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REGULAR ARTICLE

Flexible-boundary QM/MM calculations: II. Partial charge transfer across the QM/MM boundary that passes through a covalent bond

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Abstract Recently, based on the principle of electronic chemical potential equalization and the principle of charge conservation, we proposed a flexible-boundary scheme that allows both partial charge transfer and self-consistent polarization between the quantum mechanical (QM) and molecular mechanical (MM) subsystems in QM/MM calculations; the scheme was applied to study the atomic charges in selected ion–solvent complexes. In the present contribution, we further extend the flexible-boundary treatment to handle the QM/MM boundary passing through covalent bonds. We find that the flexible-boundary redistributed charge and dipole schemes yield reasonable agreement with full-QM calculations for a number of molecular ions and amino acids with charged side chains. Using the full-QM results as reference, the mean unsigned deviations are computed to be 0.06 e for atomic partial charges of the QM atoms, 0.11 e for the amounts of charge transfer between the QM and MM subsystems, and 0.016 Å for the lengths of the covalent bonds that directly connect the QM and MM subsystems. The results indicate the importance of accounting for partial charge transfer across the QM/MM boundary when the QM subsystems are charged.

Keywords Combined QM/MM · Partial charge transfer · Electronegativity equalization · Boundary treatments

1 Introduction

Combined quantum-mechanical/molecular-mechanical (QM/MM) calculations [1–19] are very popular nowadays. Although the formularization and implementation vary, most QM/MM schemes, however, suffer noticeably from two limitations. First, no partial charge transfer is allowed between the QM and MM subsystems, and second, reclassifying the atoms into the QM and MM subsystems cannot be done once the QM/MM boundary is set. For many applications, those two limitations do not raise problems. However, they do impose difficulties in certain applications, for example, simulations of ion transport in bulk solvent or through ion channels. In such simulations, one would like to treat the ion and its first solvation shell (solvent molecules and/or coordinating residues) by QM and to describe the environment at the MM level. Because of the large charge on the QM subsystem, partial charge transfer is expected between the QM and MM subsystems; the extreme case will be that the QM subsystem consists of the ion only for which significant charge transfer to the MM subsystem will almost surely happen. Moreover, during the trajectory propagation, it is very likely that the first solvation shell exchanges atoms/groups with the environment; since the reclassification of QM and MM atoms is not permitted, one has to include in the QM subsystem all possible atoms that the ion will pass by. The result is that a very large QM subsystem must be used, which limits the QM level of theory and simulation time that can be employed.

It is desirable to develop an "open-boundary" QM/MM method that allows the QM and MM subsystems to exchange atoms and partial charges on the fly during molecular dynamics simulation. In pursuing this goal, Heyden et al. [20] developed two adaptive partitioning

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schemes that enable smooth transitions for atoms entering and leaving the high-level (QM) subsystem while conserving energy and momentum; the conversation of energy and momentum prevents the artifact of sampling an unknown, possibly non-equilibrium ensemble [20–22]. Recently, we [23] proposed a flexible-boundary scheme that allows both partial charge transfer and self-consistent polarization between the QM and MM subsystems on the basis of the electronic chemical potential equalization principle [24, 25] and the charge conservation principle. We have demonstrated that, when applied to a number of ions (including polyatomic ions) in complex with water molecules, the flexible-boundary QM/MM calculations yield atomic charges in good agreement with full-QM calculations [23]. In those ion–solvent complexes, the ions were described at the QM level, and the solvent molecules were treated by MM; the QM/MM boundary did not pass though a covalent bond. In the present study, we further combine the flexible-boundary treatment with the redistributed charge (RC) scheme and the redistributed charge and dipole (RCD) scheme [26], which were previously developed to handle the QM/MM boundary passing through covalent bonds. Doing so leads to two new schemes, the flexible-boundary redistributed charge (FBRC) scheme and the flexible-boundary redistributed charge and dipole (FBRCD) scheme, both of which can handle partial charge transfer between the QM and MM subsystems that are connected by covalent bonds. The two new schemes are assessed by examining the atomic partial charges of the QM atoms, the amount of charge transfer between the QM and MM subsystems, and the optimized geometries for a number of molecular ions and amino acids with charged side chains [26].

2 Theory

The RC and RCD schemes [26] were developed based on the idea of classical analogs to the quantum description of the electron density in the vicinity of the QM/MM boundary passing through a covalent bond in the generalized hybrid orbital (GHO) theory [27, 28]. The MM point charge at the M1 atom (an MM atom that is directly bonded to a QM atom) is redistributed evenly onto the mid-points of the M1–M2 bonds, where M2 is an MM atom that is directly bonded to the M1 atom. In the RCD scheme, both the redistributed charges and the M2 charges are further modified in order to preserve the M1–M2 bond dipoles. Improvement to the RC and RCD schemes led to the polarized-boundary RC (PBRC) and polarized-boundary RCD (PBRCD) schemes [29], both of which iteratively adjust the MM charges near the boundary based on the electronegativity equalization principle [24, 25] and the charge conservation principle until self-consistence is achieved for the charge distributions in both the QM and MM subsystems. The adjustment of the MM charges accounts for the polarization of the MM subsystem by the QM subsystem, which is often significant only for MM atoms near the QM/MM boundary. A number of classical electronegativity equalization models [24, 25, 30–37] are available in the literature, and three of them [30, 31, 33] have been modified and implemented in our QMMM [38] program for this purpose.

As an attempt to further improve the PBRC and PBRCD methods, we propose in the present study the FBRC and FBRCD schemes, which incorporate the flexible-boundary treatment described in Ref. [23] into the RC and RCD models, respectively. In the flexible-boundary treatment, the primary system (PS, i.e., the QM subsystem) is described by a statistical mixture of ensemble that consists of states of integer number of electrons, usually an oxidized state (X^+) and a reduced state (X) [24, 25]. The PS exchanges electrons with the secondary system (SS, i.e., the MM subsystem), which serves as a reservoir of electrons [23, 39]. 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 [23]. At equilibrium, one has

$$\mu(\mathrm{SS}) = \mu(\mathrm{e}^-) = -I(\mathrm{X}) + k_{\mathrm{B}}T\ln[(1 - x_+)/x_+] + E_{\mathrm{cali}}, \tag{1}$$

where μ(SS) is the electronic chemical potential of the SS calculated by a classical electronegativity equalization model, $\mu(\mathrm{e}^-)$ is the “calibrated” electronic chemical potential computed by QM, $I(\mathrm{X}) = [E(\mathrm{X}^+) - E(\mathrm{X})]$ is the ionization energy of the reduced state X of the PS computed by QM, k_{B} is the Boltzmann constant, T is temperature in Kelvin, x_+ is the molar fraction of the oxidized state X^+ of the PS, and the calibration term E_{cali} is introduced to account for the different zeroes of electronic chemical potentials of the PS between the QM calculations and the calculations by the classical electronegativity equalization model. More specifically, E_{cali} is determined as the difference between I(X) and μ(PS) at $x_+ = 0.5$, where μ(PS) is the electronegativity of the PS calculated by the classical electronegativity equalization model. At $x_+ = 0.5$, the logarithms term in Eq. 1 due to the entropy contribution vanishes. Equation 1 applies conveniently to systems where the oxidized state of the PS is a cation (e.g., $X^+ = Na^+$). For a system where the reduced state of the PS is an anion, e.g., $X^- = Cl^-$, it is more convenient to use the following equation

$$\mu(\mathrm{SS}) = \mu(\mathrm{e}^-) = -A(\mathrm{X}) + k_{\mathrm{B}}T\ln[x_-/(1 - x_-)] + E_{\mathrm{cali}}, \tag{2}$$

where $A(\mathrm{X}) = [E(\mathrm{X}) - E(\mathrm{X}^-)]$ is the electron affinity of the oxidized state X computed by QM, and x_- is the molar fraction of the reduced state X^-. In both Eqs. 1 and 2, the temperature of electrons, T, is taken to be an empirical parameter that can be adjusted to achieve the best agreement with reference data, in view of the empirical nature of the calculations of the electronegativity by classical electronegativity equalization models [23].

The flexible-boundary QM/MM energy is taken to be the ensemble average of the QM/MM energies associated, respectively, with the oxidized and reduced states of the PS

$$E(\mathrm{QM/MM}) = x_+ E(\mathrm{QM/MM; PS = X^+}) + (1 - x_+) E(\mathrm{QM/MM; PS = X}), \quad (3)$$

or

$$E(\mathrm{QM/MM}) = x_- E(\mathrm{QM/MM; PS = X^-}) + (1 - x_-) E(\mathrm{QM/MM; PS = X}), \quad (4)$$

depending on the selection of the oxidized and reduced states of the PS. Note that the oxidized and reduced states of the PS are always embedded in the same set of MM charges. At a given geometry, the QM/MM gradient with the converged MM charges is evaluated by taking energy derivatives with respect to coordinates. More details about the flexible-boundary treatment can be found in Ref. [23] and will not be repeated here.

In the FBRC and FBRCD treatments, the PS is capped by H atoms. Following the protocol [29] in the PBRC (PBRCD) treatment, the FBRC (FBRCD) scheme constrains the redistributed M1 charges to their values in the RC (RCD) schemes during the flexible-boundary calculations; such constraints were found necessary to avoid producing unreasonably large charges near the QM/MM boundary [29]. In contrast to the practice in Ref. [23] that the electronic temperature parameter T was selected manually to obtain good agreement between the PS charges by QM/MM calculations and the reference data (the PS charges by full-QM computation), the present study determines T in a different way. If Eq. 1 is employed, T is selected such that the following relation is satisfied:

$$\mathrm{d}\mu(\mathrm{CPS})/\mathrm{d}q = \mathrm{d}\mu(\mathrm{e}^-)/\mathrm{d}q|_{x_+=0.5}, \quad (5)$$

where $\mu(\mathrm{CPS})$ is the electronegativity of the CPS computed by the classical electronegativity equalization model, and $q = q(\mathrm{CPS}) = x_+ q(\mathrm{X}^+) + (1 - x_+) q(\mathrm{X})$, i.e., we force $\mu(\mathrm{CPS})$ and $\mu(\mathrm{e}^-)$ have the same slopes at $x_+ = 0.5$, in addition to have the same zeros of energy at this point. The curve of $\mu(\mathrm{CPS})$ versus q is in fact a straight line, whose slope can be computed by

$$\mathrm{d}\mu(\mathrm{CPS})/\mathrm{d}q = \left[\mu(\mathrm{X}) - \mu(\mathrm{X})^+\right] / [q(\mathrm{X}) - q(\mathrm{X}^+)], \quad (6)$$

where $\mu(\mathrm{X})$ and $\mu(\mathrm{X}^+)$ are classically computed chemical potentials of the reduced and oxidized states, respectively. Meanwhile, it can be shown that

$$\mathrm{d}\mu(\mathrm{e}^-)/\mathrm{d}q\,|_{x_+=0.5} = 4k_\mathrm{B}T \,/\, [q(\mathrm{X}) - q(\mathrm{X}^+)], \quad (7)$$

and

$$\mathrm{d}^2\mu(\mathrm{e}^-)/\mathrm{d}q^2\,|_{x_+=0.5} = 0. \quad (8)$$

This leads to

$$[\mu(\mathrm{X}) - \mu(\mathrm{X}^+)] = 4k_\mathrm{B}T. \quad (9)$$

Similarly, if Eq. 2 is applied, one has

$$[\mu(\mathrm{X}^-) - \mu(\mathrm{X})] = 4k_\mathrm{B}T. \quad (10)$$

In our implementation, T is therefore determined automatically by the QMMM [40] program according to Eq. 9 or 10.

3 Computation

The FBRC and FBRCD schemes have been implemented in a new version of the QMMM [40] program. Both schemes were assessed by comparing the atomic partial charges of the PS atoms, the amounts of charge transferred between the PS and SS, and the optimized geometries with full-QM calculations on the entire systems. The test suite includes molecular ions and amino acids with charged side chains. Each amino acid is capped by an acetyl (Ace) group at the N-terminal and by an *N*-methylamine (NMe) at the C-terminal. The QM/MM boundary is indicated by a dash line between the SS and PS for each molecular ion in Table 2. For each amino acid, the QM/MM boundary passes through the C_α–C_β bond; the backbone is the SS, and the side chain is the PS.

Two QM levels of theory have been tested, which are HF/MIDI! [41, 42] and B3LYP/6-31G(d) [43–47]. The MM force field is OPLS-AA [48–53]. For the molecular ions, we have tested two kinds of MM charges as the initial charges assigned to the SS atoms: the OPLS-AA charges and ESP charges (i.e., charges fitted to electrostatic potentials using the Merz-Kollman [54, 55] algorithm as obtained previously in the study [26] of the RC and RCD schemes). For the amino acids, only the OPLS-AA charges are employed for the SS atoms. 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 [56] program is employed for QM calculations, TINKER [57] is used for MM calculations, and QMMM [40] is utilized for QM/MM calculations. Both the QM and QM/MM geometries are optimized by using the Gaussian03 program. No symmetry constraint is imposed. The classical electronegativity equalization calculations are carried out by employing the modified QEq-SCT model [29, 33].

4 Results and discussion

4.1 Atomic partial charges of the CPS atoms

We list the atomic partial charges of the CPS atoms in Table S1 in the electronic supplementary material for all model systems in the test suite. The full-QM calculations are also included for comparison, where the partial charges on the PS atoms are given. Please note that the hydrogen-link (HL) atoms, which appear only in the QM/MM calculations, carry certain amounts of charges. It is well known that the "atomic partial charge" is generally not experimentally measureable, and it is debatable that one set of charges is more "correct" than another. To this end, we have documented both the Löwdin [58] charges and Mulliken [59] charges. In general, the Mulliken charges are notably larger in magnitude than the Löwdin charges. In particular, Mulliken charges larger than 1.0 e have been observed in the calculations with QM = HF/MIDI! for the C atoms in the COO^- groups in $CH_3CH_2COO^-$ and Ace–Glu^-–NMe.

The performance by the flexible-boundary treatments is assessed by the mean signed deviations (MSD) and mean unsigned deviations (MUD) tabulated in Table 1, which are computed by using the full-QM results as reference and by averaging over all molecular ions (or amino acids) in the test suite for a given type of QM/MM calculations. It can be seen that the performance of FBRC and FBRCD are very similar, with minor difference in all listed MUD ($\leq$0.005 e). Also, the calculations for the molecular ions initiated with OPLS-AA charges and initiated with ESP charges give roughly the same MSD and MUD. We notice that the MUD computed by using the Mulliken charges as reference are larger than the MUD computed by using the Löwdin charges as reference; this can be attributed to the generally larger values of the Mulliken charges than of the Löwdin charges. The performances by both QM levels of theory are rather similar, implying weak dependence on the selected QM level of theory. Averaging all the MUD listed in Table 1 leads to an average MUD (called AMUD) of 0.06 e, which can be taken as a measure of the accuracy in the atomic partial charge of the CPS achieved by the current implementation of the flexible-boundary treatments.

In Ref. [23], we reported an AMUD of 0.16 e for the atomic partial charges when applied the flexible-boundary

Table 1 Mean signed deviations (MSD) and mean unsigned deviations (MUD) for the atomic partial charges (in e) at the CPS atoms

	Löwdin[a]				Mulliken[b]			
	OPLS[c]		ESP[d]		OPLS[c]		ESP[d]	
	FBRC	FBRCD	FBRC	FBRCD	FBRC	FBRCD	FBRC	FBRCD
QM = HF/MIDI!								
Molecular ions								
MSD	0.005	0.003	0.010	0.014	–0.017	–0.019	–0.010	–0.004
MUD	0.050	0.053	0.048	0.053	0.075	0.080	0.072	0.074
Amino acids								
MSD	–0.002	0.0004	n/a	n/a	–0.010	–0.006	n/a	n/a
MUD	0.039	0.037	n/a	n/a	0.034	0.033	n/a	n/a
QM = B3LYP/6-31G(d)								
Molecular ions								
MSD	–0.010	–0.013	–0.006	–0.003	–0.014	–0.015	–0.007	–0.001
MUD	0.065	0.063	0.065	0.066	0.078	0.081	0.077	0.077
Amino acids								
MSD	–0.005	–0.003	n/a	n/a	–0.004	0.0001	n/a	n/a
MUD	0.022	0.022	n/a	n/a	0.032	0.030	n/a	n/a

The MM is OPLS-AA

[a] Full-QM Löwdin charges as reference data

[b] Full-QM Mulliken charges as reference data

[c] Calculations initiated by using OPLS-AA charges as the MM charges

[d] Calculations initiated by using ESP charges as the MM charges

treatment to study ion–solvent complexes. That value (0.16 e) was, however, computed for both the PS and SS atoms. If only the PS atoms were considered, the AMUD was 0.13 e, which is still substantially bigger than the AMUD obtained in this work (0.06 e) for the molecular ions and amino acids. This is because there are more PS atoms in the model systems tested here than in the ion–solvent complexes studies in Ref. [23]. In general, atomic partial charges on PS atoms distance from the QM/MM boundary display better agreement between the QM/MM calculations and full-QM calculations, and having more such atoms reduces the MUD and AMUD.

4.2 Charge transfer between the CPS and SS

First, we look at the total charge on the CPS. Table 2 shows the total charges on CPS calculated by the flexible-boundary QM/MM treatments for the molecular ions and for the amino acids, respectively. The total charges on the PS by full-QM calculations are also included for comparison. The FBRC and FBRCD schemes have obtained reasonable agreement with full-QM calculations for all molecular ions except CF_3–CH_2O^-, and again, both QM levels of theory give very similar results. For CF_3–CH_2O^-, the full-QM calculations show that the majority of the

Table 2 Total charges (in e) on the PS (or CPS in the QM/MM cases)

	Full-QM		QM/MM			
	Löwdin	Mulliken	OPLS-AA[a]		ESP[b]	
			FBRC	FBRCD	FBRC	FBRCD
QM = HF/MIDI!						
Molecular ions						
CH_3–CH_2O^-	–0.821	–0.771	–0.789	–0.793	–0.839	–0.788
CH_3–CH_2S^-	–0.906	–0.886	–0.789	–0.855	–0.788	–0.790
CH_3–CH_2COO^-	–0.942	–0.949	–0.927	–0.934	–0.924	–0.926
CF_3–CH_2O^-	–0.829	–0.798	–0.360	–0.399	–0.298	–0.323
CH_3–$CH_2NH_3^+$	0.901	0.836	0.804	0.794	0.810	0.808
CH_2OH–CH_2O^-	–0.807	–0.762	–0.802	–0.799	–0.800	–0.731
CH_2OH–CH_2S^-	–0.889	–0.869	–0.728	–0.725	–0.726	–0.723
Amino acids						
Ace–Lys^+–NMe	0.990	1.015	0.988	0.987	n/a	n/a
Ace–Tyr^-–NMe	–0.917	–0.868	–0.888	–0.892	n/a	n/a
Ace–Glu^-–NMe	–0.908	–0.844	–0.771	–0.773	n/a	n/a
Ace–His^+–NMe	0.955	0.981	0.940	0.940	n/a	n/a
QM = B3LYP/6-31G(d)						
Molecular ions						
CH_3–CH_2O^-	–0.807	–0.773	–0.793	–0.851	–0.791	–0.792
CH_3–CH_2S^-	–0.908	–0.897	–0.789	–0.792	–0.785	–0.787
CH_3–CH_2COO^-	–0.932	–0.902	–0.886	–0.895	–0.880	–0.927
CF_3–CH_2O^-	–0.763	–0.832	–0.282	–0.395	–0.297	–0.320
CH_3–$CH_2NH_3^+$	0.891	0.854	0.805	0.796	0.814	0.811
CH_2OH–CH_2O^-	–0.798	–0.754	–0.799	–0.796	–0.797	–0.791
CH_2OH–CH_2S^-	–0.881	–0.873	–0.729	–0.727	–0.728	–0.725
Amino acids						
Ace–Lys^+–NMe	0.886	0.903	0.987	0.987	n/a	n/a
Ace–Tyr^-–NMe	–0.878	–0.859	–0.882	–0.886	n/a	n/a
Ace–Glu^-–NMe	–0.863	–0.840	–0.849	–0.852	n/a	n/a
Ace–His^+–NMe	0.844	0.878	0.939	0.939	n/a	n/a
MSD (Löwdin)[c]			0.081	0.066	0.104	0.106
MUD (Löwdin)[c]			0.100	0.091	0.131	0.131
MSD (Mulliken)[d]			0.064	0.050	0.096	0.098
MUD (Mulliken)[d]			0.094	0.087	0.130	0.122

The molecular ions are given as SS–PS. For the amino acids, the QM/MM boundary passes though the C_α–C_β bond, the backbone is the SS, and the side chain is the PS. The MM force field is OPLS-AA

[a] Calculations initiated by using OPLS-AA charges as the MM charges

[b] Calculations initiated by using ESP charges as the MM charges

[c] Full-QM Löwdin charges as reference data

[d] Full-QM Mulliken charges as reference data

charge (approximately –0.8 e) reside at the PS, while the QM/MM calculations display that the charge mostly locates at the SS, leaving only –0.3 to –0.4 e at the CPS. Closer examination reveals that the electronegativity of F atom in the SS is overestimated in the flexible-boundary treatments. In the QM/MM calculations, the charges at the F atoms are –0.4 to –0.5 e, and the charge at the C atom is 0.5 e, giving rise to a rather large negative charge (–0.6 to –0.7 e) at the SS. In contrast, the full-QM HF/MIDI! calculations obtain Löwdin charges –0.3 e for the F atoms and 0.7 e for the C atom, leading to a total –0.2 e charge for the CF_3 moiety. The full-QM B3LYP/6-31G(d) calculations yield Löwdin charges –0.2 e for the F atoms and 0.3 e for the C atom, also leading to a total –0.2 e charge for the CF_3 moiety. The full-QM HF/MIDI! [or B3LYP/6-31G(d)] Mulliken charges are –0.5 e (or –0.3 e) for the F atoms and 1.3 e (or 0.7 e) for the C atom in the CF_3 fragment; although the charge at the C atom is probably too large, the total charge of –0.2 e for the CF_3 moiety is similar to the Löwdin charge.

The poor QM/MM results for CF_3–CH_2O^- are probably due to the inconsistency between the QEq-SCT model parameters for the F atom and the current implementation of flexible-boundary treatments. It should be noted that we have not optimized any parameters in the classical electronegativity equalization models for the flexible-boundary treatments. Optimization of the QEq-SCT parameters will likely improve the agreement between QM and QM/MM results; however, we have not done so, because we want to examine how well the FBRC and FBRCD schemes can do employing the literature parameters. Systematic improvement of the FBRC and FBRCD schemes, including the optimization of those parameters and perhaps the modification of the classical electronegativity equalization models for the flexible-boundary treatments, will be carried out in the future.

For all amino acid model systems, the FBRC and FBRCD have obtained CPS charges in reasonably good agreement with full-QM calculations. The full-QM Mulliken charge at the CPS of Ace–Lys^+–NMe is larger than 1.0 e in the HF/MIDI! calculations, which is not realistic; such a problem is not present in the flexible-boundary treatments, because the CPS charge is an ensemble average over the selected oxidized and reduced states and will always be in the range of 0–1 e.

Averaging all the MUD listed in Table 2 yields an AMUD of 0.11 e, which indicates the accuracy in the total charge of the CPS achieved by the current implementation of the flexible-boundary treatments. Such accuracy is probably acceptable for systems with formally charged PS. It is interesting to note that the AMUD of 0.11 e obtained here is almost the same as the AMUD (0.13 e) obtained previously for the ion–solvent complexes [23], where the QM/MM boundaries do not pass through covalent bonds.

The total charge of the CPS relates to the amount of charge transfer between the CPS and the SS by $q_{\mathrm{trans}} = q_{\mathrm{formal}}(\mathrm{CPS}) - q(\mathrm{CPS})$, where $q_{\mathrm{formal}}(\mathrm{CPS})$ is the formal charge on the CPS. Similarly, the amount of charge transfer in full-QM calculations can be computed by $q_{\mathrm{trans}} = q_{\mathrm{formal}}(\mathrm{PS}) - q(\mathrm{PS})$, where $q_{\mathrm{formal}}(\mathrm{PS})$ is the formal charge on the PS. Because the formal charge on the CPS or PS is a constant, the MUD (and AMUD) in the amount of charge transfer between the CPS and SS are the same as the MUD (and AMUD) in the total charge of the CPS. Therefore, the AMUD is 0.11 e for the amounts of the transferred charge.

4.3 Geometry

The next quantity we examine is the Q1–M1 bond distances, where Q1 is a QM atom that is directly bonded to the M1 atom. Table 3 lists the Q1–M1 bond distances. We found that, in comparison with our previously developed boundary treatments, the flexible-boundary treatment improves significantly the Q1–M1 bond distance for molecular ions. Taking the calculations with QM = HF/MIDI! for example, the AMUD are 0.029 Å for the RC and RCD treatments and 0.030 Å for the PBRC and PBRCD treatments, respectively; the AMUD are computed based on the data in Table 3 in Ref. [29]. In contrast, the AMUD obtained by the FBRC and FBRCD schemes for molecular ions is 0.019 Å, an approximately 30% reduction. The most notable enhancement is observed for CF_3–CH_2O^- and CH_2OH–CH_2O^-, where atoms with significant charges are present in very close vicinity of the QM/MM boundary. For example, in the calculations with QM = HF/MIDI!, the Q1–M1 bond distance for CF_3–CH_2O^- is overestimated by 0.10 Å in the RC and the PBRC calculations and by 0.15 Å in the RCD and the PBRCD calculations [26, 29]. In comparison, the FBRC and FBRCD schemes reduce the deviations to 0.02 and 0.04 Å, respectively, even though the QEq-SCT model parameters for the F atom might not be the best ones. The better results by the flexible-boundary treatments confirm that partial charge transfer between the PS and SS is most critical when significantly charged PS atoms locate near the QM/MM boundary. This conclusion is supported by the observation that the improvement in the Q1–M1 bond distances by the FBRC and FBRCD treatments is rather small for amino acids, where the PS atoms that carry significant charges are more distant from the QM/MM boundaries. Overall, the FBRC and FBRCD schemes reproduce the full-QM Q1–M1 bond distances fairly well, and the AMUD is computed to be 0.016 Å.

Table 3 Q1–M1 bond distances (in Å)

	Full-QM	QM/MM			
		OPLS-AA[a]		ESP[b]	
		FBRC	FBRCD	FBRC	FBRCD
QM = HF/MIDI!					
Molecular ions					
CH_3–CH_2O^-	1.594	1.547	1.538	1.556	1.551
CH_3–CH_2S^-	1.550	1.524	1.517	1.529	1.527
CH_3–CH_2COO^-	1.533	1.527	1.522	1.531	1.529
CF_3–CH_2O^-	1.521	1.545	1.563	1.539	1.552
CH_3–$CH_2NH_3^+$	1.528	1.523	1.519	1.526	1.525
CH_2OH–CH_2O^-	1.561	1.564	1.572	1.568	1.574
CH_2OH–CH_2S^-	1.525	1.532	1.536	1.534	1.540
Amino acids					
Ace–Lys$^+$–NMe	1.533	1.541	1.543	n/a	n/a
Ace–Tyr$^-$–NMe	1.569	1.552	1.555	n/a	n/a
Ace–Glu$^-$–NMe	1.550	1.547	1.548	n/a	n/a
Ace–His$^+$–NMe	1.558	1.550	1.552	n/a	n/a
QM = B3LYP/6-31G(d)					
Molecular ions					
CH_3–CH_2O^-	1.571	1.556	1.545	1.564	1.560
CH_3–CH_2S^-	1.535	1.530	1.522	1.536	1.533
CH_3–CH_2COO^-	1.529	1.533	1.526	1.539	1.536
CF_3–CH_2O^-	1.550	1.570	1.594	1.565	1.576
CH_3–$CH_2NH_3^+$	1.519	1.531	1.524	1.535	1.533
CH_2OH–CH_2O^-	1.557	1.579	1.589	1.584	1.600
CH_2OH–CH_2S^-	1.519	1.541	1.547	1.544	1.553
Amino acids					
Ace–Lys$^+$–NMe	1.531	1.551	1.555	n/a	n/a
Ace–Tyr$^-$–NMe	1.569	1.562	1.568	n/a	n/a
Ace–Glu$^-$–NMe	1.553	1.556	1.559	n/a	n/a
Ace–His$^+$–NMe	1.564	1.560	1.564	n/a	n/a
MSD		0.000	0.002	0.004	0.007
MUD		0.013	0.018	0.014	0.019

The molecular ions are given as SS–PS. For the amino acids, the QM/MM boundary passes though the C_α–C_β bond, the backbone is the SS, and the side chain is the PS. The MM force field is OPLS-AA

[a] Calculations initiated by using OPLS-AA charges as the MM charges

[b] Calculations initiated by using ESP charges as the MM charges

5 Conclusion

In the present contribution, we report an attempt to combine the flexible-boundary QM/MM scheme with the RC and RCD boundary treatments. This leads to the FBRC and FBRCD schemes, both of which can model partial charge transfer and mutual polarization between the QM and MM subsystems that are connected by a covalent bond. The FBRC and FBRCD schemes are tested on a set of molecular ions and amino acids with charged side chains. Overall, reasonable agreements with full-QM calculations have been observed for the partial charges at the QM atoms (0.06 e), for the total charge on the QM subsystem or the amounts of the charge transfer between the QM and MM subsystems (0.11 e), and for the Q1–M1 bond distances (0.016 Å), where the AMUD values are given in parentheses. The results obtained here, together with the calculations on the ion–solvent complexes reported earlier [23], demonstrate the importance of accounting for the partial charge transfer across the QM/MM boundary for systems with charged QM subsystems.

In this paper, we also introduce an automatic method to determine the electronic temperature parameter by relating the electronic temperature to the difference in the classically computed electronic chemical potentials between the oxidized and reduced states of the QM subsystem. The justification is that the electronic chemical potential curves of the QM subsystem determined by QM calculations and by classical electronegativity equalization models will have the same values and slopes (with respect to the total charge at the QM subsystem) when the oxidized and reduced states are equally populated. This seems to greatly reduce the arbitrariness in the temperature parameter, as it can be seen from Table S2 in the electronic supplementary material that all QM/MM calculation with various QM levels of theory, initial MM charges, and boundary (FBRC or FBRCD) schemes yield almost identical values for the temperature parameter.

Despite the encouraging agreements above, problems remain. The first problem is the inconsistency between the QEq-SCT model parameters for some atoms (e.g., the F atom) and the current implementation of the flexible-boundary treatment. This has led to poor results in the amount of charge transfer between the QM and MM subsystems for CF_3–CH_2O^-. Moreover, the accuracy (0.11 e) in the charge transfer between the QM and MM subsystems is not very high; it is acceptable for systems with formally charged QM subsystems, but seems insufficient for systems with charge-neutral QM subsystems, which are a lot more sensitive to the variations in charge transfer due to the much smaller magnitudes of total charges (0.1 e or less) at the QM and MM subsystems. Although our main goal is to develop methods for QM/MM simulations of ion transport processes, it would be excellent if the methods can work equally well for charge-neutral molecules. Optimization of the parameters and/or modification of the classical electronegativity equalization models will likely improve the agreement between full-QM and QM/MM results, but that is not trivial. Work is needed in the future in order to enhance the accuracy of the flexible-boundary treatments.

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