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A New Method of Determining the Nonempirical Potential Functions−Application to an Ionic Fragmentation Reaction of *tert*-butyl Chloride in Aqueous Solution

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A new nonempirical method of determining the effective pair potential functions which are suitable for the molecular simulation of heterolysis reactions has been proposed. The self-energy correction due to the polarization in solution was estimated by the ab initio GB calculation which includes the solvent effect by the continuum model using the generalized Born formula, and the polarization caused by solvation was incorporated in the effective pair potential functions. The method was applied to the ionic fragmentation reaction of *t*-BuCl in aqueous solution. The effective pair potential functions between *t*-BuCl and water were determined at 12 different C−Cl distances, and expressed by analytical functions which cover the whole reaction stage, from the covalent bonding region to the dissociated free ions. The Monte Carlo simulation and statistical perturbation theory using the effective pair potential functions determined the free energy profile of the reaction with a reasonable dissociation energy.

1. Introduction

Chemical phenomena are drastically changed by transportation from gas phase to solution, and incorporation of the solvation effects into chemical models has been of great interest for several decades.[1−3] Among such methods, molecular simulations such as Monte Carlo (MC) and molecular dynamics (MD) simulations which deal with a large number of solvent molecules are widely used. In these methods, accuracy in describing the force field of the system determines the reliability of the simulation. Although a density functional theory is used as a force field in ab initio quantum mechanical (QM) MD simulations,[4] its vast computational cost is critical in moderate size reaction systems. So the molecular mechanical (MM) intermolecular pair potential functions or the QM/MM coupled potential functions are widely used to describe a large number of solvent molecules in the simulations.

A QM/MM simulation takes into account the polarization of a solute molecule induced by the molecular mechanical solvent molecules and considers the solvent effect on the electronic structure of the solute molecule dynamically. The charge transfer is not considered. A QM/MM simulation using a high level of QM calculation is not easy, and an economical QM calculation, such as PM3, has been used. In the MM simulation, the quality of the potential functions between the solute and solvent molecules is a key factor. Its economical computational cost allows researchers to carry out large scale simulations and detailed analyses for chemical phenomena in solution.

In the MM method, there are two ways to determine the intermolecular pair potential function. One is an empirical method which determines the pair potential function to reproduce a specific experimental property like the density of pure liquid. The other is a nonempirical method which is based on the intermolecular interaction energies calculated by ab initio molecular orbital (MO) theory. In this case, the pair potential function between the solute and solvent molecules is determined so as to reproduce the interaction energies calculated for the solute−solvent dimer in the vacuum state. The simulation by using this pair potential function describes system **III** in Figure 1. When the solute molecule polarizes to a large extent in solution, the ab initio energies calculated in the vacuum state are not appropriate to determine the pair potential function which describes system **IV**. Several improvements have been suggested to describe system **IV** in Figure 1; an introduction of the three-body interaction term,[5−7] a usage of parameters responsible to the force field,[7−10] and an incorporation of the polarization of the solute molecule in the effective pair potential function (EPPF) by a mean field approximation.[11−21]

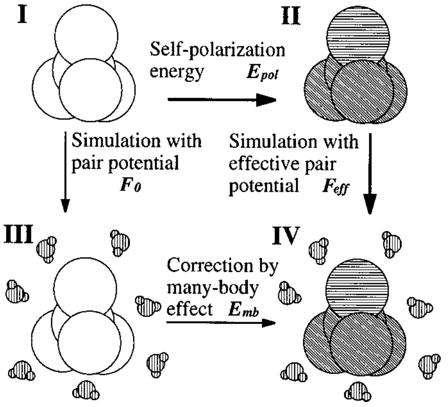

Figure 1. Schematic representation of four states of a solute−solvent system and conceptual steps to determine the solution state. The unshaded and shaded molecules mean nonpolarized and polarized molecules, respectively. **I** is the solute molecule in the gas phase and **II** is the solute molecule having the polarized electronic structure expected in solution. **I** and **II** and polarization self-energy are calculated by the ab initio GB method. **III** and **IV** are calculated by the molecular simulations. By the conventional method, pair potential functions, F_0, are determined with ab initio calculations for the nonpolarized system in the gas phase, and many-body effects are sometimes introduced to improve the pair potential function. System **IV** can be expressed by using the effective pair potential function, F_{eff}, between the polarized solute molecule and solvent which are determined in this study.

Although the polarization of a solute molecule can be incorporated in EPPF by a mean field approximation, most

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existing EPPF do not include correctly the self-polarization energy which is the energy of distortion in the electronic structure caused by solvation. For example, the pair potential functions of water determined empirically, such as TIP4P[22] and SPC[23] do not take into account the self-energy due to polarization. Berendsen et al.[24] pointed out the lack of a self-polarization energy term in SPC and improved the simulation results by including the self-polarization energy in the SPC model of water. Watanabe and Klein[25] also improved the TIP4P type potential function of water by considering the self-polarization energy.

There are several studies to determine the EPPF nonempirically. Floris et al.[11−13] proposed the nonempirical method by using a polarizable continuum model (PCM) and determined the EPPF between various mono-atomic cations and water. The calculation of the various mono-atomic cations associated by water molecules in the first and/or the second solvent shell has been employed to determine the EPPF.[14−21] In these studies of highly charged mono-atomic cations, the charge transfer is important, and the polarization of the mono-atomic cation produces little effect, and the self-polarization energy was not considered.

In the present work we propose a nonempirical method of determining the EPPF, which incorporates the polarization in the pair potential functions by the mean field approximation. It is shown that the self-polarization energy of a molecule is derived straightforwardly by the ab initio GB method,[26−30] which includes the solvent effect by the continuum model using the generalized Born (GB) formula.

The proposed method is then applied to the ionic fragmentation reaction of *tert*-butyl chloride (*t*-BuCl) in aqueous solution. According to the current view for S_N1 type dissociation of *t*-BuCl in aqueous solution,[31−33] *t*-BuCl dissociates to free ions via a contact ion pair (CIP), and then a solvent-separated ion pair (SSIP).

$$t\text{-BuCl} \rightleftharpoons \underset{\text{CIP}}{t\text{-Bu}^+\ \text{Cl}^-} \rightleftharpoons \underset{\text{SSIP}}{t\text{-Bu}^+//\text{Cl}^-} \rightleftharpoons \underset{\text{free ions}}{t\text{-Bu}^+ + \text{Cl}^-}$$

The activation free energy for the hydrolysis of *t*-BuCl was reported to be 19.6 kcal/mol.[34] The CIP and fully separated ions were considered to have the same free energy, 14.5 kcal/mol above the reactant, though the uncertainty was at least ±5 kcal/mol.[35]

Jorgensen et al.[36] investigated the potential energy profile for the ion pair region in the hydrolysis of *t*-BuCl by MC simulation. They showed a well-defined minimum for a CIP at a C−Cl distance of about 2.9 Å, and a minimum for an SSIP at 5.75 Å. Their calculation was confined to the ion pair region.

Keirstead et al.[37] carried out the empirical valence bond (EVB) simulation for the CIP formation from *t*-BuCl. Their method can treat the nonequilibrium solvation by explicitly including the coupling between an ionic state and a covalent state. They obtained a reasonable value for the free energy barrier which separates *t*-BuCl and CIP, although the CIP was predicted to be lower in energy than *t*-BuCl.

More recently, Hartsough and Merz[34] carried out the QM/MM simulation for the S_N1 heterolysis of *t*-BuCl in water using the semiempirical PM3 Hamiltonian for the solute. Their simulation covered the whole range of the reaction coordinate. They obtained a reasonable result only when the correction was taken into account in the long-range solute−solvent electrostatic interaction; a deep minimum corresponding to a CIP and a shallow minimum corresponding to an SSIP appeared at 2.9 and 6.4 Å, respectively.

To carry out the MM simulation for the whole range of this reaction, the effect of polarization of the solute molecule in aqueous solution, which is incorporated explicitly in the QM/MM and EVB simulations, should be incorporated in the EPPF. However, the determination of such EPPF cannot be obtained by ab initio calculation in the gas phase because the electron affinity of *t*-Bu$^+$, i.e., the first ionization potential of *t*-Bu group, is larger than the electron affinity of Cl and the heterolysis of *t*-BuCl does not occur in the gas phase.

The new method described in this study determines the EPPF which includes the polarization effect and makes the MM simulation over the whole range of the heterolysis of *t*-BuCl possible.

2. Method

In the MC simulation of the solution in which a solute molecule polarizes to a large extent, the pair potential functions between the solute and solvent molecules should include the effect of the polarization of the solute and solvent molecules which is caused by solvation. To determine such potential functions nonempirically, the present method takes two steps. In the first step, we calculate the polarized electronic structure of the isolated molecule using the ab initio GB method,[26−30] and estimate the self-polarization energy. In the next step, we calculate the interaction energies between the polarized solute and solvent molecules, and the parameters in the EPPF are determined to reproduce their interaction energies.

2.1. Calculation of the Polarized Electronic Structure and Self-Polarization Energy. The polarized electronic structure of a solute molecule is calculated by using the ab initio GB calculation. The Hamiltonian for the ab initio calculation with a continuum model is represented as a sum of the Hamiltonian for a solute molecule, H_0, and for the solvent effect expressed by the continuum model, H_s,

$$H = H_0 + H_s \tag{1}$$

The energy of an isolated molecule in the gas phase is expressed by H_0 and the unpolarized electronic structure, $|\Psi^{\text{gas}}\rangle$:

$$E^{\text{gas}} = \langle \Psi^{\text{gas}} | H_0 | \Psi^{\text{gas}} \rangle \tag{2}$$

The energy of a molecule in solution is obtained by using the Hamiltonian in eq 1 and the wave function for the polarized electronic structure, $|\Psi^{\text{sol}}\rangle$, by:

$$E^{\text{sol}} = \langle \Psi^{\text{sol}} | H_0 + H_s | \Psi^{\text{sol}} \rangle \tag{3}$$

which is the sum of two components,

$$E^{\text{sol}} = E_0^{\ \text{sol}} + E_s^{\ \text{sol}} \tag{4}$$

where

$$E_0^{\ \text{sol}} = \langle \Psi^{\text{sol}} | H_0 | \Psi^{\text{sol}} \rangle \tag{5}$$

$$E_s^{\ \text{sol}} = \langle \Psi^{\text{sol}} | H_s | \Psi^{\text{sol}} \rangle \tag{6}$$

E_0^{sol} is the energy of the isolated molecule having the polarized electronic structure and the difference between E_0^{sol} and the energy of the isolated molecule in the gas phase, E^{gas}, is the self-polarization energy,

$$E^{\text{pol}} = E_0^{\ \text{sol}} - E^{\text{gas}} \tag{7}$$

which is defined as the energy spent for distortion of the molecular and electronic structures by solvation.[24] Since E^{gas} is the lowest energy of the system in an isolated state, E^{pol} is positive. In other words, E^{pol} is destabilization energy.

Since E^{sol} represents the energy in solution, the usage of the EPPF determined by using E^{sol} for the solute−solvent dimer causes a double counting of the solvation energy. The interaction energy which should be used for the determination of EPPF is obtained by using E_0^{sol} instead of E^{sol}. The wave function $|\Psi^{\mathrm{sol}}\rangle$ is obtained by ab initio GB method.

2.2. Determination of the Effective Pair Potential Function. The present EPPF describes the effective interaction energy between solute and solvent molecules which is evaluated for the gas-phase Hamiltonian by using the wave function expected in the solution. Thus, the interaction energy between solute and solvent molecules is expressed as

$$E^{\mathrm{int}} = E_0^{\mathrm{sol}}(S{-}V) - (E_0^{\mathrm{sol}}(S) + E_0^{\mathrm{sol}}(V)) \tag{8}$$

where S and V represent solute and solvent molecules, respectively, and $S{-}V$ is the solute−solvent system. The subscript 0 indicates that the energy is evaluated for the gas-phase Hamiltonian. The EPPF is expressed by the Lennard-Jones(12−6) terms and the Coulomb term as

$$E_{\alpha\beta}^{\mathrm{int}} = \sum_{i\in\alpha}\sum_{j\in\beta}\left(\frac{A_{ij}}{R_{ij}^{\ 12}} - \frac{C_{ij}}{R_{ij}^{\ 6}} + \frac{Q_iQ_je^2}{R_{ij}}\right) \tag{9}$$

where α and β are molecules, i and j are interaction sites, A_{ij} and C_{ij} are the Lennard-Jones parameters between the sites i and j, Q_i is the charge of the site i, and R_{ij} is the distance between the sites i and j. The parameters Q_i, A_{ij}, and C_{ij} are determined by the least-squares fitting between the quantum mechanical interaction energy, E^{int}, and the energy of the potential function, $E_{\alpha\beta}^{\mathrm{int}}$.

The sum of the EPPF determined in this procedure,

$$\sum_{\alpha}\sum_{\beta>\alpha}E_{\alpha\beta}^{\mathrm{int}}$$

does not give the interaction energy of the solute−solvent system, and the interaction energy is obtained by adding the self-energy required to polarize the solute−solvent system,

$$\sum_{\alpha}E_{\alpha}^{\mathrm{pol}}$$

where $E_{\alpha}^{\mathrm{pol}}$ is the self-polarization energy of α molecule defined in eq 7. Thus, the total energy of the system is expressed by

$$E^{\mathrm{tot}} = \sum_{\alpha}\sum_{\beta>\alpha}E_{\alpha\beta}^{\mathrm{int}} + \sum_{\alpha}E_{\alpha}^{\mathrm{pol}} + \sum_{\alpha}E_{\alpha}^{\mathrm{gas}} \tag{10}$$

where $E_{\alpha}^{\mathrm{gas}}$ is the energy of α molecule defined in eq 2.

3. Application to the Ionic Fragmentation of *t*-BuCl

The present method was applied to the ionic fragmentation of *t*-BuCl. In the following section, we determined the EPPF between *t*-BuCl and a water molecule that covers the whole region of the C−Cl distance. By using this EPPF, Monte Carlo simulation and statistical perturbation theory (SPT) methods were carried out to calculate the free energy profile for the reaction.

TABLE 1: Parameters and Results of MC Simulation of Water

	this study[a]	TIP4P[b]	WK[c]	experiment
R_{OH} (Å)	0.9572	0.9572	0.9572	0.9572[d]
R_{OM} (Å)	0.15	0.15	0.15	
∠HOH (deg)	104.52	104.52	104.52	104.52[d]
A (kcal $Å^{12}$ mol^{-1})	960.0	774.6	1093.2	
C (kcal $Å^{6}$ mol^{-1})	30.3	24.7	34.05	
Q_M (e)	−1.156	−1.04	−1.24	
Q_H (e)	0.578	0.52	0.62	
effective interaction energy (kcal mol^{-1})	−12.45	−	−14.46	
E^{pol} (kcal mol^{-1})	2.74	−	3.97	
interaction energy (kcal mol^{-1})	−9.71	−10.07	−10.49	−9.9[e]
μ (g cm^{-3})	1.011	0.999	1.000	0.997[e]
dipole moment (Debye)	2.424[f]	2.177	2.596	1.85[e]

[a] The MC simulation carried out for the NPT ensemble (216 molecules, 1.0 atm, and 298 K). [b] Ref 22. [c] Ref 25. [d] Ref 38. [e] Ref 39. [f] This value is equal to the dipole moment calculated using the ab initio GB method with the 6-31G* basis set.

3.1. Calculation. At first, the EPPF between *t*-BuCl and a water molecule was determined. The geometry of *t*-BuCl was optimized within C_3 symmetry and local C_3 symmetry for the methyl groups for various C−Cl distances ($R_{\mathrm{C-Cl}}$) in the range of 1.70 Å ≤ $R_{\mathrm{C-Cl}}$ ≤ 9.00 Å using the ab initio GB 6-31G* method with the dielectric constants of $\epsilon = 1$ and 79 for the gas phase and aqueous solution, respectively. For each of the selected 12 C−Cl distances of *t*-BuCl, the interaction energies, E^{int}, were calculated for 126 orientations of the *t*-BuCl−H_2O system. The electron correlation plays an important role in this system,[29] and the energy was corrected using the MP2/6-31+G* calculation for the structure optimized by the HF/6-31G* calculation. In eq 9, the methyl groups were treated as united atoms. The Lennard-Jones parameters proposed by Jorgensen et al.[36] were used for the central carbon atom in *t*-Bu^{+}. From the parameters of the EPPF determined for the 12 different structures of *t*-BuCl, the EPPF which covers the whole range of the reaction coordinate was determined by interpolation.

The parameters for water in the pair potential function were newly determined in order to reproduce the dipole moment of ab initio GB 6-31G* calculation, experimental density (0.997 g/cm^3), and the pair correlation functions for water. The procedure followed the WK model[25] in which the EPPF of water was determined using a mean field approximation. The parameters and properties of the EPPF were listed in Table 1 and in Figure 2. The TIP4P[22] and WK[25] models for water were also employed to compare the solvation energies calculated by MC simulation.

The MC simulation was carried out by the NPT ensemble for one *t*-BuCl solute and 506 water molecules in a periodic rectangular cubic cell which had a variable dimension of ca. 22 × 22 × 30 Å.[40] The pressure and temperature of the system were 1.0 atm and 298 K, respectively. The interaction energies calculated by the EPPF were truncated at 10.0 Å. The change of the solvation free-energy was determined by using SPT[41,42] along the $R_{\mathrm{C-Cl}}$ stretching in steps of 0.05 Å. Double-wide sampling[42] was used and 0.10 Å of the C−Cl distance could be covered in each MC simulation.

All MO calculations were carried out using our ABINIT program and MC simulations using our SIMPLS program on HP J282 workstations and GAIA-300 personal computers.

3.2. Molecular and Electronic Structures of *t*-BuCl. The optimized molecular structures, relative energies, and charges of *t*-BuCl along the reaction coordinate are listed in Table 2.

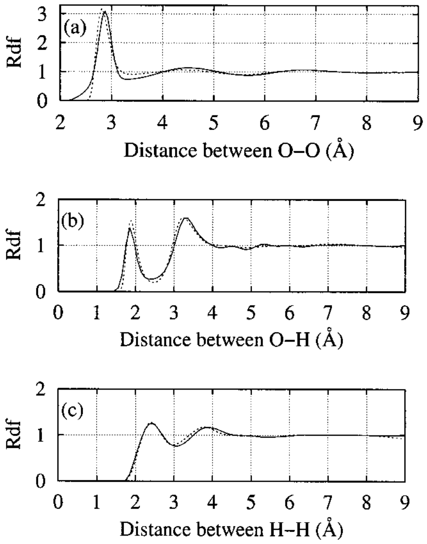

Figure 2. Calculated (a) oxygen−oxygen, (b) oxygen−hydrogen, and (c) hydrogen−hydrogen radial distribution functions of liquid water (dotted curves) obtained by using the potential function determined in the present work. The experimental data (solid curves) are from refs 44−46.

The energy minimum structure in the gas phase was found at $R_{C-Cl} = 1.83$ Å. The heterolytic C−Cl bond dissociation energy in the gas phase, which is largely method-dependent,[29] was evaluated as 150.58 kcal/mol, which was compared with the experimental value of 160 ± 6 kcal/mol.[39] The energy calculated by the MP2/6-31+G**//HF/6-31G* level was 167.17 kcal/mol, showing that the electron correlation effect stabilizes the covalent electronic state more than the ion-pair state.

Charge separation between the *t*-Bu group and Cl was almost completed at $R_{C-Cl} = 3.5$ Å, and the charges of the fragments become unit charges for $R_{C-Cl} > 3.5$ Å. The structural change was also almost completed at $R_{C-Cl} = 3.5$ Å, and the hybridization of the central carbon atom in the *t*-Bu group changed from sp^3 to sp^2; R_{C-C} became shorter by 0.05 Å and ∠ClCC became smaller by 17.3 degrees. The effect of solvation on the solute energy was the largest at $R_{C-Cl} = 2.8$ Å, where E^{pol} was 4.05 kcal/mol. At this C−Cl distance, the electronic structure is described by substantial mixing of covalent and ionic states and the destabilization of the solute molecule caused by polarization is large, because the solvation increases the contribution of the ionic state in *t*-BuCl. Inclusion of the electron correlation effect enlarges the E^{pol}, because the stabilization by the electron correlation is relatively small for the ionic electronic state which has larger contribution in solution than in the gas phase.

3.3. EPPF between *t*-BuCl and Water. The EPPF parameters of *t*-BuCl determined for the new water model are shown in Figure 3. The charge of the chlorine atom at 9.0 Å was almost a unit charge, −0.988. This was obtained without any restriction except the total charge of the system which was set to be zero, because the charges of the water model were determined to reproduce the dipole moment calculated by the ab initio GB method using the 6-31G* basis set. The corresponding values determined by using the TIP4P and WK water models were −1.098 and −0.921, respectively; they deviate from a unit charge because the charges of these water models do not reproduce the dipole moment calculated by the ab initio GB calculation. Deviation of the charge of Cl from a unit value causes a significant error in evaluation of the solvation energy of the ionic species at the dissociation limit.

TABLE 2: Relative Energies, Polarization Self-Energies (kcal/mol), Bond Lengths (Å), Bond Angles (Degrees), and Löwdin Charges of *t*-BuCl Calculated by the Ab Initio GB Method[a]

R_{C-Cl}	ΔE	E^{pol}	R_{C-C}	R_{C-H}	∠ClCC	Q_{Cl}
1.70	4.10(3.11)	0.27(−0.42)	1.534	1.085	109.1	−0.008
	4.37(2.69)		1.533	1.085	109.1	−0.012
1.80	0.19(0.00)	0.32(−0.33)	1.527	1.084	107.7	−0.082
	0.51(−0.33)		1.527	1.085	107.8	−0.094
1.83	0.00(0.01)	0.34(−0.28)	1.526	1.084	107.3	−0.103
	0.34(−0.27)		1.525	1.085	107.4	−0.119
1.90	0.76(1.21)	0.42(−0.08)	1.522	1.084	106.4	−0.155
	1.18(1.13)		1.521	1.084	106.4	−0.180
2.00	3.81(4.92)	0.62(0.47)	1.516	1.084	105.0	−0.229
	4.44(5.38)		1.515	1.084	105.0	−0.270
2.20	12.88(15.82)	1.46(2.86)	1.507	1.083	102.2	−0.378
	14.34(18.68)		1.505	1.083	102.2	−0.459
2.50	26.88(33.99)	3.29(7.91)	1.496	1.083	98.4	−0.585
	30.17(41.90)		1.492	1.082	98.3	−0.709
2.80	38.60(49.85)	4.05(9.41)	1.489	1.083	95.2	−0.744
	42.65(59.26)		1.483	1.081	95.6	−0.861
3.00	45.10(58.66)	3.78(8.38)	1.484	1.083	93.3	−0.832
	48.88(67.04)		1.479	1.081	94.3	−0.917
3.50	55.95(73.37)	3.31(5.32)	1.476	1.085	90.0	−0.946
	59.26(78.69)		1.474	1.082	91.9	−0.974
4.00	66.55(83.79)	1.88(4.20)	1.475	1.086	90.0	−0.976
	68.43(88.00)		1.474	1.082	90.0	−0.990
5.00	84.44(100.78)	1.22(2.21)	1.475	1.086	90.0	−0.997
	85.67(102.99)		1.474	1.082	90.0	−0.999
6.00	95.73(112.38)	0.86(1.05)	1.475	1.086	90.0	−1.000
	96.59(113.43)		1.475	1.082	90.0	−1.000
7.00	103.52(120.36)	0.73(0.70)	1.476	1.086	90.0	−1.000
	104.25(121.06)		1.475	1.082	90.0	−1.000
8.00	109.35(126.27)	0.69(0.62)	1.476	1.086	90.0	−1.000
	110.05(126.89)		1.475	1.082	90.0	−1.000
9.00	113.90(130.83)	0.68(0.61)	1.476	1.086	90.0	−1.000
	114.57(131.44)		1.475	1.082	90.0	−1.000
∞	150.58(167.17)	0.66(1.13)	1.476	1.086	—	−1.000
	151.24(168.30)		1.475	1.082	—	−1.000

[a] The upper values are for the gas phase ($\epsilon = 1$), and the lower values are for the aqueous solution ($\epsilon = 79$). The values were calculated at HF/6-31G*//HF/6-31G* level, and the values in parentheses were calculated at MP2/6-31+G*//HF/6-31G* level.

To apply the EPPF to the SPT calculation, the charges were expressed analytically as a function of R_{C-Cl}, $Q(R_{C-Cl})$, using the following equation,

$$Q(r) = a_1 + a_2 \exp(a_3 r^2 + a_4 r^4) + a_5 \exp(a_6 r^2) \qquad (11)$$

where a_i were fitting parameters listed in Table 3. The parameters of the Lennard-Jones terms have a minimum or a maximum near $R_{C-Cl} = 4$ Å. This characteristic feature comes from the bonding property of which changes from the covalent bond to an ionic one near this region. To represent these variations in the Lennard-Jones parameters, P_{LJ}, appropriately, the following functions were employed,

$$P_{LJ}(r) = (a_1 + a_2 r^{n_1})\, f(r{:}a_3) + (a_4 + a_5 r^{n_2})(1 - f(r{:}a_3)) \qquad (12)$$

$$f(r{:}a_3) = \frac{1}{2}(\tanh(r - a_3) + 1) \qquad (13)$$

where a_i and n_i were fitting parameters listed in Table 4.

The correlation between the energies calculated by the ab initio GB method and the EPPF determined in this work is shown in Figure 4. The standard deviation of these interaction

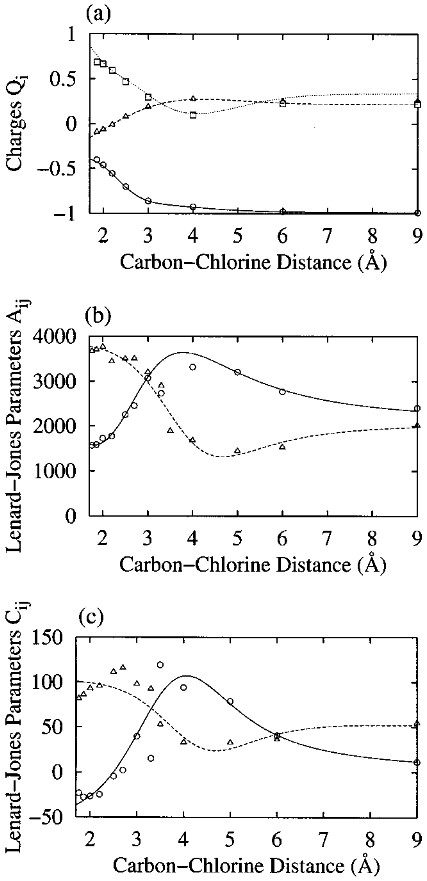

Figure 3. The parameters in the effective pair potential functions for *t*-BuCl as a function of the C−Cl distance. (a) The coulomb parameters Q_i for carbon at the center of *t* -Bu$^+$ (dotted line, squares), methyl groups (broken line, triangles), and chlorine (solid line, circles). (b) The Lennard-Jones repulsion parameters A_{ij} for methyl groups (broken line, triangles) and chlorine (solid line, circles). For carbon at the center of *t*-Bu$^+$, the fixed value of 66.8 kcal^6·mol^{-6} was used.[36] (c) The Lennard-Jones dispersion parameters C_{ij} for methyl groups (broken line, triangles) and chlorine (solid line, circles). For carbon at the center of *t*-Bu$^+$, the fixed value of 5.76 kcal^3·mol^{-3}·Å^{-3} was used.[36]

TABLE 3: Parameters for the Coulomb Term[a] in EPPF

	a_1	a_2	a_3	a_4	a_5	a_6
for chlorine	−0.988	0.264	0.358	−0.0736	0.250	−0.0935
for methyl group	0.217	−3.56	−0.150	−0.000 942	2.86	−0.139

[a] The charge for carbon at the center of *t*-Bu$^+$ was decided by $Q_C = -3Q_{Me} - Q_{Cl}$.

TABLE 4: Lennard-Jones Parameters[a] in EPPF for the Cl Atom and CH$_3$ Groups of *t*-BuCl

	a_1	a_2	a_3	a_4	a_5	n_1	n_2
Cl							
A	2130	155 000	−486	2.69	−1460	3	2
C	−4.75	1310	0.846	3.67	−52.7	2	4
CH$_3$							
A	2070	−70 200	−1.39	3.79	4040	3	5
C	48.1	337	−0.0814	4.19	101	2	5

[a] The Lennard-Jones parameters for carbon at the center of *t*-Bu$^+$ were taken from literature (ref 36).

energies was 0.73 kcal/mol, suggesting that the EPPF reproduce the ab initio GB energies well.

3.4. Energy Profile for the Ionic Fragmentation Reaction of *t*-BuCl in Aqueous Solution. The free energy profile for the ionic fragmentation of *t*-BuCl in aqueous solution, which was calculated by eq 10, is displayed in Figure 5, and the corresponding numerical data is listed in Table 5. In Figure 5, the energy of the isolated solute molecule E^{gas} was calculated by HF/6-31G*//HF/6-31G* (dotted line) or MP2/6-31+G**//HF/6-31G* (solid line) level.

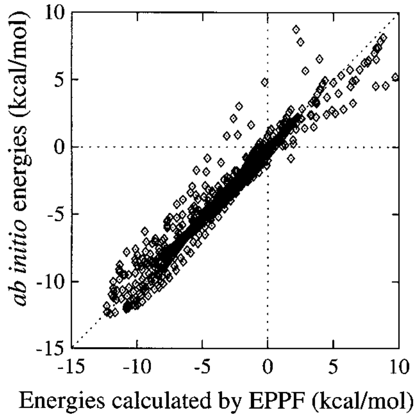

Figure 4. Comparison between the interaction energies obtained by ab initio GB calculations and the EPPF for the *t*-BuCl−H$_2$O configurations.

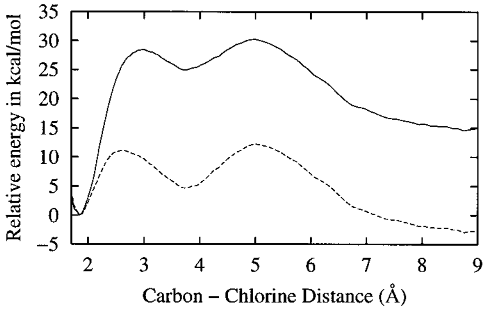

Figure 5. Free energy profile for the ionic fragmentation of *t*-BuCl plotted as a function of the carbon−chlorine distance. The energy is in kcal/mol and the distance is in Å. Solid line shows the results based on the MP2/6-31+G*//HF/6-31G* calculations, while dashed line shows the results based on the HF/6-31G*//HF/6-31G* calculations.

The energy minimum at the C−Cl distance of 1.85 Å corresponds to the *t*-BuCl molecule, and the second minimum, which appears at ca. 3.7 Å, corresponds to the CIP. The result based on the HF calculation largely underestimates the dissociation energy. In this reaction system, the inclusion of electron correlation favors the covalent state[29] and the energy profile was corrected by the MP2 calculation. The MP2 corrected relative energy of the free ions, 14.96 kcal/mol, agrees well with experiment, though the activation energy, 28.52 kcal/mol, is slightly overestimated. This overestimation may be attributed to (1) the lack of the electron correlation in the determination of the EPPF, (2) the disadvantage of the mean field approximation, and (3) the adoption of the simple form for the pair potential functions.

With respect to the first point, we carried out the MP2 and the counterpoise calculations[43] of the solute−solvent interaction energy at several C−Cl distances, and confirmed that 60−80% of the electron correlation are compensated by the basis set superposition error (BSSE).

With respect to the disadvantage of the mean field approximation, the model of Keirstead et al.[37] which is responsible for the change in solvation, may be appropriate to predict the transition state (TS$_1$) between the reactant and CIP. Our TS$_1$ is located at $R_{C-Cl} = 3.00$ Å and CIP at $R_{C-Cl} = 3.75$ Å, which

TABLE 5: Relative Energy (in kcal/mol) for the Ionic Fragmentation of *t*-BuCl

	this study[a]	ref 36	ref 37	ref 34[b]	ref 34[c]	ref 34[d]	exptl.
ΔG_{React}	0.00 (1.85 Å)	− (−)	0 (1.8 Å)	0 (1.8 Å)	0.0 (1.8 Å)	0.0 (1.8 Å)	0.0 (−)
$\Delta G_1^{\ddagger}$[e]	28.52 (3.00 Å)	− (−)	21 (2.3 Å)	× (−)	17.8 (2.3 Å)	23.4 (2.5 Å)	19.5 (−)
ΔG_{CIP}	24.92 (3.75 Å)	1.88 (2.88 Å)	−1 (2.9 Å)	× (−)	9.1 (2.9 Å)	22.9 (2.9 Å)	14.5 ± 5.0 (−)
$\Delta G_2^{\ddagger}$[f]	30.27 (5.00 Å)	4.03 (4.13 Å)	− (−)	∼57 (5.5 Å)	20.5 (5.2 Å)	23.9 (3.5 Å)	− (−)
ΔG_{SSIP}	× (−)	−2.12(5.75 Å)	− (−)	∼55 (6.5 Å)	19.3 (6.4 Å)	× (−)	− (−)
ΔG_{FreeIP}	14.96 (9.00 Å)	0.00 (10.00 Å)	− (−)	∼58 (−)	20.6 (−)	10.0 (9.0 Å)	18.5 (−)

[a] The MP2/6-31+G**//HF/6-31*G calculation. [b] Without any correction. [c] With Born correction. [d] With charge correction. [e] The relative activation free energy between reactant and CIP. [f] The relative activation free energy between CIP and free IP.

are larger than the reported values.[34,36,37] Our method can be incorporated with the empirical valence bond model like Keirstead et al.,[37] and we are planning such an extension of the present model.

It may be difficult to describe the interaction near the CIP region correctly by simple forms of pair potential functions. In this area, the molecular structure of the *t*-Bu group changes between C_{3v} and C_{3h} symmetries, and the united atom approximation of the methyl groups could not reproduce this conformational change well. This is also the reason the MP2 corrected result overestimates the energy in this area.

Hartsough and Merz[34] obtained a free energy profile of the reaction similar to that in Figure 5 by adopting the charge scaling correction; if the scaling correction was removed, the activation energy for the dissociation was vary large (∼57 kcal/mol). They used the semiempirical PM3 Hamiltonian for the solute molecule; the charges of the TIP3P model for water were not suitable for the PM3 Hamiltonian, and this is the reason the charge scaling correction was required. It is indicated that the QM/MM method, in which two different methodologies are used in each region, is hard to use to describe the solute−solvent interaction correctly.

Although the long-range Coulomb interaction plays an important role in this system, the Born correction of Hartsough and Merz[34] is not suitable, because *t*-BuCl behaves as the dipole when a long-range interaction is considered between the solute and solvent molecules.

In the present study, it was confirmed that if the TIP4P and WK models were used as the water model in the simulation, the MP2 corrected energies at $R_{C-Cl} = 9.0$ Å were ca. 2 and 71 kcal/mol relative to the reactant, respectively. These results are caused by the overestimation (TIP4P) or underestimation (WK) of the solvation energies of the ions, of which the absolute charges, 1.098 for TIP4P and 0.921 for WK, deviate largely from the unit value.

In the QM/MM simulation reported by Hartsough and Merz,[34] the dynamic solvent effect on the electronic structure of the solute molecule was considered. The main term of the solvent effect on the electronic structure of the solute molecule was the polarization term, which was induced by the molecular mechanical solvent molecules, and the effect of a charge transfer between the solute and solvent molecules was not considered. In the present method of determining the EPPF, the main term of the solvent effect on the electronic structure of the solute molecule is also the polarization term, which is induced by the continuum media, and the effect of the charge transfer is incorporated in the same amount as the conventional method of determining the pair potential function. To include the effect of the charge transfer appropriately, water molecules in the first solvent shell should be considered explicitly in the MO calculation.

4. Conclusions

A new nonempirical method is proposed which determines the pair potential functions suitable for the simulation including a highly-polarizable solute molecule. In this method, the ab initio GB calculation, which includes the solvent effect by the continuum model using generalized Born formula, was used to evaluate the interaction energy between the polarized solute and solvent molecules, and the polarization effect caused in solution was incorporated into the potential function. Though we used a simple form for the potential functions, the extension to other forms such as the empirical valence bond model is easy.

In application of this method to the ionic fragmentation reaction of *t*-BuCl, the solute−solvent potential functions could be determined as a function of the C−Cl distance over the whole range of the dissociation. For a long C−Cl distance, the ionic state of *t*-BuCl is not the ground state in the gas phase, and the potential functions which are suitable for the simulation of the heterolysis of *t*-BuCl cannot be determined by the usual calculations. The present method provides EPPF which are applicable to the simulation for the solute molecule which is highly polarizable in solution. The calculated energy profile for the reaction of *t*-BuCl elucidated experimental facts qualitatively.

Computation time for the determination of the EPPF required is very short, because the ab initio GB method adopts a simple model which consists of one solute and one solvent molecule. Thus, the method is very useful for determining the pair potential functions which are employed in solution chemistry.

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