

Polarization and Charge-Transfer Effects in Aqueous Solution via Ab Initio QM/MM Simulations

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Combined ab initio quantum mechanical and molecular mechanical (QM/MM) simulations coupled with the block-localized wave function energy decomposition (BLW-ED) method have been conducted to study the solvation of two prototypical ionic systems, acetate and methylammonium ions in aqueous solution. Calculations reveal that the electronic polarization between the targeted solutes and water is the primary many-body effect, whereas the charge-transfer term only makes a small fraction of the total solute–solvent interaction energy. In particular, the polarization effect is dominated by the solvent (water) polarization.

Introduction

Computer simulation offers a great opportunity for studying solvent effects and the mechanism of enzymatic reactions.¹ A critical component of these calculations is intermolecular potential functions that describe intermolecular interactions in the condensed phase, and ultimately determine the accuracy of computer simulations.² Traditionally, effective pairwise potentials are used, in which atomic charges are assumed to be invariant to the change of the surrounding configurations, thereby treating polarization effects in an average way. However, specific polarization energies can be significant for processes involving changes in the molecular environment such as ligand binding. Thus, inclusion of explicit polarization terms in the potential energy function is a major goal in the development of next-generation force fields.³ Furthermore, an intimately related issue is the effect of charge transfer (CT) between solute and solvent molecules, but far less is understood of its impact on condensed phase simulations.⁴ Recent studies employing linear-scaling semiempirical quantum mechanical methods showed that there is significant charge transfer between proteins and solvent with as large as two electron units migrating into aqueous solution in the solvation of a small protein (cold shock protein A).⁵ These authors estimated that the energy contribution due to charge transfer is even greater than polarization interactions. Additional studies of charge transfer have focused on charge distributions, which are known to be dependent on the procedures of the population analysis.^{6,7}

In this letter, we report specific energetic results from combined quantum mechanical and molecular mechanical (QM/MM) simulations coupled with an energy decomposition analysis. Our focus is on the interactions between ionic solutes (acetate and methylammonium ions) and water. We found that

polarization energy is the dominant many-body effect in computing intermolecular interactions, whereas charge transfer only makes small contributions.

Method

Our study of solute–solvent charge transfer and polarization is based on an energy decomposition (ED) method that was developed recently on the basis of a block-localized wave function (BLW) theory.⁸ The BLW is a variation of the ab initio valence bond (VB) method where individual resonance structures corresponding to, for example, a charge-transfer (CT) state or a non-CT state, can be uniquely characterized by Heitler–London–Slater–Pauling (HLSP) functions. The subsequent BLW-ED method allows us to evaluate the short-range charge-transfer energy, while electronic polarization effects are included using combined QM/MM simulations. An attractive feature of the BLW-ED method in comparison with other energy decomposition schemes⁹ is the construction of an intermediate diabatic state where CT among interacting monomers is quenched and the corresponding wave function is self-consistently optimized. Consequently, a physical separation of polarization and CT effects still provides reasonable results. Furthermore, the basis set superposition error (BSSE)¹⁰ is explicitly considered in the computational algorithm and attributed to the CT energy term.^{8b} The method has been applied to the study of a variety of systems, including ion–molecular interactions, Lewis acid–base complexes, and DNA base pairs.^{8c–f} Although the BLW-ED method may not work well if the basis functions lose the atomic characteristics, for example, when a complete basis on a single center for a complex system is used, we found that, from small, atom-centered basis sets such as 3-21G to medium basis sets such as aug-cc-pVTZ, the basis set dependence is insignificant. In addition, due to the cancellation between the diabatic and adiabatic states, electron correlation effects contribute little to the charge-transfer stabilization energy, as verified by the comparison between BLW-ED and ab initio VB results on the donor–acceptor complex BH_3NH_3 where the electron-transfer effect stabilizes the complex by about 30 kcal/mol.^{8d}

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In the present study, we have studied two prototypical ionic systems, acetate anion and methylammonium cation in aqueous solution, which are functional groups that have been found to have the most significant charge-transfer effect in linear-scaling QM calculations of proteins in water.

Computationally, the interaction energy with the counterpoise correction for the BSSE between a solute (X) and solvent molecules (s) is generally expressed as

$$\Delta E_{\text{tot}}^{\text{el}} = E(\Psi_{\text{Xs}}) - E(\Psi_{\text{X}}^{\circ}) - E(\Psi_{\text{s}}^{\circ}) + \text{BSSE} \quad (1)$$

where Ψ_{Xs} is the overall optimized wave function for the complex system (solution) the solute X and the solvent s, and the wave functions for the “isolated” X and s are represented by Ψ_{X}° and Ψ_{s}° , respectively.

The initial diabatic state wave function for the solution is defined as

$$\Psi_{\text{Xs}}^{\text{BLW}\circ} = \hat{A}(\Psi_{\text{X}}^{\circ}\Psi_{\text{s}}^{\circ}) \quad (2)$$

from which we derive the electrostatic energy (ΔE_{perm}) between the solute and solvent in the solution by eq 3.

$$\Delta E_{\text{perm}} = E(\Psi_{\text{Xs}}^{\text{BLW}\circ}) - E(\Psi_{\text{X}}^{\circ}) - E(\Psi_{\text{s}}^{\circ}) \quad (3)$$

where the Pauli exclusion repulsion is also included. The mutual perturbation of the solute and solvent evolves the change from the initial localized wave function ($\Psi_{\text{Xs}}^{\text{BLW}\circ}$) to the final partially localized wave function ($\Psi_{\text{Xs}}^{\text{BLW}}$), and the stabilization energy is ascribed to the polarization effect

$$\Delta E_{\text{pol}} = E(\Psi_{\text{Xs}}^{\text{BLW}}) - E(\Psi_{\text{Xs}}^{\text{BLW}\circ}) \quad (4)$$

In $\Psi_{\text{Xs}}^{\text{BLW}}$, the charge-transfer effect between solute and solvent is deactivated by its construction because each molecular orbital is expanded either in X or in s spaces, only. In fact, $\Psi_{\text{Xs}}^{\text{BLW}}$ corresponds to a diabatic (or resonance) state in terms of the resonance theory. The lift of this restriction allows electrons to move across the solute/solvent interface, and accordingly, each molecular orbital will be extended to both solute and solvent spaces, resulting in the fully delocalized state Ψ_{Xs} . This step is a charge-transfer step. The charge-transfer stabilization energy (ΔE_{CT}) is thus defined as

$$\Delta E_{\text{CT}} = E(\Psi_{\text{Xs}}) - E(\Psi_{\text{Xs}}^{\text{BLW}}) + \text{BSSE} \quad (5)$$

Overall, the total interaction energy is decomposed into electrostatic (including Pauli exclusion), electronic polarization, and charge-transfer contributions.

We can even further probe the individual polarization effect in solute and solvent by defining intermediate block-localized wave functions as

$$\Psi_{\text{Xs}}^{\text{BLW}}(\text{X}) = \hat{A}(\Psi_{\text{X}}\Psi_{\text{s}}^{\circ}) \quad (6a)$$

$$\Psi_{\text{Xs}}^{\text{BLW}}(\text{s}) = \hat{A}(\Psi_{\text{X}}^{\circ}\Psi_{\text{s}}) \quad (6b)$$

where only the orbitals in either X or s are optimized (relaxed) while the other is unperturbed. Thus, the polarization energy contribution from solute or solvent can be defined, respectively, as

$$\Delta E_{\text{pol}}^{\text{X}}(\text{Q}_s^{\circ}) = E(\Psi_{\text{Xs}}^{\text{BLW}}(\text{X})) - E(\Psi_{\text{Xs}}^{\text{BLW}\circ}) \quad (7a)$$

$$\Delta E_{\text{pol}}^{\text{s}}(\text{Q}_X^{\circ}) = E(\Psi_{\text{Xs}}^{\text{BLW}}(\text{s})) - E(\Psi_{\text{Xs}}^{\text{BLW}\circ}) \quad (7b)$$

The overall polarization energy (ΔE_{pol}) (eq 4) will be slightly greater than the sum of the individual polarization contributions (eq 7). This difference ($\Delta E_{\text{pol}}^{\text{mut}}$) reflects the mutual charge polarization between two interacting molecules, providing insight and validation of the imperfect treatment to only allow the solute polarization explicitly, while retaining solvent polarization in an average way, in combined QM/MM potentials.

Results and Discussion

The study started from statistical mechanical Monte Carlo simulations of dilute solutions, each of which consists of a solute ion and 512 water molecules in a cubic box of approximately $24.8 \times 24.8 \times 24.8 \text{ \AA}^3$. In all simulations, the isothermal–isobaric (NPT) ensemble at 25 °C and 1 atm along with periodic boundary conditions were used. The solute molecule, acetate anion or methylammonium cation, is treated quantum mechanically at the ab initio Hartree–Fock (HF) level with the 3-21G basis set,¹¹ and the solvent molecules are represented by the three-point charge model (TIP3P).¹² Each system was equilibrated for 3 million configurations by Monte Carlo sampling, and this was followed by an additional 1 million configurations of averaging, during which the coordinates of the system were saved on every 10K configurations. We used 10 configurations, separated by 100K configuration intervals, to perform the energy decomposition analysis. In the BLW-ED analysis, we used a much greater QM region that is represented by a much larger basis set, the triple-split valence basis 6-311+G(d,p) that includes polarization and diffuse functions, and included water molecules that are within 5 Å of the non-hydrogen atoms of the solute ion. The QM part thus essentially consisted of water molecules within the first two solvation layers of the ion, as determined on the basis of the relevant radial distribution functions (see Figure 1). On average, about 3.5 water molecules are found to form hydrogen bonds with the ammonium ion in the first solvation layer, while 5.6 water molecules are found to solvate the two carboxylate oxygen atoms. For the acetate system, the QM region contains 23–27 water molecules and the number of basis functions ranges from 915 to 1055, whereas, for the methylammonium solution, the QM part includes 27–32 water molecules and 1027–1202 basis functions. This large QM cluster in each configuration is embedded in the remaining solvent system, still represented by the TIP3P model. Thus, it is possible to reliably account for the charge flow across the solute/solvent interface as well as the polarization effects from distant solvent molecules. Calculations at the density functional theory (DFT) level with the same basis set indicate that the electron correlation is insignificant and accounts for additional stabilization by less than 3 kcal/mol in our cases (see the Supporting Information).

As the total interaction energy between a solute and solvent is decomposed into permanent electrostatic interaction energy (ΔE_{perm}), polarization energy (ΔE_{pol}), and charge-transfer energy (ΔE_{CT}), Figure 1 shows the fluctuations of the energy terms along the simulations. The present calculations demonstrated that, in both ionic solutions, the permanent electrostatic interaction energy not only dominates solute–solvent interactions (Table 1) but also fluctuates similarly as the total interaction energy. Polarization effects play an important role, accounting for 20 and 13% of the overall solute–solvent interaction energy for the acetate and methylammonium solutions, respectively. However, charge transfer contributes only 4.6 kcal/mol (3.9%) and 2.9 kcal/mol (2.4%) to the total interaction energy for the anion and cation solutions, respectively. The latter energetic results are mirrored by natural population analyses (NPA)¹³ on

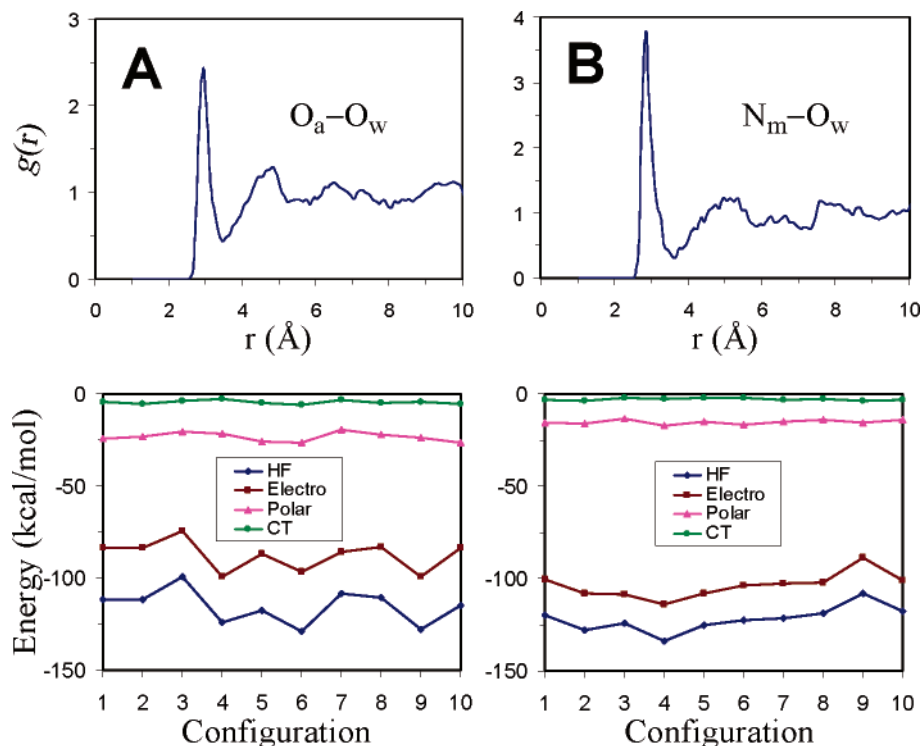


Figure 1. (A) Average acetate oxygen and water oxygen radial distribution function and the intermolecular interaction analysis between CH_3CO_2^- and aqueous solution. (B) Methylammonium nitrogen and water oxygen radial distribution function and the intermolecular interaction analysis between CH_3NH_3^+ and aqueous solution.

TABLE 1: Average Total Solute–Solvent Interaction Energy and Energy Components from Permanent Electrostatic, Polarization, and Charge-Transfer Contributions^a (Energies Are Given in kcal/mol and Charge Transfer from Solute to Solvent Is Given in Atomic Units)

solute	$\Delta E_{\text{tot}}^{\text{el}}$	ΔE_{perm}	ΔE_{pol}	ΔE_{CT}	Δq^b
CH_3CO_3^-	-115.6	-87.6	-23.3	-4.6	0.022
CH_3NH_3^+	-122.0	-103.8	-15.3	-2.9	-0.025

^a For comparison and validation of the performance of HF-QM/MM calculations, the computed total electrostatic interaction energies using DFT-QM/MM at the B3LYP/6-311+G(d,p):TIP3P level are -116.7 and -124.3 kcal/mol. ^b Atomic charges are averaged using the natural population analysis (NPA).¹⁹ Mulliken population analyses yield charge transfer of 0.469e loss and -0.178e gain for acetate and methylammonium ion, respectively. Mulliken population analyses are clearly unreliable for quantitative charge calculations.

both the HF and BLW electron densities, which reveal that the acetate ion loses about $0.022 \pm 0.005e$ to the solvent on average, while methylammonium cation gains $0.025 \pm 0.004e$ from the aqueous solution. Significantly, we found that the amounts of net charge gain and loss for a cation and an anion are small and about the same in magnitude, suggesting that it is unlikely that up to two electrons can be lost to or gained from the solvent by small proteins having a nearly equal number of anionic and cationic residues.

Since these different conclusions can have major implications in the design of new force fields, it is clearly desirable to use consistent charge analysis schemes and quantitative energy decomposition algorithms to study electronic polarization and charge-transfer effects in solute–solvent interactions. Our results, which are obtained by ab initio calculations with a large basis set along with well-defined intermediate wave functions, demonstrate that efforts in force field development shall focus on the inclusion of explicit polarization terms rather than being diverted to the consideration of charge-transfer effects. It is worthwhile to point out that there is a possibility that the charge-

TABLE 2: Computed Polarization Energies (kcal/mol) of the Solute and Solvent and Their Mutual Polarization Interactions

solute	ΔE_{pol}	$\Delta E_{\text{pol}}^{\text{x}}(Q_s^{\text{o}})$	$\Delta E_{\text{pol}}^{\text{s}}(\rho_{\text{x}}^{\text{o}})$	$\Delta E_{\text{pol}}^{\text{mut}}$
CH_3CO_3^-	-23.3	-4.7	-16.5	-2.1
CH_3NH_3^+	-15.3	-1.5	-13.2	-0.6

transfer effect may be underappreciated in our present study, since the samplings used for BLW-ED analyses are derived with combined QM/MM simulations, in which the partial charges of the solvent molecules are fixed, but they are allowed to be polarized and involved in charge flow in the energy analyses. In other words, the first one or two shells of hydration water molecules may slightly deviate from the optimal distances with the solute. One solution is to include these water molecules in the QM part in the simulations, but the ab initio QM/MM method has been parameterized against high-level ab initio results.¹⁴ Thus, it is unlikely that the results could be much different.

We also note that, in a recent study employing plane-wave function DFT and Car–Parrinello simulation techniques, Peraro et al. found that the $-\text{COO}^-$ group loses 0.1e to water and the $-\text{NH}_3^+$ group gains 0.05e from water on the basis of the *atoms in molecules* (AIM) method.⁷ That finding is in accord with our results in that the anion loses charge density, whereas the cation gains electron density from the solvent. However, due to the well-known defects in population analyses, coupled with the use of a localization procedure, which may result in quantitative differences, the focus should be on the relative amount of charges transferred.

To provide additional insights into the solute–solvent polarization effects, we investigated the individual polarization contributions from the solute and solvent separately. Table 2 lists the polarization energy of the solute by the solvent charge density in the absence of the solute ($\Delta E_{\text{pol}}^{\text{x}}(Q_s^{\text{o}})$) and the polarization energy of the solvent by the solute permanent (gas phase) charge density ($\Delta E_{\text{pol}}^{\text{s}}(\rho_{\text{x}}^{\text{o}})$). The remaining polarization

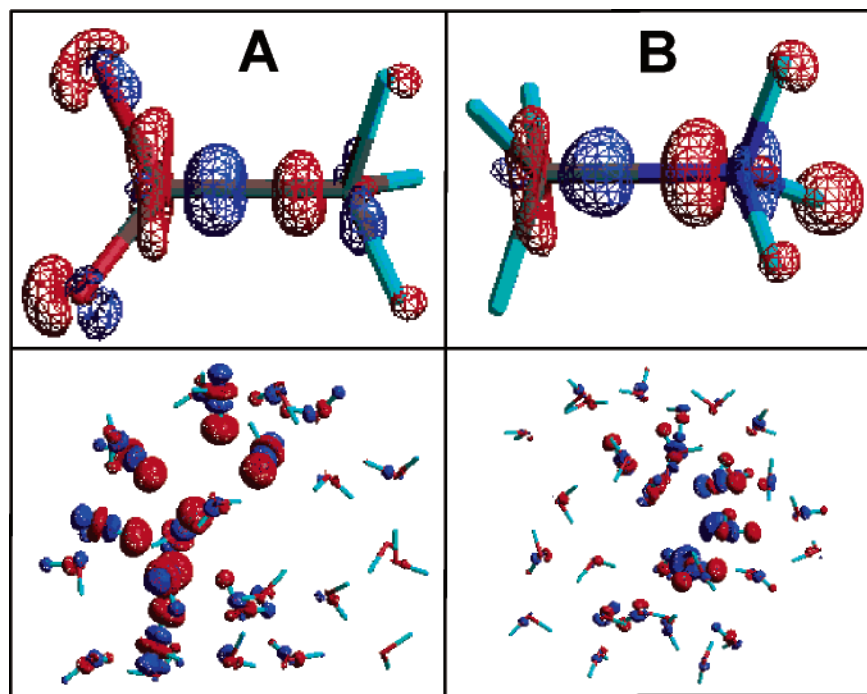


Figure 2. Snapshot electron density difference maps show the polarization of acetate (A) and methylammonium (B) ions in aqueous solution, with red color denoting electron gain and blue color denoting electron loss (isodensity 0.005 au). The upper panels show the changes of the solute electron densities, and the lower ones show the corresponding change in solvent electron density in the first solvation layer.

energy is due to further mutual interactions between the solute and solvent, which is $\Delta E_{\text{pol}}^{\text{mut}} = \Delta E_{\text{pol}} - \Delta E_{\text{pol}}^{\text{X}}(Q_s^0) - \Delta E_{\text{pol}}^{\text{S}}(\rho_s^0)$. We found that *solvent polarization* by the solute permanent charge contributes 71% of the total polarization energy for the acetate ion solution, whereas an even greater component of 86% was obtained for the methylammonium ion solution. The electronic polarization of the ions by the aqueous environment is somewhat small, with quantitative contributions of 20 and 10% for the two systems, respectively. It is interesting to note that the anion has greater polarizations than the cation, which is echoed by the polarization energy contribution to the total solute–solvent interaction energy (Table 1). The mutual effects are small, as indicated in Table 2, but they account for almost half of the solute polarization energies, suggesting that it seems insufficient to only consider the polarization of the solute by using a nonpolarizable solvent model. Furthermore, the results in Table 2 reveal that it is the solvent response that makes the largest energy contributions to polarization effects for ionic solutes. As a final note, the mutual electronic polarization of the solute and solvent can be visualized by examining the electron density difference maps between the polarized charge density and unpolarized charge densities of the solute and solvent (Figure 2). Figure 2 depicts that, for acetate solution, the polarization occurs through enhanced charge density at the carboxylate oxygens and charge depletion from the methyl group, thanks to hydrogen bonding interactions with water molecules. For the methylammonium ion solution, the opposite trend is observed, as the oxygen of water donates hydrogen bonds to the ammonium ion, pushing electrons toward the methyl substituents. For the solvent, polarization occurs to those forming H-bonds with the charged groups, as the water molecules close to the neutral methyl groups show little perturbation (Figure 1).

Concluding Remarks

In summary, combined *ab initio* QM/MM calculations coupled with BLW-ED analyses using a large basis set on the

solvation of acetate and methylammonium ions in aqueous solution demonstrate that it is the electronic polarization effects between solute and solvent that contribute dominantly to the many-body effects, whereas the charge-transfer energy only makes a fraction of the total solute–solvent interactions. We note that the present study represents only two small ions. It would be of interest to extend these studies to a much larger set of ionic systems. Although we cannot definitely exclude the possibility that the accumulation of minimal charge transfer from protein residues to solvent may lead to up to two electrons across the protein and solvent boundary, the present results show that the net gain and loss by opposite charges essentially cancels out, making the possibility of such an overall accumulated large charge transfer unlikely. Thus, it appears to be most fruitful to focus on the inclusion of explicit polarization terms, rather than charge transfer, in developing next-generation force fields for biomolecular simulations.

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Supporting Information Available: Details regarding energy terms and snapshots for the simulation models. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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