

Atomic charges in molecular mechanical force fields: A theoretical insight

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Based on quantum theory of the Coulombic interactions between a molecule and its surrounding molecules, a theoretical derivation is presented to obtain an atomic charge model. The charge model shows that the appropriate atomic charge, used for example in molecular mechanical force fields, is simply the average value of the electrostatic potential (ESP) derived charge for an isolated molecule and that obtained for the molecule in the interaction system. Computational scheme to calculate the ESP derived atomic charges of a molecule in the interaction system is presented. The method is applied to two common liquids with associated hydrogen bonds: water and methanol. The obtained theoretical atomic charges are similar to those found in the common interaction potential models, such as: SPC, TIP3P, OPLS, etc. However, for methanol they differ considerably from those obtained using the restrained ESP method.

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I. INTRODUCTION

The concept of partial atomic charges is fundamental to chemistry and molecular physics. It provides a simple and effective way to describe the electronic charge distribution in a molecule, essential in understanding the properties of the molecule. Atomic charges can be used to elucidate chemical processes and rationalize mechanisms behind chemical reactions [1]. In the calculation of intermolecular interactions, atomic charges provide a model to calculate long-ranged electrostatic interactions between the molecules.

Molecular mechanical (MM) force fields use fractional point charges on atomic sites to describe the net Coulombic interactions between molecules or so called nonbonded parts of the same molecule. This requires a careful development of the charge model. How to actually derive a set of suitable charges for MM force fields is, however, still far from clear. Although the atomic charges, derived by fitting the electrostatic potential (ESP) in the van der Waals region [2–5], can often satisfactorily be used to simulate the electrostatic interactions between the molecules, it is not clear how the polarization effects can be included quantitatively in the charge model. In the OPLS force field [6], the charge on an atom is usually considered as an empirical parameter and is optimized through liquid simulations. In the AMBER force field [7], the ESP derived atomic charges are obtained by *ab initio* quantum chemistry calculation of the gas state molecule. In order to include polarization of a molecule by the surrounding molecules in the interaction system, a suitable basis set [usually 6–31G(d)], which is assumed to provide a prepolarization description of the molecule, is often used [7–9]. Sometimes atomic charges, determined by reproducing the interaction energies and minimum geometries for some model supermolecules are also used in the development of force fields [10–12]. Clearly, the lack of a sound theoretical basis in determining a partial charge on an atomic site makes often a set of atomic charges used in one force field quite different from that found in a second force field. This can

make it particularly confusing to choose the atomic charges suitable for a molecule where there are so far no available and tested atomic charges found in the literature.

In this paper, we present a theoretical derivation, based on quantum theory of Coulombic interactions between a molecule and its surrounding molecules. The obtained resulting charge model shows that the best atomic charge for the MM force fields corresponds simply to the average of the ESP derived charge from the isolated molecule and that from the molecule in the interaction system. Also, we present a computational approach to calculate the ESP derived atomic charges of a molecule in the interaction system.

The derived formalism is further applied on liquid water and methanol: two typical hydrogen bond systems and common solvents both in experimental and computer simulation works. Because the polarization effects in these two liquids are large, it can be expected that the atomic charges in the liquid states differ considerably from those in the gas states. Another reason to choose these particular systems are the many MM force field models available for these two molecules, such as the SPC [13] and TIP3P [14] models for water, and OPLS [15] and restrained ESP (RESP) models for methanol [9]. Therefore, the atomic charges on water and methanol molecules should be two good examples to illustrate the theoretical charge model presented in this work. As an application of the method, the atomic charges on water and methanol molecules are calculated and compared with those from the widely used MM force field models.

II. THEORY AND COMPUTATIONAL DETAILS

A. Theoretical derivation

We first consider a system consisting of a single molecule *A* and its surrounding *S*.

The Hamiltonian of the system can be written as:

$$\hat{H} = \hat{H}_A^{(0)} + \hat{H}_S^{(0)} + \hat{H}_{AS}, \quad (2.1)$$

where $\hat{H}_A^{(0)}$ and $\hat{H}_S^{(0)}$ are the Hamiltonians of isolated *A* and *S*, respectively. \hat{H}_{AS} is the corresponding interaction between *A* and *S*.

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If we only consider the Coulombic interaction between the two parts and neglect the other interactions, the wave function of the system can be approximated as:

$$|\Psi\rangle = |\Phi_A\rangle|\Phi_S\rangle, \quad (2.2)$$

where $|\Phi_A\rangle$ and $|\Phi_S\rangle$ are the electronic states of A and S in the interaction system, respectively. $|\Phi_A\rangle$ only involves the coordinates of the electrons in A and $|\Phi_S\rangle$ involves those in S , thus:

$$\langle\Phi_A|\Phi_S\rangle = 0. \quad (2.3)$$

The normalization conditions for the two wave functions are:

$$\langle\Phi_A|\Phi_A\rangle = 1, \quad (2.4)$$

$$\langle\Phi_S|\Phi_S\rangle = 1. \quad (2.5)$$

The total energy of the system $E = \langle\Psi|\hat{H}|\Psi\rangle$, can be written as:

$$E = \langle\Phi_A|\hat{H}_A^{(0)}|\Phi_A\rangle + \langle\Phi_S|\hat{H}_S^{(0)}|\Phi_S\rangle + \langle\Phi_A\Phi_S|\hat{H}_{AS}|\Phi_A\Phi_S\rangle. \quad (2.6)$$

Thus, the net interaction energy between A and S , i.e., $\Delta E = E - E_A^{(0)} - E_S^{(0)}$, is:

$$\Delta E = \Delta E_A^{dist} + \Delta E_S^{dist} + \langle\Phi_A\Phi_S|\hat{H}_{AS}|\Phi_A\Phi_S\rangle, \quad (2.7)$$

where ΔE_A^{dist} and ΔE_S^{dist} can be considered as the energies required for distorting the electron distributions of A and S from their isolated states to those in the interaction system, respectively, with:

$$\Delta E_A^{dist} = \langle\Phi_A|\hat{H}_A^{(0)}|\Phi_A\rangle - E_A^{(0)}, \quad (2.8)$$

$$\Delta E_S^{dist} = \langle\Phi_S|\hat{H}_S^{(0)}|\Phi_S\rangle - E_S^{(0)}. \quad (2.9)$$

As we pointed out before, due to the limitation of the trial wave function used, only the Coulombic interactions between A and S are considered. Therefore, in Eq. (2.7), ΔE is simply the net Coulombic interaction between A and S in the interaction system. Obviously, due to the distortion of the electron distributions in A and S , ΔE is not strictly equal to the Coulombic interaction term.¹

By variationally optimizing the energy E with the restriction of the normalization conditions Eq. (2.4) and Eq. (2.5), we have the following two equations:

$$(\hat{H}_A^{(0)} + \langle\Phi_S|\hat{H}_{AS}|\Phi_S\rangle)|\Phi_A\rangle = E_A|\Phi_A\rangle, \quad (2.10)$$

$$(\hat{H}_S^{(0)} + \langle\Phi_A|\hat{H}_{AS}|\Phi_A\rangle)|\Phi_S\rangle = E_S|\Phi_S\rangle. \quad (2.11)$$

The above two equations can be considered as the eigen equations for A and S in the interaction system, respectively.

In principle, we can solve Eq. (2.10) and (2.11) self-consistently and obtain the interaction energy between A and

S . In order to obtain correct theoretical insight into the interaction energy, we try to use perturbation theory to derive further the expression for the energy.

In Eq. (2.10), $\langle\Phi_S|\hat{H}_{AS}|\Phi_S\rangle$ can be considered as the perturbation from the perturbed surrounding S to isolated molecule A . By introducing a perturbation parameter λ , we can write Eq. (2.10) as:

$$\hat{H}_A(\lambda)|\Phi_A(\lambda)\rangle = E_A(\lambda)|\Phi_A(\lambda)\rangle, \quad (2.12)$$

where

$$\hat{H}_A(\lambda) = \hat{H}_A^{(0)} + \lambda\langle\Phi_S|\hat{H}_{AS}|\Phi_S\rangle \quad (2.13)$$

and

$$|\Phi_A(\lambda)\rangle = |\Phi_A^{(0)}\rangle + \lambda|\Phi_A^{(1)}\rangle + \lambda^2|\Phi_A^{(2)}\rangle + \dots, \quad (2.14)$$

$$E_A(\lambda) = E_A^{(0)} + \lambda E_A^{(1)} + \lambda^2 E_A^{(2)} + \lambda^3 E_A^{(3)} + \dots \quad (2.15)$$

where $|\Phi_A^{(0)}\rangle$ is the wave function for the isolated molecule A . $|\Phi_A^{(1)}\rangle$ and $|\Phi_A^{(2)}\rangle$ are the first-order and second-order corrections to the wave function, respectively. $E_A^{(1)}$, $E_A^{(2)}$, and $E_A^{(3)}$ denote the first-, second-, and third-order corrections to the energy, respectively:

$$E_A^{(1)} = \langle\Phi_A^{(0)}|\langle\Phi_S|\hat{H}_{AS}|\Phi_S\rangle|\Phi_A^{(0)}\rangle, \quad (2.16)$$

$$E_A^{(2)} = \langle\Phi_A^{(0)}|\langle\Phi_S|\hat{H}_{AS}|\Phi_S\rangle|\Phi_A^{(1)}\rangle, \quad (2.17)$$

$$E_A^{(3)} = \langle\Phi_A^{(0)}|\langle\Phi_S|\hat{H}_{AS}|\Phi_S\rangle|\Phi_A^{(2)}\rangle. \quad (2.18)$$

According to the Hellmann-Feynman theorem:

$$\langle\Phi_A(\lambda)|\left|\frac{\partial\hat{H}_A(\lambda)}{\partial\lambda}\right|\Phi_A(\lambda)\rangle = \frac{\partial E_A(\lambda)}{\partial\lambda}. \quad (2.19)$$

By substituting Eq. (2.13) and Eq. (2.15) into the above equation, we have:

$$\langle\Phi_A(\lambda)|\langle\Phi_S|\hat{H}_{AS}|\Phi_S\rangle|\Phi_A(\lambda)\rangle = E_A^{(1)} + 2\lambda E_A^{(2)} + 3\lambda^2 E_A^{(3)} + \dots \quad (2.20)$$

By setting $\lambda = 1$, we get:

$$\langle\Phi_A|\langle\Phi_S|\hat{H}_{AS}|\Phi_S\rangle|\Phi_A\rangle = E_A^{(1)} + 2E_A^{(2)} + 3E_A^{(3)} + \dots \quad (2.21)$$

From Eqs. (2.10) and (2.21), we have:

$$\begin{aligned} \langle\Phi_A|\hat{H}_A^{(0)}|\Phi_A\rangle &= E_A - \langle\Phi_A|\langle\Phi_S|\hat{H}_{AS}|\Phi_S\rangle|\Phi_A\rangle \\ &= (E_A^{(0)} + E_A^{(1)} + E_A^{(2)} + E_A^{(3)} + \dots) \\ &\quad - (E_A^{(1)} + 2E_A^{(2)} + 3E_A^{(3)} + \dots) \\ &= E_A^{(0)} - E_A^{(2)} - 2E_A^{(3)} - \dots \end{aligned} \quad (2.22)$$

Therefore, the distortion energy of molecule A in the interaction system, $\Delta E_A^{dist} = \langle\Phi_A|\hat{H}_A^{(0)}|\Phi_A\rangle - E_A^{(0)}$, can be written as:

¹That is, $\langle\Phi_A\Phi_S|\hat{H}_{AS}|\Phi_A\Phi_S\rangle$.

$$\begin{aligned} \Delta E_A^{dist} = & -E_A^{(2)} - 2E_A^{(3)} - \dots = -\langle \Phi_A^{(0)} | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A^{(1)} \rangle \\ & - 2\langle \Phi_A^{(0)} | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A^{(2)} \rangle - \dots \end{aligned} \quad (2.23)$$

Interestingly, ΔE_A^{dist} is almost of the same order magnitude as the second-order perturbation energy but with opposite sign.

In the same way, we can write out the distortion energy for the surrounding S in the interaction system as:

$$\begin{aligned} \Delta E_S^{dist} = & -\langle \Phi_S^{(0)} | \langle \Phi_A | \hat{H}_{AS} | \Phi_A \rangle | \Phi_S^{(1)} \rangle \\ & - 2\langle \Phi_S^{(0)} | \langle \Phi_A | \hat{H}_{AS} | \Phi_A \rangle | \Phi_S^{(2)} \rangle - \dots \end{aligned} \quad (2.24)$$

Thus, by substituting the above two equations into Eq.

(2.7), we can write the net Coulombic interaction energy between A and S as:

$$\begin{aligned} \Delta E = & (-\langle \Phi_A^{(0)} | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A^{(1)} \rangle \\ & - 2\langle \Phi_A^{(0)} | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A^{(2)} \rangle - \dots) \\ & + (-\langle \Phi_S^{(0)} | \langle \Phi_A | \hat{H}_{AS} | \Phi_A \rangle | \Phi_S^{(1)} \rangle \\ & - 2\langle \Phi_S^{(0)} | \langle \Phi_A | \hat{H}_{AS} | \Phi_A \rangle | \Phi_S^{(2)} \rangle - \dots) \\ & + \langle \Phi_A \Phi_S | \hat{H}_{AS} | \Phi_A \Phi_S \rangle. \end{aligned} \quad (2.25)$$

Since $\langle \Phi_A \Phi_S | \hat{H}_{AS} | \Phi_A \Phi_S \rangle$ can be written as:

$$\begin{aligned} \langle \Phi_A \Phi_S | \hat{H}_{AS} | \Phi_A \Phi_S \rangle = & \frac{1}{4} \langle \Phi_A | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A \rangle + \frac{1}{4} \langle \Phi_A^{(0)} + \Phi_A^{(1)} + \Phi_A^{(2)} + \dots | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A^{(0)} + \Phi_A^{(1)} + \Phi_A^{(2)} + \dots \rangle \\ & + \frac{1}{4} \langle \Phi_S^{(0)} + \Phi_S^{(1)} + \Phi_S^{(2)} + \dots | \langle \Phi_A | \hat{H}_{AS} | \Phi_A \rangle | \Phi_S^{(0)} + \Phi_S^{(1)} + \Phi_S^{(2)} + \dots \rangle + \frac{1}{4} \langle \Phi_A^{(0)} + \Phi_A^{(1)} + \Phi_A^{(2)} + \dots | \\ & \times \langle \Phi_S^{(0)} + \Phi_S^{(1)} + \Phi_S^{(2)} + \dots | \hat{H}_{AS} | \Phi_S^{(0)} + \Phi_S^{(1)} + \Phi_S^{(2)} + \dots \rangle | \Phi_A^{(0)} + \Phi_A^{(1)} + \Phi_A^{(2)} + \dots \rangle. \end{aligned} \quad (2.26)$$

Expanding the above equation and substituting it into Eq. (2.25), we finally have:

$$\begin{aligned} \Delta E = & \frac{1}{4} (\langle \Phi_A | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A \rangle \\ & + \langle \Phi_A^{(0)} | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A^{(0)} \rangle \\ & + \langle \Phi_S^{(0)} | \langle \Phi_A | \hat{H}_{AS} | \Phi_A \rangle | \Phi_S^{(0)} \rangle \\ & + \langle \Phi_A^{(0)} | \langle \Phi_S^{(0)} | \hat{H}_{AS} | \Phi_S^{(0)} \rangle | \Phi_A^{(0)} \rangle) + O(E_A^{(3)}) + O(E_S^{(3)}), \end{aligned} \quad (2.27)$$

where $O(E_A^{(3)})$ is the third- and higher-order energy corrections to $E_A^{(0)}$, and $O(E_S^{(3)})$ to $E_S^{(0)}$, respectively.

By neglecting the third- and higher-order corrections [$O(E_A^{(3)}) + O(E_S^{(3)})$], we obtain the net Coulombic interaction energy between A and S as:

$$\begin{aligned} \Delta E = & \frac{1}{4} (\langle \Phi_A | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A \rangle \\ & + \langle \Phi_A^{(0)} | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A^{(0)} \rangle \\ & + \langle \Phi_S^{(0)} | \langle \Phi_A | \hat{H}_{AS} | \Phi_A \rangle | \Phi_S^{(0)} \rangle \\ & + \langle \Phi_A^{(0)} | \langle \Phi_S^{(0)} | \hat{H}_{AS} | \Phi_S^{(0)} \rangle | \Phi_A^{(0)} \rangle). \end{aligned} \quad (2.28)$$

Microscopically, \hat{H}_{AS} involves only the electron-electron, electron-nucleus, and nucleus-nucleus interactions between

molecule A and its surrounding S . Therefore, the physical meanings of the four terms in the right-hand side of Eq. (2.28) are obvious:

$$\langle \Phi_A | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A \rangle, \quad (2.29)$$

the electrostatic interaction between perturbed A and perturbed S .

$$\langle \Phi_A^{(0)} | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A^{(0)} \rangle, \quad (2.30)$$

the electrostatic interaction between unperturbed A and perturbed S .

$$\langle \Phi_S^{(0)} | \langle \Phi_A | \hat{H}_{AS} | \Phi_A \rangle | \Phi_S^{(0)} \rangle, \quad (2.31)$$

the electrostatic interaction between perturbed A and unperturbed S .

$$\langle \Phi_A^{(0)} | \langle \Phi_S^{(0)} | \hat{H}_{AS} | \Phi_S^{(0)} \rangle | \Phi_A^{(0)} \rangle, \quad (2.32)$$

the electrostatic interaction between unperturbed A and unperturbed S .

The next step is to use the partial atomic charges to simulate the above interaction terms. Among the atomic charge models, the charge derived by fitting the ESPs in the van der Waals region can be used to simulate the electrostatic interactions between the molecules reasonably well. Therefore, the terms in Eqs. (2.29)–(2.32) can be approximated as:

$$\langle \Phi_A | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A \rangle \approx \sum_{\alpha \in A} \sum_{\beta \in S} \frac{Q_\alpha Q_\beta}{R_{\alpha\beta}}, \quad (2.33)$$

$$\langle \Phi_A^{(0)} | \langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle | \Phi_A^{(0)} \rangle \approx \sum_{\alpha \in A} \sum_{\beta \in S} \frac{Q_\alpha^{(0)} Q_\beta}{R_{\alpha\beta}}, \quad (2.34)$$

$$\langle \Phi_S^{(0)} | \langle \Phi_A | \hat{H}_{AS} | \Phi_A \rangle | \Phi_S^{(0)} \rangle \approx \sum_{\alpha \in A} \sum_{\beta \in S} \frac{Q_\alpha Q_\beta^{(0)}}{R_{\alpha\beta}}, \quad (2.35)$$

$$\langle \Phi_A^{(0)} | \langle \Phi_S^{(0)} | \hat{H}_{AS} | \Phi_S^{(0)} \rangle | \Phi_A^{(0)} \rangle \approx \sum_{\alpha \in A} \sum_{\beta \in S} \frac{Q_\alpha^{(0)} Q_\beta^{(0)}}{R_{\alpha\beta}}, \quad (2.36)$$

where $Q_\alpha^{(0)}$ and Q_α represent the ESP derived charges on atomic site α for the unperturbed and perturbed molecule A , respectively. $Q_\beta^{(0)}$ and Q_β denote the ESP derived charges on atomic site β for the unperturbed and perturbed surrounding S , respectively. $R_{\alpha\beta}$ is the distance between α and β .

Thus, Eq. (2.28) can be written as:

$$\begin{aligned} \Delta E &= \frac{1}{4} \left(\sum_{\alpha \in A} \sum_{\beta \in S} \frac{Q_\alpha Q_\beta}{R_{\alpha\beta}} + \sum_{\alpha \in A} \sum_{\beta \in S} \frac{Q_\alpha^{(0)} Q_\beta}{R_{\alpha\beta}} \right. \\ &\quad \left. + \sum_{\alpha \in A} \sum_{\beta \in S} \frac{Q_\alpha Q_\beta^{(0)}}{R_{\alpha\beta}} + \sum_{\alpha \in A} \sum_{\beta \in S} \frac{Q_\alpha^{(0)} Q_\beta^{(0)}}{R_{\alpha\beta}} \right) \\ &= \sum_{\alpha \in A} \sum_{\beta \in S} \frac{Q_\alpha^{(eff)} Q_\beta^{(eff)}}{R_{\alpha\beta}}, \end{aligned} \quad (2.37)$$

where

$$Q_\alpha^{(eff)} = \frac{1}{2} (Q_\alpha^{(0)} + Q_\alpha) \quad (2.38)$$

and

$$Q_\beta^{(eff)} = \frac{1}{2} (Q_\beta^{(0)} + Q_\beta). \quad (2.39)$$

The result of the above derivation clearly shows that the net Coulombic interaction between molecule A and its surrounding S can be approximated as the interaction between two sets of effective charges centered on A and S , respectively. The effective charges correspond to the average of the ESP derived charges from the isolated molecule and those from the interaction system. The atomic charges are widely used in MM force fields to simulate the Coulombic interaction between the molecules. Therefore, we can conclude that the atomic charge suitable for the MM force fields also corresponds to the average of the ESP derived charge for the isolated molecule and that for the molecule in the interaction system.

It is easy to understand that the ESP charges, derived from the gas state molecule, are not quite suitable in the calculation of the intermolecular interactions because the polarization effects of the molecule by the surrounding molecules are usually not included. The reader may ask why the net Coulombic interaction between molecules could not be expressed as the electrostatic interaction among the ESP charges de-

rived from the molecules in the interaction system? The answer comes from the distortion energy of a molecule. The distortion energy is the energy required for distorting the electron distribution of a molecule from its isolated state to that in the interaction system. As can be seen from Eq. (2.7), the distortion energy can partly cancel the Coulombic interaction between the molecules and thus the net Coulombic interaction will become weaker than that calculated directly using the charge distribution in the interaction system. Therefore, the net Coulombic interaction between the molecules could be overestimated if it was expressed as the electrostatic interaction between the ESP charges derived from the molecules in the interaction system.

B. Computational details

In the following we will calculate the effective charges on water and methanol molecules as two examples to illustrate the above charge model. In order to calculate the ESP charges of water and methanol molecules in the liquid states, the configurations from the classical molecular dynamics (MD) simulations are used. The potential models used are TIP3P for water and three-sites OPLS for methanol. In the TIP3P water model, the water molecule is fixed in its experimental gas state equilibrium geometry [14]: $R_{O-H} = 0.9572 \text{ \AA}$ and $\angle(\text{H-O-H}) = 104.52^\circ$. In the three-sites OPLS methanol model, the methanol molecule is also fixed in its experimental gas state geometry [15]: $R_{O-H_O} = 0.9451 \text{ \AA}$, $R_{C-O} = 1.4246 \text{ \AA}$, $R_{C-H} = 1.0936 \text{ \AA}$, $\angle \text{COH}_O = 108.53^\circ$, and $\angle \text{HCH} = 108.63^\circ$, with point charges and Lennard-Jones parameters only on the H_O , O, and C atoms.

It has been shown that these two models could reproduce the liquid state structures adequately [14,16]. For both water and methanol, the MD simulations were carried out in the canonical NVT ensembles at room temperature (298 K). The number of molecules in each MD simulation is 256. The density is 0.997 g/cm^3 for liquid water and 0.790 g/cm^3 for liquid methanol. The time step is 1 fs. Periodic boundary conditions were used together with the minimum image convention. The cutoff distances for the intermolecular interactions are set to half of the length of the simulation boxes. For the calculation of the long-range interactions, Ewald summation [17] is also used. For each liquid, ten configurations were selected from the MD simulations at 1 ps intervals after an equilibration of 200 ps.

The calculation of the ESP charges in liquids are carried out according to an equation simplified from Eq. (2.10). In Eq. (2.10), the term: $\langle \Phi_S | \hat{H}_{AS} | \Phi_S \rangle$ represents the Coulombic interaction between molecule A and its surroundings S . Here, the simplification is made by representing the surrounding molecules as atom-centered ESP charges. Therefore, for a chosen molecule A , the corresponding Schrödinger equation is

$$\left(\hat{H}_A^{(0)} + \sum_{B \neq A} \hat{V}_{B-A} \right) | \Phi_A \rangle = E_A | \Phi_A \rangle, \quad (2.40)$$

with

TABLE I. Dipole moments (in Debye) of water and methanol molecule.

State	H ₂ O	CH ₃ OH
Gas	1.86	1.71
Liquid	2.65	2.39

$$\hat{V}_{B-A} = - \sum_{i \in A} \sum_{\beta \in B} \frac{Q_{\beta}}{r_{i\beta}} + \sum_{\alpha \in A} \sum_{\beta \in B} \frac{Z_{\alpha} Q_{\beta}}{R_{\alpha\beta}}, \quad (2.41)$$

where $\hat{H}_A^{(0)}$ is the Hamiltonian of the isolated molecule A . \hat{V}_{B-A} represents the Coulombic interaction between molecule A and its surrounding molecule B . i and α denote the electrons and nuclei in molecule A , respectively, and Z_{α} is the nuclear charge of atom α . Q_{β} denotes the ESP derived charge on atom β in molecule B . In this work, each molecule in a configuration is calculated quantum mechanically according to Eq. (2.40). The molecule that is calculated quantum mechanically is always in the center of the simulation box and the periodic boundary conditions are also used. The ESP charges are derived by fitting the molecular electrostatic potential in some region according to the Merz-Singh-Kollman scheme [4,18]. The calculation is performed in a self-consistent way until the charges on each molecule converge to $10^{-5}|e|$ unit. In order to include the electron correlation effects, the second-order Møller-Plesset perturbation theory (MP2) is used through the calculation. In the calculations, Sadlej's polarizability basis sets are used [19]. At the MP2 level, this basis set is found to give the dipole moments and polarizabilities in very good agreement with the experiments [19]. All the quantum chemistry calculation and ESP fitting presented here are carried out by GAUSSIAN98 [20]. A similar work has been done in the study of the electronic properties of a water molecule in liquid water [21].

III. RESULTS AND DISCUSSION

In Table I we list the dipole moments of water molecule and methanol molecule in the gas states and those in the liquid states, respectively. In the calculation of the gas state properties, the experimental gas state equilibrium geometries are also used. From the table, we can see that, from gas states to liquid states, the dipole moments of both molecules change greatly. The water dipole moment increases from

 TABLE II. Atomic charges and the corresponding dipole moments for H₂O

Model	q (in $ e $)		μ (in Debye)
	O	H	
Q^{gas}	-0.684	0.342	1.93
Q^{liquid}	-0.950	0.475	2.67
$\frac{1}{2}(Q^{gas} + Q^{liquid})$	-0.816	0.408	2.30
OPLS (TIP3P)	-0.834	0.417	2.35
SPC	-0.82	0.41	2.27

1.86 D to 2.65 D when it undergoes from gas state to liquid state. This has also been discussed elsewhere [21]. It is interesting that the dipole moment of methanol also increases greatly when it goes from gas state to the liquid state. In the gas state, the dipole moment is calculated to be 1.71 D. This dipole moment is in good agreement with that from the experiment [22]. In the liquid state, the dipole moments increases to 2.39 D. This corresponds to a change of 40% of the dipole moment. Therefore, in liquid methanol, the polarization effects are also large.

Table II listed the ESP derived atomic charges for water molecule. For comparison, the SPC and TIP3P charges are also listed in the table. From Table II, we can see that, for a gas state water molecule, the ESP charge for the oxygen atom is $-0.684 |e|$, much smaller in magnitude than both the SPC charge ($-0.82 |e|$) and TIP3P charge ($-0.834 |e|$). This reflects that this set of charges, derived from the gas state molecule, is not suitable for the simulation of liquid water since the polarization effects from the surrounding molecules in the liquid state are not included. On the other hand, the average charge for the oxygen atom for water molecule in the liquid state is $-0.950 |e|$, much greater in magnitude than that in the SPC and TIP3P models. Thus, comparing with the SPC and TIP3P charges, this charge seems to be too large to be used in the calculation of the intermolecular interactions. As can be seen from Table II, by averaging the charges in the gas state and those in the liquid state, we obtain that the atomic charge on oxygen is $-0.816 |e|$, and that on the hydrogen $0.408 |e|$, respectively. This set of charges is in good agreement with the SPC charges ($-0.82 |e|$ on the oxygen and $0.41 |e|$ on the hydrogen, respectively) and close to the TIP3P charges.

In Table III, we listed three sets of MM charges. The

 TABLE III. Atomic charges and the corresponding dipole moments for CH₃OH.

Model	q (in $ e $)					μ (in Debye)
	H _O	O	C	H _(l)	H _(g)	
Q^{gas}	0.391	-0.623	0.225	0.051	-0.022	1.68
Q^{liquid}	0.513	-0.811	0.334	0.020	-0.027	2.34
$\frac{1}{2}(Q^{gas} + Q^{liquid})$	0.452	-0.717	0.279	0.036	-0.025	2.00
OPLS	0.435	-0.700	0.265 ^a			2.22
H1	0.431	-0.728	0.297 ^a			2.33
RESP	0.4215	-0.6498	0.1166	0.0372	0.0372	2.14

^aUnited atom charge on the methyl group.

RESP charges [9], three-sites OPLS charges [15], and those from the three-site model of Haughney *et al.* [23] (the H1 model). The RESP charges are derived by restrained ESP fitting of the molecular ESP calculated at the Hartree-Fock 6-31G(d) level. It has been shown that the three-site OPLS model and the H1 model could give a good structure for liquid methanol [16] and the OPLS model could also give a good second virial coefficient [24]. For methanol molecule, the atomic charges on the polar area are more important than those on the nonpolar group. Therefore, it is worthwhile to compare the charges on the hydroxyl hydrogen and oxygen. Although the charges for these two atoms for a gas state methanol from this work are smaller in magnitude than those of the MM charges, the two charges for a methanol molecule in the liquid are much greater in magnitude than those of the MM charges. This reflects that neither the gas state charges nor those calculated from the liquid state could be good approximations, to be used in the calculation of the intermolecular interactions. The average of the charges for the gas state molecule and those for the molecule in the liquid are $0.452 |e|$ for the hydroxyl hydrogen and $-0.717 |e|$ for the oxygen. These two charges are close to those in the OPLS model and the H1 model. Therefore, we can expect that this set of atomic charges could be reasonably used in the calculation of intermolecular Coulombic interactions. From the table, we can find that the charges from this work do differ significantly from the RESP charges. This difference, in our opinion, may be caused by the RESP charges, derived from *ab initio* quantum chemistry calculation of the gas state molecule with a suitable basis set at the Hartree-Fock level, still could not reflect the polarization effects of the molecule by the surrounding molecules properly.

It is clear from Table II that the effective charges for water molecule from this work are slightly smaller in magnitude than those in the SPC and OPLS models. Our explanation of the difference is as follows: Empirical MM force fields use atomic charges to simulate all the electric interactions, such as electrostatic, polarization, and charge transfer interactions between the molecules. In our derivation of the intermolecular interactions, only the electrostatic and polarization interactions are considered and the charge transfer interaction is neglected. When the charge transfer effect is neglected, the effective charges thus derived would be smaller in magnitude than those in the MM force field models since the charge transfer interaction would increase the intermolecular interactions.

We would also like to point out that the effective charges we used to simulate the intermolecular interactions are derived by fitting the molecular ESP (MEP) of a molecule in the gas state and that in the interaction system. In the ESP

fitting schemes, only the MEPs on the Van der Waals surface are to be fitted. Though the Merz-Singh-Kollman scheme [4,18] is considered to be very reasonable in deriving the ESP charges suitable for reproducing the MEPs in the area that is important for the calculation of intermolecular interactions, it is possible that the charges on the atoms far away from the van der Waals surface are not well defined because they contribute little to the MEPs. This is the case for large molecules and especially for some buried atoms in large molecules. This also leads to some restrained ESP fitting schemes [9,25]. Because of this, the ESP charges even on the same molecule can differ when some restrains are added. Therefore, we believe that the effective atomic charges for water and methanol molecule presented in this work might not be unique and some adjustment in the atomic charges is also possible. This may also be part of the reason in the difference of the effective charges from this work and those in the other MM force field models.

Finally, as is well known, the ESP derived partial atomic charges depend very much on the quantum method and basis set used. Therefore, the effective charges on water and methanol molecule presented in this work are also quantum method and basis set dependent. In our calculation, MP2 quantum method and Sadlej's polarizability basis sets [19] are used. It has been shown that at the MP2 level, this basis set can reproduce the experimental dipole moments and polarizabilities accurately. For water molecule, the molecular multipole moments and polarizabilities calculated from Sadlej's basis set at the MP2 level are very close to those from the very large basis set [21]. Therefore, we believe that the results presented in the paper would be close to those from the very large basis sets.

IV. CONCLUSIONS

In this work, a theoretical derivation is presented to find the atomic charges suitable for the MM force fields. The derivation shows that the charges correspond to the average of the ESP derived charges for the isolated molecule and those for the molecule in the interaction system. The atomic charges on water and methanol molecules are also calculated to illustrate the derived charge model. It is found that the charges from this work are close to those from the widely used MM force field models. Our work is helpful in the development of the new charge model suitable for the MM force fields. The work is now in progress.

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