described at the AA level. The second term of Eq (2) is the restraining potential energy to keep the interior AA geometry of CG particle α . The nonbonded interactions, i.e., electrostatic and van der Waals (vdW) interactions, depend on the distance between two CG particles; that is

$$\begin{aligned} V^{\text{nonb}}(R_{\alpha\beta}) &= [1 - \lambda^{\text{ele}}(R_{\alpha\beta})] V_{\text{CG}}^{\text{ele}}(R_{\alpha\beta}) + \lambda^{\text{ele}}(R_{\alpha\beta}) \sum_{i \in \alpha, j \in \beta} V_{\text{AA}}^{\text{ele}}(r_{ij}) + [1 - \lambda^{\text{vdW}}(R_{\alpha\beta})] V_{\text{CG}}^{\text{vdW}}(R_{\alpha\beta}) \\ &\quad + \lambda^{\text{vdW}}(R_{\alpha\beta}) \sum_{i \in \alpha, j \in \beta} V_{\text{AA}}^{\text{vdW}}(r_{ij}), \end{aligned} \quad (3)$$

where r_{ij} is the distance between atoms i and j . Note that i must be smaller than j in the summation terms on the right hand side when α and β are the same CG particle. The coupling functions $\lambda(R_{\alpha\beta})$ can be selected as different forms. For simplicity the cutoff coupling function is used as

$$\lambda(R_{\alpha\beta}) = \begin{cases} 1 & R_{\alpha\beta} \leq R_2 \\ 0 & R_{\alpha\beta} > R_2 \end{cases}. \quad (4)$$

A more complicated coupling function can be also used to allow smooth transition between two types of energy functions and forces [23]; namely,

$$\lambda(R_{\alpha\beta}) = \begin{cases} 1 & R_{\alpha\beta} < R_1 \\ 1 - 10s^3 + 15s^4 - 6s^5 & R_1 \leq R_{\alpha\beta} \leq R_2 \\ 0 & R_{\alpha\beta} > R_2 \end{cases}, \quad (5)$$

where

$$s(R_{\alpha\beta}, R_1, R_2) = \frac{R_{\alpha\beta} - R_1}{R_2 - R_1}, \quad (6)$$

and R_1 and R_2 are the boundaries of the transition region between AA and CG models.

In order to apply the above AA+CG scheme to water model, we make another assumption that in an aqueous system each water molecule can be treated as either a donor or an acceptor of the hydrogen bond (HB) between two water molecules. The restraining potential is applied in each water dimer as

$$V_{\alpha}^{\text{rstr}} = k_b (r_{\text{OO}} - r_0)^2 H(r_{\text{OO}} - r_0) + k_{a1} (a_{\text{OHO}} - a_1)^2 H(|a_1| - |a_{\text{OHO}}|) + k_{a2} (a_{\text{OOM}} - a_2)^2 + k_d (d_{\text{MOOH}} - d_0)^2. \quad (7)$$

Here the first term is the half-side distance restraint between two oxygen atoms in dimer α , which avoids two water molecules diffusing away from each other. The second term is the half-side angle restraint on the angle maintaining the quasi-linear chain along the hydrogen bond. The rest of Eq (7) are used to keep the water dimer as a rigid geometry shown in Figure 1(b), where M is the middle point of two hydrogen atoms in the acceptor of HB. H is the Heaviside step function [26], that is, $H(x) = 1$ when $x \geq 0$ and $H(x) = 0$ when $x < 0$, and k_b , r_0 , k_{a1} , a_1 , k_{a2} , a_2 , k_d and d_0 are parameters that have been fitted to reproduce the experimental properties of bulk water.

For the nonbonded interactions in Eq (2), the resolution is determined by the distance between the middle points of two oxygen atoms in one dimer. When two water dimers are close to each other, the nonbonded interactions at the AA level are described as the TIP3P model. That is

$$V_{\text{AA}}^{\text{ele}} = V_{\text{TIP3P}}^{\text{ele}}, \quad (8)$$

and

$$V_{AA}^{vdW} = V_{TIP3P}^{vdW}. \quad (9)$$

At a long distance between two dimers, each dimer is coarse-grained as two CG particles placed in the positions of the oxygen atoms with opposite charges as $\pm Q_w$. Therefore, the electrostatic interactions between α and β at the CG level can be expanded as

$$V_{CG,\alpha\beta}^{ele} = V_{\alpha_{O1}\beta_{O1}}^{ele}(r_{\alpha_{O1}\beta_{O1}}) + V_{\alpha_{O2}\beta_{O2}}^{ele}(r_{\alpha_{O2}\beta_{O2}}) + V_{\alpha_{O1}\beta_{O2}}^{ele}(r_{\alpha_{O1}\beta_{O2}}) + V_{\alpha_{O2}\beta_{O1}}^{ele}(r_{\alpha_{O2}\beta_{O1}}), \quad (10)$$

where α_{O1} , α_{O2} , β_{O1} and β_{O2} denote the oxygen atoms of the waters as the acceptor of HB in dimer α , the donor in dimer α , the acceptor in dimer β , and the donor in dimer β , respectively, and

$$V_{\alpha_{O_i}\beta_{O_j}}^{ele}(r_{\alpha_{O_i}\beta_{O_j}}) = (2\delta_{ij} - 1) \frac{Q_w^2}{r_{\alpha_{O_i}\beta_{O_j}}}, \quad (11)$$

where $\delta_{ij} = 1$ when $i = j$ and $\delta_{ij} = 0$ when $i \neq j$. The vdW interactions completely vanish at a long distance,

$$V_{CG}^{vdW} = 0. \quad (12)$$

The coupling function with plain cutoff in Eq (4) is applied for vdW interactions, and the complicated form in Eq (5) and (6) is used for electrostatic interactions.

Combination of QM/MM and AA+CG models

In the QM/MM model, the system is split into two subsystems. One is the QM subsystem containing the active site, the other is the MM subsystem containing the rest of the molecular system. The total potential energy of the QM/MM system is written as

$$V = E_{QM} + E_{QM/MM} + E_{MM}. \quad (13)$$

Here E_{QM} is the quantum mechanical energy of the QM subsystem, and E_{MM} is the standard molecular mechanical interactions involving exclusively atoms in the MM subsystem. For our aqueous system studied in this paper no covalent interaction exists between the QM and MM subsystems, so the QM/MM interaction is simplified as

$$E_{\text{QM/MM}} = E_{\text{QM/MM}}^{\text{ele}} + E_{\text{QM/MM}}^{\text{vdW}}. \quad (14)$$

The sum of E_{QM} and $E_{\text{QM/MM}}^{\text{ele}}$ can be obtained by ab initio methods as the eigenvalue of an effective Hamiltonian as follows

$$E_{\text{QM}} + E_{\text{QM/MM}}^{\text{ele}} = \langle \Psi | \hat{H}_0 + \sum_{l \in \text{MM}} q_l v_{\text{MM}}(\mathbf{r}_l) | \Psi \rangle, \quad (15)$$

where

$$v_{\text{MM}}(\mathbf{r}_l) = \sum_{k \in \text{QM}} \frac{Z_k}{|\mathbf{r}_k - \mathbf{r}_l|} - \int d\mathbf{r}' \frac{\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}_l|}, \quad (16)$$

$\hat{H}_0$ is the Hamiltonian of the QM subsystem in vacuum, $\rho(\mathbf{r}')$ is electron density of QM subsystem, Z_k is the charge of the nuclei of QM atoms, and q_l is the point charge of MM atoms. Note that in the QM/AA/CG scheme the value of q_l is obtained from all-atom molecular mechanical force field if atom l is close to the QM subsystem or coarse-grained force field if l is far away from the QM subsystem.

In the present QM/(AA+CG) model, the Hamiltonian of QM subsystem, i.e., $\hat{H}_0$, is preserved, while the QM/MM and MM interactions are changed into a multi-resolution scheme. Thus, the key point is how to express the adaptive multi-resolution effective Hamiltonian in Eq (15). As in the previous model with the pure MM force field, each particle in the MM region should be treated at two different resolutions at the same time. This means that the MM subsystem consists of CG particles, and each CG particle consists of atoms. The QM/MM electrostatic interactions are automatically adjusted during the simulations according to the distance between the QM subsystem and the corresponding MM site. Therefore, Eq (15) is rewritten as

$$E_{\text{QM}} + E_{\text{QM/MM}}^{\text{ele}} = \langle \Psi | \hat{H}_0 + H_{\text{QM/(AA+CG)}}^{\text{ele}} | \Psi \rangle, \quad (17)$$

where

$$H_{\text{QM/(AA+CG)}}^{\text{ele}} = \sum_{\alpha \in \text{CG}} \left\{ [1 - \lambda^{\text{ele}}(R_{\alpha 0})] Q_{\alpha} v_{\text{MM}}(\mathbf{R}_{\alpha}) + \lambda^{\text{ele}}(R_{\alpha 0}) \sum_{i \in \alpha} q_i v_{\text{MM}}(\mathbf{r}_i) \right\}. \quad (18)$$

Here Q_α is the point charge of CG particle α , q_i is the point charge of atom i belonging to CG particle α , $\mathbf{R}$ and $\mathbf{r}$ are respectively the positions of CG and AA particles, and v_{MM} is defined in Eq (16). The coupling function with the form in Eq (5) and (6) is applied in Eq (18). $R_{\alpha 0}$ denotes the distance between the QM subsystem and CG particle α , which can be defined in different ways according to the boundary type of the QM/MM system. In this paper the center of mass (COM) of the QM subsystem is used as a general choice; thus

$$R_{\alpha 0} = |\mathbf{R}_\alpha - \bar{\mathbf{R}}_{\text{QM}}|, \quad (19)$$

where

$$\bar{\mathbf{R}}_{\text{QM}} = \frac{\sum_{k \in \text{QM}} m_k \mathbf{r}_k}{\sum_{k \in \text{QM}} m_k}. \quad (20)$$

The QM/MM vdW interactions in Eq (14) are treated classically as

$$E_{\text{QM/MM}}^{\text{vdW}} = \sum_{\alpha \in \text{CG}} \left\{ [1 - \lambda^{\text{vdW}}(R_{\alpha 0})] V_{\text{CG}}^{\text{vdW}}(R_{\alpha 0}) + \lambda^{\text{vdW}}(R_{\alpha 0}) \sum_{i \in \alpha} V_{\text{AA}}^{\text{vdW}}(r_{ij}) \right\}, \quad (21)$$

in which Eq (4) and (12) are respectively applied as the coupling function and the CG vdW interactions for simplicity. The AA+CG water model described in the above subsection is used as the molecular mechanical interactions, i.e., E_{MM} , in Eq (13).

Based on Eq (13) and (14), the total force acting on atoms is written as

$$\mathbf{F} = - \frac{\partial (E_{\text{QM}} + E_{\text{QM/MM}}^{\text{ele}})}{\partial \mathbf{r}} - \frac{\partial (E_{\text{QM/MM}}^{\text{vdW}} + E_{\text{MM}})}{\partial \mathbf{r}}. \quad (22)$$

Here the second term on the right side is calculated classically whether the atom belongs to the QM or MM subsystem, which has been implemented in our previous work [23]. The first term is obtained from the electronic structure calculation at each MD step. If atom $k \in \text{QM}$, it can be written as

$$\begin{aligned}
& \frac{\partial (E_{\text{QM}} + E_{\text{QM/MM}}^{\text{ele}})}{\partial \mathbf{r}_k} = \frac{\partial \langle \Psi | \hat{H}_0 + \sum_{\alpha \in \text{MM}} Q_{\alpha} v_{\text{MM}}(\mathbf{R}_{\alpha}) | \Psi \rangle}{\partial \mathbf{r}_k} \\
& + \sum_{\alpha \in \text{MM}} \left[\lambda^{\text{ele}}(R_{\alpha 0}) \frac{\partial \langle \Psi | -Q_{\alpha} v_{\text{MM}}(\mathbf{R}_{\alpha}) + \sum_{i \in \alpha} q_i v_{\text{MM}}(\mathbf{r}_i) | \Psi \rangle}{\partial \mathbf{r}_k} \right] \\
& + \sum_{\alpha \in \text{MM}} \left\{ \left[-Q_{\alpha} v(\mathbf{R}_{\alpha}) + \sum_{i \in \alpha} q_i v(\mathbf{r}_i) \right] \frac{\partial \lambda^{\text{ele}}(R_{\alpha 0})}{\partial R_{\alpha 0}} \frac{\partial R_{\alpha 0}}{\partial \mathbf{r}_k} \right\}. \quad (23)
\end{aligned}$$

Here the sum of the first and second term can be calculated directly by any electronic structure program, and $v(\mathbf{R})$ and $v(\mathbf{r})$ in the last term are the electrostatic potentials generated by the nuclei and electrons of the QM subsystem at positions $\mathbf{R}$ and $\mathbf{r}$, respectively. That is

$$v(\mathbf{R}) = \langle \Psi | v_{\text{MM}}(\mathbf{R}) | \Psi \rangle. \quad (24)$$

On the other hand, if atom $I \in \text{MM}$, the first term of Eq (22) can be expressed analytically on the basis of the Hellman-Feynman theorem as follows

$$\begin{aligned}
& \frac{\partial (E_{\text{QM}} + E_{\text{QM/MM}}^{\text{ele}})}{\partial \mathbf{r}_l} \\
& = [1 - \lambda^{\text{ele}}(R_{\alpha 0})] Q_{\alpha} \frac{\partial v(\mathbf{R}_{\alpha})}{\partial \mathbf{R}_{\alpha}} \frac{\partial \mathbf{R}_{\alpha}}{\partial \mathbf{r}_l} + \lambda^{\text{ele}}(R_{\alpha 0}) q_l \frac{\partial v(\mathbf{r}_l)}{\partial \mathbf{r}_l} \\
& + \left[-Q_{\alpha} v(\mathbf{R}_{\alpha}) + \sum_{i \in \alpha} q_i v(\mathbf{r}_i) \right] \frac{\partial \lambda^{\text{ele}}(R_{\alpha 0})}{\partial R_{\alpha 0}} \frac{\partial R_{\alpha 0}}{\partial \mathbf{r}_l}, \quad (25)
\end{aligned}$$

where α is the CG particle including atom I , $v(\mathbf{R})/\mathbf{R}$ and $v(\mathbf{r})/\mathbf{r}$ are the electrostatic fields at positions $\mathbf{R}$ and $\mathbf{r}$, respectively. Both the electrostatic potential and field can be obtained directly from the ab initio calculation. In the last term of Eq (23) and (25), $\lambda^{\text{ele}}/R_{\alpha 0}$ is calculated by Eq (5) and (6), and $R_{\alpha 0}/\mathbf{r}$ is calculated by Eq (19) and (20).

Redox potential calculation using the fractional electron approach

In this paper we applied the QM/(AA+CG) model described in previous sections to the redox potential calculation based on the fractional number of electrons approach. We aim to calculate the free energy change when one electron is removed from the electron donor group to simulate the half reaction of electron transfer, such as

where M is Fe or Ru. As implemented in the previous work [11], the fractional number of electron can be selected as the order parameter to drive the system from the reduced state to

the oxidized state and achieve efficient sampling of redox free energy by changing the number of electrons in the system gradually. According to the Janak theorem and its extension to generalized Kohn-Sham calculations [27, 28], the energy derivative with respect to the number of electrons is written as

$$\frac{\partial E}{\partial \eta} = -\epsilon_{\text{HOMO}}, \quad (27)$$

where $\eta \in [0, 1]$ is the fractional number of electrons removed from the HOMO. Note that the minus sign should be introduced on the right side of Eq (27) because the occupation number of the orbital is actually $1-\eta$. The free energy difference in Eq (26) can be obtained from direct QM/MM MD simulations combined with the thermodynamic integration (TI) method. That is

$$\Delta A = \int_0^1 \left\langle \frac{\partial E}{\partial \eta} \right\rangle_{\eta} d\eta = - \int_0^1 \langle \epsilon_{\text{HOMO}} \rangle_{\eta} d\eta. \quad (28)$$

As reported before, the FNE-TI method has been applied successfully to compute the redox potential of metal ions in aqueous solution with the all-atom TIP3P water model [11].

SIMULATION DETAILS

Hexaaquo ruthenium and iron cations, $\text{Ru}(\text{H}_2\text{O})_6^{2+/3+}$ and $\text{Fe}(\text{H}_2\text{O})_6^{2+/3+}$, were selected as the two test systems to evaluate the performance of our approach. The QM regions in both systems were defined as the central metal cation with six coordinating water molecules. The initial geometries of the complexes were optimized in the gas phase. In the QM/(AA+CG) method the QM subsystem were further solvated by 8638 water molecules (i.e., 4319 water dimers) treated by the resolution-adapted AA+CG water model. To make comparison, the QM/AA/CG model was implemented on the basis of the all-atom TIP3P and coarse-grained PW or BMW water models, employing the hexaaquo metal complex as the QM subsystem and 515 TIP3P water molecules in a droplet of 15.5 Å radius with additional distance restraints (see below). The rest of systems were then four-to-one mapped to the polarizable supra-molecular coarse-grained waters [29]. All the systems were put in a cubic box of $64 \times 64 \times 64 \text{ Å}^3$ under periodic boundary conditions.

Spin-unrestricted DFT calculations were implemented by using the BLYP exchange-correlation functional and LanL2DZ effective core potential basis set for the QM subsystem [30, 31, 32]. The vdW interactions between the QM and MM subsystems were described with the same parameters in our previous work [11]. The QM/MM electrostatic interactions were described by Eq (15) and (16), in which the point charges on MM water molecules were determined based on the AA+CG or AA/CG water model. All the parameters of AA+CG water model are listed in Table 1. These parameters of the CG model were determined to reproduce several experimental quantities of bulk water, involving the density, the

dielectric permittivity and the radial distribution functions (RDF) of oxygen-oxygen, oxygen-hydrogen and hydrogen-hydrogen pairs. It was also found by Shen and Hu that the properties of proteins can be described as well as with TIP3P model under this set of parameters (unpublished work). For the interactions between water molecules, the transition region in which the AA and CG interactions were mixed together spans from 6 to 9 Å, i.e., $R_1^{\text{MM}}=6$ Å and $R_2^{\text{MM}}=9$ Å in Eq (4), (5) and (6). For the QM/MM interactions, the coupling functions were determined by the distance between MM particles and the center of mass of QM subsystem. On account of the volume of QM subsystem, a distance of 3 Å was added to the transition region, i.e., $R_1^{\text{QM/MM}}=9$ Å and $R_2^{\text{QM/MM}}=12$ Å. The nonbonded interactions at the CG level vanish at the cutoff distance as 25 Å. In the mixed AA/CG water model, the interactions between AA waters were described by the TIP3P model [33], and the CG-CG interactions were calculated based on the parameters reported in the original papers [24, 25]. The charged AA and CG particles interact via the Coulombic energy function between point charges with a relative dielectric permittivity $\epsilon_{\text{mix}}(\text{AA-CG})$. As a result, q_i in Eq (15) should be replaced by $q_i/\epsilon_{\text{mix}}$. The values of ϵ_{mix} varied from $\epsilon_r(\text{AA-AA})$ to $\epsilon_r(\text{CG-CG})$ to adjust the AA-CG electrostatic coupling. In the TIP3P/PW model ϵ_{mix} was set as 1.45, 1.75 and 2.50, and in the TIP3P/BMW model ϵ_{mix} was set as 1.00, 1.10 and 1.30 [18]. The vdW AA-CG interactions were determined by Lennard-Jones potentials based on the parameters in the TIP3P and MARTINI force field [34, 35]. In order to keep the AA water molecules around the redox center, attractive harmonic distance restraints were applied between the oxygen atoms of the AA waters and the COM of QM subsystem with a distance larger than 15.5 Å. The force constant for the distance restraints was set to 0.25 kcal mol⁻¹ Å⁻² in each case. The cutoff distances for the vdW and electrostatic interactions between all types of particles were 12 and 25 Å, respectively, for both QM/AA/CG models.

All the MD simulations have been carried out for 50 ps after equilibration for 5 ps, which was observed as long enough for both systems to achieve equilibrium and sufficient sampling in each QM/MM model [11]. Note that the mean residence times of water molecules in the first solvation shells for $\text{Ru}(\text{H}_2\text{O})_6^{2+/3+}$ and $\text{Fe}(\text{H}_2\text{O})_6^{2+/3+}$ are much longer than the simulation time, varying from hundreds of nanoseconds to one day [36]. Therefore, it is unnecessary to consider the water exchange between the QM and MM subsystems in our case. The integration time step was set as 1 fs. Six windows with different values of FNE, i.e., $\eta = 0.0, 0.2, 0.4, 0.6, 0.8$ and 1.0, were used in the thermodynamic integration simulation. The system temperature was maintained at 300 K by a Berendsen thermostat [37]. All the calculations were performed by an in-house QM4D program package [38] combined with a modified version of GAUSSIAN 03 program [39] for the QM calculations with FNE.

RESULTS AND DISCUSSIONS

Structural properties

The initial geometries of hexaaquo ruthenium and iron cations were optimized in the gas phase with the same ab initio model. The metal oxygen radial distribution functions were subsequently obtained from the direct QM/MM MD simulations with the full all-atom

QM/MM (i.e., QM/TIP3P), QM/TIP3P/PW with $\epsilon_{\text{mix}} = 1.45$, QM/TIP3P/BMW with $\epsilon_{\text{mix}} = 1.00$ and QM/(AA+CG) models. The positions of the first peak of RDF for both ions are nearly the same in the four models. As shown in Table 2 and Figure 2, the ruthenium cations form stable octahedral complexes with average Ru-O bond distances of 2.18 Å for Ru(II) and 2.08 Å for Ru(III). The results are similar to the previous computations by the Car-Parrinello molecular dynamics as 2.18 Å for Ru(II) and 2.10 Å for Ru(III), in which the whole system was treated quantum mechanically [40]. The experimental values of Ru-O bond length are 2.12 and 2.03 Å in the reduced and oxidized states, respectively [41]. Despite the overestimation of the Ru-O distance in our simulations, the difference between two oxidation states was produced accurately. A clean separation between the first and the second solvation shell was observed from the disappearance of RDF, which starts from 2.43 and 2.29 Å for Ru(II) and Ru(III), respectively, and ends at about 3.6 Å. There might be a negligible difference that the positions of the second peak of Ru(III)-O RDF are slightly smaller in the QM/(AA+CG) model than that in QM/TIP3P, indicating a stronger interaction between the QM and MM subsystems with the presence of AA+CG waters. As shown in Table 2 and Figure 3, the average Fe-O bond distances in the octahedral iron cations are 2.03 Å for Fe(II) and 1.94 Å for Fe(III). Compared with the experimental values as 2.12 Å for Fe(II) and 1.99 Å for Fe(III) [42], our simulations overbinds the iron cations in both oxidation states, which might be attributed to the different conditions between experiment in crystal and theoretical simulations in aqueous or the error in the DFT calculation [43, 44]. The iron-oxygen RDF vanishes between the first and the second solvation shell, starting from 2.28 and 2.15 Å for Fe(II) and Fe(III), respectively, and ending at about 3.5 Å. In addition, the RDF obtained by QM/TIP3P/PW and QM/TIP3P/BMW with other values of ϵ_{mix} were consistent with that shown above for all systems (see Figures S1 and S2 in Supporting Information). It is evident from the structural properties that the QM/MM short-range interactions are almost independent of the water models used here.

Redox free energies with QM/(AA+CG) model

As listed in Table 3, the experimental redox potentials of $\text{Ru}(\text{H}_2\text{O})_6^{2+/3+}$ and $\text{Fe}(\text{H}_2\text{O})_6^{2+/3+}$ are 0.230 and 0.771 eV, respectively [45]. Since the experimental values were measured relative to the standard hydrogen electrode (SHE), the absolute SHE potential should be added to the experimental electrode potentials. However, its measurement is currently disputable with a range from 4.20 to 4.84 eV [11]. In this paper the value of the absolute SHE potential was set as 4.28 eV suggested by Kelly *et al.* [46, 47], so the experimental values of the absolute redox potentials are 4.51 eV for aqueous ruthenium with the uncertainty from the absolute SHE as 14% and 5.05 eV for aqueous iron with the uncertainty as 13%, respectively. Applying our QM/(AA+CG) model into the FNE-TI approach, the redox potential of aqueous $\text{Ru}(\text{H}_2\text{O})_6^{2+/3+}$ was calculated as 4.57 eV, and that of aqueous $\text{Fe}(\text{H}_2\text{O})_6^{2+/3+}$ was 5.09 eV. On one hand, the absolute values of redox potentials may not be physically meaningful [43, 48] due to not only the uncertainty of the experimental number but also the ion-dipole interactions between the QM and MM subsystems that artificially shift the absolute potential in the simulation box. On the other hand, the difference between the redox potentials of the two redox species, i.e., G , is

independent of the absolute value of the SHE potential and measured as 0.54 eV experimentally. The result obtained from the QM/(AA+CG) model is 0.52 eV, which is in excellent accordance with the experimental values and better than that obtained by using the QM/TIP3P model in our previous work as 0.68 eV (5.14 eV for ruthenium and 5.82 eV for iron) [11].

Additional calculations were implemented for the validation of simulations. First, the simulations with different cutoff distances at the CG level were performed. The data shown in Figure 4 indicate that the long-range electrostatic potential has converged after 25 Å. Second, five additional windows, i.e., $\eta = 0.1, 0.3, 0.5, 0.7$ and 0.9 in FNE, were applied to check the convergence of thermodynamic integration simulations. The redox potentials of aqueous ruthenium and iron were estimated as 4.59 and 5.12 eV, respectively. Thus, six windows from $\eta = 0.0$ to 1.0 are sufficient for thermodynamic integration in our case even if the free energy change between two oxidation states is quite large. It is consistent with the linear relationship between the fractional numbers of electrons and the ensemble average of ϵ_{HOMO} , which can be seen from Figure S3 in Supporting Information under the QM/(AA+CG) model and Figure 3 in Ref [11] under the all-atom QM/MM model. Finally, the NVE simulations on aqueous ruthenium(II) were carried out for 6,000 steps with the integration time step as 1 fs by using the QM/(AA+CG) model, showing a small energy drift of the total system as $0.05 \text{ kcal mol}^{-1}$, i.e., $4 \times 10^{-7} \text{ kcal mol}^{-1}$ per atom per picosecond (see Figure S4 in Supporting Information).

Two possible factors in our AA+CG water model may play a part in the difference between the results obtained by using TIP3P and AA+CG water models. One is the potentials in Eq (7) used to keep the geometry of water dimers. The accuracy of the simulations with the bundled waters is currently disputable [49]. Here we added the same restraints to the TIP3P water molecules and performed the all-atom QM/MM calculation on the redox potential for aqueous ruthenium. The result as 5.17 eV was very similar to that obtained with the unrestrained QM/TIP3P model (5.14 eV), indicating that the influence of the additional restraints can be neglected. Another key factor is the QM/MM long-range electrostatic interactions determined by the parameters of water model. Although the parameterization can be performed analytically based on the existing all-atom force field [50], the values in the present model were alternatively fitted to reproduce the experimental data of the bulk water and captured several properties as well as TIP3P model. Especially, the oxygen-oxygen RDF was found to be more consistent with the experimental results than that obtained with TIP3P (unpublished work). It should be also noted that the TIP3P water model was developed based on the simulations performed with 125 water molecules and a cutoff distance of 7.5 Å [33], which may place a limit on the long-range interactions and introduce artifacts. For example, the use of the long cutoff distance of 18 Å can lead to a spurious result during the simulation of bulk water with TIP3P model [51]. It highlights the importance of evaluating the existing water models beforehand for the simulations of electron transfer or charge transfer processes with a large electrostatic interacting distance. The present AA+CG water model is a possible solution in these cases.

One important purpose of the introduction of coarse-grained model is to reduce the computational cost of QM/MM calculations. Here we measured the average computation

times for one MD step for the Ru(II) and Ru(III) systems with different basis sets of QM calculations. All calculations were performed in serial mode on Intel Xeon E5-2620 2.4 GHz CPU. As shown in Table 4, the computational costs of the QM/(AA+CG) model are reduced by 25–30% compared to the usual QM/MM calculation with TIP3P water model. The improvement is due to the significant decrease in the number of point charges in the QM Hamiltonian, since the water dimer far away from the active site was described by two point charges in our AA+CG model rather than six point charges in the TIP3P water model. The computational savings could be even larger if combined with the semi-empirical QM methods in which the component of electrostatic QM/MM interactions is dominant [16, 52], or the accelerated MD algorithms such as the extended Born-Oppenheimer MD [53] and the multiple time step method [23, 54].

Redox free energies with other QM/AA/CG models

To compare our AA+CG approach with the existing coarse-grained force field, the redox potentials were further simulated by using the QM/TIP3P/PW and QM/TIP3P/BMW models. The strength of the electrostatic coupling between AA and CG particles could be adjusted through the relative dielectric permittivity $\epsilon_{\text{rmix}}(\text{AA-CG})$. Furthermore, the change of ϵ_{rmix} should be synchronous for the electrostatic interactions between the QM subsystem and the charged CG particles in the QM/AA/CG model. The results of QM/TIP3P/PW and QM/TIP3P/BMW are listed in Table 5. The values used for the relative dielectric permittivity was 1.00 for the AA-AA interactions and 2.50 for CG-CG interactions in the QM/TIP3P/PW model [24]. The redox potentials with $\epsilon_{\text{rmix}} = 1.45$ were respectively 4.84 and 5.05 eV for ruthenium and iron, and the difference between the redox potentials of the two redox species was 0.21 eV, which was underestimated compared with the experimental values and the calculations with the QM/TIP3P and QM/(AA+CG) models. The results with $\epsilon_{\text{rmix}} = 1.75$ and 2.50 also conflicted with the experimental values. In the QM/TIP3P/BMW model, the relative dielectric permittivity was set as 1.00 for the AA-AA interactions and 1.30 for the CG-CG interactions [25]. The redox potentials with $\epsilon_{\text{rmix}} = 1.00$ were calculated as 4.80 and 5.14 eV for ruthenium and iron, respectively, with an underestimated G as 0.34 eV. The errors of calculations with $\epsilon_{\text{rmix}} = 1.10$ and 1.30 are larger. On the whole, the redox potentials calculated by the QM/AA/CG approach, including the absolute values and the difference between two half-reactions, are less accurate than the QM/(AA+CG) approach. Only the QM/TIP3P/BMW model with $\epsilon_{\text{rmix}} = 1.00$ produced the results with an error in the order of 0.2 eV.

The coupling between AA and CG particles should be responsible for the error of QM/AA/CG model. Here we considered two factors. One is the distance restraints applied at the AA/CG boundary to keep the AA water molecules around the active site. In the QM/TIP3P/PW model with $\epsilon_{\text{rmix}} = 1.45$, the average restraint energies per TIP3P water molecule were calculated as 0.06, 0.06, 0.08 and 0.09 kcal/mol for the Ru(II), Ru(III), Fe(II) and Fe(III) systems, respectively. In the QM/TIP3P/BMW model with $\epsilon_{\text{rmix}} = 1.00$, the values were 0.12, 0.13, 0.14 and 0.13 kcal/mol for the Ru(II), Ru(III), Fe(II) and Fe(III) systems, respectively. It decays quickly with the increase of ϵ_{rmix} (see Table S1 in SI). All the numbers are smaller than the thermal energy per degree of freedom at the simulated temperature and negligible compared to the total potential energy of the systems, indicating

that the influence of the distance restraints can be ignored. Another factor is the electrostatic coupling between AA and CG particles, which remains to be explored. For example, the hybrid AA/CG model with PW or BMW was found to be very sensitive to the strength of the AA-CG electrostatic coupling, and the accurate results on the charged or polar system were difficult to obtain by adjusting ϵ_{mix} [18]. In the present QM/AA/CG models, the external electrostatic potentials generated by solvent molecules at the center of the QM subsystems were different from that obtained with the QM/(AA+CG) model except QM/TIP3P/BMW with $\epsilon_{\text{mix}} = 1.00$ (see Table S2 in SI), which was consistent with the errors on calculated redox potentials. We thus attributed the error to the QM/MM electrostatic interactions provided by the CG waters. It can be remedied by the re-parametrization on the CG water models used here or the application of other models developed recently [55, 56, 57, 58].

Possible further improvements

Several improvements can be further made on the current approach. As studied in our previous work, the nonpolarizable model for the MM solvent is an important source of error in the simulation on the electron transfer process, especially for the reorganization energy calculation [11, 13]. In this work the response to the significant change of the local electric field is also absent since it does not allow for redistribution of the MM charges near the redox center. Therefore, the all-atom polarizable water models, such as the inducible point dipole model [59, 60], the model with Drude oscillators [61, 62], and the fluctuating charge model [63, 64] can be employed into the multi-resolution approach as the fourth level. Inspired by the QM/(AA+CG) and QM/AA/CG models, the water molecules close to the redox center could be described by the polarizable model, while the rest of system could be described by the AA+CG water model. Another extension is to combine this water model with the QM/MM-MFEP method [12, 65] instead of the direct QM/MM MD used in this paper, which would lead to further enhanced efficiency due to not only the reduction in the number of background charges in the QM Hamiltonian but also the long-time MD sampling on the MM subsystem required by QM/MM-MFEP. The present QM/(AA+CG) method can be also applied to calculate the redox properties of metalloprotein in the wild type and mutation variants [66]. But two issues should be addressed at first. One is the systematic benchmark by changing the ligand or metal to check the transferability of QM/(AA+CG), for which the error from different sources of uncertainty such as DFT functional, water model, finite system size and periodic boundary effects should be separated carefully [43, 44]. Another is the parameterization on the CG nonbonded interactions between the multi-resolution water molecules and the ligands or amino acids in protein.

CONCLUSIONS

In conclusion, we developed a multi-resolution QM/(AA+CG) model that spans three levels of resolution with quantum mechanical, molecular mechanical all-atom, and coarse-grained models, in which the resolution-adaptive AA+CG water model is combined with the QM/MM method. It has been performed to calculate the redox potentials of $\text{Ru}(\text{H}_2\text{O})_6^{2+/3+}$ and $\text{Fe}(\text{H}_2\text{O})_6^{2+/3+}$ aqueous complexes by using the FNE-TI approach. The absolute redox potentials were evaluated to be 4.57 and 5.09 eV for aqueous ruthenium and iron,

respectively, leading to the difference between the redox potentials of the two redox species as 0.52 eV, which is in excellent accordance with the experimental value as 0.54 eV.

Another multi-resolution model so-called QM/AA/CG has been also implemented to make comparison. In the QM/AA/CG model, the MM atoms close to the QM subsystem are described at the AA level, while the particles far away from the active site are described at the CG level. The results were less accurate by using the all-atom TIP3P and coarse-grained PW or BMW models, which highlight the importance of modification on the existing CG water models for QM/MM electrostatic interactions. This work opens up the possibility for QM/MM simulations combined with the hybrid all-atom and coarse-grained models on large-scale biochemical systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Schematic representations of QM/(AA+CG) and QM/AA/CG models. (b) Schematic representations of resolution-adaptive AA+CG water model. All-atom water dimer is coarse-grained as two charged particles placed in the positions of the oxygen atoms. The acceptor and donor of the hydrogen bond are respectively assigned by a charge as $\pm Q_w$ at the CG level.

Figure 2.

Ruthenium–oxygen radial distribution functions of aqueous ruthenium in the reduced (left) and oxidized (right) states. Different colors represent different models (blue, QM/TIP3P; red, QM/(AA+CG); orange, QM/TIP3P/BMW with $\epsilon_{\text{mix}} = 1.00$; green, QM/TIP3P/PW with $\epsilon_{\text{mix}} = 1.45$).

Figure 3.

Iron-oxygen radial distribution functions of aqueous iron in the reduced (left) and oxidized (right) states. Different colors represent different models (blue, QM/TIP3P; red, QM/(AA +CG); orange, QM/TIP3P/BMW with $\epsilon_{\text{mix}} = 1.00$; green, QM/TIP3P/PW with $\epsilon_{\text{mix}} = 1.45$).

Figure 4. Dependence of the redox potentials of the aqueous ruthenium and iron complexes on the cutoff distance. Different colors and shapes represent different systems (blue square, ruthenium; red diamond, iron).

Table 1

Parameters in the resolution-adaptive AA+CG water model.

Parameters	Values
k_b (kcal mol ⁻¹ Å ⁻²)	8.0
k_{a1} (kcal mol ⁻¹ rad ⁻²)	8.0
k_{a2} (kcal mol ⁻¹ rad ⁻²)	8.0
k_d (kcal mol ⁻¹ rad ⁻²)	8.0
r_0 (Å)	3.10
a_1 (degree)	171.0
a_2 (degree)	123.5
d_0 (degree)	180.0
Q_w	0.21

Table 2

Average metal-oxygen bond lengths with uncertainties in parentheses of aqueous ruthenium and iron in the reduced and oxidized states calculated with all-atom QM/MM, QM/(AA+CG), QM/TIP3P/BMW ($\epsilon_{\text{mix}} = 1.00$) and QM/TIP3P/PW ($\epsilon_{\text{mix}} = 1.45$) models. Bond length units are in Å.

	TIP3P	AA + CG	TIP3P/BMW	TIP3P/PW
$\text{Ru}(\text{H}_2\text{O})_6^{2+}$	2.179 (0.006)	2.170 (0.008)	2.175 (0.008)	2.176 (0.004)
$\text{Ru}(\text{H}_2\text{O})_6^{3+}$	2.080 (0.009)	2.073 (0.008)	2.079 (0.006)	2.078 (0.008)
$\text{Fe}(\text{H}_2\text{O})_6^{2+}$	2.034 (0.004)	2.030 (0.007)	2.034 (0.007)	2.031 (0.006)
$\text{Fe}(\text{H}_2\text{O})_6^{3+}$	1.941 (0.002)	1.938 (0.007)	1.941 (0.005)	1.939 (0.002)

Table 3

Comparison of the redox potentials of the aqueous ruthenium and iron calculated with all-atom QM/MM and QM/(AA+CG) methods to experiments. Energy units are in electron-volts (eV).

	G^{expt}	$\Delta G_{\text{abs}}^{\text{expt}}$	G^{TIP3P}	$G^{\text{AA+CG}}$
$\text{Ru}(\text{H}_2\text{O})_6^{2+/3+}$	0.230 ^a	4.51 (4.4–5.1) ^b	5.14 ^c	4.57 ^d
$\text{Fe}(\text{H}_2\text{O})_6^{2+/3+}$	0.771 ^a	5.05 (5.0–5.6) ^b	5.82 ^c	5.09 ^d
G		0.54	0.68 ^c	0.52 ^d

^aExperimental values for standard electrode potentials (SHE) from Ref [45].

^bThe experimental absolute redox potentials are obtained by taking the absolute SHE potential as $\Delta G_{\text{abs}}^{\text{SHE}} = 4.28$ eV. The minimum and maximum values are also listed in parentheses with the range of $\Delta G_{\text{abs}}^{\text{SHE}}$ from 4.20 to 4.84 eV.

^cSee Ref. [11].

^dResults in this work.

Table 4

Average CPU times (second) for one MD step with computational savings (% , in parenthesis) of all-atom QM/MM and QM/(AA+CG) simulations on aqueous ruthenium complex with different basis sets.

	$\text{Ru}(\text{H}_2\text{O})_6^{2+}$		$\text{Ru}(\text{H}_2\text{O})_6^{3+}$	
	QM/MM	QM/(AA+CG)	QM/MM	QM/(AA+CG)
LanL2DZ	65	46 (29)	66	48 (27)
SDD	84	63 (25)	88	65 (26)
LanL2DZ + 6-31G(d) ^a	92	65 (29)	94	71 (24)
LanL2DZ + cc-pVDZ ^b	135	98 (27)	144	106 (26)

^aLanL2DZ for Ru and 6-31G(d) for O and H.

^bLanL2DZ for Ru and cc-pVDZ for O and H.

Table 5

Redox potentials of the aqueous ruthenium and iron calculated with QM/TIP3P/PW and QM/TIP3P/BMW methods by varying $\epsilon_{\text{rmix}}(\text{AA-CC})$. Energy units are in electron-volts (eV).

ϵ_{rmix}	TIP3P/PW				TIP3P/BMW			
	1.45	1.75	2.50	1.00	1.10	1.30	1.10	1.30
Ru (H ₂ O) ₆ ^{2+/3+}	4.84	5.43	6.17	4.80	5.39	5.76		
Fe (H ₂ O) ₆ ^{2+/3+}	5.05	5.65	6.39	5.14	5.64	6.01		
<i>G</i>	0.21	0.22	0.22	0.34	0.25	0.25		