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Flexible-Boundary Quantum-Mechanical/ Molecular-Mechanical Calculations: Partial Charge Transfer between the Quantum-Mechanical and Molecular-Mechanical Subsystems

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Abstract: Based on the principle of electronic chemical potential equalization, we propose a flexible-boundary scheme to account for partial charge transfers between the quantum-mechanical (QM) and molecular-mechanical (MM) subsystems in combined QM/MM calculations. The QM subsystem is viewed as an open system with a fluctuating number of electrons and is described by a statistical mixture of ensemble that consists of states of integer number of electrons. The MM subsystem serves as a reservoir that exchanges electrons with the QM subsystem. The electronic chemical potential of the MM subsystem varies whenever charges flow in or out, until equilibrium is established for the electronic chemical potentials between the QM and MM subsystems. Our scheme is demonstrated by calculations of the partial atomic charges for 7 small model systems, each consisting of a singly charged ion and a water molecule, as well as for the Eigen cation, a model system for the solvated structure of hydronium ion in water. Encouraging results are obtained for the partial atomic charges, which are in reasonable agreement with full-QM calculations on those model systems. The averaged mean unsigned deviations between the QM/MM and full-QM calculations are 0.16 e for the partial atomic charges of the entire systems and 0.13 e for the amount of charge transferred between the QM and MM subsystems.

I. Introduction

In combined quantum-mechanical and molecular-mechanical (QM/MM)[1−15] calculations, the entire system (ES) is often partitioned into a small and localized primary system (PS) and its surroundings called secondary system (SS). The PS is treated at the quantum-mechanics (QM) level of theory. The SS, which is modeled at the molecular mechanics (MM) level, interacts with the PS and affects its electronic structure. The PS is also called the QM subsystem, and the SS is also known as the MM subsystem. The QM/MM energy for the entire system (ES) can be formally defined as the sum of the QM energy of the PS, the MM energy of the SS, and the QM/MM interaction energy between them.

$$E(\text{QM/MM;ES}) = E(\text{QM;PS}) + E(\text{MM;SS}) + E(\text{QM/MM;PS}|\text{SS}) \quad (1)$$

The inclusion in eq 1 of the interactions between the PS and its surroundings (the SS) is a key issue in the QM/MM methodology.

The interactions between the PS and the SS include bonded interactions, van der Waals interactions, and electrostatic interactions. A given bonded interaction, if presented, is often included at the MM level if it involves at least an SS atom, and the van der Waals interactions are typically evaluated at the MM level. The treatment for electrostatic interactions varies in different QM/MM schemes.[16] The first category is the mechanical-embedding schemes,[16] where the electrostatic interactions between the PS and SS are computed at the MM level, e.g., by Coulomb's law employing atomic charges assigned to both the PS and SS atoms, and the QM

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calculations for the PS are performed in the gas phase. In the second category of electrostatic-embedding schemes,[16] QM computations for the PS that are carried out with the inclusion of charge distribution of the SS, which is done by including in the QM Hamiltonian the operators that describe the electrostatic interaction between the nuclei and electrons of the PS and the MM partial atomic charges of the SS. The use of the MM partial atomic charges is convenient and popular, but more sophisticated representations of the SS charge density including distributed multipoles and the effective fragment potential[17] have also been developed. Today, most QM/MM implementations are electrostatic-embedding. The third class of embedding schemes is called self-consistent mutual-polarized-embedding schemes[16] or polarized-embedding schemes for short. In the polarized-embedding schemes, the PS and SS will polarize each other until their charge distributions are self-consistent. A number of studies[1,2,16,18−31] have been carried out to develop polarized-embedding QM/MM schemes by combining the commonly used unpolarizable MM potentials (such as AMBER,[32] CHARMM,[33] and OPLS-AA[34−39]) with classical polarization models.[19,40−52] The basic idea is similar to reaction field theory, although the response is now given by a discrete model incorporating the atomic polarizability of individual SS atoms instead of by a continuum. Employing polarization models[19,42−44] based on the principle of electronegativity equalization[53,54] to account for the flexibility of charge redistribution in the SS, we[31] recently developed the polarized-boundary redistributed charge scheme and polarized-boundary redistributed charge and dipole scheme; both schemes permit the mutual polarizations between the PS and SS near the QM/MM boundary.

It is of interest to further develop embedding schemes that permit fractional (or whole) charges flow between the PS and SS. Such treatments, which can be called flexible-boundary embedding schemes, account for both mutual polarization and charge transfer between the PS and SS and are in principle even more realistic than the polarized-boundary embedding schemes. For flexible-boundary embedding calculations, one needs an algorithm that describes the electronic structure of a quantum system with fractional electrons and a prescription that determines how much charge should be transferred between the quantum and classic mechanical subsystems.

Gogonea and Merz (GM)[55,56] have proposed a combined quantum-mechanical/Poisson−Boltzmann equation approach to study the charge transfer between ions and a solvent medium treated as a dielectric continuum. In the GM treatment, the charge being transferred is represented by a surface charge density at the dielectric interface, which modifies the boundary condition for which the Poisson−Boltzmann equation is solved. The ions are described by an effective QM Hamiltonian that resembles Dewar's half-electron method[57,58] but with subtle differences in handling the electron−electron repulsion term. The self-consistent QM calculations are carried out in terms of the density matrix by adding electron density to the LUMO (in the case of charge transferred to ions) or by subtracting electron density from the HOMO (in the case of charge transferred to solvent). The amount of charge being transferred is deter-

mined variationally subject to the criterion of the free energy including the environment.

Tavernelli, Vuilleumier, and Sprik (TVS)[59] proposed another scheme that can potentially be adapted to handle fractional charge transfer between the PS and SS in the QM/MM calculations. Their method, which is called the grand-canonical molecular dynamics method, can be traced back to the treatment of fractional particle number of electrons in density function theory by Perdew, Parr, Levy, and Balduz (PPLB).[60] The TVS scheme models the exchange of electrons between a molecule and a reservoir of fixed chemical potential by a modification of the Car−Parrinello[61] method allowing for fluctuating numbers of electrons under constraints of fixed electronic chemical potential. The molecular dynamics simulations involve multiple diabatic potentials energy surfaces where each surface corresponds to a system with a strictly integer number of electrons, e.g., a surface for the reduced state whose charge is 0 and a surface for the oxidized state whose charge is +1 e. Thermochemical properties in a molecular dynamics run were computed by a weighted average of the partition functions for the two oxidation states; in other words, one avoids treating a fractional number of electrons by moving the system on an effective (adiabatic) potential that is a weighted average of diabatic potential surfaces corresponding to integer numbers of electrons. The weights are determined by the chemical potential and the mole fraction of the cations. This provides a more justifiable treatment of electron exchange, but it has been criticized[62] because of the need for a uniform background charge.

Both the GM[55,56] method and the TVS[59] method can in principle be adapted to be used in the flexible-boundary QM/MM methodology. It is conceptually straightforward to replace the Poisson−Boltzmann equation for the solvent medium that is treated as a dielectric continuum in the GM method by the electronegativity equalization models for the SS atoms in the boundary region. That is, the surroundings of the PS are treated explicitly by a discrete model of individual SS atoms in the flexible-boundary QM/MM scheme instead of by a continuum in the GM method. The calculations will provide a single set of molecular orbitals and other quantities (e.g., atomic charges) that are easy to interpret. The drawback is that one needs to modify QM codes so as to implement the half-electron treatments. Moreover, due to its empirical nature, the half-electron treatment is difficult to extend to more advanced QM theories such as coupled-cluster theory.[63] In contrast, a treatment based on the TVS method should not require modification to QM codes, and therefore more advanced QM theories can be used. The artificial uniform background charge is not a requirement in the QM/MM boundary treatment, although it is needed in the TVS method for molecular dynamics simulations of a system with finite net charge employing periodic boundary condition. To make use of the TVS method, one must figure out what the electron reservoir is and how to treat the exchange of electrons between the PS and the reservoir. The disadvantage of this approach is that the picture of the PS fluctuating between two (reduced and oxidized) potential energy surfaces is not so straightforward to grasp.

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In the present contribution, we make an attempt to develop the flexible-boundary QM/MM based on the principle of electronic chemical potential equalization. The basic idea is similar to the TVS method, with the difference that the electronic chemical potential of the surroundings (SS) in our treatment varies whenever charges flow in or out. The charge-transfer ceases when equilibrium is established for electronic chemical potentials between the PS and SS, and iterative treatments are required to achieve self-consistence. Our flexible-boundary QM/MM scheme can also be considered as an extension of the classical electronegativity-equalization models, such as the charge equalization (QEq) method proposed by Rappé and Goddard,[44] to the treatment of hybrid quantum-classical systems. In this article, we apply this flexible-boundary treatment to QM/MM calculations on model systems where the QM/MM boundary does not pass through a covalent bond; in particular, we study partial charge transfers between a formally singly charged ion, which is the PS, and a (or several) formally charge-neutral water molecule(s), which is the SS. The cases where the QM/MM boundary does pass through one or more covalent bonds are deferred to future studies. The methodology is described in section II, the computations are carried out in section III, and the results are given in section IV. Discussions are presented in section V, and conclusions are drawn in section VI.

II. Methodology

II.A. Electronegativity Equalization Models. The principle of electronic chemical potential equalization, or electronegativity equalization, has been extensively discussed in literature, and various models have been proposed.[19,42–48,53,54] One of such models is the charge equalization (QEq) method proposed by Rappé and Goddard.[44] In our recent development of the polarized-boundary QM/MM schemes,[31] we employed (with modifications) the QEq model with a shielded Coulomb term (SCT)[44] to account for the charge redistribution within the SS atoms near the QM/MM boundary in response to the electric field generated by the PS. The modified QEq-SCT method is used in the present study of flexible-boundary treatments for the determination of charges for the SS atoms. Below, we give a brief description for our modified QEq-SCT implementation; more details can be found in ref 31 and are not repeated here.

In our polarized-boundary QM/MM implementation,[31] we allow the SS to be separated into two parts. The first part is polarizable, and it normally consists of atoms near the QM/MM boundary (although this is not a requirement). The second part, if presented, normally consists of atoms distance from the PS and is not polarized in the QM/MM calculations. In our study, the first part is called the (polarizable) boundary group, and the second part is called the unpolarized group. The original QEq-SCT method was modified in order to take into account the external electric field generated by the PS and by the unpolarized group of the SS; in the absence of the external electric field, our treatment is identical to the original QEq-SCT scheme. (In ref 31 where the QM/MM boundary passed through covalent bonds, the PS is capped by hydrogen atoms, giving rise to a Capped PS, or CPS.)

The modified atomic potential at atom A of charge Q_A in the (polarizable) boundary group is given by

$$\chi_A(Q_1 \cdots Q_N) = \chi_A^0 + J_{AA}^0 Q_A + U_{A,PS} + \sum_C J_{AC} Q_C + \sum_{A \neq B} J_{AB} Q_B \quad (2)$$

where χ_A^0 is the electronegativity of this isolated atom, J_{AA}^0 is the Coulomb repulsion integral of two electrons residing at the same isolated atom, the electric field at the position of atom A due to the PS is $U_{A,PS}$, J_{AC} is the Coulomb interaction integral between unit charges on centers A and C, C denotes an unpolarized SS atom, the charge at the center C is Q_C, J_{AB} is the Coulomb interaction integral between unit charges on centers A and B, and B is another atom of charge Q_B in the polarizable boundary group. The principle of electronegativity equalization leads to

$$\bar{\chi} = \chi_1 = \cdots = \chi_N \quad (3)$$

where $\bar{\chi}$ is the common value. The principle of charge conservation imposes a constraint on the total charge

$$Q_{tot} = \sum_{i=1}^{N} Q_i \quad (4)$$

The common value of the atomic chemical potential and the atomic charges in the boundary group are computed by solving eqs 3 and 4.

Here, we re-emphasized that our treatments only change the MM background charges in the embedded-QM calculations and do not affect the pure MM calculations, for which the original MM charges are used.[31] Our treatments are, in a sense, optimizations of selected charge parameters in the effective QM Hamiltonian for the operators that describe the electrostatic interaction between the PS and the SS. On the other hand, the MM charges are part of an MM force field, which is parametrized to be used as a whole; the charge parameters are cross correlated with parameters for the other (bonded and van der Waals) interactions. Although the effective SS charge parameters in the embedded-QM calculations and the MM charge parameters in an MM force field share some similarity, and we indeed often use MM charge parameters as effective SS charge parameters in embedded-QM calculations, these two sets of charges are different in nature. For this reason, we feel that it is not appropriate to use charges optimized from the polarized-QM calculations for the MM calculations.

II.B. Partial Charge Transfer between the PS and SS. Following the PPLB argument,[60] we consider the PS as an open system with a fluctuating number of electrons, which is described by a statistical mixture of ensemble that consists of states of integer number of electrons. The SS serves as a reservoir that exchanges electrons with the PS. Unlike the reservoir of fixed chemical potential in the TVS[59] model, the electronic chemical potential of the SS in the flexible-boundary QM/MM scheme varies whenever charges flow in or out. Based on the principle of electronic chemical potential equalization, the charge transfer will continue until the electronic chemical potentials in the PS and SS become

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equal. Iterative treatments are therefore required to achieve self-consistence.

In the simplest situation, the PS consists of only two states, i.e., a reduced state (X) and an oxidized state (X^+). An example is the neutral sodium atom Na and the sodium cation Na^+. The oxidized state is of charge $q(X^+)$, and its molar fraction is x_+. The reduced state is of charge $q(X)$, and its molar fraction is $x = 1 - x_+$. Let us denote the charges on the ES, PS, and SS as $q(ES)$, $q(PS)$, and $q(SS)$, respectively. Apparently, one has

$$q(PS) = [x_+ q(X^+) + (1 - x_+) q(X)] \qquad (5)$$

$$q(ES) = q(PS) + q(SS) \qquad (6)$$

As the same in the TVS treatment,[59] we assume the existence of equilibrium of PS ionization $X^+ + e^- \leftrightarrow X$. This leads to

$$\mu(X^+) + \mu(e^-) = \mu(X) \qquad (7)$$

Here, $\mu(X^+)$ is the chemical potential of X^+, $\mu(e^-)$ is the chemical potential of the free electrons, and $\mu(X)$ is the chemical potentials of X. Following the same procedure outlined in ref 59, we separate the chemical potential of a component species A into the contribution of an energetic term $\mu^0(A)$ and an ideal gas contribution, and eq 7 can be rewritten as

$$\mu(e^-) = \mu^0(X) - \mu^0(X^+) + k_BT \ln\left(\frac{x}{x_+}\right) \qquad (8)$$

and

$$\mu^0(X) - \mu^0(X^+) = -I(X) = -[E(X^+) - E(X)] \qquad (9)$$

where $I(X)$ is the ionization potential of the reduced state X. In our flexible-boundary treatment, $I(X)$ is computed for the PS as the gas-phase energy difference between its reduced state and its oxidized state. Here, we have made an approximation by assuming that $I(X)$ obtained for the PS in the gas-phase is equal to $I(X)$ for the PS in the presence of the SS. Now assuming that the free electrons are in equilibrium of the electrons in the reservoir (SS),

$$\mu(e^-) = \mu(SS) = \mu \qquad (10)$$

we reach an equation similar to eq 3 in ref 59:

$$\mu(SS) = -I(X) + k_BT \ln\left(\frac{1 - x_+}{x_+}\right) \qquad (11)$$

The electronic chemical potential of the SS, $\mu(SS)$, is related to the chemical potential for charge transfer, or electronegativity χ, of the SS by

$$\mu(SS) = -\chi \qquad (12)$$

The electronegativity of the SS, χ, can be computed by employing the (modified) QEq-SCT scheme described in section II.A. Equation 11 is the central equation in our flexible-boundary treatment, which must be satisfied when the equilibrium is established for electron exchange between the PS and SS.

In some cases, it is more convenient to denote the reduced state as X^- and the oxidized state as X, such as the Cl^- anion and the Cl atom. Using such notations, one can rewrite eq 11 as follows

$$\mu(SS) = -A(X) + k_BT \ln\left(\frac{x_-}{1 - x_-}\right) \qquad (13)$$

where x_- is the molar fraction of X^-, and $A(X) = [E(X) - E(X^-)]$ is the electron affinity of X. For the sake of brevity, unless otherwise indicated, we will focus our discussion on eq 11 with the notations of X for the reduced state and X^+ for the oxidized state.

Two issues need to be addressed here. First, the temperature T in eq 11 is the temperature for electrons, which is not necessarily the same as the temperature that describes nuclear motions (vibration, rotation, and translation). It is probably better to view T in eq 11 as an empirical parameter adjustable to achieve the best agreement with reference data; this is especially true when considering the empirical nature of the calculations of the electronegativity by the QEq-SCT scheme. The second issue is the different zeroes of electronic chemical potentials between QM calculations and QEq-SCT calculations, which require calibration before comparisons can be made. Note that the logarithm term in eq 11 disappears when $x_+ = 0.5$, and the calibration can be done as follows: First, one computes the electronegativity χ_{cali} by the QEq-SCT method for the PS with a charge of $q(PS) = 0.5\ q(X^+) + 0.5\ q(X)$; for example, because $q(Na) = 0$ and $q(Na^+) = 1$ e, χ_{cali} will be calculated for the PS of a charge of 0.5 e, or $Na^{+0.5}$. An energy term E_{cali} is determined by comparing χ_{cali} and the ionization energy $I(X)$ for the PS:

$$-I(X) + E_{cali} = -\chi_{cali} \qquad (14)$$

The energy term E_{cali} is then added to eq 11, yielding

$$\mu(SS) = -I(X) + k_BT \ln\left(\frac{1 - x_+}{x_+}\right) + E_{cali} \qquad (15)$$
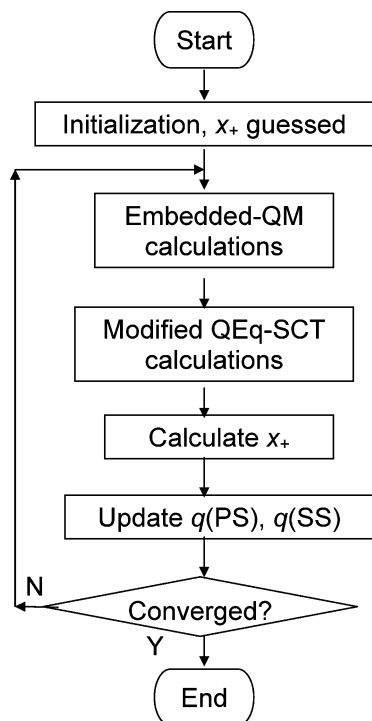
The flexible-boundary treatment needs an iterative procedure for self-consistent calculations. For example, the procedure can start with a guessed molar fraction x_+ for the oxidized state X^+ and enters the cycle of polarized-boundary calculations, where the electrostatic potential at an SS atom A due to the PS, $U_{A,PS}$ in eq 2, is computed as an ensemble average of the electrostatic potentials due to the oxidized and reduced states of the PS:

$$U_{A,PS} = x_+ U_{A,PS}(X^+) + (1 - x_+)U_{A,PS}(X) \qquad (16)$$

After the polarization-boundary calculations converge, one computes the electronic chemical potential of the SS, $\mu(SS)$. With the newly obtained $\mu(SS)$, the molar fraction x_+ is updated according to eq 11, and a new cycle of polarization-boundary calculations are performed. The loop continues until self-consistency is achieved, i.e., the variations in the amount of charge transferred between the PS and SS are smaller than preset thresholds.

The iterative procedure described above is easy to understand and straightforward to implement but is not

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              │   calculations      │
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              │  Modified QEq-SCT   │
              │   calculations      │
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              ┌────────────────────┐
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              │ Update q(PS), q(SS) │
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Figure 1. Flowchart for flexible-boundary calculations.

efficient. We have therefore adopted a more efficient procedure where the molar fraction x_+ is updated at every iteration within the cycle of polarization-boundary calculations. (A flow chart is shown in Figure 1.) The self-consistence requires both the convergence in the amount of charge transferred between the PS and SS and the convergence in the partial atomic charges at the SS atoms. Implemented as such, only one cycle of polarized-boundary calculations is needed, and the computational cost for the flexible-boundary calculations is approximately twice the cost for the polarized-boundary calculations (since one has to do embedded-QM calculations for both oxidation states in the flexible-boundary calculations).

III. Computation

The method is demonstrated by studying the partial atomic charges for model systems. First, we study 7 small model systems that each consists of a singly charged ion and a water molecule; these model systems are denoted [A...B], where A = Li^+, Na^+, K^+, NH_4^+, F^-, Cl^-, and HS^- is the PS, and B = H_2O is the SS. Second, we study a larger model system, the Eigen cation $H_9O_4^+$, which is a proposed solvation structure for the hydronium ion H_3O^+ in water; in the Eigen cation, the central H_3O^+ moiety is the PS, and the three hydrogen-bonded neighbor H_2O molecules compose the SS. In total, we have therefore included 8 model systems in the test calculations. The formal charges for the PS are +1 e in [$Li^+\cdots H_2O$], [$Na^+\cdots H_2O$], [$K^+\cdots H_2O$], [$NH_4^+\cdots H_2O$], and the Eigen cation, and are −1 e in [$F^-\cdots H_2O$], [$Cl^-\cdots H_2O$], and [$HS^-\cdots H_2O$], respectively. Note that the PS in [$NH_4^+\cdots H_2O$], the Eigen cation, and [$HS^-\cdots H_2O$] are polyatomic ions.

We compute and compare three types of partial atomic charges: (1) the charges determined by applying the QEq-

SCT model to the entire (model) systems, which are denoted QEq-SCT-ES charges, (2) two sets of full-QM calculated charges, which include the charges obtained by fitting to the electrostatic potential (ESP) using the Merz−Singh−Kollman[64,65] scheme, and the charges given by Löwdin[66] population analysis, and (3) two sets of QM/MM charges obtained by the flexible-boundary calculations. The two sets of QM/MM partial atomic charges are identical to each other except for the partial atomic charges for the polyatomic PS. In the first set of QM/MM charges (denoted QM/MM-1), the partial atomic charges for the polyatomic PS are ensemble-averaged ESP charges over the reduced and oxidized states, while in the second set of QM/MM charges (denoted QM/MM-2), the partial atomic charges for the polyatomic PS are ensemble-averaged Löwdin charges. Both QM/MM-1 and QM/MM-2 possess the same charges for monatomic PS, which are computed based on the total charges of the SS and according to the principle of charge conservation (eq 6). In both QM/MM-1 and QM/MM-2, the partial atomic charges for the SS are obtained by the modified QEq-SCT scheme.

It is well-known that partial atomic charges are not experimentally measurable quantities, and there is ambiguity in which set of charges is more "correct" than the other. Indeed, we have found in our calculations that, at the employed level of theory, the partial atomic charges predicted by the QEq-SCT-ES and full-QM calculations sometimes disagree with one's intuition. For example, the Na center in [$Na^+\cdots H_2O$] is assigned a partial positive charge large than +1 e. However, the partial atomic charge is a very useful concept that provides important information about the charge distributions within a model system, and we feel that it is instructive to make the comparisons between the charges obtained by reference (QEq-SCT-ES and full-QM) calculations and by the flexible-boundary QM/MM calculations. Since this work is the first step toward the full development of the flexible-boundary QM/MM embedding scheme, we aim mainly at achieving a qualitative (or semiquantitative) agreement between the full-QM and QM/MM charges; the methodology is to be refined in the future in order to accomplish more accurate quantitative calculations.

For a given model system and level of theory, the total amount of partial charge transferred between the PS and the SS is computed as

$$q_{trans} = q_{formal}(PS) - q(PS) \qquad (17)$$

i.e., as the difference between the formal charge of the PS and the actually calculated charge of the PS. Note that QM/MM-1 and QM/MM-2 are identical in q_{trans}.

The QM level of theory is the B3LYP[67−69] density functional model with the 6−31++G(d,p) basis set.[70−74] The MM force field is OPLS-AA.[34−39] Convergence thresholds for the flexible-boundary treatment are as follows: the maximum change in the SS partial atomic charge less than 0.005 e, root-mean-square variation in the SS partial atomic charge less than 0.002 e, and the amount of charge flowing between PS and SS less than 0.005 e. For the present study, the *Gaussian03*[75] program is employed for QM calculations, TINKER[76] is used for MM calculations, and the

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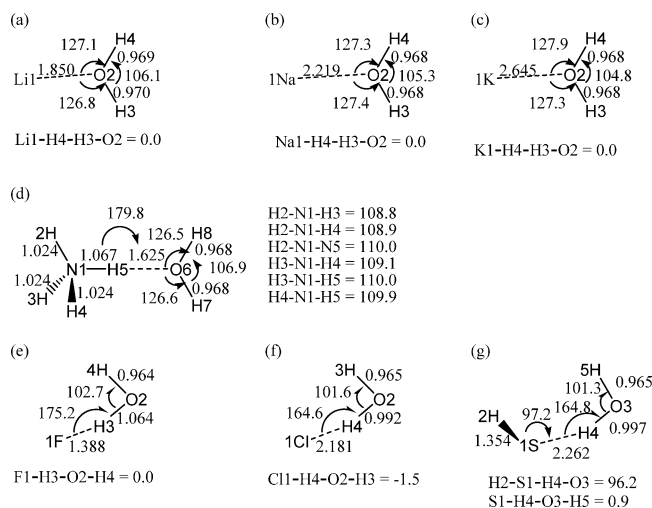
Figure 2. Critical geometric data for small model systems [A···B], where A = Li$^+$, Na$^+$, K$^+$, NH$_4^+$, F$^-$, Cl$^-$, and HS$^-$ is the PS in (a)−(g), respectively, and B = H$_2$O is the SS. Distances are in Å, and angles and dihedrals are in deg. The geometries are optimized at the B3LYP/6-31++G(d,p) level of theory without symmetry constraints.
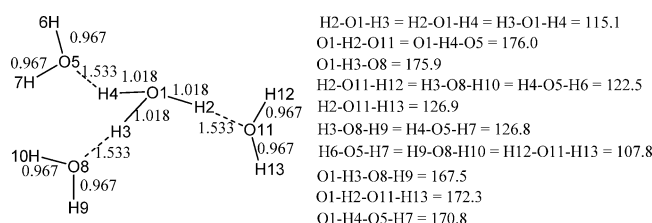
Figure 3. Critical geometric data for the Eigen cation H$_9$O$_4^+$, where the central H$_3$O$^+$ moiety is the PS and the three hydrogen-bonding neighbor H$_2$O molecules are the SS. Distances are in Å, and angles and dihedrals are in deg. The geometry is optimized at the B3LYP/6-31++G(d,p) level of theory without symmetry constraints.

QMMM[77] program is utilized for QM/MM calculations. The geometries are the full-QM geometries optimized by using the *Gaussian03* program with the (5D, 7F) option for basis sets. No symmetric constraints are imposed in geometry optimizations. The QEq-SCT parameters are taken from ref 44.

IV. Results

The optimized geometries are illustrated in Figure 2 for the small model systems [A···B] and in Figure 3 for the Eigen cation. Table 1 tabulates the partial atomic charges for the small model systems [A···B], while the charges for the Eigen cation are collected in Table 2. No full-QM ESP charge is available for [K$^+$···H$_2$O] due to the lack of parameter (the Merz−Kollman atomic radius) for potassium in the ESP charge calculations. Table 3 gives the mean unsigned deviations (MUD) for the partial atomic charges between the QM/MM calculations and the full-QM calculations; for a given temperature and QM/MM charge set, the MUD is averaged over all 8 model systems, except that [K$^+$···H$_2$O] is excluded from the calculations for QM/MM-1. The amounts of the charges transferred between the PS and the SS are listed in Table 4, for which the MUD and mean signed

deviations (MSD) between the QM/MM calculations and the full-QM calculations are presented in Table 5. Note that in the calculations of the MUD and MSE, we always compare the QM/MM-1 charges with the full-QM ESP charges while compare the QM/MM-2 charges with the full-QM Löwdin charges. The electronic chemical potential $\mu(e^-)$ at $T = 30\,000$ K is shown in Figure 4 for a statistical (Na, Na$^+$) mixture of ensemble of charge q, along with the molar fractions x of Na and x_+ of Na$^+$. Also plotted in Figure 4 is the electronegativity χ calculated by the QEq-SCT method for Na^{+q}, where $0 \leq q \leq 1$. In Figure 5, we display $\mu(e^-)$ for the [Na$^+$···H$_2$O] model system at three temperatures 10 000 K, 30 000 K, and 50 000 K, all indicated by dashed lines, as well as $\mu(SS)$, indicated by a solid line. The convergence of the QM/MM calculated charges is demonstrated in Figure 6 for [Na$^+$···H$_2$O] at $T = 30\,000$ K.

V. Discussion

V.A. Case Study for [Na$^+$···H$_2$O]. The small model system [Na$^+$···H$_2$O] is one of the simplest systems in the test calculations. In this section, we choose it to illustrate the concepts and to examine the difficulties that we have come across in the calculations.

The optimized geometry for [Na$^+$···H$_2$O] is planar, as shown in Figure 2(b). As listed in Table 1, the QEq-SCT-ES calculations (for the entire system) imply that some positive charge is transferred from H$_2$O to Na$^+$, such that the Na1 center carries a charge of +1.16 e. This sounds somewhat unusual, as the result contradicts one's intuition. We have found that such unusual charges appear when the Na$^+$ moiety is close to the H$_2$O moiety. As shown in Table S6 in the Supporting Information, the charge at the Na1 center increases monotonically as the Na$^+$ and H$_2$O moieties approach each other and exceeds +1 e when the Na−O distance reduces to 3.5 Å or shorter. The unusual results have also been obtained for [Li$^+$···H$_2$O] and [K$^+$···H$_2$O] at their optimized geometries, as indicated in Table 1. The reason could be that we have used the simplified SCT treatment to calculate the Coulomb integration in order to reduce computational costs; this SCT treatment was not recommended in the original QEq paper[29] but has been shown to yield quite reasonable charges for many systems.[31,44] On the other hand, we point out that even the full-QM charges are not free of this kind of artifact, either—the full-QM ESP charge at the Na1 center is also larger than +1 e, although to a much smaller extent (by 0.003 e). The full-QM Löwdin charges seem quite reasonable for this system, where +0.84 e is assigned to the Na1 center; but we have noticed that the full-QM Löwdin charge at the K1 center in [K$^+$···H$_2$O] is +1.018 e (Table 1), again unusually larger than +1 e. For the H$_2$O moiety, the partial atomic charges obtained by the QEq-SCT-ES, full-QM ESP, and full-QM Löwdin calculations agree qualitatively with each other.

In the flexible-boundary QM/MM treatment for the [Na$^+$···H$_2$O] model system, we consider Na as the reduced state and Na$^+$ as the oxidized state for the PS, since the Na^{2+} state is likely too high in energy to be involved. (The same consideration has been applied to the other systems whose PS has a formal charge of +1 e.) Therefore, the PS is

Table 1. Partial Atomic Charges for 7 Small Model Systems [A···B][a]

		full-QM		QM/MM		
	QEq-SCT-ES	ESP	Löwdin	$T = 10\,000$	$T = 30\,000$	$T = 50\,000$
				Li$^+$···H$_2$O		
Li1	1.212	0.896	0.712	0.999	0.918	0.821
O2	−0.759	−0.706	−0.265	−0.782	−0.754	−0.718
H3	0.273	0.405	0.276	0.405	0.430	0.460
H4	0.274	0.405	0.276	0.379	0.405	0.437
				Na$^+$···H$_2$O		
Na1	1.155	1.003	0.838	0.999	0.920	0.824
O2	−0.693	−1.053	−0.358	−0.765	−0.738	−0.703
H3	0.269	0.525	0.260	0.395	0.420	0.450
H4	0.269	0.525	0.260	0.371	0.397	0.429
				K$^+$···H$_2$O		
K1	1.237	n/a	1.018	0.999	0.926	0.832
O2	−0.687	n/a	−0.513	−0.716	−0.691	−0.660
H3	0.224	n/a	0.248	0.367	0.391	0.421
H4	0.225	n/a	0.248	0.350	0.375	0.407
				NH$_4^+$···H$_2$O[b]		
N1	−0.581	−0.963	−0.068	−0.722/−0.049	−0.255/−0.068	0.058/−0.077
H2	0.328	0.445	0.239	0.402/0.234	0.259/0.208	0.180/0.203
H3	0.328	0.443	0.239	0.402/0.234	0.260/0.209	0.180/0.204
H4	0.328	0.444	0.239	0.403/0.235	0.262/0.210	0.183/0.205
H5	0.343	0.663	0.252	0.462/0.292	0.244/0.211	0.082/0.150
O6	−0.551	−1.134	−0.416	−0.666	−0.603	−0.571
H7	0.402	0.552	0.257	0.358	0.416	0.445
H8	0.402	0.550	0.257	0.362	0.417	0.441
				F$^-$···H$_2$O		
F1	−0.677	−0.890	−0.812	−0.999	−0.917	−0.803
O2	−0.657	−1.038	−0.634	−0.639	−0.637	−0.634
H3	0.237	0.582	0.262	0.518	0.445	0.345
H4	0.097	0.346	0.184	0.121	0.109	0.092
				Cl$^-$···H$_2$O		
Cl1	−0.706	−0.873	−0.865	−0.994	−0.842	−0.729
O2	−0.641	−0.724	−0.541	−0.519	−0.523	−0.523
H3	0.137	0.337	0.201	0.239	0.206	0.184
H4	0.209	0.260	0.205	0.274	0.158	0.068
				HS$^-$···H$_2$O[b]		
S1	−0.628	−1.045	−0.835	−1.079/−0.934	−0.889/−0.752	−0.809/−0.675
H2	0.007	0.099	0.006	0.148/0.002	0.145/0.007	0.143/0.009
O3	−0.653	−0.946	−0.555	−0.634	−0.656	−0.665
H4	0.164	0.520	0.191	0.390	0.276	0.228
H5	0.109	0.372	0.194	0.176	0.125	0.103

[a] A is the PS, and B is the SS. Geometries and atom labels are given in Figure 2. The QEq-SCT-ES charges are obtained by doing QEq-SCT calculations for the entire model systems. No full-QM ESP charges are available for [K$^+$···H$_2$O] due to the lack of parameter (the Merz−Kollman atomic radius) for potassium in the ESP charge calculations. QM/MM charges are obtained by the flexible-boundary calculations, where the atomic charges for polyatomic PS are ensemble-averaged ESP charges in QM/MM-1 and ensemble-averaged Löwdin charges in QM/MM-2. For monatomic PS, QM/MM-1 and QM/MM-2 charges are identical. The QM/MM charges for the SS are determined by employing the modified QEq-SCT procedure. Charges are in e, and temperatures are in K. [b] For the PS, QM/MM charges are given as (QM/MM-1)/(QM/MM-2).

described by a pair of oxidation states (Na, Na$^+$). Our first question is as follows: for such a statistical (Na, Na$^+$) mixture of ensemble, how will the electronic chemical potential $\mu(e^-)$ change if the charge q varies from 0 to +1 e. As can be seen in Figure 4, the $\mu(e^-)$ curve computed at $T = 30\,000$ K changes its value sharply when q approaches 0 or +1 e. Such characteristics have already been demonstrated in previous works,[59,60] which approaches the well-known "staircase" shape at $T = 0$ with discontinuity at

integer charges. As expected, the molar fractions for Na and Na$^+$ are linear functions of the charge of the mixture q. Next, we ask how $\mu(e^-)$ differs from χ, the electronegativity calculated by the QEq-SCT method for Na^{+q}, where $0 \leq q \leq 1$. The $-\chi$ curve, which is also plotted in Figure 3, turns out to be a linear function of q. Besides the different shapes, $-\chi$ and $\mu(e^-)$ differ in values at $x^+ = 0.5$, where Na and Na$^+$ are equally likely; the difference is about 0.01 au: $-\chi = -0.1889$ au, and $\mu(e^-) = -0.1987$ au. As pointed out in

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Table 2. Partial Atomic Charges for the Eigen Cation[a]

		Full-QM		QM/MM		
	QEq-SCT-ES	ESP	Löwdin	$T = 10\,000$	$T = 30\,000$	$T = 50\,000$
O1	−0.643	−0.857	−0.188	−0.651/−0.098	−0.542/−0.123	−0.514/−0.129
H2	0.394	0.609	0.268	0.515/0.328	0.412/0.266	0.386/0.250
H3	0.394	0.594	0.268	0.513/0.326	0.409/0.263	0.382/0.247
H4	0.394	0.608	0.268	0.495/0.315	0.363/0.235	0.330/0.216
O5	−0.575	−1.040	−0.382	−0.643	−0.603	−0.593
H6	0.366	0.529	0.256	0.326	0.353	0.360
H7	0.362	0.525	0.254	0.389	0.403	0.406
O8	−0.575	−1.029	−0.382	−0.680	−0.642	−0.632
H9	0.362	0.521	0.254	0.390	0.403	0.406
H10	0.366	0.527	0.256	0.319	0.342	0.348
O11	−0.575	−1.039	−0.382	−0.697	−0.658	−0.648
H12	0.366	0.529	0.256	0.331	0.354	0.359
H13	0.362	0.523	0.254	0.393	0.406	0.409

[a] Geometry and atom labels are given in Figure 3. The central H_3O^+ moiety is the PS, and the three hydrogen-bonding neighbor H_2O molecules are the SS. QEq-SCT-ES charges are obtained by doing QEq-SCT calculations for the entire system. The QM/MM charges are obtained by the flexible-boundary calculations, where the atomic charges for the PS are ensemble-averaged ESP charges in QM/MM-1 and ensemble-averaged Löwdin charges in QM/MM-2. For the PS, QM/MM charges are given as (QM/MM-1)/(QM/MM-2). The QM/MM charges for the SS are determined by employing the modified QEq-SCT procedure. Charges are in e, and temperatures are in K.

Table 3. Mean Unsigned Deviations for Partial Atomic Charges between QM/MM Calculations and Full-QM Calculations [a]

	$T = 10\,000$	$T = 30\,000$	$T = 50\,000$
QM/MM-1[b]	0.161	0.202	0.238
QM/MM-2[c]	0.126	0.113	0.117
average[d]	0.144	0.158	0.178

[a] Average over the 7 small model systems [A···B] and the Eigen cation, except that [K⁺···H_2O] is excluded from the calculations for QM/MM-1. Charges are in e, and temperatures are in K. [b] QM/MM-1 charges versus full-QM ESP charges. [c] QM/MM-2 charges versus full-QM Löwdin charges. [d] Average over QM/MM-1 and QM/MM-2.

section II.B, a calibration step must be taken to account for this difference (different zeros). In the rest of this paper, we only refer to the calibrated $\mu(e^-)$, unless otherwise indicated.

The central ideal of the flexible-boundary treatment is electronic chemical potential equalization, i.e., the PS and the SS should have the same electronic chemical potentials when charge-transfer ceases. This is illustrated in Figure 5 by the crossing between the $\mu(e^-)$ and $\mu(SS)$ curves, both plotted as functions of $q(PS)$. Note that $\mu(SS)$ is determined in the polarized-boundary QM/MM calculations, where the PS and SS polarize each other until self-consistence. Inspection of the graph suggests that the $\mu(SS)$ and $\mu(e^-)$ curves cross at $q(PS) = +1.00$ e, $+0.91$ e, and $+0.82$ e at $T = 10\,000$ K, $30\,000$ K, and $50\,000$ K, respectively. It is conceivable that by varying the temperature T, one can obtain $[Na^{+q}···H_2O^{+(1-q)}]$ with the amount of transferred charge $(1 - q)$ in best agreement with reference data, although we have not made such an effort to optimize the temperature parameter in the present study.

We find that the flexible-boundary QM/MM calculations employing the iterative procedure described in section II.B converge within 4 iterations. For example, at $T = 30\,000$ K, the QM/MM charges converge in 4 iterations (Figure 6). Going from iteration 3 to iteration 4, the magnitude of variation in charge is 0.001 e at the Na1 center and less than

0.001 e at the O2, H3, and H4 centers. Such convergence behavior is typical in our calculations for all the model systems.

V.B. Case Study for [HS⁻···H_2O]. Unlike Na^+, HS^- is a polyatomic anion. The optimized geometry for $[HS^-···H_2O]$ shown in Figure 2(g) reveals that the S1 center is closer to one hydrogen of the water than to the other; in particular, the S1−H4 distance, which is shorter, is 2.262 Å. As listed in Table 1, all three reference calculations assign significant negative charges (-0.63 e ~ -1.05 e) at the S1 center and small positive charges ($+0.01$ e $\sim +0.10$ e) at the H2 center for the PS. The charges at the H4 and H5 centers are the same (0.19 e) in the full-QM Löwdin calculations but differ from each other in the QEq-SCT-ES calculations (by 0.05 e) and in the full-QM ESP calculations (by 0.15 e). Both the QEq-SCT-ES and the full-QM calculations suggest that negative charge is transferred from the HS^- moiety to the H_2O moiety.

For the flexible-boundary QM/MM calculations on this system, we consider the PS as a statistical (HS, HS^-) mixture of ensemble, as we feel that the HS^{2-} state is of rather high energy and is unlikely to contribute. (The same consideration has been applied to the other systems where the PS has -1 e formal charge.) The QM/MM partial atomic charges depend on the employed temperature parameter, but overall they agree reasonably well with the reference calculations. For the PS, both QM/MM-1 and QM/MM-2 assign significant negative charges (-0.68 e ~ -1.08 e) at the S1 center and small positive charge ($<+0.15$ e) at the H2 center. Interestingly, in both QM/MM-1 and QM/MM-2, the charge at the H2 center varies negligibly (less than 0.01 e) between $T = 10\,000$ K and $T = 50\,000$ K. Turned to the SS, the H4 center, which is the closest to the PS, shows large variations from $+0.39$ e at $T = 10\,000$ K to $+0.23$ e at $T = 50\,000$ K. Smaller variations are observed for the H5 center, which is two bonds further away from the PS: the charge decreases from $+0.18$ e to $+0.10$ e when T increases from $10\,000$ K to $50\,000$ K. The QM/MM charges for the PS and SS suggest

***Table 4.*** Partial Charges Transferred from the PS to the SS[a]

		full−QM		QM/MM		
	QEq-SCT-ES	ESP	Löwdin	$T =$ 10 000	$T =$ 30 000	$T =$ 50 000
$Li^+\cdots H_2O$	−0.212	0.104	0.288	0.001	0.082	0.179
$Na^+\cdots H_2O$	−0.155	−0.003	0.162	0.001	0.080	0.176
$K^+\cdots H_2O$	−0.237	n/a	−0.008	0.001	0.074	0.168
$NH_4^+\cdots H_2O$	0.254	−0.032	0.099	0.053	0.230	0.317
$F^-\cdots H_2O$	−0.323	−0.110	−0.188	−0.001	−0.083	−0.197
$Cl^-\cdots H_2O$	−0.294	−0.127	−0.135	−0.006	−0.158	−0.271
$HS^-\cdots H_2O$	−0.379	−0.054	−0.171	−0.069	−0.256	−0.334
Eigen cation	0.461	0.046	0.384	0.128	0.358	0.416

[a] For the first 7 small model systems [A⋯B], A is the PS, and B is the SS. For the Eigen cation, the central H_3O^+ moiety is the PS, and the three hydrogen-bonding neighbor H_2O molecules are the SS. The amount of transferred charge is computed as the difference between the formal charge and the actually calculated charge of the PS. Charges are in e, and temperatures are in K.
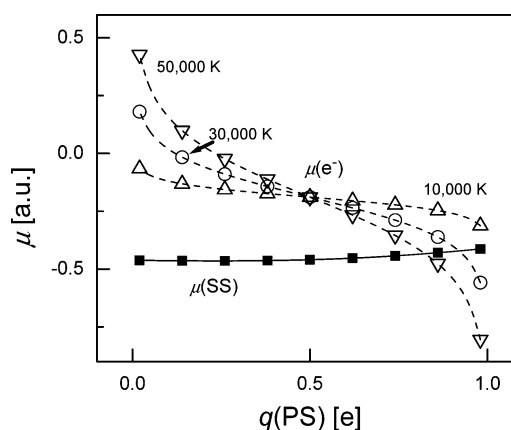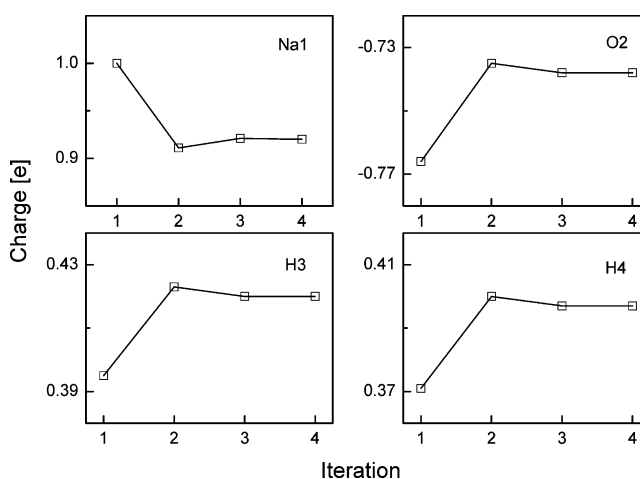
Table 5. Mean Unsigned Deviations (MUD) and Mean Signed Deviations (MSD) for Partial Charges Transferred from the PS to the SS[a]

	MUD			MSD		
	$T =$ 10 000	$T =$ 30 000	$T =$ 50 000	$T =$ 10 000	$T =$ 30 000	$T =$ 50 000
QM/MM-1[b]	0.074	0.134	0.212	0.040	0.061	0.066
QM/MM-2[c]	0.167	0.094	0.097	−0.047	−0.026	−0.022
average[d]	0.121	0.114	0.155	−0.004	0.018	0.012

[a] Signed deviations between QM/MM calculations and reference data are determined by q_{trans}(QM/MM) − q_{trans}(reference), where the reference is full-QM ESP and full-QM Löwdin for QM/MM-1 and QM/MM-2, respectively. Mean deviations are averaged over the 7 small model systems [A⋯B] and the Eigen cation, except that [$K^+\cdots H_2O$] is excluded from the calculations for QM/MM-1. Charges are in e, and temperatures are in K. [b] QM/MM-1 charges versus full-QM ESP charges. [c] QM/MM-2 charges versus full-QM Löwdin charges. [d] Average over QM/MM-1 and QM/MM-2.
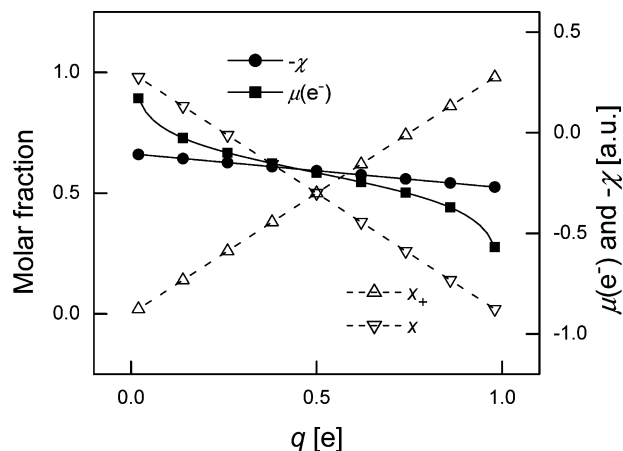
Figure 4. Electronic chemical potential $\mu(e^-)$ at $T = 30\ 000$ K, molar fractions x for Na, and molar fraction x_+ for Na^+, all computed for a statistical (Na, Na^+) mixture of ensemble, and electronegativity χ calculated by the QEq-SCT method for Na^{+q}, where $0 \leq q \leq 1$.

Figure 5. Electronic chemical potentials $\mu(e^-)$ at three temperatures of 10 000 K, 30 000 K, and 50 000 K, and μ-(SS) determined by the modified QEq-SCT method in the QM/MM calculations, all computed for the [$Na^+\cdots H_2O$] model system and expressed as functions of the charge of the PS.

Figure 6. Convergence of the QM/MM calculated charges for [$Na^+\cdots H_2O$] at $T = 30\ 000$ K.

that some negative charge is transferred from HS^- to H_2O, in line with the QEq-SCT-ES and full-QM calculations. The amount of the transferred charge by QM/MM calculations depends on the temperature parameter, which is quite small (−0.07 e) at $T = 10\ 000$ K, but increases rapidly to −0.33 e at $T = 50\ 000$ K.

V.C. Overall Assessment. In general, the partial atomic charges are computed quite reasonably by the flexible-boundary QM/MM scheme. The results depend on the employed temperature parameter, but for all the three temperatures (10 000 K, 30 000 K, and 50 000 K) we have tested, the results are qualitatively similar. Furthermore, the QM/MM charges agree reasonably with the reference data.

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Not surprisingly, for polyatomic PS, the QM/MM-1 charges resemble the full-QM ESP charges, while the QM/MM-2 charges look similar to the full-QM Löwdin charges; this trend is especially evident in the case of the Eigen cation. As to the partial atomic charges for the SS, the QM/MM calculations and QEq-SCT-ES calculations normally produce quite similar results. As far as the charge transferred between the PS and SS is concerned, the QM/MM calculations predict the direction of charge flow in agreement with our chemical intuitions: for the systems where the PS has a formal charge of +1 e (−1 e), QM/MM calculations predicted that partial positive (negative) charges are transferred to the SS; we however must admit that such predictions are consistent with our choice of the reduced and oxidized states for the PS.

It is not easy to give definite quantitative assessment on the overall performance of the flexible-boundary QM/MM calculations, because the three sets of reference data (QEq-SCT-ES charges, full-QM ESP charges, and full-QM Löwdin charges) vary considerably. Nevertheless, we attempt to address this issue by examining the MUD for the partial atomic charges as well as the MUD for the amount of charge transferred between the PS and SS. Table 3 shows that, for the partial atomic charges, the MUD varies between 0.11 and 0.24 e for the three tested temperatures. Averaging the MUD first over QM/MM-1 and QM/MM-2 and then over the three tested temperatures, we obtain an averaged MUD of 0.16 e, which can be used as a rough indication of the accuracy for the QM/MM-calculated partial atomic charges. In terms of the amount of charge transferred between the PS and SS, as displayed in Table 5, the MUD is in the range of 0.07−0.21 e, and the averaged MUD is 0.13 e. Overall, those deviations are rather moderate, and they imply that our flexible-boundary treatment is able to semiquantitatively describe the charge-transfer cross the QM/MM boundary.

V.D. Involving More Oxidation States. The two-state (reduced and oxidized states) treatment outlined in section II.B can in principle be extended to involve three or more states. In the case of three states, one can assume for the PS the equilibrium between e⁻, X, X⁺, and X⁻,[59] which leads to (a more detailed description is given in the Supporting Information)

$$q(\text{PS}) = (q(\text{X}^+)e^{-\mu+I/kT} + q(\text{X}^-)e^{\mu+A/kT} +$$
$$q(\text{X}))/(e^{-\mu+I/kT} + e^{\mu+A/kT} + 1) \quad (18)$$

where $\mu(\text{SS})$ is denoted by μ, $I(\text{X})$ is denoted by I, and $A(\text{X})$ is denoted by A for short. Note that

$$\mu = \frac{1}{2}\left[-I - A + k_\text{B}T \ln\left(\frac{x_-}{x_+}\right)\right] \quad (19)$$

The logarithm term in eq 19 disappears when $x_+ = x_-$. The calibration can be therefore done by comparing the electronegativity χ_cali for the PS of the state X with the Mulliken[78−80] absolute electronegativity μ_M

$$\mu_\text{M} + E_\text{cali} = -\chi_\text{cali} \quad (20)$$

$$\mu_\text{M} = -\frac{1}{2}[I(\text{X}) + A(\text{X})] \quad (21)$$

VI. Conclusion

In this work, we propose a flexible-boundary scheme to account for partial charge transfers between the PS and SS for QM/MM calculations. The scheme is based on the principle of electronic chemical potential equalization. The PS, which is described by a statistical mixture of ensemble that consists of states of integer number of electrons, exchanges electrons with the SS, which serves as a reservoir of electrons. The electronic chemical potential of the SS varies when charges flow in or out until equilibrium is established for the electronic chemical potentials between the PS and SS. Our scheme is tested by calculations of the partial atomic charges for 8 model systems. The QM/MM calculated charges agree with full-QM calculations reasonably well. The averaged mean unsigned deviations (over two set of QM/MM charges and three temperatures) between the QM/MM calculations and full-QM calculations are rather moderate: 0.16 e for partial atomic charges for the entire systems and 0.13 e for the amount of charges transferred between the PS and SS.

The flexible-boundary treatment requires embedded-QM calculations for each involved oxidation state. In contrast, a polarized-embedding QM/MM calculation requires embedded-QM calculations for only one specific oxidation state. The flexible-boundary treatment provides enhanced accuracy but is computationally more expensive. Fortunately, in most cases, it is sufficient to consider only two oxidation states, as the other oxidation states are generally much higher in energy and contribute negligibly. Thus, for most applications, the computational costs will increase by approximately a factor of 2, which is still within the acceptable range.

Future work is needed to refine and improve the flexible-boundary treatment. First, analytic gradients should be implemented to facilitate geometry optimizations and molecular dynamics simulations. Second, in our current implementation of the flexible-boundary treatment, the MM parameters such as partial atomic charges and van der Waals parameters are not reoptimized for pure-MM calculations. In future studies, it is desirable to refine those MM parameters for a more self-consistent description of the interactions between the PS and SS. Such a refinement will improve geometry and other molecular properties.

Supporting Information Available: Optimized geometries and atomic charges for H_2O, HS^-, NH_4^+, and H_3O^+ in the gas phase (Table S1), Cartesian coordinates for the optimized geometry of the 7 small model systems and of the Eigen cation, along with the absolute energies, HOMO energies, and LUMO energies (Table S2), for the PS the $\mu(\text{e}^-)$ at $T = 30\,000$ K, molar fractions of the reduced and oxidized states, and the gas-phase electronegativity χ (Table S3), crossing of $\mu(\text{e}^-)$ and $\mu(\text{SS})$ for the model systems

(Table S4), convergence of the QM/MM calculated charges (Table S5), QEq-SCT-ES charges calculated for $[Na^+\cdots H_2O]$ as functions of the Na$-$O distance (Table S6), and more details about the extension of the flexible-boundary treatment involving three oxidation states. This material is available free of charge via the Internet at http://pubs.acs.org.

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