PCCP

Accepted Manuscript

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Efficient approach to include molecular polarizations using charge and atom dipole response kernels to calculate free energy gradients in QM/MM scheme

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ABSTRACT:

An efficient approach to evaluate free energy gradients (FEGs) within the quantum mechanical/molecular mechanical (QM/MM) framework has been proposed to clarify reaction processes on the free energy surface (FES) in molecular assemblies. The method is based on response kernel approximations denoted as the charge and the atom dipole response kernel (CDRK) model that include explicitly induced atom dipoles. The CDRK model was able to reproduce polarization effects for both electrostatic interactions between QM and MM regions and internal energies in the QM region obtained by conventional QM/MM methods. In contrast to charge response kernel (CRK) models, CDRK models could be applied to various kinds of molecules, even linear or planer molecules, without using imaginary interaction sites. Use of the CDRK model enabled us to obtain FEGs on QM atoms in significantly reduced computational time. It was also clearly demonstrated that the time development of QM forces of the solvated propylene carbonate radical cation ($PC^{\cdot +}$) provided reliable results for 1 ns molecular dynamics (MD) simulation, which were quantitatively in good agreement with expensive QM/MM results. Using FEG and nudged elastic band (NEB) methods, we found two optimized reaction paths on the FES for decomposed reactions to generate CO_2 molecules from $PC^{\cdot +}$, whose reaction is known as one of the degradation mechanisms in the lithium-ion battery. Two of these reactions proceed through an identical intermediate structure whose molecular dipole moment is larger than the reactant to be stabilized in the solvent, which has a high relative dielectric constant. Thus, in order to prevent the decomposed reaction, $PC^{\cdot +}$ should be modified to have a smaller dipole moment along two reaction paths.

1. INTRODUCTION

Free energy analyses of chemical reactions are important to understand reaction mechanisms in large systems such as solutions or biomolecules at a given temperature. In order to obtain reliable information about the FES using computer simulations, high quality potential functions are required. Since *ab initio* molecular orbital (MO) calculations are quite expensive for large systems, less costly QM/MM methods[1-4] have recently become popular for evaluating the physical properties of those systems. Using MD simulations, molecular structures on the FES can be explored by the FEG method[5], which can also be applied to optimize structures on FES. Since it has been suggested that FEG is equivalent to the ensemble average of energy gradients for a focused region, the QM region can easily be optimized on FES by the FEG method in a QM/MM framework. In typical calculations, to obtain FEGs, the QM region is frozen during the MD simulation of the surrounding MM region in order to generate MM ensembles at a given temperature. Even though the QM/MM approach could save the computational time to obtain energies and forces in the QM region, it is still time-consuming to generate FEGs as it requires quite large number of gradient calculations in the QM region. It is noteworthy that polarized charges of the QM region significantly affect the environmental electrostatic field (ESF), which determines the time development of the surrounding MM molecules.

Morita et al.[6-9] proposed mathematical expressions to represent the polarized charges of molecules based on a CRK approximation[10-12], instead of conventional *ab initio* MO calculations. In these expressions, polarized charges were described by the change of electrostatic potentials (ESPs) on atomic sites affected by environmental charge distributions. Subsequently, using the CRK approximation, Yang et al.[13,14] derived the QM internal energy representation to evaluate forces on QM atoms and applied this to the enzyme 4-OT to optimize a reaction path using the FEG and the NEB[15] methods. In principle CRK models would be valuable computational approaches to evaluate polarization effects in the QM region because fluctuations of QM forces can readily be obtained without MO calculations during MD simulations of MM regions if CRK approximations were reliable enough for a given QM molecule.

Despite the benefits of CRK approximations, there exist potential disadvantages for some molecules. Especially for linear or planar molecules, there is no response site that is perpendicular to the bond or the molecular plane, preventing us from expressing the molecular polarization for such directions as was suggested by

Tsutsumi et al.[16] To apply CRK approximations to these molecules, imaginary interaction sites should be placed perpendicular to the bond or above/below the molecular plane. While these modifications could improve the representation of polarization effects of molecules[7-9,16], the given position of imaginary sites influences upon calculated results. For example, electrostatic interactions become infinitely large when a charged atom would approach to the imaginary site, since the imaginary sites should have no van der Waals (vdW) radius to avoid the deformation of the molecular shape. These unfavorable situations sometimes occur at interaction sites without repulsive vdW parameters in MD simulations. In addition, it is more complicated how to divide energy gradients on imaginary sites into real QM atoms especially when QM structures are flexible.

To eliminate such difficulties, the concept of induced atom polarizations[17] will be introduced explicitly as a part of the molecular polarization instead of introducing imaginary response sites in the present manuscript. In principle, the molecular polarization of the QM region is based on deformations of MOs. The polarization of MOs between widely separated atoms can be approximately represented by the rearrangement of effective atomic charges among QM atoms. However, it is difficult to evaluate local polarizations of MOs around given atoms by only the rearrangement of atomic charges. Accordingly, both CRK and atom dipole response kernel models, presently denoted as the CDRK model[18], are introduced to reproduce MO polarizations in detail. For the sake of convenience, a simple numerical computational approach will be proposed to obtain matrix elements of all required response kernels. The total energy expression related to induced charges and atom dipoles in the QM region will be divided into QM internal and electrostatic interaction energies between QM and MM regions by the second order Taylor expansion. It is important to keep in mind that the CDRK model includes both the conventional CRK and the atom dipole moment response kernels. Thus, in the following discussions, both terminologies, CRK and CDRK, will be used to compare calculated results of each component. To adopt the CDRK model on the FEG calculations, the gradients of internal and electrostatic energies will also be formulated.

In order to demonstrate the efficiency and the reliability of the CDRK model, induced energies and forces by the CDRK model will be compared initially with those obtained by expensive *ab initio* MO methods for simple molecules hydrogen, carbon dioxide, water, benzene, and ethylene. The model will then be applied to the decomposed reaction of $PC^{\cdot +}$ in PC solution using FEG and NEB approximations[3]. This reaction is reported to occur at the anode surface in the lithium-ion battery during charging processes, which is known as one of the degradation reactions in the life of a battery.

2. THEORY AND COMPUTATIONAL METHODS

2.1 QM/MM energy

In the QM/MM treatment of the reactive solute molecule in solution, the total energy of the system $E_{\mathrm{QM/MM}}$ can be written by

$$E_{\mathrm{QM/MM}} = E_{\mathrm{QM}} + E_{\mathrm{QM/MM}}^{\mathrm{est}} + E_{\mathrm{QM/MM}}^{\mathrm{vdW}} + E_{\mathrm{MM}}\ , \tag{1}$$

where E_{QM} is the internal energy of the QM region under the external ESF originating from surrounding MM molecules, while E_{MM} means MM energies in the MM region. $E_{\mathrm{QM/MM}}^{\mathrm{est}}$ and $E_{\mathrm{QM/MM}}^{\mathrm{vdW}}$ represent interaction energies between QM and MM systems, i.e., the electrostatic and vdW interactions, respectively. According to the standard QM/MM scheme, both E_{MM} and $E_{\mathrm{QM/MM}}^{\mathrm{vdW}}$ are calculated by using conventional MM potentials, while E_{QM} and $E_{\mathrm{QM/MM}}^{\mathrm{est}}$ are evaluated simultaneously by *ab initio* MO calculations in order to take polarization effects into considerations. Thus, the energy obtained by MO calculations with environmental point charges can be written as

$$\left\langle \psi \left| \mathbf{H}_{\mathrm{eff}} \right| \psi \right\rangle = E_{\mathrm{QM}}\left(\mathbf{r}, v, \mathbf{E}\right) + E_{\mathrm{QM/MM}}^{\mathrm{est}}\left(\mathbf{r}, v, \mathbf{E}\right), \tag{2}$$

where ψ and $\mathbf{H}_{\mathrm{eff}}$ are the polarized wave function of the QM region and the effective Hamiltonian of the QM region with environmental point charges in the MM region, respectively. $\mathbf{r}$ represents positions of QM particles. v and $\mathbf{E}$ represent ESPs and ESFs, respectively, on QM atoms induced by MM charge distributions.

$$v(\mathbf{r}) = \sum_{m \in \mathrm{MM}} \frac{q_m}{\left|\mathbf{r}_m^{\mathrm{MM}} - \mathbf{r}\right|}, \tag{3}$$

$$\mathbf{E}_s(\mathbf{r}) = -\frac{\partial v(\mathbf{r})}{\partial \mathbf{r}^s}, \qquad s \in x, y, z \tag{4}$$

where, $\mathbf{r}_m^{\mathrm{MM}}$ and q_m are the position and the charge, respectively, of m -th MM atom.

Thus, eqn (2) is rewritten to represent QM internal energy.

$$E_{\mathrm{QM}}\left(\mathbf{r}, v, \mathbf{E}\right) = \left\langle \psi \left| \mathbf{H}_{\mathrm{eff}} \right| \psi \right\rangle - E_{\mathrm{QM/MM}}^{\mathrm{est}}\left(\mathbf{r}, v, \mathbf{E}\right). \tag{5}$$

2.1.1 Electrostatic interaction and QM internal energy with molecular polarization due to MM atoms

Including polarized charges and atom dipoles, we can write the expression for the electrostatic interaction between QM and MM regions as

$$E_{\mathrm{QM/MM}}^{\mathrm{est}}(\mathbf{r}, v, \mathbf{E}) = \sum_{a \in \mathrm{QM}} Q_a v(\mathbf{r}_a) - \mu_a \mathbf{E}(\mathbf{r}_a), \tag{6}$$

where

$$Q_a = Q_a^{\mathrm{ref}} + \sum_{b \in \mathrm{QM}} \chi_{ab} \Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right) + \sum_{b \in \mathrm{QM}} \sum_{s \in x,y,z} \kappa_{a,sb} \Delta \mathbf{r}_b^s \tag{7}$$

and

$$\mu_a^t = \mu_a^{t,\mathrm{ref}} + \sum_{b \in \mathrm{QM}} \sum_{s \in x,y,z} \zeta_{ta,sb} \Delta \mathbf{E}^s\left(\mathbf{r}_b^{\mathrm{ref}}\right) + \sum_{b \in \mathrm{QM}} \sum_{s \in x,y,z} \gamma_{ta,sb} \Delta \mathbf{r}_b^s, \qquad t \in x, y, z \tag{8}$$

The first and the second terms on the right-hand side of eqn (6) are charge-charge and atom dipole-charge interactions between QM and MM regions, respectively. Q_a is the atomic charge and $\boldsymbol{\mu}_a$ is the atom dipole on a-th QM atom at the coordinate $\mathbf{r}_a$. The properties with the superscript 'ref' denote reference properties, which mean the corresponding values without any perturbations such as external ESPs, ESFs and QM deformations. Thus, $\Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right) = v\left(\mathbf{r}_a^{\mathrm{ref}}\right) - v^{\mathrm{ref}}\left(\mathbf{r}_a^{\mathrm{ref}}\right)$, $\Delta \mathbf{E}^s\left(\mathbf{r}_a^{\mathrm{ref}}\right) = \mathbf{E}^s\left(\mathbf{r}_a^{\mathrm{ref}}\right) - \mathbf{E}^{s,\mathrm{ref}}\left(\mathbf{r}_a^{\mathrm{ref}}\right)$, and $\Delta \mathbf{r}_a^s = \mathbf{r}_a^s - \mathbf{r}_a^{s,\mathrm{ref}}$ $(s \in x, y, z)$ represent differences of the ESP, the ESF, and the QM structure, respectively, from non-perturbed values. Four response kernels in eqns (7) and (8) are given by

$$\chi_{ab} = \frac{\partial Q_a}{\partial v(\mathbf{r}_b)}, \tag{9}$$

$$\zeta_{ta,sb} = \frac{\partial \mu_a^t}{\partial \mathbf{E}^s(\mathbf{r}_b)}, \tag{10}$$

$$\kappa_{a,sb} = \frac{\partial Q_a}{\partial \mathbf{r}_b^s}, \tag{11}$$

$$\gamma_{ta,sb} = \frac{\partial \mu_a^t}{\partial \mathbf{r}_b^s}, \tag{12}$$

where χ_{ab} and $\zeta_{ta,sb}$ are CRK and atom dipole response kernel matrix elements, respectively. The matrix $\boldsymbol{\zeta}$ does not mean atom polarizability but atom polarizability tensor because the subscript b is running all over QM atoms for a-th QM atom in eqn (8). Two kernels $\boldsymbol{\kappa}$ and $\boldsymbol{\gamma}$ are structure-related response kernels.

Using these kernels, the electrostatic interaction of eqn (6) with the frozen QM structure can be expanded as

$$E^{\mathrm{est}}_{\mathrm{QM/MM}}(\mathbf{r},v,\mathbf{E}) = \sum_a \left[v(\mathbf{r}_a)\left\{ Q_a^{\mathrm{ref}} + \sum_b \chi_{ab}\Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right)\right\}\right.$$

$$\left. - \sum_{t\in x,y,z} \mathbf{E}^t(\mathbf{r}_a)\left\{ \mu_a^{t,\mathrm{ref}} + \sum_b \sum_{s\in x,y,z} \zeta_{ta,sb}\Delta\mathbf{E}^s\left(\mathbf{r}_b^{\mathrm{ref}}\right)\right\}\right. \tag{13}$$

Adapting the second-order Taylor expansion on QM internal energies with the frozen QM structure (see Appendix in details), we have the following equations;

$$\begin{aligned} &E_{\mathrm{QM}}(\mathbf{r},v,\mathbf{E}) \cong E_{\mathrm{QM}}\left(\mathbf{r}^{\mathrm{ref}},v^{\mathrm{ref}},\mathbf{E}^{\mathrm{ref}}\right) \\ &-\sum_{a,b}\chi_{ba}v^{\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right)\Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right) - \frac{1}{2}\sum_{a,b}\chi_{ba}\Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right)\Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right) \\ &+\sum_{a,b}\sum_{s,t\in x,y,z}\zeta_{sb,ta}\mathbf{E}^{s,\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right)\Delta\mathbf{E}^t\left(\mathbf{r}_a^{\mathrm{ref}}\right) + \frac{1}{2}\sum_{a,b}\sum_{s,t\in x,y,z}\zeta_{sb,ta}\Delta\mathbf{E}^t\left(\mathbf{r}_a^{\mathrm{ref}}\right)\Delta\mathbf{E}^s\left(\mathbf{r}_b^{\mathrm{ref}}\right) \end{aligned} \tag{14}$$

2.1.2 Energy gradient representation of QM and MM atoms

The first derivative of eqn (2) with respect to QM coordinates with the frozen QM structure (see Appendix in details) is written as

$$\begin{aligned} &\frac{\partial\left\{E_{\mathrm{QM}}(\mathbf{r},v,\mathbf{E}) + E^{\mathrm{est}}_{\mathrm{QM/MM}}(\mathbf{r},v,\mathbf{E})\right\}}{\partial\mathbf{r}_a^p} = \left.\frac{\partial\langle\psi|\mathbf{H}_{\mathrm{eff}}|\psi\rangle}{\partial\mathbf{r}_a^p}\right|_{\mathbf{r}^{\mathrm{ref}},v^{\mathrm{ref}},\mathbf{E}^{\mathrm{ref}}} \\ &+\left\{Q_a^{\mathrm{ref}} + \sum_b\chi_{ab}\Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right) + \sum_b\sum_{s\in x,y,z}\kappa_{a,sb}\Delta\mathbf{r}_b^s\right\}\left\{\frac{\partial v(\mathbf{r}_a)}{\partial\mathbf{r}_a^p} - \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_a)}{\partial\mathbf{r}_a^p}\right|_{\mathbf{r}^{\mathrm{ref}}}\right\} \\ &-\sum_{t\in x,y,z}\left\{\mu_a^{t,\mathrm{ref}} + \sum_b\sum_{s\in x,y,z}\zeta_{ta,sb}\Delta\mathbf{E}^s\left(\mathbf{r}_b^{\mathrm{ref}}\right) + \sum_b\sum_{s\in x,y,z}\gamma_{ta,sb}\Delta\mathbf{r}_b^s\right\}\left\{\frac{\partial\mathbf{E}^t(\mathbf{r}_a)}{\partial\mathbf{r}_a^p} - \left.\frac{\partial\mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_a)}{\partial\mathbf{r}_a^p}\right|_{\mathbf{r}^{\mathrm{ref}}}\right\} \\ &+\sum_b\kappa_{b,pa}\left[v(\mathbf{r}_b) - v^{\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right)\right] \\ &-\sum_b\sum_{s\in x,y,z}\gamma_{sb,pa}\left[\mathbf{E}^s(\mathbf{r}_b) - \mathbf{E}^{s,\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right)\right] \end{aligned} \tag{15}$$

where, $\partial A/\partial x|_{\mathbf{r}^{\mathrm{ref}}}$ means the partial derivative of A with respect to x at the QM structure $\mathbf{r}^{\mathrm{ref}}$.

In order to evaluate energy gradients by eqn (15), four kernels χ_{ab}, $\kappa_{a,sb}$, $\zeta_{ta,sb}$, and $\gamma_{ta,sb}$ at a given QM structure are required. In this manuscript, these kernels were constructed by simplified numerical methods as follows. For the CRK matrix χ_{ab}, induced charges $\Delta Q_{a,i}$ are evaluated by *ab initio* MO calculations for an isolated QM molecule with an appended *i*-th point charge q_i^{add}, which is referred to as the test charge placed at the position $\mathbf{r}_i^{\mathrm{add}}$ within a given range of distance r_p from the closest QM atom (see Fig. 1). In addition, induced ESPs on a-th QM atoms $\Delta v_{a,i}$ are also evaluated in the same environment. The ChelpG charge is a reasonable choice to calculate $\Delta Q_{a,i}$ since induced charges should reproduce ESPs around the QM region obtained by MO calculations. These calculations are repeated until a large number of $\{\Delta Q_{a,i}, \Delta v_{a,i}\}$ sets have been obtained for different positions $\mathbf{r}_i^{\mathrm{add}}$ of the test charge, which are randomly distributed around the QM region as depicted in Fig. 1 in this study. If M sets of data are calculated for a molecule of N atoms, $N \times M$ matrix $\Delta\mathbf{Q}$ is related to both $N \times N$ matrix $\boldsymbol{\chi}$ and $N \times M$ matrix $\Delta\mathbf{V}$.

$$\Delta\mathbf{Q} = \boldsymbol{\chi}\Delta\mathbf{V} \tag{16}$$

Accordingly, the CRK matrix $\boldsymbol{\chi}$ can immediately be obtained. In the same fashion, the response kernel $\boldsymbol{\zeta}$ can be obtained by evaluating $\Delta\mu_{a,i}^{r}$ and $\Delta E_{a,i}$ instead of matrices $\Delta Q_{a,i}$ and $\Delta v_{a,i}$. Since definitions of structure related response kernels $\boldsymbol{\kappa}$ and $\boldsymbol{\gamma}$ are straightforward, they can be calculated easily and directly with only a small amount of displacement for each QM atom. Although the number of data sets M should be large enough compared to the number of atoms N in the QM region to avoid the linear dependency in data sets, a small number of M can reduce the computational cost. Thus, $M = 5 \times N$ were adapted in this study. For an acceptable net charge of the test charge q_i^{add}, the approximated absolute value of the ChelpG charge of oxygen in water molecule was used: $q_i^{\mathrm{add}} = \pm 0.8e$, while response kernels should be independent to the test charge under the linear response approximation. In order to extract electrostatic properties from MO calculations, test charges should be placed rather distant from QM atoms, since electrostatic interactions are rather long range interactions. The distances r_p were randomly generated in the range of $5\text{Å} \le r_p \le 10\text{Å}$. Once four response kernels have been obtained, atomic charges and atom dipole moments can be readily evaluated by eqns (7) and (8) under the linear response approximation using external ESPs, external ESFs on QM atoms originated from any MM environments, and structure displacements of QM atoms. This is because all generated response kernels are proportional constants of $\Delta\mathbf{Q}$ (or $\Delta\boldsymbol{\mu}$) to the intensity of $\Delta\mathbf{V}$ (or $\Delta\mathbf{E}$).

On the other hand, energy gradients of electrostatic interaction energies between QM and MM regions on MM atoms can be expressed using basic formulations of charge-charge and charge-dipole interactions between QM and MM atoms.

$$\frac{\partial E^{\mathrm{est}}_{\mathrm{QM/MM}}}{\partial \mathbf{r}_{\mathrm{MM}}} = -\sum_{a\in \mathrm{QM}} \frac{Q_a q_{\mathrm{MM}}\left(\mathbf{r}_a - \mathbf{r}^{\mathrm{MM}}\right)}{\left|\mathbf{r}^{\mathrm{MM}} - \mathbf{r}_a\right|^3} + q_{\mathrm{MM}}\left[\frac{\boldsymbol{\mu}_a}{\left|\mathbf{r}^{\mathrm{MM}} - \mathbf{r}_a\right|^3} - \boldsymbol{\mu}_a \cdot \left(\mathbf{r}^{\mathrm{MM}} - \mathbf{r}_a\right)\frac{3\left(\mathbf{r}^{\mathrm{MM}} - \mathbf{r}_a\right)}{\left|\mathbf{r}^{\mathrm{MM}} - \mathbf{r}_a\right|^5}\right] \tag{17}$$

2.2 Free energy gradient calculation

FEG[5] on QM atoms can be expressed as

$$\frac{\mathrm{d}A}{\mathrm{d}\mathbf{r}} = \left\langle \frac{\mathrm{d}E}{\mathrm{d}\mathbf{r}} \right\rangle_{\mathrm{MM}}, \tag{18}$$

where A is the free energy of the system, E the total energy of the system, and $\langle X \rangle_{\mathrm{MM}}$ means the ensemble average of X over MM configurations appeared at a given temperature. Since we can use a fixed response kernel for a fixed QM structure during the MD simulation of the MM region, the response kernel approximation is a cheaper approach to evaluate FEGs of the QM region to include polarization effects.

To obtain FEGs of $\mathrm{PC}^{\cdot +}$ in PC solution, MD simulations were performed at a temperature of 300 K and pressure of 1 atm using the Amber-Gaussian interface program[19] based on Amber 9[20] and Gaussian09[21] packages, whose details were described in our previous paper[19]. In MD simulations, whole energy components in eqn (1) were calculated. In each step of the QM optimization, MM regions were equilibrated for 30 ps with a 1.0 fs time step. FEGs of the QM region were then calculated by averaging QM forces for 300 ps MD simulation of the MM region with the frozen QM structure. Long-range electrostatic interactions were evaluated by means of the particle mesh Ewald method, where Lennard-Jones forces and real-space electrostatics were cut off at 8.0 Å.

3. RESULTS AND DISCUSSION

3.1 Simple molecules: hydrogen, carbon dioxide, water, benzene, and ethylene

CRK matrix elements generated by numerical procedures for the optimized structure of water molecule were summarized in Table 1 for different kinds of wavefunctions with 6-311G(2d,2p) basis sets. While the Hartree Fock (HF) wavefunction provided rather smaller matrix elements indicating smaller polarizations, other theoretical levels resembled each other and agreed well with those previously reported by Iuchi et al.[25]. As seen in Table 1, the numerical approach to make the CRK matrix could be applied for a given theoretical level of QM calculation, while the generated CRK matrix does not satisfy the molecular symmetry rigorously since test charges were randomly distributed around the molecule without being restricted by the molecular symmetry. Similar to the CRK matrix, the atom dipole response kernel matrix was also constructed to reproduce ESPs around the molecule. Though ChelpG charges can be used to evaluate induced charges for constructing response kernels, it is difficult to determine atom dipole moments simultaneously with ChelpG charges to reproduce ESPs around molecules. For example, if a +1.0e was placed on the C2 axis of water molecule 5.0 angstroms away from the oxygen atom opposite to the hydrogen atom, the ChelpG charge of oxygen atom becomes unreasonably small (i.e., -1.4e with the atom dipole moment, and -0.8e without it). Since distance dependencies of ESPs by the point charge differs from those by the dipole, we evaluated ChelpG charges first, before obtaining induced atom dipoles to reproduce ESPs of MO calculations.

The electrostatic interaction energies between water molecule and external test charges evaluated by response kernels were in good agreement with those obtained by expensive QM calculations, as shown in Fig. 2a. This fact indicates that the induced electrostatic interactions can be described mainly by the charge rearrangement among atoms, which can be represented by the CRK model. Nevertheless, the CDRK model could also reproduce induced QM internal energies by MO calculations, which are equivalent to the positive deformation energies of MOs, in contrast to the CRK model as shown in Fig. 2b. In this study, induced QM internal energies by MO calculations were obtained by subtracting electrostatic interactions from total induced energies.

Fig. 3 and supplemental Fig. S1 compared induced forces on both QM atoms (eqn (15)) and test charges between response kernel approximations and MO calculations for water molecule. The structure-related kernels $\boldsymbol{\kappa}$ and $\boldsymbol{\gamma}$ are important for evaluating induced forces on QM atoms since geometrical deformations also realize substantial charge reorganizations in the molecule, which significantly contribute to energy gradients on QM atoms under the external electric field, even though the QM molecule is frozen. It is obvious that atom dipole moment cannot be neglected for linear or planer molecules such as H_2 and/or benzene molecules as shown in Figs 4 and 5. CDRK models have apparently improved these energies and forces without introducing imaginary response sites.

This fact suggests that the CDRK model can be applied to a wide range of molecules having linear or planer moieties, which is important for reaction path optimizations because the structures of intermediates and/or products would not usually be clearly understood. In supplemental Figs S2 and S3, induced energies and forces for CO_2 and ethylene molecules were also depicted, in which CDRK methods also significantly improved induced internal energies. In particular, when dealing with carbon atoms with π orbitals, it is important to consider polarizations along the out-of-plane direction.

The comparison results of calculated induced energies between CDRK and CRK with imaginary sites for CO_2 molecule are shown in the supplemental Fig. S4 in order to demonstrate the dependency of positions of imaginary sites in the CRK model. Using CDRK models, we could eliminate such problems so that energies and forces can be formally determined without fictitious imaginary sites.

3.2 Decomposition reaction of propylene carbonate (PC) radical cation

In order to demonstrate the efficiencies of the CDRK model to obtain FEGs, the decomposition reaction of PC radical cation[22] has been analyzed. PC molecules have been widely used as an electrolytic solution in the lithium-ion battery[23,24]. However, during battery charging processes, it is decomposed at the anode surface into CO_2, aceton or propanal molecules [22-24]. Since the rate limiting step was reported to be the CO_2 production reaction[22], we have focused attention on the CO_2 production reaction from $PC^{\cdot +}$. Although the energy barrier of the decomposed reaction was evaluated to be 10.7 kcal/mol in the gas phase using the B3LYP/6-311++G(d) approximation[22], the corresponding value using the M06-2x[26]/6-311G(d) calculation is 17.1 kcal/mol, which is in good agreement with the CCSD(T)/aug-cc-pVDZ//M06-2x/6-311++G(d,p) level of 17.4 kcal/mol. Accordingly, the M06-2x/6-311G(d) level of theory was applied in this manuscript to save the computational time.

The unit cell for MD simulation was prepared to have a $PC^{\cdot +}$, 512 neutral PC molecules, and a PF_6^- anion for the charge neutralization, in which QM and MM regions contained a $PC^{\cdot +}$ and remaining molecules as environments, respectively. Fig. 6 shows time developments of CDRK-derived forces of QM atoms in PC1$^{\cdot +}$ compared with MO results for structures obtained for 1000 ps MD simulation of the MM region. Only the two components with the largest fluctuations are depicted in these figures. The other forces are given in supplemental materials. Despite including a large number of environmental molecules, fluctuations of the forces of QM atoms provided essentially the same behavior as MO-calculated results during thermal fluctuations of the MM region, which suggests that FEGs evaluated by the CDRK model can quantitatively reproduce MO results for even longer simulations.

Table 2 summarizes the computational time needed to obtain FEGs for PC$^{\cdot +}$ on quad core i7 3.2GHz CPU. Since we have performed 330 psec MD simulation to obtain FEGs in each optimization step of the QM region, the computational time was evaluated for the same time scale in Table 2. If we use conventional QM/MM MD simulations for FEG evaluations, almost three months of the computational time would be required at the M06-2x/6-311G(d) level. To obtain the free energy optimized structure, many optimization cycles are usually required, which means that optimizations on the FES are not practicable by using the FEG method with conventional QM/MM MD simulation except for quite small molecules. On the other hand, reliable FEGs can be evaluated in only 5 hours approximately once CDRK is constructed, with additional 2 hours for response kernel preparations. Therefore, the CDRK model enabled us to optimize QM structures and reaction paths on the FES for a wide range of molecules within a reasonable computational time. This advantage should be emphasized for calculations using a high level of theory and large basis sets such as MP2/aug-cc-pVDZ for the QM region as seen in Table 2.

Using the FEG and the CDRK model, the reaction path on the FES could be optimized in conjunction with the NEB (FEG-NEB) method[3,13,14]. In the NEB approach, the reaction path is represented by the chain of conformations connecting from the reactant PC$^{\cdot +}$ to the product PC1$^{\cdot +}$ as shown in Fig. 7, in which the generated CO_2 is electrically neutral and is bounds to the residual structure in PC1$^{\cdot +}$. The n-th image structure in the chain of conformation is denoted as IMn in this paper. Thus, 24 structures from IM1 (PC$^{\cdot +}$) to IM24 (PC1$^{\cdot +}$) were optimized by the quick-min argorithm[27] and the NEB method, where the positions of the C1 atom in IMn were restricted to be equally separated along the reaction path, which means the interatomic distance between C1 and O3 atoms (R(C1-O3)) was chosen as the primary reaction coordinate. It is noticed that all response kernels for intermediate structures are constructed individually. The free energy profiles for the optimized reaction path denoted as path 1 are shown in Fig. 8, in which the root-mean-square forces on QM atoms were converged to be less than 1.1×10^{-3} hartree/bohr. Since the relative dielectric constant of PC was known to be $\varepsilon = 64.4$[28], the polarizable continuum medium (PCM) model calculations were also performed at FEG-NEB optimized structures in order to compare the free energy profile with FEG-NEB results. However, PCM relative energy profiles are similar to those for PCM optimized structures. For example, the relative energy at the PCM optimized transition state, which is close to IM16, and relative energies at the PCM optimized product, which is close to IM24, are 12.4 kcal/mol and 11.1 kcal/mol by PCM calculations, respectively. In the physical meaning, FEG calculations considering explicit solvent molecules by the MD simulation are considered to be more reliable than PCM models, and can also be applied to optimize reaction paths on the FES, even for heterogeneous systems, which are difficult to evaluate by the PCM model with unavailable experimental dielectric constant. It was confirmed that both computational methods showed similar qualitative behaviors, though relative free energy values are somewhat different. In addition, free energy curves were not smooth at two positions in Fig. 8: IM1→IM2 and IM6→IM7. Apparently, some interatomic distances such as *R*(C3-C5) and *R*(C1-O12) changed suddenly as seen in Fig. 9, while the monotonic increase of *R*(C1-O13) from 1.3 to 2.3 angstroms represents the dissociation process of CO_2. The interatomic distance *R*(C3-C5) increased at IM2, which means that the covalent bond between C3 and C5 weakened at the early stage of the dissociation process, and concurrently, *R*(C3-O12) and *R*(C1-O12) were decreased and increased, respectively. Thus, the covalent bond between C3 and O12 at IM2 tends to have the double bond character than the corresponding distance at $PC^{\cdot+}$. In contrast, *R*(C3-C5) decreases at IM7 to recover the bonding character of $PC^{\cdot+}$. These structural changes suggest that the primary reaction coordinate altered to *R*(C3-C5) on both IM1→IM2 and IM6→IM7. However, in the current NEB computation, *R*(C1-O13) was chosen as the CO_2 dissociation reaction coordinate and the other structural coordinates were fully minimized to follow the reaction path on FES. This is the reason why the free energy profile contains two unsmooth changes in Fig. 8. These are not limitations of the CDRK and FEG methods, but are substantial difficulties in the simple NEB optimization technique for the system with conjugated reaction coordinates. Nonetheless, NEB optimization techniques can be used to obtain intermediate structures along the reaction process.

3.3 Alternative decomposed reaction path for propylene carbonate (PC) radical cation

In order to explore another decomposed reaction path, FEG-NEB optimizations were performed from the different initial chain of conformations, since the optimized reaction path by the NEB method sometimes depends on initial structures. The alternative decomposed reaction path denoted as the path 2 could be found, whose reaction profile and key structures are illustrated in Figs 10 and 11, respectively, together with the reaction path 1. In contrast to the previous study by Xing et al.[22], the intermediate structure M2$^{\cdot +}$ was definitely found in this study in both decomposed reaction pathways. The structure M2$^{\cdot +}$ is stable in the PC solution with high dielectric constant, while it is not found in the gas phase, because the dipole moment based on the charge centroid of M2$^{\cdot +}$ is 8.0 debye, which is significantly larger than that of PC$^{\cdot +}$ (2.7 debye). This is the reason why M2$^{\cdot +}$ could be stabilized in the PC solution. In reaction path 1, the other intermediate structure M1$^{\cdot +}$ was obtained between the PC1$^{\cdot +}$ and M2$^{\cdot +}$ structures, where the methyl group is weakly bound to the C3 atom in PC with an interatomic distance of R(C3-C5) = 1.73Å. On the other hand, the bond distance R(C3-C5) is almost constant in reaction path 2 and R(C2-O13) decreases as R(C1-O13) increases. In Figs 10 and 11, transition state structures TS1$^{\cdot +}$ and TS2$^{\cdot +}$ were optimized using the PCM model since these transition structures unfortunately could not be addressed using the simple NEB method. Two reaction paths found in this paper show that decomposed reactions are accelerated in the PC solution than in the gas phase, which influences the degradation mechanism in the lithium-ion battery due to the lowering of the activation energy in the medium with the high dielectric constant. In order to prevent CO_2 evolution in the battery, appropriate substituents should be introduced in PC molecules to have lower dipole moments along the reaction processes provided in Fig. 10. These results confirm that FEG-NEB techniques in conjunction with the CDRK model are practicable approaches to find reaction mechanisms with some intermediate structures on the FES.

Fig. 12a depict the time development of atom polarizations contributing to the whole polarization effects in QM forces on the C1 atom (See Fig. 7) in FEG calculations using the CDRK model. Although atom polarization effects seem to be small compared to whole polarization effects, as is expected, it becomes relatively large in some environmental MM configurations. The amount of the atom polarization was evaluated to be 25.3% on average. Thus, it is reasonable to conclude that atom polarizations affect the surrounding MM distributions in FEG calculations. Fig. 12b shows the radial distribution function g(O4-O4) between O4 atoms in QM and MM regions with and without atom polarizations. It is clear that the height of the first peak increases and moves toward shorter distances by including atom dipole moments, which means that the atom polarization of the O4 atom is induced to stabilize interactions with surrounding MM molecules. These results suggest that atom polarizations of QM atoms should be considered in order to generate reliable MM distributions surrounding QM atoms, which also reflect on induced QM forces. Although more suitable optimization algorithms are necessary for locating TS structures[29] by FEGs, the CDRK model is confirmed to be a powerful tool for evaluating FEGs for a wide range of molecules and for optimizing reaction pathways on the FES.

4. CONCLUDING REMARKS

The response kernel model with explicit induced atom dipoles denoted as the CDRK model has been proposed to calculate FEGs of QM regions in the context of a QM/MM framework. CDRK models can be applied to a wide range of molecules, even for linear or planer molecules, in contrast to the conventional CRK approach, which requires imaginary interaction sites to include out-of-plane polarization effects. Induced internal energies and forces of the QM region, which were derived by the second order Taylor expansion, were considerably improved to reproduce results calculated by expensive MO methods. FEG calculations by MD simulations are very time consuming when using conventional QM/MM methods because ensemble averages of polarized QM forces affected by surrounding MM atoms are required. However, FEGs can be calculated more efficiently by the CDRK model than with conventional QM/MM calculations, even for high level wavefunctions and basis sets retaining comparable qualities. Thus, CDRK models were applied to calculate FEGs to evaluate the decomposition reaction of propylene carbonate radical cation $\mathrm{PC1}^{\cdot+}$ by optimizing reaction paths on the FES using the NEB technique. In PC decomposition reactions, the amount of atom polarizations in QM forces was evaluated to be 25.3% on average against the whole polarizations. It was also confirmed that atom polarizations of QM atoms affect the distribution of surrounding MM molecules. We found two decomposed reaction pathways on the FES at 300K. In both pathways, reactions proceed through an identical intermediate structure, which is stabilized by a PC solution with a high relative dielectric constant because the dipole moment of the intermediate structure is much higher than that of $\mathrm{PC1}^{\cdot+}$. In order to improve the lifetime of the solvent PC, it is suggested that $\mathrm{PC}^{\cdot+}$ molecule should be modified to have appropriate substituents for lowering dipole moments along two reaction pathways.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported partly by the a Grant-in-Aid for Science Research from the Ministry of Education, Culture, Sport, Science and Technology (MEXT) in Japan (No. 23550021), and also by Core Research for Evolutional Science and Technology (CREST) “High Performance Computing for Multi-scale and Multi-physics Phenomena” and “Establishment of Molecular Technology to towards the Creation of New Functions” from the Japan Science and Technology Agency (JST) and also by a MEXT program “Elements Strategy Initiative to Form Core Research Center” (since 2012), Japan.

APPENDIX

A.1 Representation of QM internal energy and its gradient and the electrostatic interaction energy between QM and MM regions using the CDRK model

Based on the Hellmann-Feynman theorem, we have

$$\frac{\partial\langle\psi|\mathbf{H}_{\text{eff}}|\psi\rangle}{\partial v(\mathbf{r}_a)} = \left\langle\psi\left|\frac{\partial\mathbf{H}_{\text{eff}}}{\partial v(\mathbf{r}_a)}\right|\psi\right\rangle \cong \left\langle\psi\left|\frac{\partial}{\partial v(\mathbf{r}_a)}\left(\mathbf{H}_{\text{QM}} + \sum_{a\in QM}\left[Q_a v(\mathbf{r}_a) - \sum_{r\in x,y,z}\mu_a^r\mathbf{E}^r(\mathbf{r}_a)\right]\right)\right|\psi\right\rangle = Q_a, \tag{A1}$$

and

$$\frac{\partial\langle\psi|\mathbf{H}_{\text{eff}}|\psi\rangle}{\partial \mathbf{E}^r(\mathbf{r}_a)} = \left\langle\psi\left|\frac{\partial\mathbf{H}_{\text{eff}}}{\partial \mathbf{E}^r(\mathbf{r}_a)}\right|\psi\right\rangle \cong \left\langle\psi\left|\frac{\partial}{\partial \mathbf{E}^r(\mathbf{r}_a)}\left(\mathbf{H}_{\text{QM}} + \sum_{a\in QM}\left[Q_a v(\mathbf{r}_a) - \sum_{r\in x,y,z}\mu_a^r\mathbf{E}^r(\mathbf{r}_a)\right]\right)\right|\psi\right\rangle = -\mu_a^r, \tag{A2}$$

where, ψ is the polarized wave function of the QM region. $\mathbf{H}_{\text{eff}}$ the effective Hamiltonian of the QM region including isolated QM Hamiltonian $\mathbf{H}_{\text{QM}}$ and ESP from MM regions. Q_a and μ_a^r are the atomic charge and the component $r \in x, y, z$ of the atom dipole on a-th QM atom, respectively. External ESPs and ESFs at the position of a-th QM atom $\mathbf{r}_a$ are represented by $v(\mathbf{r}_a)$ and $\mathbf{E}^r(\mathbf{r}_a)$, respectively.

Then, response kernels can be written as the following expressions:

$$\chi_{ab} = \frac{\partial Q_a}{\partial v(\mathbf{r}_b)} = \frac{\partial^2\langle\psi|\mathbf{H}_{\text{eff}}|\psi\rangle}{\partial v(\mathbf{r}_a)\partial v(\mathbf{r}_b)} \tag{A3}$$

$$\kappa_{a,rb} = \frac{\partial Q_a}{\partial \mathbf{r}_b^r} = \frac{\partial^2\langle\psi|\mathbf{H}_{\text{eff}}|\psi\rangle}{\partial v(\mathbf{r}_a)\partial \mathbf{r}_b^r} \tag{A4}$$

$$\zeta_{ra,sb} = \frac{\partial \mu_a^r}{\partial \mathbf{E}^s(\mathbf{r}_b)} = -\frac{\partial^2\langle\psi|\mathbf{H}_{\text{eff}}|\psi\rangle}{\partial \mathbf{E}^s(\mathbf{r}_a)\partial \mathbf{E}^s(\mathbf{r}_b)} \tag{A5}$$

$$\gamma_{ra,sb} = \frac{\partial \mu_a^r}{\partial \mathbf{r}_b^s} = -\frac{\partial^2\langle\psi|\mathbf{H}_{\text{eff}}|\psi\rangle}{\partial \mathbf{E}^r(\mathbf{r}_a)\partial \mathbf{r}_b^s} \tag{A6}$$

Using eqns (7) and (8), electrostatic interactions between QM and MM region are given by

$$\begin{aligned} E_{\text{QM/MM}}^{\text{est}}(\mathbf{r}, v, \mathbf{E}) = \sum_a \Bigg[& v(\mathbf{r}_a)\left\{Q_a^{\text{ref}} + \sum_b \chi_{ab}\Delta v(\mathbf{r}_b^{\text{ref}}) + \sum_b \sum_{s\in x,y,z}\kappa_{a,sb}\Delta\mathbf{r}_b^s\right\} \\ & - \sum_{r\in x,y,z}\mathbf{E}^r(\mathbf{r}_a)\left\{\mu_a^{r,\text{ref}} + \sum_b\sum_s \zeta_{ra,sb}\Delta\mathbf{E}^s(\mathbf{r}_b^{\text{ref}}) + \sum_b\sum_{s\in x,y,z}\gamma_{ra,sb}\Delta\mathbf{r}_b^s\right\}\Bigg] \end{aligned} \tag{A7}$$

QM internal energy is expanded by the second order Taylor expansion as

$$
\begin{aligned}
E_{\mathrm{QM}}(\mathbf{r}, v, \mathbf{E}) \cong{} & E_{\mathrm{QM}}\left(\mathbf{r}^{\mathrm{ref}}, v^{\mathrm{ref}}, \mathbf{E}^{\mathrm{ref}}\right)+\sum_{a} \sum_{r \in x,y,z} \left.\frac{\partial E_{\mathrm{QM}}}{\partial \mathbf{r}_a^r}\right|_{\mathrm{ref}} \Delta \mathbf{r}_a^r+\frac{1}{2} \sum_{a,b} \sum_{r,s \in x,y,z} \left.\frac{\partial^2 E_{\mathrm{QM}}}{\partial \mathbf{r}_a^r \partial \mathbf{r}_b^s}\right|_{\mathrm{ref}} \Delta \mathbf{r}_a^r \Delta \mathbf{r}_b^s \\
& +\sum_{a} \left.\frac{\partial E_{\mathrm{QM}}}{\partial v(\mathbf{r}_a)}\right|_{\mathrm{ref}} \Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right)+\frac{1}{2} \sum_{a,b} \left.\frac{\partial^2 E_{\mathrm{QM}}}{\partial v(\mathbf{r}_a) \partial v(\mathbf{r}_b)}\right|_{\mathrm{ref}} \Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right) \\
& +\sum_{a} \sum_{r \in x,y,z} \left.\frac{\partial E_{\mathrm{QM}}}{\partial \mathbf{E}^r(\mathbf{r}_a)}\right|_{\mathrm{ref}} \Delta \mathbf{E}^r\left(\mathbf{r}_a^{\mathrm{ref}}\right)+\frac{1}{2} \sum_{a,b} \sum_{r,s \in x,y,z} \left.\frac{\partial^2 E_{\mathrm{QM}}}{\partial \mathbf{E}^r(\mathbf{r}_a) \partial \mathbf{E}^s(\mathbf{r}_b)}\right|_{\mathrm{ref}} \Delta \mathbf{E}^r\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta \mathbf{E}^s\left(\mathbf{r}_b^{\mathrm{ref}}\right) \\
& +\sum_{a,b} \sum_{r \in x,y,z} \left.\frac{\partial^2 E_{\mathrm{QM}}}{\partial v(\mathbf{r}_a) \partial \mathbf{r}_b^r}\right|_{\mathrm{ref}} \Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta \mathbf{r}_b^r+\sum_{a,b} \sum_{r \in x,y,z} \left.\frac{\partial^2 E_{\mathrm{QM}}}{\partial v(\mathbf{r}_a) \partial \mathbf{E}^r(\mathbf{r}_b)}\right|_{\mathrm{ref}} \Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta \mathbf{E}^r\left(\mathbf{r}_b^{\mathrm{ref}}\right) \\
& +\sum_{a,b} \sum_{r,s \in x,y,z} \left.\frac{\partial^2 E_{\mathrm{QM}}}{\partial \mathbf{E}^r(\mathbf{r}_a) \partial \mathbf{r}_b^s}\right|_{\mathrm{ref}} \Delta \mathbf{E}^r\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta \mathbf{r}_b^s
\end{aligned}
\tag{A8}
$$

Then, E_{QM} is substituted by eqn (5) so that

$$
\begin{aligned}
E_{\mathrm{QM}}(\mathbf{r}, v, \mathbf{E}) \cong{} & E_{\mathrm{QM}}\left(\mathbf{r}^{\mathrm{ref}}, v^{\mathrm{ref}}, \mathbf{E}^{\mathrm{ref}}\right) \\
& +\sum_{a} \sum_{r \in x,y,z} \Bigg[\left.\frac{\partial \langle \psi | \mathbf{H}_{\mathrm{eff}} | \psi \rangle}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}, v^{\mathrm{ref}}, \mathbf{E}^{\mathrm{ref}}} -\sum_{b} v^{\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right) \kappa_{b,ra} - Q_a^{\mathrm{ref}} \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \\
& +\sum_{b} \sum_{s \in x,y,z} \gamma_{sb,ra} \mathbf{E}^{s,\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right)+\sum_{s \in x,y,z} \mu_a^{s,\mathrm{ref}} \left.\frac{\partial \mathbf{E}^{s,\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \Bigg] \Delta \mathbf{r}_a^r \\
& +\frac{1}{2} \sum_{a,b} \sum_{r,s \in x,y,z} \Bigg[\left.\frac{\partial^2 \langle \psi | \mathbf{H}_{\mathrm{eff}} | \psi \rangle}{\partial \mathbf{r}_a^r \partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}, v^{\mathrm{ref}}, \mathbf{E}^{\mathrm{ref}}} - \kappa_{b,ra} \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_b)}{\partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} - \kappa_{a,sb} \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} - Q_a^{\mathrm{ref}} \left.\frac{\partial^2 v^{\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r \partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} \delta_{ab} \\
& +\sum_{t \in x,y,z} \gamma_{tb,ra} \left.\frac{\partial \mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_b)}{\partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} +\sum_{t \in x,y,z} \gamma_{ta,sb} \left.\frac{\partial \mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} +\sum_{t \in x,y,z} \mu_a^{t,\mathrm{ref}} \left.\frac{\partial^2 \mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r \partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} \delta_{ab} \Bigg] \Delta \mathbf{r}_a^r \Delta \mathbf{r}_b^s \\
& -\sum_{a,b} \chi_{ba} v^{\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right) \Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right)-\frac{1}{2} \sum_{a,b} \chi_{ba} \Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right) \\
& +\sum_{a,b} \sum_{r,s \in x,y,z} \zeta_{sb,ra} \mathbf{E}^{s,\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right) \Delta \mathbf{E}^r\left(\mathbf{r}_a^{\mathrm{ref}}\right)+\frac{1}{2} \sum_{a,b} \sum_{r,s \in x,y,z} \zeta_{sb,ra} \Delta \mathbf{E}^r\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta \mathbf{E}^s\left(\mathbf{r}_b^{\mathrm{ref}}\right) \\
& -\sum_{a,b} \sum_{r \in x,y,z} \chi_{ba} \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_b)}{\partial \mathbf{r}_b^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta \mathbf{r}_b^r +\sum_{a,b} \sum_{r,s,t \in x,y,z} \zeta_{tb,ra} \left.\frac{\partial \mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_b)}{\partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} \Delta \mathbf{E}^r\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta \mathbf{r}_b^s
\end{aligned}
\tag{A9}
$$

where, $\left.\partial A / \partial x\right|_{\mathbf{r}^{\mathrm{ref}}}$ means the partial derivative of A with respect to x at the structure $\mathbf{r}^{\mathrm{ref}}$. Adapting the linear approximation on Q and μ, their second derivatives become zero. If the QM structure is frozen, a simplified form can be derived from eqn (A9) as

$$\begin{aligned}
E_{\mathrm{QM}}(\mathbf{r}, v, \mathbf{E}) &\cong E_{\mathrm{QM}}\left(\mathbf{r}^{\mathrm{ref}}, v^{\mathrm{ref}}, \mathbf{E}^{\mathrm{ref}}\right) \\
&- \sum_{a,b} \chi_{ba} v^{\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right) \Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right) - \frac{1}{2} \sum_{a,b} \chi_{ba} \Delta v\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right) \\
&+ \sum_{a,b} \sum_{r,s \in x,y,z} \zeta_{sb,ra} \mathbf{E}^{s,\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right) \Delta \mathbf{E}^{r}\left(\mathbf{r}_a^{\mathrm{ref}}\right) + \frac{1}{2} \sum_{a,b} \sum_{r,s \in x,y,z} \zeta_{sb,ra} \Delta \mathbf{E}^{r}\left(\mathbf{r}_a^{\mathrm{ref}}\right) \Delta \mathbf{E}^{s}\left(\mathbf{r}_b^{\mathrm{ref}}\right)
\end{aligned} \tag{A10}$$

Using eqn (A9), the gradient of QM internal energies are expressed as

$$\begin{aligned}
\frac{\partial E_{\mathrm{QM}}(\mathbf{r}, v, \mathbf{E})}{\partial \mathbf{r}_\alpha^r} &= \left.\frac{\partial \langle \psi | \mathbf{H}_{\mathrm{eff}} | \psi \rangle}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}, v^{\mathrm{ref}}, \mathbf{E}^{\mathrm{ref}}} - \sum_b v^{\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right) \kappa_{b,ra} - Q_a^{\mathrm{ref}} \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \\
&+ \sum_b \sum_{s \in x,y,z} \gamma_{sb,ra} \mathbf{E}^{s,\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right) + \sum_{s \in x,y,z} \mu_a^{s,\mathrm{ref}} \left.\frac{\partial \mathbf{E}^{s,\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \\
&+ \sum_b \sum_{s \in x,y,z} \Bigg[\left.\frac{\partial^2 \langle \psi | \mathbf{H}_{\mathrm{eff}} | \psi \rangle}{\partial \mathbf{r}_a^r \partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}, v^{\mathrm{ref}}, \mathbf{E}^{\mathrm{ref}}} - \kappa_{b,ra} \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_b)}{\partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} - \kappa_{a,sb} \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} - Q_a^{\mathrm{ref}} \left.\frac{\partial^2 v^{\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r \partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} \delta_{ab} \\
&+ \sum_{t \in x,y,z} \gamma_{tb,ra} \left.\frac{\partial \mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_b)}{\partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} + \sum_{t \in x,y,z} \gamma_{ta,sb} \left.\frac{\partial \mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} + \sum_{t \in x,y,z} \mu_a^{t,\mathrm{ref}} \left.\frac{\partial^2 \mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r \partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} \delta_{ab} \Bigg] \Delta \mathbf{r}_b^s \\
&- \sum_b \chi_{ba} v^{\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right) \left.\frac{\partial v(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} - \sum_b \chi_{ba} \Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right) \left.\frac{\partial v(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \\
&+ \sum_b \sum_{s,t \in x,y,z} \zeta_{sb,ta} \mathbf{E}^{s,\mathrm{ref}}\left(\mathbf{r}_b^{\mathrm{ref}}\right) \left.\frac{\partial \mathbf{E}^{t}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} + \sum_b \sum_{s,t \in x,y,z} \zeta_{sb,ta} \Delta \mathbf{E}^{s}\left(\mathbf{r}_b^{\mathrm{ref}}\right) \left.\frac{\partial \mathbf{E}^{t}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \\
&- \sum_b \sum_{s \in x,y,z} \chi_{ba} \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_b)}{\partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} \left.\frac{\partial v(\mathbf{r}_a)}{\partial \mathbf{r}_a^s}\right|_{\mathbf{r}^{\mathrm{ref}}} \Delta \mathbf{r}_b^s - \sum_b \chi_{ab} \left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right) \\
&+ \sum_b \sum_{s,t,u \in x,y,z} \zeta_{tb,ua} \left.\frac{\partial \mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_b)}{\partial \mathbf{r}_b^s}\right|_{\mathbf{r}^{\mathrm{ref}}} \left.\frac{\partial \mathbf{E}^{u}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \Delta \mathbf{r}_b^s + \sum_b \sum_{s,t \in x,y,z} \zeta_{ta,sb} \left.\frac{\partial \mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} \Delta \mathbf{E}^{s}\left(\mathbf{r}_b^{\mathrm{ref}}\right)
\end{aligned} \tag{A11}$$

In addition, the energy gradient of the electrostatic interaction is represented from eqn (A7) by

$$\begin{aligned}
\frac{\partial E_{\mathrm{QM/MM}}^{\mathrm{est}}(\mathbf{r}, v, \mathbf{E})}{\partial \mathbf{r}_a^r} &= \frac{\partial v(\mathbf{r}_a)}{\partial \mathbf{r}_a^r} \left\{ Q_a^{\mathrm{ref}} + \sum_b \chi_{ab} \Delta v\left(\mathbf{r}_b^{\mathrm{ref}}\right) + \sum_b \sum_{s \in x,y,z} \kappa_{a,sb} \Delta \mathbf{r}_b^s \right\} + \sum_b v(\mathbf{r}_b) \left\{ \chi_{ba} \left.\frac{\partial v(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} + \kappa_{b,ra} \right\} \\
&- \sum_{t \in x,y,z} \frac{\partial \mathbf{E}^t(\mathbf{r}_a)}{\partial \mathbf{r}_a^r} \left\{ \mu_a^{t,\mathrm{ref}} + \sum_b \sum_s \zeta_{ta,sb} \Delta \mathbf{E}^s\left(\mathbf{r}_b^{\mathrm{ref}}\right) + \sum_b \sum_{s \in x,y,z} \gamma_{ta,sb} \Delta \mathbf{r}_b^s \right\} - \sum_b \sum_{s \in x,y,z} \mathbf{E}^s(\mathbf{r}_b) \left\{ \sum_{t \in x,y,z} \zeta_{sb,ta} \left.\frac{\partial \mathbf{E}^t(\mathbf{r}_a)}{\partial \mathbf{r}_a^r}\right|_{\mathbf{r}^{\mathrm{ref}}} + \gamma_{sb,ra} \right\}
\end{aligned} \tag{A12}$$

Using eqns (A10) and (A11), the energy gradient of QM atoms is expressed as

$$
\begin{aligned}
&\frac{\partial\left\{E_{\mathrm{QM}}(\mathbf{r},v,\mathbf{E})+E_{\mathrm{QM/MM}}^{\mathrm{est}}(\mathbf{r},v,\mathbf{E})\right\}}{\partial\mathbf{r}_{\alpha}^{r}}=\left.\frac{\partial\langle\psi|\mathbf{H}_{\mathrm{eff}}|\psi\rangle}{\partial\mathbf{r}_{a}^{r}}\right|_{\mathbf{r}^{\mathrm{ref}},v^{\mathrm{ref}},\mathbf{E}^{\mathrm{ref}}}\\
&+\sum_{b}\sum_{s\in x,y,z}\left[\left.\frac{\partial^{2}\langle\psi|\mathbf{H}_{\mathrm{eff}}|\psi\rangle}{\partial\mathbf{r}_{a}^{r}\partial\mathbf{r}_{b}^{s}}\right|_{\mathbf{r}^{\mathrm{ref}},v^{\mathrm{ref}},\mathbf{E}^{\mathrm{ref}}}-\kappa_{b,ra}\left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_{b})}{\partial\mathbf{r}_{b}^{s}}\right|_{\mathbf{r}^{\mathrm{ref}}}-Q_{a}^{\mathrm{ref}}\left.\frac{\partial^{2}v^{\mathrm{ref}}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}\partial\mathbf{r}_{b}^{s}}\right|_{\mathbf{r}^{\mathrm{ref}}}\delta_{ab}-\chi_{ba}\left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_{b})}{\partial\mathbf{r}_{b}^{s}}\right|_{\mathbf{r}^{\mathrm{ref}}}\left.\frac{\partial v(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{s}}\right|_{\mathbf{r}^{\mathrm{ref}}}\right.\\
&\left.+\sum_{t\in x,y,z}\gamma_{tb,ra}\left.\frac{\partial\mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_{b})}{\partial\mathbf{r}_{b}^{s}}\right|_{\mathbf{r}^{\mathrm{ref}}}+\sum_{t\in x,y,z}\mu_{a}^{t,\mathrm{ref}}\left.\frac{\partial^{2}\mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}\partial\mathbf{r}_{b}^{s}}\right|_{\mathbf{r}^{\mathrm{ref}}}\delta_{ab}+\sum_{t,u\in x,y,z}\zeta_{tb,ua}\left.\frac{\partial\mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_{b})}{\partial\mathbf{r}_{b}^{s}}\right|_{\mathbf{r}^{\mathrm{ref}}}\left.\frac{\partial\mathbf{E}^{u}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}\right|_{\mathbf{r}^{\mathrm{ref}}}\right]\Delta\mathbf{r}_{b}^{s}\\
&+\left\{Q_{a}^{\mathrm{ref}}+\sum_{b}\chi_{ab}\Delta v(\mathbf{r}_{b}^{\mathrm{ref}})+\sum_{b}\sum_{s\in x,y,z}\kappa_{a,sb}\Delta\mathbf{r}_{b}^{s}\right\}\left\{\frac{\partial v(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}-\left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}\right|_{\mathbf{r}^{\mathrm{ref}}}\right\}\\
&-\sum_{t\in x,y,z}\left\{\mu_{a}^{t,\mathrm{ref}}+\sum_{b}\sum_{s\in x,y,z}\zeta_{ta,sb}\Delta\mathbf{E}^{s}(\mathbf{r}_{b}^{\mathrm{ref}})+\sum_{b}\sum_{s\in x,y,z}\gamma_{ta,sb}\Delta\mathbf{r}_{b}^{s}\right\}\left\{\frac{\partial\mathbf{E}^{t}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}-\left.\frac{\partial\mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}\right|_{\mathbf{r}^{\mathrm{ref}}}\right\}\\
&+\sum_{b}\kappa_{b,ra}\left[v(\mathbf{r}_{b})-v^{\mathrm{ref}}(\mathbf{r}_{b}^{\mathrm{ref}})\right]-\sum_{b}\sum_{s\in x,y,z}\gamma_{sb,ra}\left[\mathbf{E}^{s}(\mathbf{r}_{b})-\mathbf{E}^{s,\mathrm{ref}}(\mathbf{r}_{b}^{\mathrm{ref}})\right]\\
&+\sum_{b}\chi_{ba}\left.\frac{\partial v(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}\right|_{\mathbf{r}^{\mathrm{ref}}}\left[v(\mathbf{r}_{b})-v(\mathbf{r}_{b}^{\mathrm{ref}})\right]-\sum_{b}\sum_{s,t\in x,y,z}\zeta_{sb,ta}\left.\frac{\partial\mathbf{E}^{t}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}\right|_{\mathbf{r}^{\mathrm{ref}}}\left[\mathbf{E}^{s}(\mathbf{r}_{b})-\mathbf{E}^{s}(\mathbf{r}_{b}^{\mathrm{ref}})\right]
\end{aligned}
\tag{A13}
$$

If the QM structure is frozen, eqn (A13) becomes a simplified form as

$$
\begin{aligned}
&\frac{\partial\left\{E_{\mathrm{QM}}(\mathbf{r},v,\mathbf{E})+E_{\mathrm{QM/MM}}^{\mathrm{est}}(\mathbf{r},v,\mathbf{E})\right\}}{\partial\mathbf{r}_{\alpha}^{r}}=\left.\frac{\partial\langle\psi|\mathbf{H}_{\mathrm{eff}}|\psi\rangle}{\partial\mathbf{r}_{a}^{r}}\right|_{\mathbf{r}^{\mathrm{ref}},v^{\mathrm{ref}},\mathbf{E}^{\mathrm{ref}}}\\
&+\left\{Q_{a}^{\mathrm{ref}}+\sum_{b}\chi_{ab}\Delta v(\mathbf{r}_{b}^{\mathrm{ref}})+\sum_{b}\sum_{s\in x,y,z}\kappa_{a,sb}\Delta\mathbf{r}_{b}^{s}\right\}\left\{\frac{\partial v(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}-\left.\frac{\partial v^{\mathrm{ref}}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}\right|_{\mathbf{r}^{\mathrm{ref}}}\right\}\\
&-\sum_{t\in x,y,z}\left\{\mu_{a}^{t,\mathrm{ref}}+\sum_{b}\sum_{s\in x,y,z}\zeta_{ta,sb}\Delta\mathbf{E}^{s}(\mathbf{r}_{b}^{\mathrm{ref}})+\sum_{b}\sum_{s\in x,y,z}\gamma_{ta,sb}\Delta\mathbf{r}_{b}^{s}\right\}\left\{\frac{\partial\mathbf{E}^{t}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}-\left.\frac{\partial\mathbf{E}^{t,\mathrm{ref}}(\mathbf{r}_{a})}{\partial\mathbf{r}_{a}^{r}}\right|_{\mathbf{r}^{\mathrm{ref}}}\right\}\\
&+\sum_{b}\kappa_{b,ra}\left[v(\mathbf{r}_{b})-v^{\mathrm{ref}}(\mathbf{r}_{b}^{\mathrm{ref}})\right]\\
&-\sum_{b}\sum_{s\in x,y,z}\gamma_{sb,ra}\left[\mathbf{E}^{s}(\mathbf{r}_{b})-\mathbf{E}^{s,\mathrm{ref}}(\mathbf{r}_{b}^{\mathrm{ref}})\right]
\end{aligned}
\tag{A14}
$$

REFERENCES

1 M.Svensson, S.Humbel, R.D.J.Froese, T.Matsubara, S.Sieber, and K.Morokuma, *J. Phys. Chem.*, 1996, **100**, 19357-19363.

2 T.Asada, K.Ohta, T.Matsushita, and S.Koseki, *Theo. Chem. Acc.*, 2011, **130**, 439-44.

3 N.Takenaka, Y.Kitamura, Y.Koyano, T.Asada and M.Nagaoka, *Theo. Chem. Acc.*, 2011, **130**, 215-226.

4 J.Xu, J.Z.H.Zhang, and Y.Xiang, *J. Am. Chem. Soc.*, 2012, **134**, 16424-16429.

5 M.Nagaoka, N.Okuyama-Yoshida, and T.Yamabe, *J. Phys. Chem. A*, 1998, **102**, 8202-8208.

6 A.Morita and S.Kato, *J. Am. Chem. Soc.*, 1997, **119**, 4021-4032.

7 T.Ishiyama and A.Morita, *J. Chem. Phys.*, 2009, **131**, 244714.

8 T.Ishiyama and A.Morita, *J. Phys. Chem. C*, 2007, **111**, 721-737.

9 T.Ishiyama, T.Imamura and A.Morita, *Chem. Rev.*, 2014, **114**, 8447-8470.

10 M. Isegawa and S. Kato, *J. Chem. Theory Comput.*, 2009, **5**, 2809-2821.

11 H. Nakamura, T. Ohto, and Y. Nagata, *J. Chem. Theory Comput.*, 2013, **9**, 1193-1201.

12 Y. Nagata, *Chemphychem.*, 2010, **11**, 474-479.

13 Z.Lu and W.Yang, *J. Chem.P hys.*, 2004, **121**, 89-100.

14 H.Hu, Z.Lu, J.M.Parks, S.K.Burger and W.Yang, *J. Chem. Phys.*, 2008, **128**, 034105.

15 G.Mills and H.Jónsson, *Chem. Phys. Lett.*, 1994, **72**, 1124-1127.

16 J.Tsutsumi, H.Yoshida, R.Murdey, S.Kato and N.Sato, *J. Phys. Chem. A*, 2009, **113**, 9207-9212.

17 C.Voisin and A.Cartier, *J.Mol.Struct.(Theochem)*, 1993, **286**, 35-45.

18 T.Asada, K.Ando, and S.Koseki, *AIP conf. proc.*, 2015, in press.

19 T.Okamoto, K.Yamada, Y.Koyano, T.Asada, N.Koga, M.Nagaoka, *J. Comp. Chem.*, 2011, **32**, 932-942.

20 D.A. Case, T.A. Darden, T.E. Cheatham, III, C.L. Simmerling, J. Wang, R.E. Duke, R.Luo, K.M. Merz, D.A. Pearlman, M. Crowley, R.C. Walker, W. Zhang, B. Wang, S.Hayik, A. Roitberg, G. Seabra, K.F. Wong, F. Paesani, X. Wu, S. Brozell, V. Tsui, H.Gohlke, L. Yang, C. Tan, J. Mongan, V. Hornak, G. Cui, P. Beroza, D.H. Mathews, C.Schafmeister, W.S. Ross, and P.A. Kollman, AMBER 9, University of California, San Francisco, 2006.

21 Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

22 L.Xing, C.Wang, W.Li, M.Xu, X.Meng and S.Zhao, *J. Phys. Chem. B*, 2009, **113**, 5181-5187.

23 M.Arakawa and J.Yamaki, *J. Power Sources*, 1995, **54**, 250-254.

24 J.Ufheil, A.Würsig, O.D.Schneider and P.Novák, *Electrochem. Commun.*, 2004, **7**, 1380-1384.

25 S.Iuchi, A.Morita, and S.Kato, *J. Phys. Chem. B*, 2002, **106**, 3466-3476.

26 Y.Zhao and D.G.Truhlar, *Theor. Chem. Account*, 2008, **120**, 215-241.

27 D.Sheppard, R.Terrell and G.Henkelman, *J. Chem. Phys.*, 2008, **128**, 134106.

28 W.C.West, J.F.Whitacre, N.Leifer, S.Greenbaum, M.Smart, R.Bugga, M.Blanco and S.R.Narayanan, *J. Elec. Soc.*, 2007, **154**, A929-A936.

29 N.Gonzalez-Garcia, J.Pu, A.Gonzalez-Lafont, J.M.Lluch and D.G.Truhlar, *J. Chem. Theory Comput.*, 2006, **2**, 895-904.