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Computational Studies of Aliphatic Amine Basicity

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Computational studies have been used to examine the structural and energetic effects of adding small numbers of water molecules to ammonia, methylamine, dimethylamine, and trimethylamine, and their respective ammoniums ions using the effective fragment potential method. Distinct structural effects with only a few fragment water molecules are revealed. The complexity of structures increases with the number of water fragments with the water fragments forming complex networks. Structural and energetic effects are used to probe the so-called anomalous basicity effect of ammonia and the methylamines on going from the gas phase to aqueous solution.

Introduction

Recognition of the importance of steric effects in determining the basicity order of various amines was reported in the 1940s by H. C. Brown.[1−4] The notion that the size of the acid and base contributed to the basicity order was elegantly demonstrated in studies of methyl- and ethylamines with different acids. Brown reported that the order of basicity of methylamines with the aqueous proton or trimethylborane is $(CH_3)_2NH > CH_3NH_2 > (CH_3)_3N > NH_3$ in contrast with the order expected if inductive contributions dominate $[(CH_3)_3N > (CH_3)_2NH > CH_3NH_2 > NH_3]$. This is often called an anomalous order, meaning any order not mirroring the inductive one. The more sterically demanding acid, tri(*tert*-butyl)borane, gives another order altogether $[CH_3NH_2 > NH_3 > (CH_3)_2NH > (CH_3)_3N]$ as do ethylamines: for $HCl_{(g)}$ and aqueous HCl, $(CH_3CH_2)_2NH > CH_3CH_2NH_2 > (CH_3CH_2)_3N > NH_3$; for trimethylborane, $(CH_3CH_2)_2NH > CH_3CH_2NH_2 > NH_3 > (CH_3CH_2)_3N$; for tri(*tert*-butyl)borane, $NH_3 > (CH_3CH_2)_2NH > CH_3CH_2NH_2 > (CH_3CH_2)_3N$. Brown clearly recognized not only the importance of the size of the interacting species in gas-phase acid−base reactions, but the complicated nature of the aqueous solvent effects.

During the intervening years, numerous studies of amine basicity (and corresponding solvent effects) give testament to the fundamental importance of understanding aliphatic amine basicity.[1,5,6] Although current understanding of the factors contributing to aliphatic amine basicity in both the gas and condensed phase is very sophisticated, details related to the specific, structural nature of acid−aliphatic amine interactions are still lacking. The road to this point has been charted by both gas-phase studies of aliphatic amine basicity[7,8] and detailed analyses of the thermodynamic factors controlling interaction.[9,10]

Munson demonstrated in 1965 not only that the gas-phase basicities of the methylamines followed the inductive order $[(CH_3)_3N > (CH_3)_2NH > CH_3NH_2 > NH_3]$, and that increasing basicity with methyl substitution occurred for series of ethers/alcohols, aldehydes/ketones, and carboxylic acids as well.[7] Subsequent comprehensive studies of gas phase basicities and acidities of a wide range of compounds by Brauman and co-workers considerably broadened the scope of gas-phase alkyl substitution effects and established the importance of polarizability as a stabilizing effect in alkyl groups in the gas phase.[11,12] Thus, increasing the number and complexity of alkyl substituents in a regular molecular series in the gas phase can have the effect of stabilizing a positive charge and increasing basicity (the amines[8]) or of stabilizing a negative charge and increasing acidity (the alcohols[12,13]), both by mechanisms that are dominated by polarizability ($\approx 1/r^4$) effects.[11] In addition to the increase in amine basicity with both methyl and ethyl substitution, these workers showed that larger, more polarizable alkyl groups increase amine basicity [e.g. $(CH_3)_3CNH_2 > (CH_3)_3CCH_2NH_2 > (CH_3)_2CHNH_2 > CH_3CH_2CH_2NH_2 > CH_3CH_2NH_2$]. While the observation by Brown in 1945 that hydrogen chloride and aqueous HCl gave the same

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basicity ordering for ethylamines (anomalous) may seem inconsistent with gas-phase results, Brauman, Riveros, and Blair suggest that this is a solution effect, recognizing that the Brown's experiments were carried out in solution at low temperature.[8]

Once the intrinsic basicity ordering of alkylamines and suitable explanations for alkyl substituent effects were established in the gas phase, the process of understanding the anomalous basicities of amines in polar solution could be addressed in new ways. Taft, Arnett, Beauchamp, and co-workers carried out detailed thermodynamic analyses of the anomalous basicity order of amines in a series of studies that were made possible by complete gas phase and solution "dissection" of water ionization and amine/ammonium ion solvation.[9,14−17] Despite the care and determination of these workers, it is fair to say that the factors that typically contribute to the anomalous basicity effects of alkylamine in polar solvents such as water are small and not easily applied de novo. The situation is adequately expressed by "the inverted order of aqueous base strength arises from slight differences in the rate of change of the thermodynamic properties in response to progressive alkyl substitution".[14]

Another trenchant analysis of the thermodynamic factors involved in methylamine basicity by Aue, Webb, and Bowers emphasizes the importance of electrostatic effects in both the enthalpic and entropic contributions to the anomalous effect.[18,19] There is a large attenuation of the effect of methyl substitution on going from the gas phase to aqueous medium, which results largely from an electrostatic solvation enthalpy term for the ammonium ions. These authors indicate that the enthalpic contribution to the anomalous effect results from the competition between the intrinsic base strengthening of methyl substitution and the larger base weakening electrostatic solvation term of the ammonium ions, which depends strongly on their effective radius and ionic charge density. The free energy change must take account of entropic changes as well, and these are dominated by an electrostatic $T\Delta S^{el}$ term for the ammonium ions. This term, in addition to a small symmetry entropy term, leads to increasing base strength with methyl substitution and "oppose the strong base-weakening effect of the electrostatic term..."[18] This analysis shows that the many of the enthalpic and entropic terms cancel, leading to a situation (1) where the solution free energies of ammonia and the methylamines are within 2 kcal/mol and (2) in which very small differences seemingly control the basicity ordering of methylamines.

Application of the modified Drago ECW equation has been used to examine interactions between amines and various specific acids, $H(H_2O)_n^+$, and represents another approach to understanding anomalous amine basicity behavior.[6,10] Based on gas-phase studies by Meot-Ner and co-workers that provide proton affinities for methyl- and ethylamines and $H(H_2O)_n^+$, the ECW relationship can be used to obtain enthalpy estimates of the appropriate acid−base reactions based on the relative importance of gas-phase electrostatic and covalent interactions between the amines and acids.[10,20−23] As the value of n in $H(H_2O)_n^+$ increases from 0 to 6, the strength of the gas phase electrostatic amine−acid interactions increases while covalent interactions attenuate. The interplay between varying electrostatic and covalent parameters for the amines and acids (as n varies) not only suggests the dominance of electrostatic interactions in the enthalpic changes in these acid−base reactions, but gives insight into the anomalous basicity ordering. It is suggested that the unique characteristics of each base and acid are sufficient to explain anomalous behavior without the necessity of invoking solvent effects.[24]

Although there is a measure of satisfaction in understanding the thermodynamic relationships that control alkylamine basicity, it is incomplete because of the paucity of additional information about the structural characteristics of the acid−base interactions, particularly when only a few water molecules are 'present' as part of an amine−acid interaction. Nevertheless, there are various literature indications of the importance of only a few waters in alkylamine/alkylammonium studies.[9,10,20−22,25−28] Trotman−Dickenson in 1949 suggested that ammonium/alkylammonium ions were more strongly solvated at hydrogen.[25] Thus, ammonium ion could be primarily solvated by four solvent molecules, while the trimethylammonium ion could be primarily solvated by only one. Since this solvation effect opposes the alkyl inductive effect, it was suggested that the opposing effects could help explain the anomalous basicity behavior of alkylamines. Although Arnett has indicated that this approach in "mostly correct", Aue, Webb, and Bowers indicate that the Trotman−Dickenson approach "neglects hydrophobic effects and electrostatic effects which we have shown to be important" for ammonium ions[16,17,18] It has also been suggested that small numbers of water molecules play an important role in determining the solvation energies of ammonium and hydronium[29] ions, where as few as four molecules of water for ammonium and three for hydronium seem to be important.[9]

Both Kebarle and co-workers and Meot-Ner have shown in the gas phase that the hydration enthalpies of onium ions (N- and O-types) begin to approach bulk behavior in the first few hydration stages.[20,22,26] Studies by Chang, Lee, and co-workers using both vibrational

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(23) Note that proton affinity is defined as $-\Delta H$ for $B_{(g)} + H^+ \rightarrow BH^+_{(g)}$.

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(29) Hydronium ion is being used in the broadest sense here to mean $H(H_2O)_n^+$.

predissociation spectroscopy and high-level ab initio computations address some structural issues when small numbers of water molecules cluster with ammonium, methylammonium, and hydronium ions.[27,28] These studies not only distinguish experimentally between various isomers of "small-number-of-water" clusters, but provide important structural characteristics for $NH_4^+(H_2O)_n$ with $n = 3-6$ from B3LYP/6-31+G(d) computations.[28,30] Earlier MO computations examining the hydration of various alkylammonium ions were carried out at lower levels of theory and yield conflicting results.[10]

A more complete understanding of the anomalous behavior of aliphatic amines in water might result from comprehensive structural studies of aliphatic amines and their corresponding ammonium ions with a few water molecules, particularly because several studies have indicated the approach to bulk behavior with only a few solvent molecules. Although we are unaware of any experimental studies of this type, there has been active research, both experimental and computational, on small water clusters $[(H_2O)_n]$,[31−40] water interacting with other small molecules,[32,41−50] other ion/water clusters,[51−67] and proton transfer.[68−73] In addition, the molecular details of solvation have begun to be elucidated in studies of the dissolution of strong electrolytes such as HCl, HBr, HI, and NaCl in water, which reveal the importance of contact and solvent-separated ion pairs as dissociation occurs.[54,74−77] A study of the weak acid HF by Ando and Hynes also stresses the importance of contact and solvent-separated ion pairs, but, in addition, indicates that a barrier to contact ion pair formation is present.[70]

Computational studies of the anomalous amine basicity effect by Hirata, Silla, Geerlings and their respective coworkers emphasize energetic aspects of the anomaly without being able to probe structural characteristics specifically.[78−81] Thus, Hirata and co-workers use the reference interaction site method under self-consistent field conditions method (RISM-SCF) and report the radial distribution functions of the waters of hydrated ammonia, methylamine, dimethylamine, trimethylamine, and their respective ammonium ions. The first solvation shell is at approximately 3 Å for the methylamines and the methylammonium ions. By separating the free energy contribution of the solute from that of the solvent for the acid−base interaction (eq 1, where A = amine), the source of the anomalous

$$A + H^+ \rightarrow A{-}H^+ \qquad (1)$$

behavior is said to result because the free energy of trimethylamine does not decrease as much compared to that of dimethylamine as dimethylamine does relative to methylamine.

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Silla and co-workers using a simple cavitation model with water as the continuous dielectric calculated the free energies for the methylamines (eq 1).[80] They found that their computations most favorably matched with experiment when double-ζ plus heavy atom polarization function basis sets were used. In a later study, the anomalous experimental trends were reproduced by Silla and co-workers by combining quantum computations of the solute with the polarizable continuum model (PCM)[82] of the solvent.[79] In agreement with Drago and co-workers, this study suggested the importance of electrostatic interactions in understanding the anomalous behavior, but the anomalous order could not be reproduced when the solute computations were carried out at HF/6-31G(d). Instead a reasonable level of electron correlation, namely, MP4(SDTQ)/6-31G(d) was required to obtain results mirroring experiment. Geerlings and co-workers in a related study have recently used the SCI−PCM (self-consistent isodensity polarized continuum model)[82] to probe the anomalous alkylamine basicity ordering.[81] The SCI−PCM approach incorporates better coupling between the solvent cavity (an isodensity surface) and the electron density of the solute. This study, where several solvents were considered, reproduced the anomalous ordering for methylamines.

The computational studies just described to model solute−solvent interactions do so either by treating the statistical distribution of the solvent around the solute, where the coupling between solute and solvent is electrostatic, or by treating the solvent as a bulk component whose dielectric properties affect the interactions. These and related methods vary in sophistication and often have been quite successful in modeling the bulk behavior of solvents. An inherent deficiency of such methods is that they cannot probe solute−solvent or solvent−solvent molecular interactions.[83−88] Various other computational methods can reveal these interactions, from costly ab initio quantum mechanical methods to more modest molecular mechanics ones. Each extreme has its advantages, depending on the size and nature of the system to be studied. When large systems with many solvent interactions are to be studied, an ab initio treatment, while desirable, can be practically impossible. As a result, a number of computational methods in which a quantum mechanical 'core' interacts with a solvent that is variously modeled have been developed. Among the interacting solvent models are ones that are strictly molecular mechanical and ones that are more sophisticated, being based more fundamentally in quantum mechanics. One such model is the effective fragment potential (EFP) method developed by Gordon and co-workers, where each solvent molecule is treated explicitly as a perturbation of the 'core' Hamiltonian.[40,54,89−96] In the EFP model, the interaction between the quantum mechanical 'core' (the so-called active region) and an individual solvent fragment is treated by adding one-electron potential terms to the active region Hamiltonian.

Since computational methods such as the EFP model can provide information about individual solute−solvent and solvent−solvent interactions, their utilization is expected to reveal important molecular details about solvation as well as additional information about properties and processes that differ in gas and condensed phase.[93] The anomalous alkylamine basicity effect counts among the latter, where particularly relevant questions surface for a computational study of the anomalous effect, namely: (1) what structural characteristics do the solvated amines and ammonium ions display, (2) are there structural differences among these that could help explain the anomalous behavior, (3) in structural terms, to what extent can small numbers of protic solvent molecules be said to contribute to 'bulk' solvent properties, and (4) how many protic solvent molecules are required for the anomalous behavior? To address these questions, an EFP model basicity study of ammonia, the methylamines, and their corresponding ammonium ions has been undertaken. These results are reported herein. In addition, a recent application of the EFP method to ammonia/water clusters will be discussed subsequently.[96]

Computational Methods

A. Effective Fragment Potential Method. The EFP model developed by Gordon and co-workers has been described in detail and need be summarized only briefly here.[40,54,89−92] The system is described by the Hamiltonian,

$$H = H_{\mathrm{AR}} + V$$

in which H_{AR} is the ab initio Hamiltonian of the active region (the solutes being ammonia, methylamine, dimethylamine, trimethylamine, and their corresponding ammonium ions in this study) and V is the potential due to a solvent fragment (water in this study). In the current EFP formulation, V consists of one-electron terms that describe the (1) electrostatic (Coulombic), (2) polarization, and (3) exchange repulsion/charge-transfer interactions between solute and solvent and between solvent and solvent. Although the internal geometry of a water fragment is fixed in the EFP method, its relative position with respect to the solute is not. Implementation of the EFP method in the GAMESS suite of programs allows the use of analytical gradients for systems consisting of solute and fragment(s) as well as vibrational frequency analysis by means of numerical differences of the analytical gradients. Thus, geometric and energetic, as well as reaction path, information can be obtained for solute−fragment systems.

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B. Computational Details. Calculations on ammonia, methylamine, dimethylamine, trimethylamine, and their corresponding ammonium ions have been used to probe the anomalous amine effect since these solutes not only show this behavior experimentally, but are small enough to be amenable to high-level ab initio computation. Since the proton is the common feature in amine basicity (eq 1), relative basicities can be obtained by ignoring the energy of the proton, whether bare or solvated; this assumes that $H^+(H_2O)_n$ is solvated to the same extent in the presence of the various amines/ammonium ions. The fragment calculations have been carried out in the active amine and ammonium ion regions at the restricted Hartree−Fock (RHF) level of theory with the 6-31++G(d,p) basis set, while the water fragments have been modeled using the EFP method just described (hereafter abbreviated as the EFP method). This particular basis set was chosen as the largest that practically could be used for systems of the size studied. For each $RR'R''N(H_2O)_n$ and $RR'R''NH^+(H_2O)_n$, full geometry optimizations (with the fixed fragment geometry restriction vide supra) were carried out from various initial geometries (R = all combinations of CH_3 and H for ammonia, methylamine, dimethylamine, trimethylamine, and their corresponding ammonium ions) (n = 0, 1, 2, 3, 4, 5, 6, 10, and 14.). The initial geometries were systematically chosen to explore the potential surface as widely as possibly.

As the number of fragment waters increases, the number of possible initial geometries dramatically increases as does the number of optimized structures. When large numbers of structures were examined, it became clear that the potential energy surface for a given amine or ammonium ion with a fixed number of fragments is quite flat. Numerical Hessians (matrix of energy second derivatives) of the lowest energy structures as well as others of similar energy were obtained from finite double differences of analytical derivatives and used to determine the nature of such structures (minima = positive definite Hessian); nth order saddle point = n negative eigenvalues). The structures discussed herein all are minima whose vibrational analysis has been used to correct energies for zero point vibrational contributions (ZPC). These data are reported as enthalpies at 0 K. They have not been corrected for temperature effects, since the flat nature of the potential energy surfaces makes the normal rigid rotor−harmonic oscillator approximations for the entropy contributions suspect. Because the basicity values reported herein are $\Delta H_{(0°,\mathrm{eq1})}$ and because the computations have not been carried out with highly correlated wave functions, they are not expected to be accurate, although relative $\Delta H_{(0°,\mathrm{acid})}$ values obtained for methanol and *tert*-butyl alcohol under these conditions proved useful.[93] Many minima have been found with some of the larger water molecule species. Although their energies can vary by a few kcal (except in cases where the structural characteristics suggest that a particular species is not to be considered), using the lowest energy species is justified from previous experience in studies of alcohol acidity reversal.[93] There is no measure of whether the global minima have been found, which is why so many structures have been examined.

All computations were carried out using the GAMESS suite of programs.[97] MacMolPlot has been used to visualize the molecular structures.[98]

Results and Discussion

A. Structural Considerations: Amines. EFP-optimized structures of ammonia, methylamine, dimethylamine, and trimethylamine were obtained at the RHF level of theory using the 6-31++G(d,p) basis set for the active region and the EFP method for the water fragments with n = 0, 1, 2, 3, 4, 5, 6, 10, and 14. Many initial geometries were optimized for each n value, particularly when n is ≥ 6, and, as anticipated,[93] many stable structures were obtained. The data presented herein are those from the most stable structures found for each value of n. Several general structural characteristics are revealed in these computations: (1) the active region structures for ammonia, methylamine, dimethylamine, and trimethylamine are unaffected by the number of fragment waters (bond distances are 1.00−1.01 Å for N−H, 1.08−1.09 Å for C−H, and 1.45−1.46 Å for C−N),[99−103] (2) the bonding distance between amine N and fragment water ($N\cdots H_2O$) varies in a small range (1.86−2.20 Å) for all values of n, (3) the bonding distance between water fragments ($H_2O\cdots H_2O$) varies in a small range (1.79−2.16 Å) for all values of n, and (4) the bonding distance between amine NH and fragment water ($NH\cdots OH_2$) varies in a small range (2.10−2.18 Å) for all values of n. (The $N\cdots H_2O$, $H_2O\cdots H_2O$, and $NH\cdots OH_2$ hydrogen-bonding distances have been defined as ≤2.20 Å in this study.)

The general complexity of each amine structure increases with increasing numbers of water fragments. This is expected based on the results of many experimental and computational studies of water clusters $[(H_2O)_n]$.[31−39,104] In this study, ammonia with one fragment (NH_3-1F) has its nonbonded water hydrogen eclipsed with an amine hydrogen with a $N\cdots HO$ angle that is not quite linear (177°). Although none of the NH_3-nF structures has a linear $N\cdots HO$ angle (the range is 158−178°), there is no obvious trend that relates this angle and n. Instead, it appears that other demands, particularly the building of the water network, dominate the structural characteristics of each species.

Both NH_3-3F and NH_3-4F have cyclic structures with each water making only one H-bond (Figure 1S, A, in Supporting Information); in these, N is an H-bond acceptor and N−H is an H-bond donor and the hydrogens of the fragment waters make only one H-bond. Such cyclic structures are interesting to consider in light of what is known about water clusters[31−39,104] and related earlier work examining small numbers of water molecules (both EFP fragments and RHF waters) with methanol and *tert*-butyl alcohol.[93] That the lowest energy structures of $(H_2O)_n$ for n = 3−5 are cyclic and larger n values give rise to more structural possibilities is well established. The first "three-dimensional" structures of $(H_2O)_n$ were obtained for $(H_2O)_6$, where several low energy species have been reported.[37] What distinguishes the more complex from the cyclic structures is the number of H-bonds that the water molecules make. In cyclic structures, only one hydrogen atom of each water is an H-bond

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[100] Typical experimental bond distances for ammonia, methylamine, dimethylamine, and trimethylamine are N−H, 1.01−1.02 Å; C−N, 1.45−1.47 Å; C−H, 1.09 Å.

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donor; in more complex structures, some water molecules have both hydrogen atoms that are H-bond donors. For the $n = 6$: the prism structure has three waters that are doubly H-bonded, the cage structure has two doubly H-bonded waters, the book structure has one, and, in the cyclic structure, each water is singly H-bonded. Methanol and *tert*-butyl alcohol have cyclic structures for $n = 2$ and 3 with the alcohol O−H substituting for a water; these correspond with structures for $(H_2O)_3$ and $(H_2O)_4$.[93] The lowest energy structure for methanol and *tert*-butyl alcohol when $n = 5$ corresponds with the book isomer of the water hexamer.

NH_3-5F, in which it might be expected that the N−H bond would become part of a "water-hexamer-like" structure, instead has NH_3 H-bonded to a cyclic water tetramer with an additional water appended. Although NH_3-6F is the first solvated ammonia in which a water fragment makes more than one H-bond, the ammonia is not incorporated into the water structural framework, instead being pendant to it (Figure 1S, B). The NH_3-10F structure is more complex still, having four waters making two H-bonds as well as a $NH\cdots OH_2$ bond; NH_3-14F has six waters making two H-bonds as well as two $N\cdots H_2O$ and one $NH\cdots OH_2$ bond (Table 1S, in Supporting Information). A recent study by Geerlings and co-workers explores the solvation of ammonia using the EFP method.[96] The structures reported here are similar to theirs, although, for $n = 5$ and 6, the structures reported here have ammonia pendant to a water cluster (the structures similar to those reported[96] are less than 0.5 kcal/mol higher in energy).

All the $N\cdots HO$ angles for methylamine, dimethylamine, and trimethylamine with n fragments [CH_3NH_2-nF, $(CH_3)_2NH$-nF, and $(CH_3)_3N$-nF] are nonlinear, and, like the NH_3-nF structures, show no obvious trends relating the nonlinearity with n. With CH_3NH_2-nF, $(CH_3)_2NH$-nF, and $(CH_3)_3N$-nF, the complexity of structures increases with n. For CH_3NH_2-nF and $(CH_3)_2NH$-nF, the $n = 3$ and 4 structures are cyclic (Figure 1S, C). Larger n values lead to three-dimensional networks (Figure 1S, D; Table 1S). In all of these cases, the amine N acts as an H-bonding donor; in many cases, the N−H is an H-bond acceptor (Table 1S). In some examples, where it appears like H-bonded is occurring only through N (ammonia for $n = 5$ and 6, methylamine for $n = 10$ and 14, and dimethylamine for $n = 5$ and 6), the $NH\cdots OH_2$ bonds are just beyond the limit of ≤ 2.20 Å used to define H-bonds herein (Figure 1, E). For $(CH_3)_3N$-nF with no N−H to bonds, there are no cyclic structures, although the waters are arranged in cyclic arrays for $n = 4$, 5, and 6 with nitrogen H-bonding to a water fragment ($N\cdots H_2O$) (Figure 1S, F).

B. Structural Considerations: Ammonium Ions. EFP optimized structures of ammonium, methylammonium, dimethylammonium, and trimethylammonium were obtained at the RHF level of theory using the 6-31++G(d,p) basis set for the active region and the EFP method for the water fragments with $n = 0$, 1, 2, 3, 4, 5, 6, 10, and 14. starting from a variety of structures. Because such structures are dominated by the ionic character of the nitrogen center, the water fragments are expected to be arranged differently than in the amines. The immediately striking difference between the amine and the ammonium ions is that water fragments bond directly with each N−H of the ammonium ions, after which increasing the number of fragment waters begins to build a complex water network. Thus, there are close $NH^+\cdots OH_2$ bonds, depending on the number of N−H bonds of the ammonium ion (four for NH_4^+, three for $CH_3NH_3^+$-nF, two for $(CH_3)_2NH_2^+$-nF, and one for $(CH_3)_3NH^+$-nF) (Figure 2S, A, in Supporting Information). As the number of water fragments increases further, the water structure builds (Figure 2S, B−D). The general structural characteristics of ammonium ions revealed by these computations show that: (1) the bond distances for ammonium, methylammonium, dimethylammonium, and trimethylammonium in the active region are unaffected by the number of fragment waters (bond distances are 1.01−1.02 Å for N−H, 1.08 Å for C−H, and 1.48−1.51 Å for C−N), (2) the bonding distance between the ammonium NH^+ and fragment water ($NH^+\cdots OH_2$) varies in a small range (1.74−2.12 Å) for all values of n, and (3) the bonding distance between water fragments ($H_2O\cdots H_2O$) varies in a small range (1.85−2.20 Å) for all values of n. [The $NH\cdots OH_2$ and $H_2O\cdots H_2O$ hydrogen-bonding distances have been defined as ≤ 2.20 Å.] In contrast with negatively charged methoxide and *tert*-butoxide, the ammonium ions shown no variation of bond lengths in the active region as more water fragments are added.[93]

TABLE 1. $NCH\cdots OH_2$ Bond Distances of Ammonium Ions (H-bonding distance ≤ 2.8 Å)

number of water fragments	$NCH\cdots OH_2$ Bond Distances (Å)[a]
Methylammonium Ion	
10	2.71, 2.79
14	2.51
Dimethylammonium Ion	
6	2.55, 2.54
10	2.55, 2.70, 2.77
14	2.49, 2.54, 2.59, 2.66, 2.70
Trimethylammonium Ion	
6	2.38, 2.44, 2.62, 2.70
10	2.33, 2.52, 2.60,2.62, 2.64, 2.64
14	2.43, 2.48, 2.49, 2.51, 2.54

[a] Carried out at EFP/6-31++G(d,p)//6-31++G(d,p).

The $NH^+\cdots O$ angle to the water fragment in NH_4^+-1F is nearly linear (177°). As the number of waters increases for NH_4^+-nF, the $NH\cdots O$ angle changes. Although these H-bonds are nearly linear through $n = 4$ (177−179°), they are significantly nonlinear when the water structure becomes more complex. When $n = 6$, one water fragment is bound to N^+−H and not to other water fragments. The $NH^+\cdots O$ angle corresponding to that water is 178°; the other three $NH^+\cdots O$ angles, corresponding to water fragments in a small water cluster network, are 154, 158, and 161°. For larger ammonium structures (NH_4^+-nF with $n = 10$ and 14), the $NH^+\cdots O$ angle varies between 140 and 177° with all but one angle deviating far from linearity. The $NH^+\cdots O$ angles in the methylammonium ions behave similarly. It is clear that the demands of building complex water structures generally outweigh any tendency toward linear $NH^+\cdots O$ bonds.

Once the requisite number of $NH^+\cdots OH_2$ bonds have formed, the water structures build in various ways (Tables 1S and 1). When $n = 4$ in $CH_3NH_3^+$-nF, a cyclic water structure that involves two N−H bonds and three waters is found (the other water is bound to the third

N−H) (Figure 2S, B). As n increases ($n = 10$ and 14), the water structures become three-dimensional with some water fragments making hydrogen-bonds through both of their hydrogen atoms (Table 1S). These three-dimensional structures become more and more complex (Figure 2S, D), eventually to the point where the water fragments 'wrap-around' the hydrophobic methyl groups. 'Wrapped-around' water fragments are common for dimethyl- and trimethylammonium ions with $n = 6$, 10, and 14. The 'wrap-around' $CH\cdots OH_2$ bond distances for methyl-, dimethyl-, and trimethylammonium ions range from 2.33 to 2.79 Å (where the 'wrap around' $CH\cdots OH_2$ hydrogen-bonding distances have been defined as ≤2.80 Å) (Table 1). Such "wrap-around" structures are not surprising in view of the known importance of hydrophobic interactions in the solvation of both methylamines and their corresponding ammonium ions.[18] Trimethylammonium ions, because they only have one N−H, begin building water structures in a different way. For $n = 4$, a cyclic water fragment 'trimer' appends to the N−H (Figure 2S, E) while for $n = 6$ the N−H is attached to a water tetramer that itself has two other water fragment attachments. In the $n = 10$ structure, a four- and five-membered ring is joined by a water fragment that is a member of the four-membered ring (Figure 2S, F).

Several computation studies of ammonium ions relating to the structural characteristics reported here have been published.[10,27,28,105,106] Ikuta in 1983 demonstrated that small numbers of water molecules are H-bonded to ammonium and methylammonium through the available N−H bonds ($NH\cdots OH_2$).[105] Using higher level computations, Deakyne has studied a number of ammonium-water clusters.[106] Still more recently, Wang, Lee, and co-workers have examined water clusters of ammonium ion with as many as six waters.[27,28] The structures obtained by these workers and those reported here are similar, although the EFP structures tend to have more complex water fragment H-bonding. The lowest energy structure reported by Wang, Lee, and co-workers for the ammonium and five waters has one water bound to each N−H with the additional water H-bonded to one of these water molecules. The similar EFP structure is about 2 kcal/mol less stable, with the lowest energy structure having two N−H bonds in a ring with three waters fragments and the two other water fragments exocyclic and bound to the two other N−H bonds. For $n = 6$, Wang, Lee, and co-workers report that their lowest energy structure is a cyclic cluster of ammonium with three water molecules and three additional exocyclic water molecules (two bound to the N−H bonds and the other bound to the opposite water. The similar EFP structure is about 1 kcal/mol less stable while the lowest energy structure, as indicated earlier, has a complex water cluster structure (Figure 2S, B).

C. Energy Considerations. Table 2 presents the lowest relative ZPC energies of ammonia, methylamine, dimethylamine, trimethylamine, and their corresponding ammonium ions for $n = 0$, 1, 2, 3, 4, 5, 6, 10, and 14. These represent a measure of the basicity of each amine for different n values.

In previously discussing the application of the EFP method to the anomalous basicity effect for the series of methylamines, one question to be addressed was "how many protic solvent molecules are required for the anomalous behavior". There are particular methodological drawbacks to asking this question:

(1) Because of the flat potential energy surfaces of the solvated species, the normal rigid rotor−harmonic oscillator approximations for the entropy contributions are suspect, making it imprudent to estimate free energy changes. While earlier discussion of the work of Aue, Webb, and Bowers has indicated both the importance of entropy effects and their subtle and small nature, their work emphasizes as well the importance of large enthalpic contributions to basicity of methylamines.[18,19]

(2) The EFP method underestimates the number of water molecules necessary to describe the acidity reversal of aliphatic alcohols in earlier work.[93]

Although examination of the structural characteristics of the both the amine and ammonium species in the last section suggest that entropy effects are important and the number of water fragments studied herein is limited to 14 by necessity, it is instructive nevertheless to examine the data in Table 2 to assess the importance of the possible limits of the EFP method under these limitations.

The relative energy data show that (1) all the amine and ammonium ions species become more stable as n increases, (2) the ammonium ions are stabilized by fragment waters to a greater extent than are the amines (range of 137 versus 86 kcal/mol), (3) the amines are stabilized to about the same extent with increasing n as methyl substitution increases, and (4) the ammonium ions stabilization with increasing n decreases as methyl substitution increases (trimethylammonium ion is stabilized by water fragments less than dimethylammonium ion). These results are consistent with the suggestion of Aue, Webb, and Bowers that the electrostatic term for methylammonium ions dominates their solvation enthalpy analysis and that methylammonium ions solvation enthalpies decrease with increasing ion size.[18,19]

Examination of the amine relative energy changes as n increases are similar for ammonia, methylamine, dimethylamine, and trimethylamine. In each case, waters decrease the energy by 4−8 kcal/mol per water fragment. The data reported here for ammonia are consistent with those reported by Geerlings and co-workers in which extensive studies have been made of the variation of energy of ammonia with incremental fragment additions, although they reported incremental water additions to ammonia that are slightly greater than those indicated in Table 2.[96]

For the ammonium ions, the first waters decrease the energy by a larger amount, 12−18 kcal/mol per water fragment, but the point where additional waters have a smaller effect depends on the structure of the ammonium ion (after four for ammonium, three for methylammonium, two for dimethylammonium, and one for trimethylammonium). These trends are indications of the importance of the stronger interactions that the first few fragment waters have with the amine and ammonium ions studied. They particularly make sense in light of the structural features discussed in the last section. Thus, the addition of water fragments gives increasing structural complexity as waters are added, but is not highly

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TABLE 2. Relative Energy Data of Amines and Ammonium Ions and Basicities of Amines

no. of water fragments	relative ZPC energy of amine (kcal/mol)	relative ZPC energy of ammonium ion (kcal/mol)	$\Delta H_{(0\mathrm{K,eq\ 1})}$ (kcal/mol)
	Ammonia/Ammonium Ion		
0[a]	0.0	0.0	206
1[b]	−3.9	−17.8	220
2[b]	−8.5	−33.2	231
3[b]	−15.1	−46.4	238
4[b]	−20.8	−57.8	243
5[b]	−24.5	−66.5	248
6[b]	−32.2	−73.1	247
10[b]	−57.6	−104.3	253
14[b]	−81.5	−136.6	261
	Methylamine/Methylammonium Ion		
0[a]	0.0	0.0	218
1[c]	−4.3	−16.0	229
2[c]	−9.1	−30.1	239
3[c]	−15.8	−42.5	244
4[c]	−21.5	−48.0	244
5[c]	−27.2	−58.1	249
6[c]	−34.4	−66.9	250
10[c]	−59.4	−98.6	257
14[c]	−83.9	−127.8	262
	Dimethylamine/Dimethylammonium Ion		
0[a]	0.0	0.0	225
1[d]	−4.2	−15.0	236
2[d]	−9.3	−28.2	244
3[d]	−16.1	−38.1	247
4[d]	−21.9	−46.1	249
5[d]	−27.9	−53.8	251
6[d]	−33.9	−61.0	252
10[d]	−61.0	92.2	256
14[d]	−83.9	−118.7	260
	Trimethylamine/Trimethylammonium Ion		
0[a]	0.0	0.0	230
1[e]	−4.1	−14.2	240
2[e]	−8.8	−23.5	245
3[e]	−14.3	−31.3	247
4[e]	−21.0	−38.9	248
5[e]	−27.3	−45.8	249
6[e]	−33.2	−55.6	252
10[e]	−60.0	−85.7	256
14[e]	−85.5	−112.1	257

[a] Carried out at 6-31++G(d,p)//6-31++G(d,p) [b] Carried out at EFP/6-31++G(d,p), relative to −56.16441 Hartree for ammonia and −56.49305 for ammonium ion (zero point corrected). [c] Carried out at EFP/6-31++G(d,p)//6-31++G(d,p), relative to −95.15810 Hartree for methylamine and −95.50491 for methylammonium ion (zero point corrected). [d] Carried out at EFP/6-31++G(d,p)//6-31++G(d,p), relative to −134.15695 Hartree for dimethylamine and −134.51563 for dimethylammonium ion (zero point corrected). [e] Carried out at EFP/6-31++G(d,p)//6-31++G(d,p), relative to −173.15813 Hartree for trimethylamine and −173.52447 for trimethylammonium ion (zero point corrected).

dependent on amine structure, while, for the ammonium ions, the building complexity is directly related to the number of N−H bonds. Thus, more highly methyl-substituted ammonium ions are less well stabilized by water fragments than are less methyl-substituted ammonium ions undoubtedly because the polar water fragments cannot interact as strongly with the 'methyl-shielded' charged region near the nitrogen. The $\Delta H_{(0°,\mathrm{eq1})}$ trends are to be examined with caution in view of the (1) importance of small and subtle entropic effects and (2) earlier results on aliphatic alcohol acidity in which the EFP data capture the acidity reversal, but higher level calculations, while indicating the beginning of these trends, do not actually reveal the acidity reversal. Here, where the basicity differences of the methylamines are quite small in water, the EFP data are not expected to show anomalous effects particularly well, although, perhaps surprisingly, the $n = 14$ results has an anomalous amine basicity order of $NH_3 \approx CH_3NH_2 > (CH_3)_2NH > (CH_3)_3N$. Since experimental studies clearly indicate that anomalous orders are a reflection of subtle and small steric, hydrophobic, and solvent effects, it is not surprising that such effects are seen in the EFP enthalpy computations. However, neither is it surprising that no major factor(s) can explain the anomalous amine basicity behavior.

Concluding Remarks

Structural complexity of water-solvated ammonia, methylamine, dimethylamine, trimethylamine, and their corresponding ammonium ions increases as each water fragment is added. Many stable structures have been found, which generally differ in energy only slightly, particularly for fragment numbers ≥6. There are many structural similarities among the amines as methyl groups replace hydrogen. Not surprisingly, the amine structures are governed largely by H-bonding with increasing complexity being a simple measure of the increasing number of H-bonding possibilities. Small solvated ammonium ion structures are governed by the charge on nitrogen, but, as the number of fragment waters increases, structural complexity (H-bonding possibilities) does as well. As the water structure 'grows' in the methylammonium ions, water molecules begin to interact ('wrap around') with the methyl groups in several cases (hydrophobic interactions). The energies of all the amines and ammonium ions considered decrease as the number water fragments is increased as expected. The basicity differences of the methylamines are very small in water, suggesting that anomalous effects cannot be sorted out with only small numbers of water fragments and/or without a careful analysis of entropy effects. The accumulated wisdom that subtle structural and solvation effects govern the anomalous basicity effect, while unsatisfying in some ways, is clearly reflected in the computations reported here.

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Supporting Information Available: Figures of structures as well as various tables are included as Supporting Information. These include Table 1S, which indicates the number and types of H-bonded waters for all the computed structures as well as tables containing EFP/6-31++G(d,p)//6-31++G(d,p) energies and the optimized Cartesian coordinates for all reported structures. Figures 1S and 2S show typical amine and ammonium ion structures with various numbers of water fragments. This information can be obtained free of charge via the Internet at http://pubs.acs.org.

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