J. Phys. Chem. A **2004,** *108,* 4277−4282

Studies of Solvation Free Energies of Methylammoniums and Irregular Basicity Ordering of Methylamines in Aqueous Solution by a Combined Discrete-Continuum Model

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Received: December 4, 2003; In Final Form: February 17, 2004

The solvation free energies of $Me_nNH_{4-n}^+$ ($n = 0$, 1, 2, and 3) have been computed by means of a combined discrete-continuum model, in which the ionic solute and the solvent molecules in the first layers around the hydrogen atoms or protons bonded to the nitrogen atom are treated quantum mechanically and the remaining solvent is simulated by a continuum model. The results show that the discrete-continuum model can predict the solvation free energies of charged species within the chemical accuracy. On the basis of the computed solvation free energies, we further explore the nature of the irregular order in basicity of a series of methylamines in aqueous solution. Analyses reveal that the short-range solute−solvent interactions play a very important role in the inversion of basicity.

1. Introduction

The determination of the free energy change associated with the process of ionic solvation has been the subject of numerous theoretical and computational studies.[1−12] Theories for both implicit and explicit solvation models have been developed and applied widely. In the implicit continuum theory,[1,4] the solute is treated by the quantum mechanics, but embedded in a dielectric continuum of permittivity equal to that of the solvent. The continuum models have been the most popular and convenient approaches for the description of solvents in computational chemistry due to its high efficiency and implementation in popular quantum mechanical calculation software. These models provide a very easy and accurate way to treat the extremely important and strong long-rang solute−solvent interactions that dominate many solvation phenomena. However, it is also known that the strong and specific solute−solvent interactions are not completely accounted for by the continuum models. In particular, hydrogen bonding, which is a short-range force, is not completely predictable from bulk electrostatics. An alternative discrete approach is to treat solvent molecules explicitly at the molecular mechanical (MM) level, with the solute at either the same MM level or more advanced quantum mechanical (QM) level. The solvation free energy is derived by subsequent Monte Carlo simulations.[2,6,8] This kind of combined QM/MM method is very useful for inspecting specific solvent effects on the solute electronic structure, although it is considerably computation-demanding compared with the continuum models, particularly when a few solvent molecules are added to the QM part together with the solute molecule. A compromise between the implicit and explicit models is to include the first-shell solvent molecules around the solute into the QM part, but the rest of the bulk solvent is treated with the continuum theory. In this case specific solute−solvent interactions, mainly the hydrogen bonding ones, are retained at the ab initio level, while long-range interactions are introduced through the continuum model. Such a combined discrete-continuum model,[13] also known as cluster-continuum,[14] semicontinuum,[15] or supermolecule-continuum model,[16] is more economic and efficient, especially in the case where the solvent and the solute are strongly bound, such as the ionic solvation. In addition, the discrete-continuum model can provide insight into many fundamental details where continuum models fail to provide unique pictures.

One kind of interesting phenomenon related to the solvation free energy is the acid/base equilibrium. The prediction of basicity remains extraordinarily hard, due to the difficulties in computing accurate gas-phase protonation free energies and solvation free energies of charged species.[17] For example, the inversion of the basicities of methylamines when passing from the gas phase to aqueous solution continues to be a challenging research topic.[18−28] The gas-phase basicities increase with successive methyl substitutions due to the inductive effect of methyl groups,[29] whereas the sequence is $Me_2NH > MeNH_2 > Me_3N > NH_3$ in aqueous solution,[30,31] although the differences of their basicities are very small. Obviously, the basicity ordering inversion should be attributed to the solvent effect,[18−28] thus the accurate computation of the solvation free energies is essential in the determination of the basicity in solution and rationalization of the basicity irregularities. Many computational studies have been conducted to probe the basicities of methylamines in solution, but the reproduction of this subtle trend was shown to be difficult. In the process of continuing investigations, however, an interesting controversy has arisen about whether the interpretation of the abnormal basicity order should be principally based on hydrogen bonds or on electrostatic interactions.[21,23−25] On the basis of the supermolecule approach calculations, Galera et al.[21] claimed that the number and strength of hydrogen bonds play a critical role in the inversion of basicity. However, this explanation is not persuasive, since the long-range interactions arising from bulk solvent molecules beyond the first solvation shell are ignored, and this type of long-range interaction could have significant impact, particularly on ions.

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10.1021/jp0377127 CCC: $27.50

SCHEME 1: Thermodynamic Cycle Considered for Calculating Solvation Free Energies of the Solutes in Water

$$\begin{tikzcd}
S(g) + nH_2O(g) \arrow[r, "\Delta G^*_{clust}"] & S(H_2O)_n\,(g) \arrow[d, "\Delta G^*_{solv}(S(H_2O)_n)"] \\
S(g) + \text{water} \arrow[u, "n(\Delta G_{vap})"] \arrow[r, "\Delta G^*_{solv}(S)"'] & S(H_2O)_n\,(aq)
\end{tikzcd}$$

By taking into account the electron correlations up to the MP4 level, Tunon and co-workers[23] successfully reproduced the irregular order in basicities with the continuum PCM method. Based on the computational results, Tunon et al. further concluded that the electrostatic interactions between the solute and the solvent are more important than the specific hydrogen bonds. But this statement was disproved by Kawata and co-workers,[24,25] who argued that the continuum models have no way to incorporate the hydrogen bond interactions. They demonstrated that qualitatively similar results with those of Tunon et al. can be derived based on the microscopic solvent model without considering the electron correlations. Therefore, it remains an open question for further studies whether specific or long-range solute−solvent interactions exert a more significant effect on the irregularity of the basicities of methylamines.

In this work, we apply the combined discrete-continuum solvation model to the solvation free energies of methyl-substituted ammonium ions in an attempt to assess the accuracy and usefulness of the model. Our focus is whether and how much the results can be improved by explicitly considering one or more solvent molecules with the solute at the quantum mechanical level which are embedded in a continuum solvation model, compared with the conventional practice of inserting the solute only in the continuum models. In addition, the basicities of a series of methylamines in aqueous solution are computed with the combined discrete-continuum solvation model and the nature of their irregular order is probed. The contributions to free energy changes are analyzed entirely from a microscopic point of view.

2. Method and Computational Details

2.1. Thermodynamic Calculations. The discrete-continuum model has been applied to the calculations of the solvation free energies of ionic solutes from the thermodynamic cycle presented in Scheme 1. Thus solvation free energies are calculated as (S denotes the solute)

$$\Delta G^*_{solv}(S) = n\Delta G_{vap} + \Delta G^*_{clust} + \Delta G^*_{solv}(S(H_2O)_n) \quad (1)$$

where $n\Delta G_{vap}$ is the Gibbs free energy required to move n water molecules from the pure liquid phase to the gas phase to form the cluster with the solute, ΔG^*_{clust} is the free energy of formation of the cluster $S(H_2O)_n$ in the standard state (1 mol/L), and $\Delta G^*_{solv}(S(H_2O)_n)$ is the solvation free energy of the cluster corresponding to the long-range interactions of the hydrated cluster embedded in a cavity, which refers to the process of gas (1 mol/L) → solution (1 mol/L).[32] For the free energy of vaporization of water, we have used the experimental data of 2.05 kcal/mol for ΔG_{vap}.[33] It should be noted that the vaporization occurs under the pressure of 1 atm and thus an expansion work term $P\Delta V$ has been added to the Gibbs free energy.

SCHEME 2: Thermodynamic Cycle for the Calculation of the Basicity in Solution ($\Delta G_{prot,aq}$)

$$\begin{tikzcd}
B(g) \arrow[d, "\Delta G^0_{solv}(B)"'] & + & H^+(g) \arrow[d, "\Delta G^0_{solv}(H^+)"] \arrow[r, "\Delta G^0_{prot,g}"] & BH^+(g) \arrow[d, "\Delta G^0_{solv}(BH^+)"] \\
B(aq) & + & H^+(aq) \arrow[r, "\Delta G^0_{prot,aq}"'] & BH^+(aq)
\end{tikzcd}$$

Similarly, the computation of basicity, defined as the Gibbs free energy for the protonation of a base, can be carried out by the thermodynamic cycle shown in Scheme 2. The free energy of protonation ($\Delta G^0_{prot,aq}$), related to the concept of basicity in solution, can subsequently be calculated as

$$\Delta G^0_{prot,aq} = \Delta G^0_{prot,g} + \Delta G^0_{solv}(BH^+) - \Delta G^0_{solv}(B) - \Delta G^0_{solv}(H^+) \quad (2)$$

where the first term is the free energy of protonation in the gas phase and the other three terms are the solvation free energies of the neutral and protonated amines and the proton. Since the solvation of the proton term $\Delta G^0_{solv}(H^+)$ exists in all amine basicity calculations and will not affect the ordering of the basicity, we simply used the value of −260.5 kcal/mol given for $\Delta G^0_{solv}(H^+)$ by Aue et al.,[31] although a slightly improved value (−264.0 kcal/mol) has been recommended recently.[34]

2.2. Computational Details. The ab initio molecular orbital calculations were performed with the GAUSSIAN 98 software.[35] Equilibrium geometries in the gaseous phase were optimized at the MP2/6-311+G(d,p) level. Frequency calculations have been carried out to characterize the stationary points and derive the thermal, rotational, and vibrational contributions to the free energy by using standard procedures. Basis set superposition errors (BSSE) have been estimated in several cases by the computation of counterpoise corrections.[36]

The solvation energies of neutral species and bare ions by the bulk solvent were calculated respectively by the continuum PCM,[37] IEFPCM,[38] and IPCM[39] methods in conjunction with the MP2/6-311+G(d,p) wave function and a dielectric constant of 78.39, corresponding to water at 298.15 K. In the IPCM calculations, a 0.004 au isodensity surface was used to define the cavity. In the continuum model calculations of neutral systems, the gaseous phase optimal geometries were used, as it has been shown in previous work[23,40] that changes in the geometrical parameters due to the inclusion of the solvent effect are relatively minor. For ionic clusters, i.e. methylammoniums with the first hydration shell, gas-phase stationary structures were reoptimized in aqueous solution by using the continuum PCM method at the HF/6-31+G(d) level. Furthermore, single-point calculations were done including electron correlation with the IEFPCM method at the MP2/6-311+G(d,p) level. These calculations were applied in the computation of solvation free energies and basicities in aqueous solution, as illustrated in the previous section.

3. Results and Discussion

3.1. Structural and Electronic Properties. For the number of discrete solvent molecules to be used in the discrete-continuum model, the general approach is to consider the first solvation shell with discrete molecules while the rest of the solvent is described by the continuum models. A recent study by Caskey et al.[27] reveals that the ionic character of the nitrogen center significantly influences the hydration structures, and the

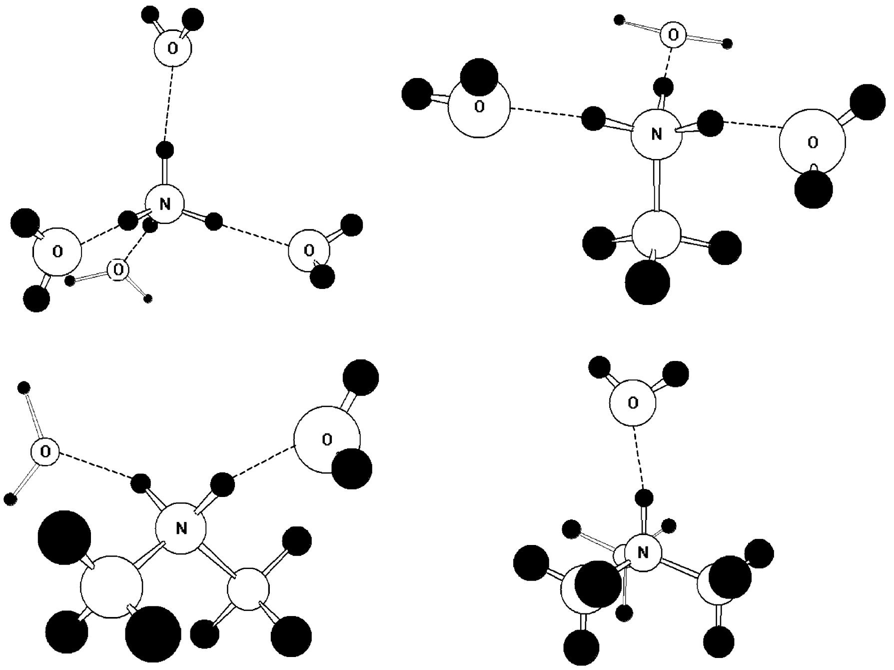

Figure 1. Optimized geometries for $NH_4(H_2O)_4^+$, $MeNH_3(H_2O)_3^+$, $Me_2NH_2(H_2O)_2^+$, and $Me_3NH(H_2O)^+$ clusters in aqueous solution.

water fragments bond directly with the hydrogen atoms or protons attaching to the nitrogen center in methylammoniums ions. Therefore the minimum number of water molecules in the first solvation shells around the positively charged centers of methylammoniums depends on the number of N−H bonds (i.e., four for NH_4^+, three for $MeNH_3^+$, two for $Me_2NH_2^+$, and one for Me_3NH^+). Although there is a controversy regarding the number of water molecules in the first solvation shell of NH_4^+,[41] we note that each (N−)H forms only one hydrogen bond with water in ideal situations (e.g., gaseous phases or crystals) and increasing the number of water molecules in the first solvation shell will significantly complicate the search of the representative ground-state structure and, as an alternative, molecular dynamics simulations must be performed to get the solvation free energy. For the sake of simplicity, here we put four water molecules around the NH_4^+, which can form four strong hydrogen bonds and consequently recover the majority of short-range solvent−solute interactions with the remaining interactions accounted for by the continuum model. Optimized geometries for $NH_4(H_2O)_4^+$, $MeNH_3(H_2O)_3^+$, $Me_2NH_2(H_2O)_2^+$, and $Me_3NH(H_2O)^+$ clusters in a continuum are shown in Figure 1. Selected geometric parameters and charge distribution from the computations in vacuo to in solution are listed in Table 1 for comparison.

TABLE 1: Selected Bond Distances (Å) and Mulliken Charges (electrons) on Atoms for the Targeted Structures in the Gas Phase and in Solution at the HF/6-31+G* Level

solute	R(N−H)	R(N···O)	P(N)	P(C)	P(O)
		optimized in the gas phase			
NH_4^+	1.013		−1.06		
$MeNH_3^+$	1.011		−1.00	−0.38	
$Me_2NH_2^+$	1.009		−0.86	−0.39	
Me_3NH^+	1.009		−0.73	−0.39	
$NH_4(H_2O)_4^+$	1.017	2.931	−1.30		−1.07
$MeNH_3(H_2O)_3^+$	1.016	2.924	−1.20	−0.36	−1.08
$Me_2NH_2(H_2O)_2^+$	1.016	2.915	−0.98	−0.39	−1.08
$Me_3NH(H_2O)^+$	1.016	2.905	−0.79	−0.39	−1.07
		optimized in aqueous solution			
NH_4^+	1.018		−1.11		
$MeNH_3^+$	1.017		−1.02	−0.39	
$Me_2NH_2^+$	1.018		−0.85	−0.41	
Me_3NH^+	1.022		−0.69	−0.43	
$NH_4(H_2O)_4^+$	1.017	2.905−2.914	−1.30		−1.13
$MeNH_3(H_2O)_3^+$	1.015−1.017	2.879−2.887	−1.15	−0.39	−1.13
$Me_2NH_2(H_2O)_2^+$	1.014	2.863−2.877	−0.88	−0.43	−1.13
$Me_3NH(H_2O)^+$	1.017	2.845	−0.72	−0.43	−1.13

From Table 1, it can be found that the change of structures owing to the solvent effect is modest in magnitude. This is in agreement with previous works.[23,40] However, the small structural changes still reflect interesting features for the specific and long-range solute−solvent interactions and demonstrate the discrepancy between the combined discrete-continuum solvation model and conventional continuum model. When either specific (solute plus a few water molecules) or long-range interaction (solute in continuum media) is taken into account, the N−H bonds in the ammonium ions always lengthen due to their respective polarization effects. In the cases where both types of interactions (supermolecule in a continuum media) are simultaneously considered, N−H bonds are still longer than those in vacuo, but slightly shorter than those in a pure discrete model or in a pure continuum model. In addition, the N−O distances in a combined discrete-continuum model are shorter than those in a pure discrete model. These results can be interpreted on the basis of the charge distributions (or polarization). Mulliken population analyses on the pure discrete model and the combined discrete-continuum model indicate that the water molecules experience electron density polariztion toward the oxygen side due to the solvent effect. The partial charges on the oxygen atoms are increased from ca. −1.07 to ca. −1.13, which subsequently strengthens the N−H···O hydrogen bonds and leads to the shortening of N−H distances and N−O distances. Compared with the structural parameters in Table 1, we find that the N−O distance is the most sensitive or variable one. The relatively big changes of the N−O distances from the pure discrete model to the combined discrete-continuum model highlight the importance of short-range interactions between the solute and solvent and the necessity of reoptimization of the structures in solution.

For the ammonium ions, population analyses reveal that the partial charges on the nitrogen atoms are enhanced compared to the gas phase due to the electrostatic field generated by the

TABLE 2: Solvation Free Energy and Its Components within the Discrete-Continuum Model[a] (kcal/mol)

solute	ΔG_{vap}	ΔG^*_{clust}	$\Delta G^*_{solv}(S(H_2O)_n)$	$\Delta G^*_{solv}(S)$
NH_4^+	5.92	−32.76	−53.78	−80.62
$MeNH_3^+$	4.44	−22.24	−53.10	−70.90
$Me_2NH_2^+$	2.96	−13.71	−52.46	−63.21
Me_3NH^+	1.48	−7.35	−52.13	−58.00

[a] The IEFPCM model with a MP2/6-311+G(d,p) wave function was used for the continuum calculations.

TABLE 3: Comparison of Calculated and Experimental Solvation Free Energies of Methylamines in Aqueous Solution and Errors in Parentheses (kcal/mol)

solute	PCM	IEFPCM	IPCM	exptl[a]
NH_3	−5.13(−0.82)	−4.51(−0.20)	−4.61(−0.30)	−4.31
$MeNH_2$	−5.72(−1.15)	−5.19(−0.62)	−3.75(0.82)	−4.57
Me_2NH	−7.95(−3.67)	−4.92(−0.64)	−3.11(1.17)	−4.28
Me_3N	−5.26(−2.03)	−3.36(−0.13)	−2.64(0.59)	−3.23

[a] Reference 44.

solvent in all three models. Furthermore, in the pure continuum model the nitrogen partial charges are close to the values in the gas phase, since there is no charge transfer between the solute and the bulk solvent. However, both discrete and discrete-continuum models predict similar partial charges on the N atoms due to the charge transfers between the solute and explicit water molecules, which are −0.04e, −0.02e, −0.01e, and 0.01e for $NH_4(H_2O)_4^+$, $MeNH_3(H_2O)_3^+$, $Me_2NH_2(H_2O)_2^+$, and $Me_3NH(H_2O)^+$, respectively, in the discrete-continuum model. A large discrepancy for the partial charges on the N atoms is observed between the pure continuum model and the combined discrete-continuum mode. Therefore, we conclude that the major drawback of the continuum model is the neglect of electron exchanges between solute and its surrounding solvent molecules.

3.2. Solvation Free Energy. Solvation free energies of methylammoniums have been obtained from the thermodynamic cycle presented in Scheme 1. The relevant data and the calculated solvation free energies are summarized in Table 2. It can be seen that along with the successive methyl substitution, continuum contributions ($\Delta G^*_{solv}(S(H_2O)_n)$) remain nearly constant throughout the series, while discrete contributions ($\Delta G_{vap} + \Delta G^*_{clust}$) decrease significantly due to the reduction of the number of hydrogen bonds. Although the continuum contributions are larger than the discrete contributions, the direct solute−solvent interactions are still considerably strong and important, with about 7 kcal/mol per water fragment. Thus, the specific solute−solvent interactions are important and should be considered explicitly.

Tables 3 and 4 compared the calculated solvation free energies of methylamines and methylammoniums in aqueous solution with experiments. As Pliego and Riveros have shown,[14] this solvation free energy can be computed with good accuracy for neutral molecules but not for ions due to the existence of strong solute−solvent interactions which complicate the calculation accuracies. For the neutral molecules, the solvation free energies calculated by means of the IEFPCM method are in very good agreement with experimental results with errors less than 1 kcal/mol. The PCM results are slightly poorer, particularly for Me_2NH and Me_3N. For the methylammonium ions, the experimental results are still controversial, as they are dependent on the absolute value of the solvation free energy of proton ($\Delta G^0_{solv}(H^+)$), which itself remains a controversial issue. Pearson[42] and Florian and Warshel[43] compiled the solvation free energies of ions using $\Delta G^0_{solv}(H^+) = -259.5$ kcal/mol, while Pliego and Riveros[44] adopted a value of $\Delta G^0_{solv}(H^+) = -264.0$ kcal/mol. In our calculations, PCM and IEFPCM results are extremely close, although there are large discrepancies for the neutral molecules. These results support the experimental values of Pearson,[42] but the IPCM results seem more consistent with the values of Florian et al.[43] Besides, the combined discrete-continuum model, with the first solvation shell explicitly considered, is also consistent with results of continuum PCM and IEFPCM methods and is shown to be good enough to predict solvation free energies of charged species, as the errors are lower than 4%. However, for the methylammonium ions since the PCM and IEFPCM calculations lead to close results which are in accord with the experimental values, the use of discrete models with a few explicit water molecules plus the continuum IEFPCM method does not result in a better evaluation of the solvation free energies. In fact, comparing the results of the discrete-continuum model and pure continuum methods, we find that for NH_4^+, the error in the discrete-continuum model is more pronounced than that in the continuum PCM and IEFPCM methods, while the error trend reverses for Me_3NH^+. Therefore it seems that the combined discrete-continuum model introduces errors due to discrete contributions, while it annihilates the errors in continuum methods. On the basis of the above analyses of error sources, it can be inferred that the discrete-continuum model may not be suitable for the treatment of neutral molecules unless at very high levels, since it is considerably difficult to calculate the weak solute−solvent interactions accurately.

To further evaluate the discrete-continuum model, we calculated the solvation free energy of NH_4^+ by changing the number of water molecules explicitly considered, and the results are presented in Table 5. Clearly, when the first solvation shell of NH_4^+ are simplified by four discrete water molecules which satisfy each N−H bond by forming a hydrogen bond, the solvation energy is in good agreement with the experimental value. When the first solvation shell of NH_4^+ is not completely filled with the water molecules, the errors slightly go up. Previous studies concluded that the use of a discrete model with more solvent molecules beyond the first solvation shell plus a continuum does not lead to a better evaluation of the solvation energy.[23,45] Our results suggest that the inclusion of solvent molecules in the first solvation shell, which strongly interact with ionic solutes, is necessary.

3.3. Basicity. As pointed out in the pretext, the determination of the basicity scale in solution involves the calculation of

TABLE 4: Comparison of Calculated and Experimental Solvation Free Energies of Methylammoniums in Aqueous Solution (kcal/mol)

solute	discrete-continuum	PCM	IEFPCM	IPCM	discrete-continuum[a]	experimental		
						Pliego et al.[b]	Pearson[c]	Florian et al.[d]
NH_4^+	−80.62	−80.44	−80.41	−84.15	−79.38	−84.9 ± 0.7	−79	−81 ± 5
$MeNH_3^+$	−70.90	−70.28	−70.94	−73.63	−72.69	−75.2 ± 0.7	−70	−73 ± 5
$Me_2NH_2^+$	−63.21	−64.03	−65.83	−65.21		−67.9 ± 0.7	−63	−66 ± 5
Me_3NH^+	−58.00	−58.38	−59.55	−59.27		−61.7 ± 0.7	−56	−59 ± 5

[a] Reference 14. [b] Reference 44. [c] Reference 42. [d] Reference 43.

TABLE 5: Solvation Free Energy for the Different $NH_4((H_2O)_n^+$ Clusters and Its Components within the Discrete-Continuum Model (kcal/mol)

solute	nH$_2$O	ΔG_{vap}	ΔG^*_{clust}	$\Delta G^*_{solv}(S(H_2O)_n)$	$\Delta G^*_{solv}(S)$
NH_4^+	4	5.92	−32.76	−53.78	−80.62
NH_4^+	3	4.44	−30.08	−57.83	−83.47
NH_4^+	2	2.96	−21.89	−63.77	−82.70
NH_4^+	1	1.48	−13.09	−70.95	−82.56

solvation free energy ΔG^0_{solv} and its algebraic addition to the gas-phase protonation energy. Table 6 lists the gas-phase protonation free energies ($\Delta G^0_{prot,g}$) of methylamines calculated at the MP2 and G3 levels. Experimental values given by Eades et al.[46] are also presented for comparison. Among the two sets of data obtained at the MP2 and G3 levels, the relative values at the MP2 level are closer to the experimental values, although the discrepancies (2−3 kcal/mol) are still notable compared with the small differences among the protonation free energies of methylamines. The BSSE corrections at the MP2 level tend to increase the discrepancy between the calculated protonation free energy of NH_3 and the experimental value due to the overestimation of the BSSE by the counterpoise method at correlated levels.[47] As a consequence, although the calculated absolute values of other methylamines at the MP2 level are in better agreement with experimental results, e.g., the deviations of absolute values are −2.09, −1.85, and −1.88 kcal/mol for $MeNH_2$, Me_2NH, and Me_3N, respectively, their relative values compared to ammonium deviate from the experimental values by around 2−4 kcal/mol. At the G3 level the calculated absolute values are similar to those at the MP2 level apart from NH_3, and their relative values are even slightly larger than those at the MP2 level. Therefore in the current work the MP2 results are used for further calculations of the basicities in aqueous solution.

The protonation free energies of methylamines in aqueous solution together with the energy contributions as shown in Scheme 2 are present in Table 7. Obviously, the ordering of the calculated basicity in solution is different from the ordering in the gas phase. Although the errors of the calculated gas basicities have little effect on the correct estimation of in-solution basicity ordering and the calculated solvation free energies are in reasonable agreement with the experimental values, the irregular order of the basicities of methylamines in aqueous solution cannot be reproduced as the discrepancy of the basicities of methylamines in aqueous solution is very modest. The errors of calculated results, i.e., the gas-phase basicities and solvation free energies, are more or less larger than the relative values of in-solution basicities of methylamines.

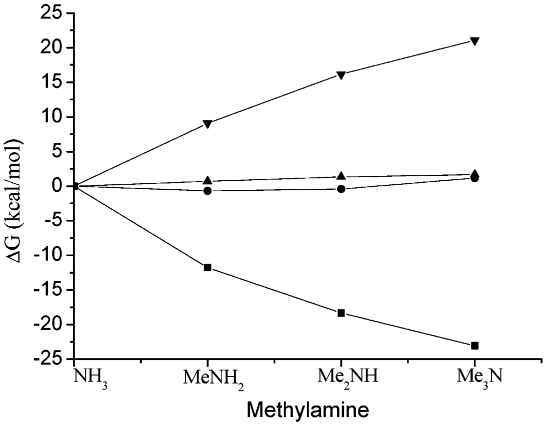

Figure 2. $\Delta G^0_{prot,g}$(■), ΔG^*_{solv}(B) (●), $\Delta G^*_{solv}(S(H_2O)_n)$ (▲), and $\Delta G_{vap} + \Delta G^*_{clust}$(▼) relative to the NH_3/NH_4^+ system for each methylamine.

An important issue, apart from the correct estimation of absolute energies, is the rational understanding of the origin of basicity inversion in solution. Essentially, the inductive effect and the electrostatic interaction with the solvent can explain most of the differences between the basicity orderings of methylamines in vacuo and in solution. The substitution of hydrogen atoms in ammonia by methyl groups has these two effects on the free energy of protonation in solution. On one hand, there is only one effect namely the inductive effect present in vacuo. The inductive effect of the methyl group causes the stabilization of conjugate acids of methylamines. The basicities of methylamines thus increase with the successive methyl substitutions. On the other hand, in solution the substitution of methyl groups decreases the stabilization of conjugate acids caused by the solvent effect, due to the continuing loss of strong hydrogen bonds. As a consequence, the subtle balance between the two contributions determines the irregular order of basicity of methylamines. Our computations indicate that both $\Delta G^0_{prot,g}$ and ΔG^0_{solv} have monotonic behaviors with the methyl substitutions. Whereas $\Delta G^0_{prot,g}$ decreases along the series from NH_3 to $N(CH_3)_3$, ΔG^0_{solv} increases. Thus, it seems that the irregular basicity ordering of methylamines in solution can be explained from a delicate equilibrium between the protonation energies in vacuo and solvation energies. Regarding the solvation terms, Figure 2 shows that along with the successive methyl substitution, continuum contributions ($\Delta G^*_{solv}(S(H_2O)_n)$) which depend on the size and shape of cavity remain nearly constant throughout the series, and discrete contributions ($\Delta G_{vap} + \Delta G^*_{clust}$) decrease significantly due to the changes of the

TABLE 6: Comparison of Calculated and Experimental Free Energy Changes upon Protonation in the Gas Phase (kcal/mol)

solute	MP2		MP2 (BSSE)		G3		experimental [a]	
	ΔG	ΔG_{rel}	ΔG	ΔG_{rel}	ΔG	ΔG_{rel}	ΔG	ΔG_{rel}
NH_3	−196.51	0.0	−193.98	0.0	−195.73	0.0	−197	0.0
$MeNH_2$	−208.29	−11.78	−207.15	−13.17	−208.13	−12.4	−206.2	−9.1
Me_2NH	−214.85	−18.34	−214.79	−20.81	−214.97	−19.24	−213	−16.0
Me_3N	−219.58	−23.07	−220.21	−26.23	−219.89	−24.16	−217.7	−20.7

[a] Reference 46.

TABLE 7: Protonation Free Energies in Aqueous Solution (kcal/mol)

solute	$\Delta G^0_{solv}(H^+)$	$\Delta G^*_{solv}(B)$	$\Delta G^*_{solv}(BH^+)$	$\Delta G^0_{prot,g}$	$\Delta G^0_{prot,aq}$	$\Delta G^0_{prot,aq}$(exptl)[a]
NH_3	−260.5	−4.51	−80.62	−196.51	−12.12	−12.61
$MeNH_2$	−260.5	−5.19	−70.90	−208.29	−13.50	−14.53
Me_2NH	−260.5	−4.92	−63.21	−214.85	−12.64	−14.70
Me_3N	−260.5	−3.36	−58.00	−219.58	−13.72	−13.37

[a] Reference 31.

number of hydrogen bonds. Thus, our results suggest that the specific solute–solvent interactions, mainly the hydrogen bonds, play a very important role in the irregular ordering of the basicity of methylamines in aqueous solution. The correct prediction of the basicity order of methylamines in water requires an accurate treatment of the short-range hydrogen bonds between methylamines and water molecules.

4. Conclusions

In this paper the solvation free energies of methylammoniums ions have been calculated by means of the combined discrete-continuum model in which the specific solute–solvent interactions are described at the quantum mechanical level, while the long-range interactions are introduced through an electrostatic model. This hybrid model was shown to be good enough to predict the solvation free energies of charged species. However, for the methylammoniums, since the PCM and IEFPCM results are in close agreement with the experimental values, the combined discrete-continuum model does not lead to a better evaluation of solvation free energies compared to conventional continuum models. The irregular order in basicity of a series of methylamines in aqueous solution has also been investigated. Since the errors of calculated gas-phase basicities and solvation free energies are larger than the relative values of in-solution basicities, the combined discrete-continuum model cannot completely reproduce the subtle trend of the basicity of methylamine in aqueous solution. However, the origins of the discrepancy between our computed data and experimental results are explored based on the various energy contributions to the protonation energies of methylamine in water. On the basis of the discrete-continuum model employed in this work, we believe that the specific solute–solvent interactions play a very important role in the inversion of basicity of methylamines.

Acknowledgment. This work is supported by the Natural Science Foundation of China and Western Michigan University (Y.M.).

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