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Electrostatic Interaction of the Electrostatic-Embedding and Mechanical-Embedding Schemes for QM/MM Calculations

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Abstract: The geometries of the system including two waters have been optimized by the full quantum calculations with the constraints of the O—O distance. The HF and B3LYP density function levels with STO-3G, 6-31G, 6-31G*, and 6-31++G** four basis sets were used in the optimizations. At the optimized geometries, the QM/MM single point interaction energies of the electrostatic-embedding and mechanical-embedding schemes were calculated. The QM/MM interaction energies were compared with the full quantum calculations. The results reveal that the basis sets could be important in the QM/MM calculations. The QM/MM method of the two schemes could not accurately describe the energy of the structure. The electrostatic and VDW interaction energy between QM and MM regions of the electrostatic-embedding scheme is better than that of the mechanical-embedding scheme at the 6-31G and 6-31G* levels. At the 6-31++G** level, the energies of the two schemes are in good agreement with the full quantum calculations. Present investigation suggests that the electrostatic-embedding scheme could be more suitable in the QM/MM simulations of very large systems, e.g. emzyme reaction. The cutoff radius of the electrostatic-embedding scheme is at least $25a_0$.

AMS subject classifications: 80A50, 92C40

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Combined quantum-mechanical and molecular-mechanical (QM/MM) method has been widely applied in the investigations of the complex large systems over the past decade [1-5]. In the method, the full system is partitioned into the reactive region which is treated at the quantum mechanical (QM) level and the region of surrounding environment which is treated at the molecular mechanics (MM) level. In principal, the approach combines the QM accuracy with the MM low computational cost. The total QM/MM energy of the full system can be given by the sum of the QM energy, the MM energy, and the QM/MM interaction energy between the QM and MM regions [5].

$$E(\mathrm{QM/MM}) = E(\mathrm{QM}) + E(\mathrm{MM}) + E_{int}(\mathrm{QM–MM}), \quad (1)$$

E(QM), E(MM) and E_{int}(QM–MM) correspond to QM region energy, MM region energy, and inteaction energy between QM and MM regions, respectively. E(QM) can be obtained by the the calculations of electronic-structure program. E(MM) is given by the compuations of MM force fields. The calculation of E_{int}(QM–MM) is more complex and a center of the QM/MM methodology. The interaction energy includes the bonding interactions, van der Waals (VDW) interactions, and electrostatic interactions. As the QM/MM boundary cutting the covalent bond, the special treating models (e.g. link atom [6-9], localized orbital [10-13], pseudo-atom model [14-16] *etc*) are required to saturate the dangling bond. In general, the van der Waals interactions are evaluated by the MM calculations. The treatment of electrostatic interactions has the different schemes in various QM/MM calculations. The schemes have been classified by Bakowies and Thiel into two general types which refer to the mechanical-embedding (ME) and electrostatic-embedding (EE) [17].

In ME scheme, QM energy is calculated in the gas phase. The electrostatic interactions between the QM and MM regions are computed by Coulomb's law of the MM level using atomic charges on the QM and MM atoms. In EE scheme, the point charges on the MM atoms are involved in QM Hamiltonian operators. It means that the electrostatic interaction of the scheme between the QM and MM regions is calculated at QM level. In the treatment, QM region is polarized by MM region, but MM region is not polarized by QM region. Recently, several mutual polarized embedding schemes were developed to allow the polarization of QM and MM regions with each other [18-23]. Theoretically, the electrostatic interaction computed by the EE scheme is more accurate than that of the ME scheme. Nevertheless, the MM partial atomic charges are generally used in the QM/MM schemes to describe the MM atomic charge density because most MM force fields contain the charge parameters to compute the electrostatic interactions at the MM level. The MM partial atomic charges are a part of the parameters for a whole MM force field which also includes the van der Waals parameters etc. It suggests that the charge parameters are fitted to calculate the

MM electrostatic interaction energies, and not designed for the QM/MM computations. Although many QM/MM calculations have successfully used the two schemes to investigate the large systems, the detailed discussion of the electrostatic interaction for the EE and ME schemes is absent. The accuracy of the two schemes to describe the electrostatic interaction in the calculation is also ambiguous.

We scan the potential energy surfaces (PES) of the system consisting of two water molecules *A* and *B* along the O—O distance to investigate the interaction energy between the QM and MM parts in the QM/MM calculations. The geometry of the full system was optimized by full QM with the constraints of the O—O distance. At the each optimized geometry, the QM/MM SP calculations using the ME and EE schemes, in which water *A* is treated by QM and water *B* is MM, were carried out. Two models were used to calculate the interaction between water *A* and *B*. In the first model, the full QM and QM/MM interaction energies between two waters can be defined by

$$E_{int}^{a}(\mathrm{QM};AB) = E(\mathrm{QM};AB) - E_{1}(\mathrm{QM};A) - E_{1}(\mathrm{QM};B), \quad (2)$$

$$E_{int}^{a}(\mathrm{QM/MM};AB) = E(\mathrm{QM/MM};AB) - E_{1}(\mathrm{QM};A) - E_{1}(\mathrm{MM};B), \quad (3)$$

where $E(\mathrm{QM};AB)$ and $E(\mathrm{QM/MM};AB)$ are the full QM and AM/MM single point (SP) total energy of *AB* molecule consisting of two waters at the full QM optimized geometry, respectively. $E_1(\mathrm{QM};A)$, $E_1(\mathrm{QM};B)$, and $E_1(\mathrm{MM};B)$ are the referenced energies. We first optimized the geometry of the isolated water molecue by full QM. At the optimized geometries, we calculated the full QM SP energies $E_1(\mathrm{QM};A)$ and $E_1(\mathrm{QM};B)$ and MM SP energy $E_1(\mathrm{MM};B)$. In the second model, the full QM and QM/MM interaction energies between two waters are given by

$$E_{int}^{b}(\mathrm{QM};AB) = E(\mathrm{QM};AB) - E_{2}(\mathrm{QM};A) - E_{2}(\mathrm{QM};B), \quad (4)$$

$$E_{int}^{b}(\mathrm{QM/MM};AB) = E(\mathrm{QM/MM};AB) - E_{2}(\mathrm{QM};A) - E_{2}(\mathrm{MM};B), \quad (5)$$

Here the geometries of monomeric water *A* and *B* to compute the referenced energies were taken from the structure of *AB* molecule by full QM constrained optimizations. $E_2(\mathrm{QM};A)$ and $E_2(\mathrm{QM};B)$ are the full QM SP energies of monomeric water *A* and *B*. $E_2(\mathrm{MM};B)$ is the MM SP energy at the geometry of monomeric water *B*.

In the present computation, the full QM calculations were doned by the Turbomole 6.3 program [24]. The ChemShell 3.4 package was used in the QM/MM calculations[25]. MM water was treated by the TIP3P model[26]. We performed the QM calculations at the HF [27] and B3LYP [28] density function levels using four basis sets including the STO-3G [29], 6-31G [30], 6-31G*[31], and 6-31++G**[32] to study the effect of the methods of electronic structure theory and basis on the interaction energy between two waters. The step size of the PES scan by the constrained full QM optimization is 0.1 a_0. The DL-FIND optimizer implemented in the ChemShell package was applied to optimize the geometries [33].

As a system including two waters, one water molecule can be polarized by the other. The polarization would induce the change of the water molecular structure. The interaction energies E_{int}^{a}(QM;*AB*) and E_{int}^{a}(QM/MM;*AB*) of the first model contains the energy produced by the structural change[34]. Moreover, the interaction energy also includes the electrostatic and VDW interactions between two waters. For the QM/MM SP computations applying the ME and EE schemes, the referenced energies E_1(QM;*A*) and E_1(MM;*B*) are equal. VDW interaction and the energy produced by the change of the water molecular structure for the EE calculations are the same with those for the ME scheme at the geometry of the constrained optimization. Thus, it could be concluded that the deviation of the interaction energy E_{int}^{a}(QM/MM;*AB*) should be caused by the methodology to treat the electrostatic interaction between two waters in the QM/MM calculations of the EE and ME schemes.

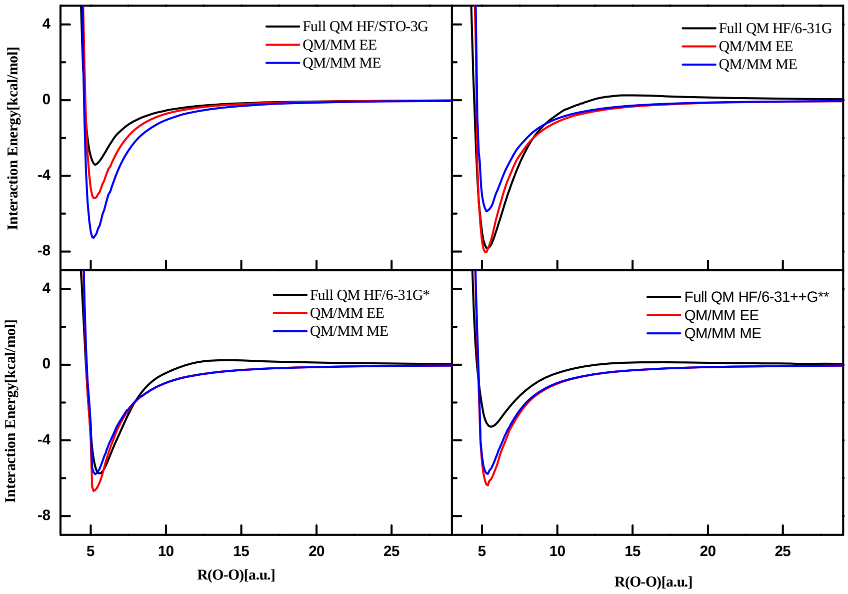

Figure 1: Interaction energies Einta (QM; AB) and Einta (QM/MM; AB) of the full QM and QM/MM calculations as a function of the O—O distance. The energies contain the contribution of the structural change and the electrostatic and VDW interactions between two waters.

Figure 1 shows the interaction energies E_{int}^{a} (QM; *AB*) and E_{int}^{a} (QM/MM; *AB*) of the full QM and QM/MM calculations as a function of the O—O distance. Full QM results indicate that the interaction energy between two waters is very small at larger O—O distance, e.g. >25a_0. It suggests that the mutual polarization between two waters could be negligible when the O—O distance is longer than 25a_0. Consequently, the EE and ME QM/MM results are well consistent with the full QM calculations. The interaction energies E_{int}^a (QM/MM; AB) of the EE and ME QM/MM calculations have an evident difference only near the equilibrium position, at which E_{int}^a (QM/MM; AB) has a minimum. The deviation would decrease as the basis set enlarges. Particularly, the interaction energies of the EE and ME scheme at the 6-31++G** level are very close. Observing the **Figure 1**, it could be found that the calculations using HF and B3LYP density function give the similar results. However, the mutual polarization between two waters becomes more important when the O—O distance is shorter than 25a_0. The interaction energies E_{int}^a (QM/MM; AB) of the QM/MM calculations obviously disagree with the full QM results.

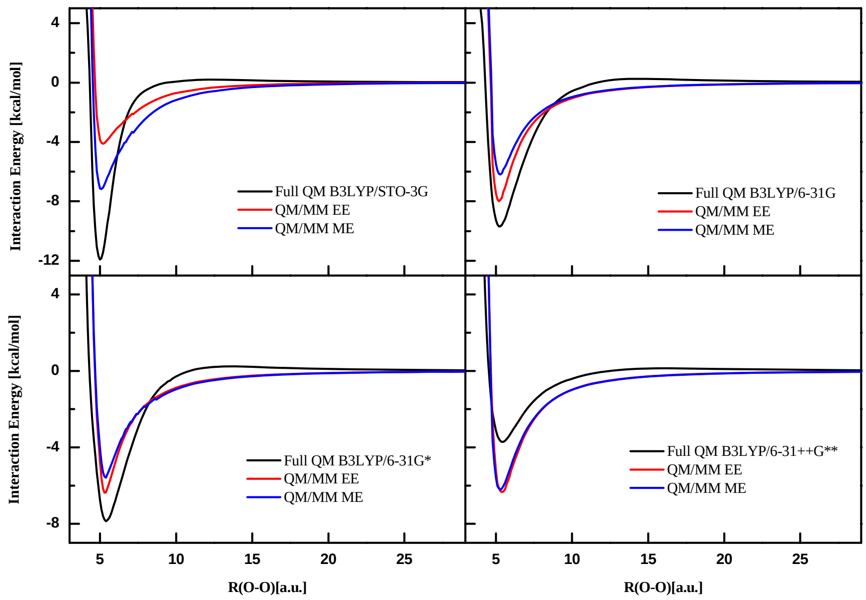

Figure 2: Interaction energies Eintb(QM;AB) and Eintb(QM/MM;AB) including of the electrostatic and VDW interactions between two waters as a function of the O—O distance. The full QM and QM/MM results are plotted.

The deviation of the interaction energies E_{int}^a (QM; AB) and E_{int}^a (QM/MM; AB) for the full QM and QM/MM calculations could partly comes from the contribution of the water structure change based on the defination. In order to further investigate the electrostatic interaction in the two QM/MM schemes, we computed the the interaction energies E_{int}^b (QM; AB) and E_{int}^b (QM/MM; AB) of the second model which only contains the the electrostatic and VDW interactions between two waters. **Figure 2** displays the interaction energy E_{int}^{b} (QM; *AB*) and E_{int}^{b} (QM/MM; *AB*) of the full QM and QM/MM calculations. The electrostatic interaction between two waters could be affected by the method and basis of the electric structure in the QM/MM calculations. The results using the HF and B3LYP levels using four basis sets are presented. As shown in the figure, the QM/MM interaction energy E_{int}^{b} (QM/MM; *AB*) at the 6-31G and 6-31G* levels is in good agreement with that of full QM when the O—O distance is longer than 15a_0. At the 6-31++G** level, the full QM and QM/MM results are very close. It is noticeably different from the interaction energy of the first model. The resutl reveals that QM/MM calculations could not exactly reproduced the contribution of the structure change when the polarization between two waters is more important. An essential factor that creates the inaccuracy for the energy of the structure change could be the parameters of the TIP3P water model. The parameters are fitted based on the classical Monte Carlo simulations. Therefore, the energy of the water structure change at the geometry of the shorter O—O distance could not be correctly described.

The QM/MM calculations of the EE and ME schemes by the the HF and B3LYP levels with the small basis (STO-3G, 6-31G, and 6-31G*) could not accurately give the electrostatic interaction between two waters near the equilibrious geometries. Because the QM/MM calculations of the EE scheme using the STO-3G basis underestimate the polarization between the background charges and QM atoms, the interaction energy E_{int}^{b} (QM/MM; *AB*) of the EE scheme is larger than that of the ME scheme. The result of the 6-31G, and 6-31G* basis is reverse. At the 6-31++G** level, the interaction energy E_{int}^{b} (QM/MM; *AB*) of the EE scheme is close to the ME QM/MM calculations. It seems that the results could not be affected by the method of the electronic structure calculations.

In summary, we investigate the interaction energy of the QM/MM calculations using the EE and ME schemes in present work. The full QM and QM/MM calculations were performed using the HF and B3LYP levels using four basis sets. We compared the QM/MM results with the full QM calculations. It could be found that the basis could be very important in the QM/MM calculations. The calculations at the HF and B3LYP levels give the similar results. Furthermore, the present investigation suggests that the QM/MM computations of the two schemes could not correctly give the energy of the structure except for the large O—O distance. At the 6-31++G** level, the electrostatic and VDW interactions between two waters computed by the QM/MM EE and ME schemes are very close. The QM/MM electrostatic and VDW interactions consist with the full QM calculations. For the QM/MM computations at the 6-31G and 6-31G* levels, the electrostatic and VDW interaction energy of the EE scheme is better than the ME scheme. However, the charge parameters of QM region are not well fitted in some QM/MM simulations, e.g. emzyme reaction. The

QM/MM ME calculations could not correctly compute the electrostatic interaction energy between QM and MM regions. Therefore, the EE scheme is more suitable in most QM/MM calculations. For very large systems, the QM calculations embedded in the background point charges could not include all the charges due to the expensive computational cost. The cutoff radius is an important parameter in the EE scheme to determine the charge number which is involved in the embedded QM calculation. The present calculations imply that the cutoff radius is at least $25a_0$.

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