Ion Pair Interactions in Aqueous Solution: Self-Consistent Reaction Field (SCRF) Calculations with Some Explicit Water Molecules

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Ion pair interactions in aqueous solution and the role of explicit water molecules have been investigated using ab initio self-consistent reaction field (SCRF) calculations with and without some explicit water molecules. Both the Polarizable Continuum Model (PCM) and the Self-Consistent Isodensity surface Polarizable Continuum Model (SCIPCM) were used for this study. The results suggest that the inclusion of explicit water molecules on hydrogen bonding sites on a solute and the use of a continuum model to complete the hydration environment is more accurate than a continuum model alone. This procedure is also computationally more economical than an explicit bulk water model to represent ion pair interactions in aqueous solution. The results also demonstrate that the SCIPCM method is superior to the PCM method for the interaction of ion pairs, and that the PCM method should not be used for oppositely charged ion pairs until further improvements are introduced.

1. Introduction

Charged groups on the exterior of folded proteins behave quite differently from those in the interior of the folded protein because of the presence of water molecules that play a crucial role in determining the structure and function of biological molecules.[1−4] Although ion pairs observed in proteins are mainly oppositely charged,[5−7] pairings of like-charged groups have often been found in crystal structures.[8−12] Several computational approaches[12−21] to the hydration of ion pairs, based on semiempirical or empirical potential energy functions, have indicated that the stability of hydrated like-charged ion pairs becomes more favorable as the ions approach each other because the network of water molecules stabilizes clusters of like charge. In this work, we have investigated the stability of ion pairs in aqueous solution and the role of explicit water molecules using the Polarizable Continuum Model (PCM)[22] and the Self-Consistent Isodensity Surface Polarizable Continuum Model (SCIPCM),[23] which are based on ab initio quantum mechanical molecular orbital calculations and have been used widely.

The PCM method has been quite successful and works well in treating neutral molecules,[24,25] single ions,[26,27] pK_a calculations,[28] and S_N2 reactions.[29,30] Some calculations[31,32] have been carried out for a single solute with the PCM model, plus explicit water molecules. Recently, hydration energies have been reported for ion-pair interactions using the PCM method,[33,34] but they show nonphysical behavior; for example, when oppositely charged molecules interact, their hydration energy is positive (i.e., repulsive) and does not converge to zero at long distances of separation of the interacting solutes. Initially, we tried to use the PCM method to extend our calculations of ref 33, which showed that the interactions between liked-charged ion pairs in aqueous solution are attractive, to study the role of some explicit water molecules. After extensive calculations with the PCM method with some explicit water molecules, we found that there are problems with this method for the interaction between oppositely charged molecules, as already indicated. For this reason, we introduced the SCIPCM method with and without explicit water molecules, and the results are compared with the results from the PCM method.

In this paper, we show (1) how ions interact with each other in pairs in aqueous solution and how the interactions differ from those in the gas phase, (2) what the role of explicit water is when the solute molecule has a hydrogen-bonding site in a continuum solvation model (this is accomplished by using some explicit water molecules hydrogen-bonded to the solute), and (3) how the description of the interactions within ion pairs in aqueous solution is improved compared with that when the PCM or SCIPCM method is used without explicit water molecules. We also show what the relative accuracies of the PCM and SCIPCM method are and which method should be used for treating interactions between ionic species.

2. Models and Technical Details

Acetate and methylammonium ions were chosen as simplified models for the ionizable side chains of proteins such as Asp, Glu, and Lys. To start the calculations with reliable geometries for the ionic monomers, the geometries of the acetate and methylammonium ionic monomers were optimized in the gas phase with a 6-311++G** basis set at the MP2 level of quantum theory using Gaussian94.[35] With these geometries, the interaction energy was calculated with a 6-31++G** basis set at the Hartree−Fock (HF) level of quantum theory for the three types of ion pairs at various solute−solute distances, defined in Figure 1. The results would not be different if HF/6-

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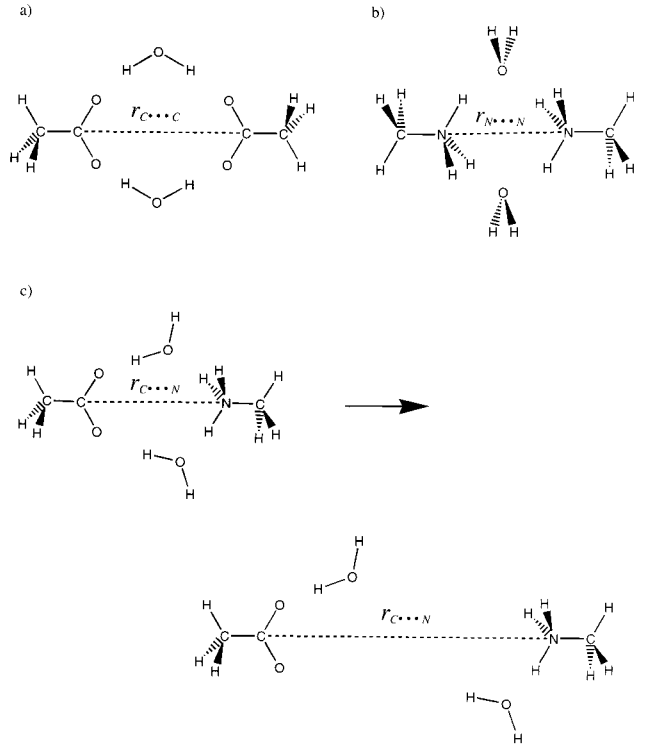

Figure 1. Ion pairs with symmetric water bridges. (a) acetate−acetate (ACAC); (b) methylammonium−methylammonium (AMAM); and (c) acetate−methylammonium(ACAM). As illustrated in (c), which also applies to (a) and (b), when the solutes move apart, each retains only one hydrogen-bonded water molecule.

31++G** geometries or any experimental geometries were used because the geometries of the monomers in the interactions were fixed during the calculations of the interaction energies. The solvation energy depends directly on the cavity surface of the molecule rather than on the geometry. The differences in cavity surface between the geometries from the different levels of calculation are negligibly small.

Our goal here is to show that a pair of two like-charged ions can exhibit an energy minimum at a short distance rather than to show the exact amount of energy involved. Better energies would be obtainable by considering the basis set superposition error or a higher level of quantum mechanical theory, but there would probably be no difference in the trends. Because the electrons in the ions are highly polarized (polarizable) and diffused (diffusable), we used more polarization and diffuse basis sets rather than a higher level of theory such as MP2 or a basis set superposition error correction.

Six types of calculations were carried out in the gas phase and/or in aqueous solution: (1) only ion pairs in the gas phase (GAS), (2) ion pairs with explicit water molecules in the gas phase (GAS/W), (3) ion pairs in the PCM (PCM), (4) ion pairs with explicit water in the PCM (PCM/W), (5) ion pairs in the SCIPCM (SCIPCM), and (6) ion pairs with explicit water in the SCIPCM (SPCICM/W). Both the PCM and SCIPCM are continuum models only. When explicit water molecules were used in the GAS/W, PCM/W, and SCIPCM/W calculations, each solute carried one water molecule at various interionic distances (illustrated in Figure 1c), and the position of the water was optimized with a 6-31++G** basis set at the HF level of quantum theory in the gas phase (GAS/W) while the geometries of the ions and water were fixed; the geometries were then used for the PCM/W and SCIPCM/W methods for the solvation energy calculations.

The stabilization energy of an ion pair, $E^{S,X}_{A-B}(r_{AB})$, is defined as

$$E^{S,X}_{A-B}(r_{AB}) = E^{X}_{A-B}(r_{AB}) - (E^{X}_{A} + E^{X}_{B}) \qquad (1)$$

where A and B represent the ions A and B, respectively; X is the index to designate the phase (i.e., GAS, GAS/W, PCM, PCM/W, SCIPCM, or SCIPCM/W); r_{AB} is the distance between ions A and B as defined in Figure 1. $E^{X}_{A-B}(r_{AB})$ is the energy of the ion pair at the separation r_{AB} in phase X; and E^{X}_{A} and E^{X}_{B} are the energies of ions A and B, respectively, in phase X. The sum of E^{X}_{A} and E^{X}_{B} corresponds to the reference state of the energy of ion pair A-B in phase X. The superscript S stands for *stabilization energy*.

3. Results and Discussion

The stabilization energies of the ion pairs (ACAC, AMAM, ACAM) in one set of phases (GAS, GAS/W, PCM, PCM/W) are plotted against the interionic distances in Figure 2, and in another set of phases (GAS, GAS/W, SCIPCM, SCIPCM/W) are plotted in Figure 3. For comparison, GAS and GAS/W data are plotted for both sets.

Instead of considering all possible orientations of the water molecules, we used a symmetry constraint for the water molecules, as shown in Figure 1c. Most of the irregularities in the curves arise from the symmetry constraint. The irregularities that can be seen for ACAM with GAS/W at distances between 8 and 10 Å in Figure 2c and 3c arise from the interaction between water molecules. Because a constraint is applied, because each ion retains only one hydrogen-bonded water molecule, we broke the interaction between water molecules. When we did not apply such a constraint, the acetate ion carried two water molecules at distances >10 Å, whereas the methylammonium ion carried none because the interaction between waters is stronger than that between water and methylammonium.

Because gas-phase geometries (GAS/W) were used for the solvation energy calculations (PCM/W and SCIPCM/W), the points on the curves for PCM/W and SCIPCM/W may not be connected to the minimum energy path, which led to the irregularities in the PCM/W and SCIPCM/W curves.

In Figure 2a, the stabilization energies of ACAC are plotted against the interionic distances, $r_{C\cdots C}$. Although GAS/W shows a minimum at 6.5 Å with an energy of 51.2 kcal/mol, both GAS/W and GAS show that the complex is very repulsive at short distance and the energy goes to zero as the distance, $r_{C\cdots C}$, goes to infinity. PCM is much lower in energy but still shows a repulsive behavior at short distances. PCM/W shows a minimum at 6.4 Å, with an energy of −3.7 kcal/mol. In Figure 2b, AMAM shows the same tendency as ACAC in Figure 2a.

In Figure 2c, the energies of GAS and GAS/W for ACAM are very attractive, with energies of −116.6 kcal/mol at 2.9 Å and −107.6 kcal/mol at 3.2 Å, respectively, whereas PCM and PCM/W are repulsive (>0 kcal/mol), with energies of 14.9 kcal/mol at 3.3 Å and 12.9 kcal/mol at 3.6 Å, respectively. This result implies that the oppositely charged ion pair (ACAM) is very unstable in aqueous solution, which is physically unrealistic for two reasons. First, in general, solvent-exposed salt bridges seem to play a role in stabilizing proteins, though small compared with the contributions from salt bridges that are completely or partially buried,[36−39] and solvent-exposed salt bridges still contribute to the stabilization (perhaps reflecting the presence of the nearby low-dielectric protein). Also, although pairings of like-charged groups have often been found in crystal

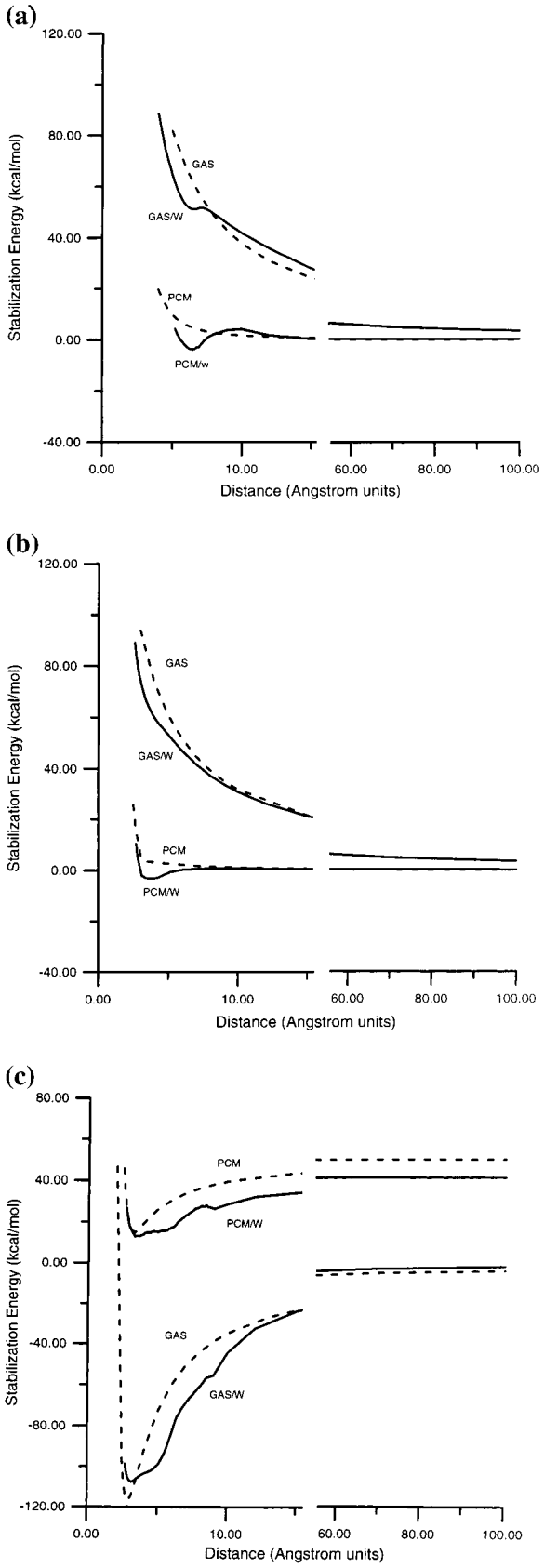

Figure 2. Stabilization energy, $E^{S,X}$ in the various phases (GAS, GAS/W, PCM, and PCM/W) of (a) acetate pair (ACAC), (b) methylammonium pair (AMAM), and (c) acetate−methylammonium pair (ACAM).

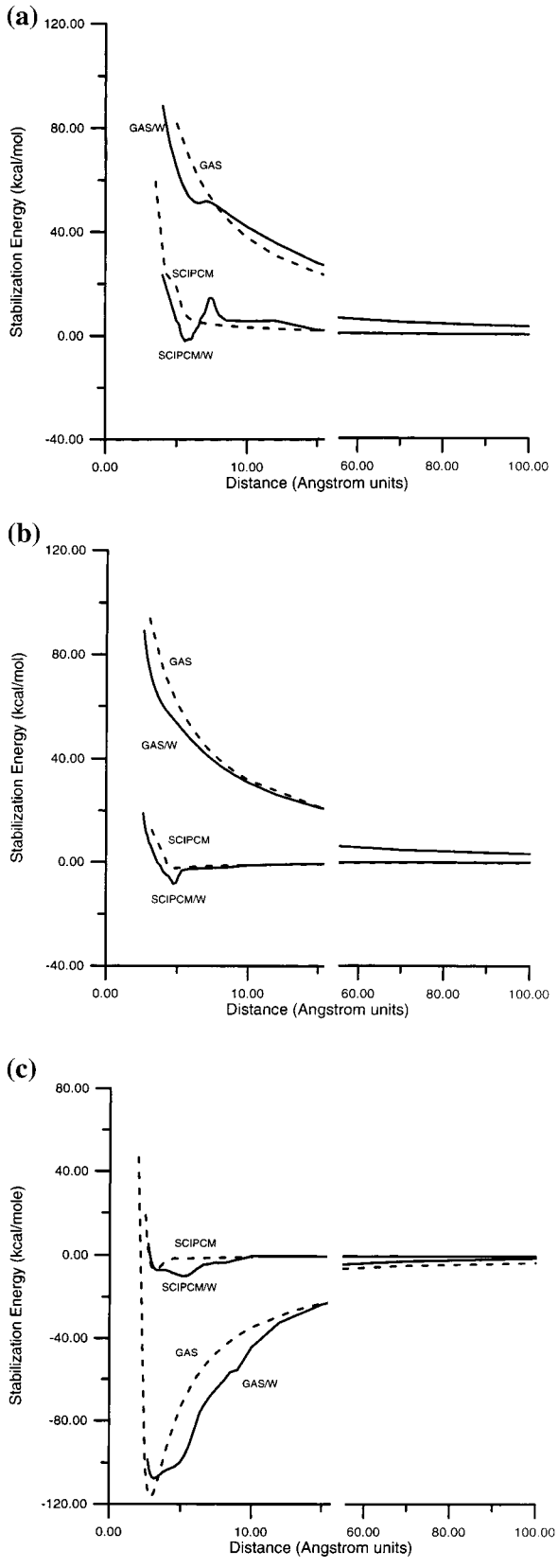

Figure 3. Stabilization energy, $E^{S,X}$ in the various phases (GAS, GAS/W, SCIPCM, and SCIPCM/W) of (a) acetate pair (ACAC), (b) methylammonium pair (AMAM), and (c) acetate−methylammonium pair (ACAM).

structures of proteins, the majority of ion pairs observed in proteins are oppositely charged,[5−7] which means that the pairing of oppositely charged ions is energetically still favorable and should have negative stabilization energies. Second, the energies of PCM and PCM/W should converge to zero as the distance goes to infinity because we define the reference state as the sum of E_A^X and E_B^X. However, the energies in Figure 2c converge to 50 kcal/mol for the PCM model and to 30 kcal/

mol for the PCM/W model. This result is not the only one that shows this tendency. No et al.[33] (in Figure 3 of that paper) and, more recently, Barril et al.[34] (in Table 3 of that paper) also showed positive free energies for this ion pair. Thus, our results do not reflect a misuse of the PCM method but rather that there are problems inherent in this method.

The PCM method has a critical defect that has been reported as a "tail error" by several authors.[40−45] In the PCM method, it is assumed that the whole solute charge distribution lies within the cavity boundary, which is 1.2 times that of the van der Waals radius. In quantum mechanical calculations, the electronic contribution to the solute charge distribution fades away exponentially rather than being confined within the fixed cavity. The situation becomes worse when anions are treated because the cavity is defined on the basis of the neutral state, and anions have more electrons than the neutral species and even more than cations; thus, electrons in anions have a greater chance to be located outside of the cavity.

Recently, a renormalization procedure was applied to a newer version of PCM and tested for an S_N2 reaction.[30] The procedure was successful in treating the tail errors of the system [$Cl^- + CH_3Cl$], which has a total charge of −1, but the procedure has not been tested for the oppositely charged system that has a total charge of zero. The methods that use renormalization procedures (namely, CPCM or IEFPCM) are presented in Gaussian 98. The CPCM and IEFPCM methods differ from PCM, the latter being available in Gaussian 94. Although the later version, Gaussian 98, includes PCM, the latter is also present unchanged in Gaussian 98. Our purpose in using Gaussian 94 was to provide general guidelines for treating ion-pair interactions with SCRF calculations. It is thus not clear why the convergence problem occurs only with oppositely charged ion pairs (ACAM) in the PCM model.

For this reason, we used another method, the so-called SCIPCM. In this model, the cavity boundary is defined by an isoelectrondensity surface that is determined self-consistently in the SCF procedure. Because the SCIPCM method does not require explicit atomic radii, the free energy of solvation depends strongly on the isodensity value used. In this study, we used the solute cavity defined by the isodensity surface with a value of 0.0004 au.[35]

The results are shown in Figure 3. In Figure 3a, SCIPCM/W shows a minimum at 5.6 Å with an energy of −2.0 kcal/mol, whereas SCIPCM shows a repulsive and energetically unfavorable behavior at all the distances. The SCIPCM/W result is consistent with the works of Dang and Pettitt[17] and of Buckner and Jorgensen,[19] which show that two negatively charged ion pairs are in close contact in aqueous solution. SCIPCM without explicit water molecules does not seem to be good enough to represent the ion-pair interactions in aqueous solution, especially for the two negatively charged ion pairs. One interesting result is that SCIPCM/W shows a maximum at 7.4 Å, with an energy of 14.5 kcal/mol, which is caused by the inflation of cavities (see later discussion in this section). In Figure 3b, SCIPCM shows a minimum at 4.6 Å, with an energy of −2.4 kcal/mol, and SCIPCM/W has a minimum energy of −8.6 kcal/mol at 4.7 Å. The energy is lower than that of ACAC. In Figure 3c, SCIPCM and SCIPCM/W have minima and converge to zero as the distance goes to infinity. SCIPCM has a minimum energy of −7.5 kcal/mol at 3.2 Å and SCIPCM/W has a minimum of −10.2 kcal/mol at 5.2 Å. These values are lower than those for AMAM and even much lower than those for ACAC, which implies that pairing of oppositely charged ions is more favorable than pairing of like-charged ions in aqueous solution. Also, this situation differs from the results reported previously.[33,34]

Some caveats must be applied to the discussion just presented because the polar groups remaining, after the hydrogen bonds in the complex are broken at large separation distance, would each hydrogen bond to other water molecules (which is not taken into account in the simplified model of Figure 1). Inclusion of only two water molecules is not a proper treatment of a single solvation shell. Addition of more water molecules would be required to produce more quantitative results. However, the inclusion of more water molecules would require a proper definition of their most favorable orientations. To avoid this difficulty, we used only two water molecules. It would be expected, however, that the continuum water present in the model would fulfill the role of such additional water molecules to some extent, so that the quantum mechanical calculations would capture the main features of complex formation between the monomers considered here. In this study, we have demonstrated that the presence of even two water molecules can account for the existence of a minimum at a short distance between two like-charged molecules, which cannot be seen in an SCRF or normal continuum model alone.

It is of interest to note that minima of AMAM (two positive ions) is much lower, −8.6 kcal/mol, than that of ACAC (two negative ions), −2.0 kcal/mol, in the SCIPCM/W curves. It is difficult to account for the preferred stability of two positive ions compared with two negative ions, but perhaps this behavior is related to the different hydration properties of positive and negative ions.[46,47]

Although the SCIPCM method is more realistic than the PCM method, it still has problems. One problem is the "inflation of cavity" that was noticed by Truong and Stefanovich.[29] As can be seen in Figure 3a, there is a maximum for ACAC at 7.4 Å, with an energy of 14.5 kcal/mol. The energy is larger than that for breaking a hydrogen bond between water and acetate. This barrier can be explained by the inflation of the isodensity contour that is caused by the electron density redistribution from the oxygen of acetate to the hydrogen of water. This inflation is maximized for the case of ACAC because water molecules make four equivalent hydrogen bonds to acetate. And, as already mentioned, SCIPCM alone without explicit water molecules cannot represent the minima of negatively charged ion pairs, whereas the SCIPCM/W result is consistent with the works of Dang and Pettitt[17] and of Buckner and Jorgensen[19] that show that two negatively charged ion pairs are in close contact in aqueous solution.

The solvation energy of SCIPCM does not include the cavitation energy. Because we are interested in the stabilization energy rather than the solvation energy itself, the absence of cavitation energy for both the reference solvation energy (solvation energy of monomers) and the interaction energy should not be a problem when comparing the relative interaction energies of ion pairs.

4. Conclusions

Those potential energy functions based on gas phase data cannot represent the interaction of molecules in solution, including not only the magnitude that can be adjusted by varying the dielectric constant but also the attractive or repulsive behavior. As can be seen in Figure 3b, SCIPCM leads to negative values. These values cannot be adjusted by introducing a dielectric constant unless we use a negative value for the dielectric constant, which has no physical meaning.

The SCIPCM method without explicit water molecules was quite successful in representing the interaction between mol-

ecules in solution. However, because this method lacks an orientation effect and specific hydrogen bonding, it still shows no minima, especially for ACAC (in Figure 3a) which shows an opposite behavior compared with SCIPCM/W.

With SCIPCM/W, the results show that like-charged ion pairs are also favorable (energies <0 kcal/mol), and ACAM is more favorable than ACAC or AMAM. These results are quite different from those obtained with only SCIPCM for ACAC, and differ even more from those in the gas phase. It is obvious that a simple electrostatic model in the gas phase does not account for structure and stability. Furthermore, an accurate description of interactions with water plays a major role in the prediction of structure and stability; that is, the structure and stability of an ion pair cannot be accounted for by simply adding a pair interaction between a solute and a water molecule to a gas-phase potential function (GAS/W) or by using only the SCIPCM method. In particular, such potentials cannot adequately describe phenomena in aqueous solution if these potential functions are used to study protein folding. It is obvious that water molecules are significantly polarizable, and account should be taken of this property. Our work demonstrated that it is both accurate and computationally economical to treat explicit water for hydrogen bonding sites with a solute and to use a continuum model to complete the treatment of hydration. Such a model, with specific hydrogen-bonded water molecules in an otherwise continuum water hydration layer, had been proposed by Hodes et al.,[48] and this work supports this approach with ab initio calculations.

The PCM method does not represent the interaction between oppositely charged ions well because of its inherent defect in the definition of the cavity. Presumably, this result arises from the fact that the PCM method uses a fixed atomic cavity that is 1.2 times that of the van der Waals radius. It is obvious that the atomic cavity should change according to the solute charge. By comparison, the SCIPCM method defines its cavity by the isosurface of electron density of the solute which means that it takes full account of the charges of the molecules. This aspect of the SCIPCM method demonstrates that it is superior to the PCM method for the interaction of ions in pairs and that the PCM method should not be used for oppositely charged ion pairs until further improvements are introduced.

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