Ionic Hydrogen Bond Networks and Ion Solvation 1. An Efficient Monte Carlo / Quantum Mechanical Method for Structural Search and Energy Computations: Ammonium/Water

Yi-Lei Zhao,*[a,b] Michael Meot-Ner (Mautner),[a,c] Carlos Gonzalez[a]

[a]Physical and Chemical Properties Division, National Institute of Standards and Technology, Gaithersburg, MD 20877, [b]College of Life Science and Biotechnology, Shanghai Jiao Tong University, Shanghai, 200030, [c]Department of Chemistry, Virginia Commonwealth University, Richmond, VA 23284 and Department of Chemistry, University of Canterbury, Christchurch 8001, New Zealand

Email: yi-lei.zhao@nist.gov

Tel: (301) 975-2111

Fax: (301) 869-4020

Abstract: Hydrogen bond networks about solvated ions can form many alternative structures, requiring extensive conformational searches with accurate but affordable energy computation. Using Monte Carlo searches plus geometry optimizations with a computationally efficient density functional-based tight-binding (DFTB) method, we compute the stepwise hydration energy of the ammonium ion in $NH_4^+(H_2O)_n$ clusters ($n = 1$-8), for which experimental data are available. The resulting structure from the conformational search for each n was compared to those optimized by the MM3 and

OPLA-AA force fields in the Monte Carlo processes, and then re-optimized with quantum chemistry methods including HF, MP2 and DFT. The binding energies were further calculated with the CBS-Q, CBS-QB3, and CBS-APNO methods. Calculated geometries and charge densities for the clusters are also presented. The assessments show that the calculated DFTB binding energies reproduce the experimental values as well as the energies predicted by highly correlated (and significantly more expensive from the computational point of view) *ab initio* quantum chemical methods. These encouraging results suggest that the computational procedure presented in this work should be useful for simulating relatively large ion/solvent systems.

Introduction:

The solvation of ions is fundamental to many natural and industrial processes such as acid/base equilibrium, catalysis, electrolytes, and chemistry in ionizing astrochemical environments. Ion-solvent interactions involve strong ionic hydrogen bond networks, as reviewed recently.[1,2] In biology, ion solvation is important in enzyme activity, protein and RNA and DNA folding, and membrane transport.[3-5] These functions involve ionic sites, such as protonated amine functions, that are partially or fully solvated. Understanding of N^+-H---water ionic hydrogen bonding will help to understand the functions of protonated basic amino acid residues such as His, Lys, Arg, N-terminal amine, and protonated amino terminals of zwitterions at active sites of proteins and amino sugars, and the ammonium ion itself that constitutes a biological reservoir of ammonia[6].

Fundamental understanding of ion solvation requires addressing the following questions:

- The nature of the bonding between the ion and the nearest solvent molecules (orbital interactions, electrostatic, resonance charge-transfer, covalent contributions, as well as energy and geometry of the inner solvent shell)

- The relation between clusters amenable to computation and experiment, and bulk solvation

- Structure of the outer solvent shells;

- How far does the effect of the ion extend into the solvent?

- How many solvent molecules are required in quantum chemistry for convergence to macroscopic solvation?

- For organic ions, what is the relation between solvation of charged head-groups and of hydrophobic substituents?

- How to extrapolate from clusters to obtain single-ion solvation energies, and how do these results compare with experimental values?

- What are the contributions of various physical factors (dielectric, cavity, hydrogen bonding as well as "hydrophilic" and "hydrophobic" terms) to the solvation of ions with diverse structures?

In the present series of papers, we shall combine advanced computational methods and available experimental data to address these questions in the case of solvation of organic and biological ions. In this paper, the first of the series, we present an efficient computational procedure for performing conformational searches combined with energy calculations for ammonium-water cluster ions containing $1 - 8$ H_2O

molecules, to model ion-solvent interactions in the inner solvent shells near the ammonium ion. In following papers, we shall extend this approach to larger clusters and more complex ions.

Fundamental properties of ammonium-water hydrogen bonds can be addressed by combining experiments using mass spectrometry and state-of-the-art quantum chemical methodologies to study protonated $BH^+(H_2O)_n$ clusters (B = NH_3 and alkylamines).[7-10] The properties of these clusters provide significant insights into intimate ion-solvent interactions in the inner shells, and allow a systematic stepwise approach toward macroscopic solvation.[1]

Experimentally, the stepwise hydration energies of ammonium have been measured with a series of equilibriums (1).[10-13]

$$NH_4^+(H_2O)_{n-1} + H_2O \rightarrow NH_4^+(H_2O)_n \qquad (1)$$

The stepwise hydration energies (i.e. reaction enthalpies) for the first seven molecules of water to ammonium are shown in Table 1 below. The stepwise hydration energies decrease from 84.5 ± 1.5 kJ/mol for the first H_2O molecule (two recent data sets) until they approach and then undershoot the limiting value at infinity, 44 kJ/mol, which is the macroscopic bulk enthalpy of water.[14]

The fact that the stepwise hydration enthalpies for $n = 6$ and 7 (38 and 35 kJ/mol as listed in Table 1) undershoot the macroscopic limit (and then reach it again at large n) suggests that the binding energies may oscillate about the limiting value with further increasing n, as observed in measurements on the solvation of proton.[15] Some structural

information for the observable clusters $NH_4^+(H_2O)_n$ (n = 2 to 6) has been proposed based on vibrational predissociation spectroscopy.[10] In particular, hydrogen-bonded single and double rings have been suggested for clusters containing 3 – 6 cluster water molecules.[16]

Theoretical calculations provide a useful complementary tool to study the geometries and energetics of ionic hydrogen bonds.[2,17-19] Calculations can expand the experimental data to large clusters and more isomers and at the same time, they can provide fine details of their potential energy surfaces. For example, the structure and dynamics of ammonium in aqueous solution have been studied extensively with classical[20] and *ab initio* [21-23] (with a small cluster model n ≤ 5) molecular simulations, to compute bulk solvation energies and to rationalize the fast rotation[21] of ammonium within strongly binding water cages. In addition, simple electrostatic models have shown that NH_4^+ appears isotropic to the solvent beyond about 3.5 Å, making such rotation possible.[24]

Theoretical approaches to solvation and hydrogen bonding:

Stepwise hydration can be calculated based on the reaction energy of (1):

$$\Delta E = E_{NH4+(H2O)n} - E_{NH4+(H2O)(n-1)} - E_{H2O} \qquad (2)$$

For cluster sizes *n* of up to 5 H_2O molecules, experiments show that the stepwise hydration energy approaches the macroscopic water condensation enthalpy of 44 kJ/mol, and then fluctuate around the value in the cases of *n > 5*. In principle, this might allow extrapolating from clusters to full bulk solvation energies in truly single-ion systems.[1] A systematic theoretical study based on reliable and accurate quantum chemical

methodologies may help assess the validity of this approach and explain its thermochemical and electronic structure basis.

As indicated before, a full quantum chemical treatment of $NH_4^+(H_2O)_n$ clusters using conventional *ab initio* electronic structure methods is limited to a relatively small number of H_2O molecules given that the complexity and the large number of local minima in the potential energy surface significantly increases with n,[17] making the calculations prohibitively expensive from the computational point of view.

Classical molecular dynamics simulations (CMD), based on molecular mechanics (MM) force fields constitute one of the most computationally efficient methods to study large ion/solvent assemblies in solvation and biology. In general, MM force fields treating the different interatomic interactions in a molecular system are expressed as a sum of functions describing bond stretches, chemical angle changes, rotations about chemical bonds (torsions), electrostatic and non-bonded interactions, as well as hydrogen-bonding. Most of force fields use either fixed charges or bond dipoles to compute the electrostatic interaction components, while others include empirical terms that consider polarizable atomic charges and multipole electrostatics.[25-28] In addition, some MM approaches include an extra term comprising a Lennard-Jones structural formulation in order to explicitly treat hydrogen bonds. It has been found that TIP[29] and SPC[30] MM water models with parameters treating the mixed electrostatics-hydrogen bond interactions, perform reasonably well in protein simulations. Despite their success, MM force fields based on fixed-charge models do not account for important quantum effects such as polarization and resonant charge-transfer that sometimes can dominate the dynamics and thermochemistry of water-solute interactions. More recently, force fields

including charge polarization have been developed. The most popular approaches in this area have been the use of a fluctuating charge model with the CHARMm force field and the OPLS/PFF force field based on polarizable dipoles by Brooks and collaborators.[31,32] As pointed out by Friesner[33,34], despite initial encouraging results obtained in the simulation of 22 small proteins and also on 2 ns CMD simulation of the bovine pancreatic trypsin inhibitor (BPTI), further work leading to a systematic improvement and validation of these methods is necessary. In this work, we use the OPLS-AA[20] and MM3[28] models in our simulations for NH_4^+ - water clusters.

In principle, conventional electronic structure calculations based on highly correlated *ab initio* methodologies provide a systematic approach that can accurately treat quantum effects such as charge-transfer, polarization, charge density fluctuations and dispersion forces, important in the proper description of solvent-solute interactions. However, the use of these methodologies is limited by the complexity of the potential energy surfaces of relatively large systems. Despite major advances in the development of efficient computational algorithms and the advent of powerful hardware, state-of-the-art quantum chemical calculations can only be used to compute single-point energy calculations of molecules of up to 100 atoms, and their use to probe molecular conformations and the dynamics of molecules in solution is hampered by their prohibitive computational cost. Thus, in the case of $NH_4^+(H_2O)_n$ clusters, performing a comprehensive conformational search with *ab initio* calculations already becomes impractical for n > 4, even with very computationally efficient density functional theory methods (DFT).[17-19]

Recently, a more efficient parametric Hamiltonian quantum mechanical method based on density functional theory has been developed. The self-consistent charge density functional theory-based tight binding (SCC-DFTB) method, developed by Frauenheim and co-workers, belongs to the class of semi-empirical methods that is related to a second-order expansion of the DFT total energy, E, with respect to charge density variation:[35]

$$E = \sum_{i}^{occ} \left\langle \phi_i \middle| \hat{H}^0 \middle| \phi_i \right\rangle + \frac{1}{2} \sum_{A,B} \gamma_{AB} \Delta q_A \Delta q_B + E_{rep} \qquad (3)$$

In Equation (3), the first term corresponds to the sum-over-states of a one-electron Kohn-Sham type Hamiltonian parameterized from a well known reference electron density, the second term depends on the coulomb-correlation-exchange kernel representing a second-order correction due to charge density fluctuations from a reference value, and E_{rep} contains corrections for double-counting in the sum-over-states and the ion-ion repulsion (fitted with a polynomial or spline function). With a proper treatment on the eigenvalue solver, computational complexity can scale linearly with the size of the system as in the DFTB+ program,[36] making it feasible to conduct conformational searches of relatively large systems such as ammonium-water clusters with n > 4.

In this work, we assess the performance of DFTB+ as well as the MM force fields OPLS-AA and MM3 in the conformational search of NH_4^+-$(H_2O)_n$ (n = 1-8) to generate global minimum energy structures which are used in the calculation of stepwise hydration energies with these models and conventional *ab initio* quantum chemical methodologies. These results are compared directly with the experimental values available in the literature.[11-13]

Computational Methods:

a. Conformational Searches

Basin-hopping (Monte Carlo plus minimization) was used for the conformational search of the NH_4^+-$(H_2O)_n$ clusters in this work.[37] At each Monte Carlo step, a randomly selected molecule (water or ammonium) was subjected to random translational and rotational moves.[38] A three-dimensional uniformly distributed random unit vector (v_x, v_y, v_z) for the translational move and a four-dimensional Hamiltonian quaternion (q_0, q_1, q_2, q_3) for the orientational move were generated with the Marsaglia algorithm.[39] The Hamiltonian-quaternion approach has successfully been employed for computing CCl_4 spherical potentials.[40] The relationship between the rotation Eulerian angles (ϕ, θ, φ) and the quaternion is given by the following expression:

$$
\begin{aligned}
q_0 &= \cos\frac{\theta}{2}\cos\left(\frac{\phi+\varphi}{2}\right) \\
q_1 &= \sin\frac{\theta}{2}\cos\left(\frac{\phi-\varphi}{2}\right) \\
q_2 &= \sin\frac{\theta}{2}\sin\left(\frac{\phi-\varphi}{2}\right) \\
q_3 &= \cos\frac{\theta}{2}\sin\left(\frac{\phi+\varphi}{2}\right)
\end{aligned}
\tag{4}
$$

Making use of these relations, the rotational matrix $\underset{\sim}{R}$ can be efficiently computed by the following relation:

$$
\underset{\sim}{R} = \begin{pmatrix}
q_o^2+q_1^2-q_2^2-q_3^2 & 2(q_1q_2-q_0q_3) & 2(q_1q_3+q_0q_2) \\
2(q_1q_2+q_0q_3) & q_o^2-q_1^2+q_2^2-q_3^2 & 2(q_2q_3-q_0q_1) \\
2(q_1q_3-q_0q_2) & 2(q_2q_3+q_0q_1) & q_o^2-q_1^2-q_2^2+q_3^2
\end{pmatrix}
\tag{5}
$$

The molecular system was placed inside a cubic box with a length approximately equal to 10-20 Å (depending on the cluster size), avoiding vaporization/dissociation in the

simulations. The maximum Cartesian displacements for each move were constrained to obtain acceptance probabilities of ~ 40% for new configurations. After each Monte Carlo move, an energy minimization with either the force field or tight-binding approach is conducted, and the final structure is accepted or rejected according to the Metropolis sampling at 300 K.[41] In the case of the MM3 and OPLS-AA force fields, a local version of the TINKER molecular modeling software (version 4.2) was used to perform the conformational search.[42-44] The TINKER Monte Carlo module was modified in order to treat molecular clusters. An RMS gradient stopping criterion was set to 0.04 kJ mol^{-1} Å^{-1} for the energy minimization.

In the case of the tight-binding energy minimization, the DFTB+ software package (version 1.01) was used to optimize the structures produced by the Monte Carlo conformational search.[35] A python script was implemented for interfacing a locally developed Monte Carlo routine to the DFTB+ program. The tight-binding parameters were set as follows: stopping criterion for the SCC was set to 1.0 x 10^{-6} a.u., while the maximum number of SCC cycles was set to 1000. The default configuration for the Broyden charge mixing method was adopted. In addition, s and p Slater atomic orbitals for nitrogen and oxygen, and only s type for hydrogen, using mio-0-1 set (as-is) of the Slater-Koster parameters were used.[45] We note that dispersion constants from this reference have been tested for biological system.[46]

Lowest energy configurations corresponding to NH_4^+-$(H_2O)_n$ (n = 1 − 8) clusters were obtained by this procedure. Specifically, for each cluster size n the Monte Carlo procedure was applied until the conformation with the lowest energy (within an energy

variation of ±0.1 kJ/mol) was obtained ten times, and this was then selected as the operational global minimum energy conformation of the cluster.

b. Quantum chemistry calculations

The global structures obtained from the Monte Carlo procedure described above were re-optimized using a variety of quantum chemical methodologies including: the semi-empirical methods AM1[47] and PM3[48], Hartree-Fock (HF), the gradient corrected exchange-correlation DFT functional PBE[49], second-order Möeller-Plesset Perturbation Theory[50] (MP2), the Complete Basis Set model (CBS) proposed by Petersson and collaborators[51], as well as the Gaussian-2[52] (G2) and Gaussian-3[53] (G3) methods. In the case of the HF, PBE and MP2, Dunning's augmented triple-zeta correlation consistent basis sets[54] aug-cc-pVTZ were used (herein HF/aug-cc-pVTZ, PBE/aug-cc-pVTZ and MP2/aug-cc-pVTZ respectively). All calculations were carried out with the Gaussian 03[55] (version D.01) suite of programs. In addition, atomic charges were computed performing natural bond orbital (NBO) analysis[56] in the case of the HF and PBE[49] wave functions. In the case of the DFTB+ calculations, the charges were obtained via Mulliken analysis. We note that the CBSs and G2/G3 results include thermal corrections (RT, ~ 2.4 kJ/mol) at 298 K.

In summary, the computational procedure adopted in this work for searching the lowest energy structures of the NH_4^+-$(H_2O)_n$ clusters follows the following steps:

(1) For each cluster *n,* a starting geometry is selected by adding one more water molecule to the previous cluster (n-1) (starting with the unsolvated NH_4^+ ion).

(2) Using a Monte-Carlo move, a new conformation is formed.

(3) The minimized energy of the new conformation is calculated by the tight-binding method (or, alternatively, with MM3 or OPLS-AA force fields).

(4) The cluster energy in step (3) is compared with the cluster energy from the previous cycle for the same cluster size n. If the new energy is lower, this energy and the corresponding geometry are saved, and the previous value is discarded.

(5) Steps (2-4) are repeated until the lowest energy (within $\pm$ 0.1 kJ/mol) for a given n appears 10 times. This energy is used as the global minimum energy, and the structure corresponding to this energy from the last computation cycle is considered as the global lowest energy structure for cluster size n.

(6) Using the last structure from step (5), the optimized geometry and energy are re-computed with various quantum mechanical methods.

(7) Steps (1-6) are repeated for the next cluster size

Results and Discussion

  a. **Stepwise hydration energies from MM and DFTB+ calculations and comparison with experimental values**

Figure 1 depicts the stepwise hydration energies for $NH_4^+(H_2O)_n$ as a function of the cluster size n, computed at 0 K using the global minima obtained by the search procedure described above using the MM3 and OPLS-AA force fields and the tight binding DFTB+ quantum chemistry model. The corresponding experimental data obtained from three sources in the NIST Cluster Ion database,[57] are also plotted in Figure 1 for comparison.
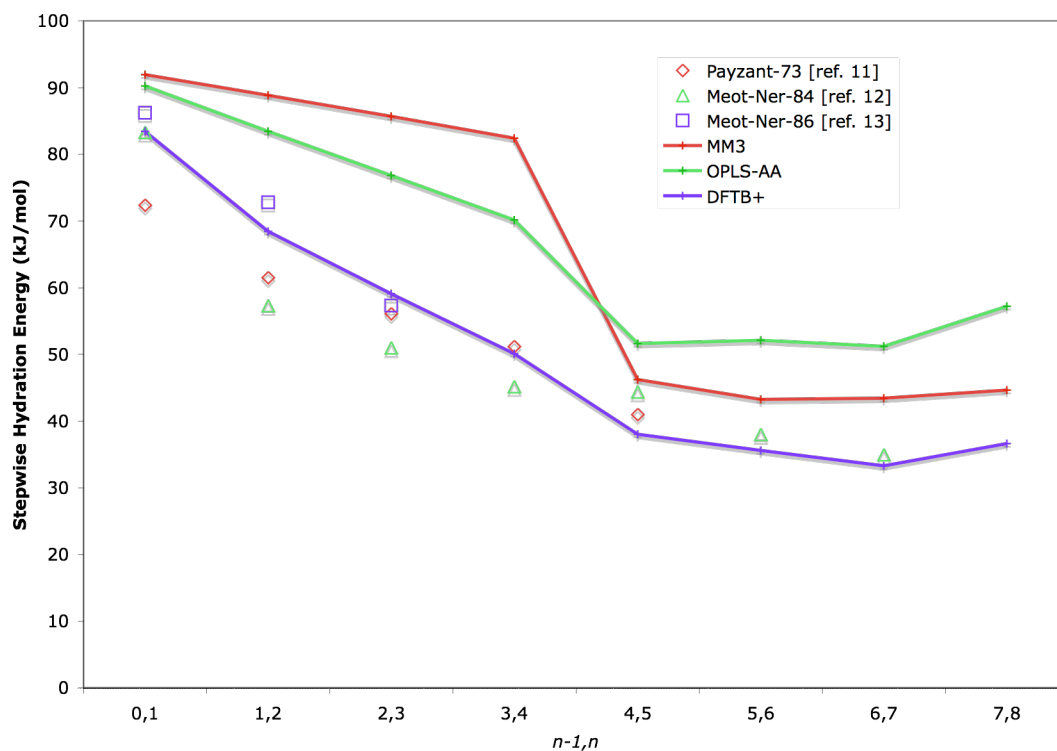
Figure 1. The calculated stepwise hydration energies (lines) with the MM3 (red), OPLS-AA (green), and DFTB (blue), compared with the experimental enthalpies (points: Payzant-73[11], diamond; Meot-Ner-84[12], triangle; Meot-Ner-86[13], square).

As observed in Figure 1, the DFTB+ results agree remarkably well with experiment. The calculated stepwise hydration energies are within the range of experimental values, within 2 kJ/mol of the latest experimental series for $n = 1 - 3$, and within less than 5 kJ/mol of all the average experimental values. Experimental uncertainties are estimated as about ± 6 kJ/mol based on these measurements, and The DFTB+ binding energies show a mean absolute deviation of 6.4 kJ/mol versus the high-level CBS calculations in Table 1.

Note that the first hydration shell includes four H_2O molecules that bind directly to the N^+-H hydrogens. The fifth H_2O molecule must lie in the second shell, bonded to the first shell by a water-water hydrogen bond or bonds. In a clustering series, such hydration shell filling by the *n*-th ligand molecule can lead to a significant change in the slope of the stepwise hydration energy (i.e., the decrease in the hydration energy of the *n* to the (*n*+1) solvent molecule $\Delta H_{n,n+1} - \Delta H_{n-1,n}$, is significantly larger than that of the decrease in the hydration energy of the *n*-1 to *n* solvent molecule, $\Delta H_{n-1,n} - \Delta H_{n-2,n-1}$).[13] In the present work, the stepwise hydration energy decrease computed with the DFTB+ between *n* = 4 and 5 was found to be 12 ± 6 kJ/mol, slightly larger than the decrease of 9 ± 6 kJ/mol in going from n = 3 to 4 (see Fig. 1). This may indicate a very small hydration shell-filling effect at n = 4.

The shell-filling effects may not be observed when the binding energies are already converging to the limiting bulk value of about $\Delta H_{vap,water}$ = 44 kJ/mol within the calculation uncertainty (~ 6 kJ/mol). This is likely the case in the present system, where $\Delta H_{3,4}$ and $\Delta H_{4,5}$ are both near this value and the binding energy cannot decrease much below this macroscopic limit as those in the force fields. In this case, the inner-shell binding energy of water to the ion at step *n* is similar to the outer-shell water-water bonding energy at step *n+1*.

The DFTB+ predictions are in good agreement with experimental results, which show no significant shell-filling effects for the $NH_4^+(H_2O)_n$ series in the experimental uncertainty (~ 6 kJ/mol).[13] In 1973, Payzant and coworkers reported the energy gap of 10 kJ/mol for *n* = 4 to 5, close to the average change of 7 kJ/mol for *n* = 1 to 4; in 1984 Meot-Ner investigated the $NH_4^+(H_2O)_n$ system extensively for up to *n* = 7 with mass

spectroscopy, obtaining a negligible gap of 1 kJ/mol from $n = 4$ to 5. (Figure 1 and Table 1)

In stark contrast to the DFTB+ calculations and the experimental results, the stepwise hydration energies computed with the force fields MM3 and OPLS-AA show an abrupt drop in the region of n= 4 to 5. As observed in Figure 1, the MM3 and OPLS-AA force field simulations group the stepwise hydration energies into an inner hydration shell of water ($n = 1$-4), and an outer shell ($n = 5$-8). The predicted stepwise hydration energy gaps between the two groups are 36 kJ/mol (MM3) and 18 kJ/mol (OPLS-AA). In addition, the stepwise hydration energies computed with the MM3 and OPLS-AA force fields are found to decrease much more slowly for the first four H_2O molecules than the experimental values, decreasing by a factor of 3.4 - 3.8 % (MM3), and by 7.5 − 8.7 % (OPLS-AA) for each additional H_2O molecule. It appears therefore that these force-field models do not reproduce well the hydration behavior of these clusters observed experimentally. This supports the need for efficient computational procedures based on quantum mechanical calculations such as the ones proposed in this work.

b. **Structures of Solvated Ammonium Ion Clusters**

Figure 2 shows minimum energy structures for $n = 4$ to 8 computed with the Monte Carlo conformational search using the MM3, OPLS-AA force fields and the DFTB+ quantum chemistry model. The corresponding structures for $n = 1$ to 3 (not shown) can be obtained by removing water molecules from the $n = 4$ cluster.

For $n > 4$, the cluster structures predicted by the MM3 force field are significantly different from the ones obtained with OPLS-AA and DFTB+. In the MM3 structures, ammonium is found to coordinate to more than four molecules of water for $n = 5 - 8$ (sometimes as many as 7 as in the case of $n = 7$), in contrast to the structures predicted by OPLS-AA and DFTB+. These additional water molecules coordinated to the ammonium ion in the MM3 structures exhibit unusual N---O distances (< 2.6 Å), even shorter than the ionic hydrogen bonding N---O distances (~ 2.7 Å).

With the exception of the cases where $n = 6$ and 7, the OPLS-AA and DFTB+ methods yield similar geometries, with DFTB+ predicting slightly longer (by ~0.1 Å) hydrogen bonds.
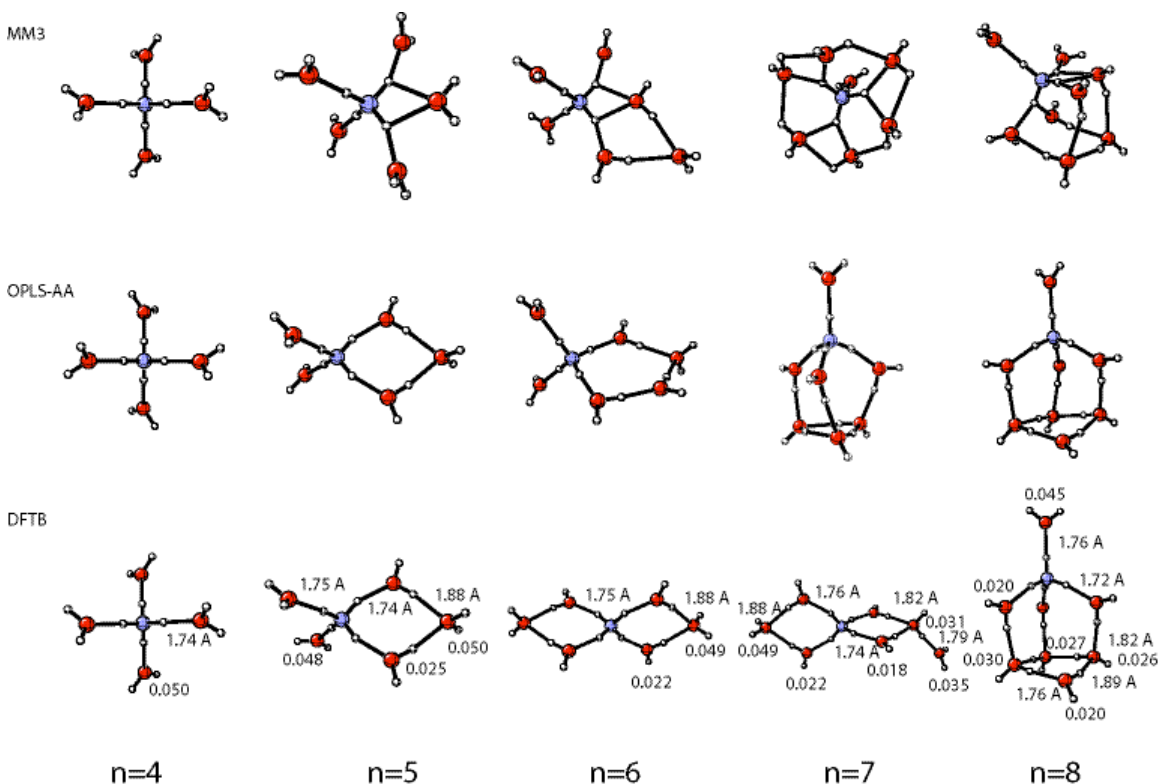

Figure 2. The clusters $NH_4^+(H_2O)_n$, $n = 4$ to 8, obtained from the Monte Carlo conformational search, with the MM3, OPLS-AA, and DFTB+ methods. (Lines are

16

added where atom-atom distances are less than sums of the corresponding van der Waals radii. The total DFTB+ charges on the water molecules and the hydrogen bond distances are shown.)

In addition, the prediction of four-membered (heavy atom) ring structures in clusters with $n = 5 - 8$ by OPLS-AA and DFTB+ is in excellent agreement with infrared spectroscopic experiments.[58] As can be observed in Fig. 2, while OPLS-AA predicts the formation of 3-D network structures for n $\geq$ 7, the DFTB+ calculations predict the formation of these network structures in clusters with n $\geq$ 8. Three-dimensional cage structures have been identified previously in protonated water clusters.[15,37]

In the case of $n = 6$, re-optimization of the OPLS-AA structure with DFTB+ does not lead to significant changes in the original OPLS-AA structure which was found to lie approximately 3.5 kJ/mol above the bi-cyclic structure identified by the DFTB+ search as the global minimum. Similar results were obtained with *ab initio* CBS-QB3 calculations. In the case of n = 7, re-optimization of the OPLS-AA structure at the DFTB+ level of theory leads to a 3-D network structure very similar to the original OPLS-AA structure which is only 0.6 kJ/mol less stable than the tight-binding global minimum. Calculations at the CBS-QB3 level indicate that the 3-D cage structure is actually lower in energy than the bicyclic structure by 8.9 kJ/mol. These results suggest that the formation of 3-D cage structures in $NH_4^+(H_2O)_n$ clusters start at n $\geq$ 7 and that the combination of computationally efficient methodologies based in the OPLS-AA force field and efficient quantum chemistry methodologies such as DFTB+ provide a reliable and efficient computational tool to probe the potential energy surfaces of these clusters.

Thus, our quantum mechanical calculations use the DFTB global minima structures, plus the OPLS-AA global minima of $n = 6$ and 7, as the starting geometries.

c. Quantum chemical calculations of stepwise hydration energies

The stepwise hydration energies for $NH_4^+(H_2O)_n$ ($n = 1-8$) computed with DFTB+ as well as with different semi-empirical and *ab initio* levels of theory are listed in Table 1. The semi-empirical and *ab initio* hydration energies were computed after re-optimization of the low energy structures obtained by the Monte Carlo search using the DFTB+ quantum chemistry methodology. The experimental hydration energies are also listed for comparison purposes. In the case of $n = 6$ and 7, the lowest energy structures obtained with OPLS-AA were also re-optimized with the different quantum chemistry methods and the resulting hydration energies are listed in parentheses.

Table 1. Stepwise hydration energies (in kJ/mol) for NH_4^+-$(H_2O)_n$ clusters (n = 1-8) computed at the AM1, PM3, HF/aug-cc-pVTZ, PBE/aug-cc-pVTZ, MP2/aug-cc-pVDZ, CBS-QB3, CBS-Q, and CBS-APNO levels of theory using the lowest energy structures obtained with the Monte Carlo search procedure proposed in this work combined the DFTB+ quantum chemistry method. Values in parentheses were computed after re-optimization of the OPLS-AA lowest energy structures.

n =	1	2	3	4	5	6	7	8
Exp.	86.2[c] 83.3[b] 72.4[a]	72.8[c] 61.5[a] 57.3[b]	57.3[c] 56.1[a] 51.0[b]	51.0[a] 45.2[b]	44.4[b] 41.0[a]	38.0[b]	35.0[b]	___
AM1	64.0	59.5	45.4	51.4	28.4	38.5 (46.5)	30.9 (34.7)	43.7
PM3	56.4	50.7	45.0	39.5	40.8	39.7 (29.1)	42.5 (29.5)	36.8
DFTB+	83.4	68.4	59.1	50.1	38.0	35.6 (32.1)	33.3 (32.7)	36.6
HF	76.4	64.5	55.4	47.6	41.2	40.6 (34.1)	36.3 (32.9)	36.0
PBE	89.7	71.6	59.6	50.1	53.8	51.5 (44.8)	48.4 (51.5)	62.7
MP2	86.6	72.6	62.6	54.3	56.9	55.3 (43.7)	47.5 (47.5)	61.5
CBS-QB3	80.2	65.6	55.5	47 .7	44.8	42.2 (33.1)	33.8 (42.7)	51.1
CBS-Q	79.2	65.1	55.4	47.4	47.5	46.2 (34.6)	39.0 (44.3)	47.5
CBS-APNO	80.7	68.2	52.7	46.8	___	___	___	___

Experimental enthalpies: a) ref. [11], b) ref. [12], c) ref. [13]; and G2/G3 results (*n* = 1-3, not listed) are in a similar accuracy as those from the CBSs methods.

The results listed in Table 1 show that the tight-binding results closely reproduce the high-level quantum mechanical calculations. For the cases of *n* ≤ 7, the DFTB+ approach, as well as the *ab initio* methods HF, CBS-QB3, CBS-Q and CBS-APNO

predict hydration energies with a relatively small deviation (within ± 3 kJ/mol) with respect to the average values of the available experimental results as reported in the literature. The hydration energies computed at the PBE/aug-cc-pVTZ and MP2/aug-cc-pVDZ levels of theory, lie closer to the upper bound of the experimental values, likely overestimating the binding energy. In addition, it is found that the semi-empirical methods, AM1 and PM3, predict significantly lower values than the above first-principles calculations, casting serious doubts on their ability to properly describe the ion-water interactions in the clusters under study.

For the isomers of $n = 6$, all quantum mechanical methods, expect for AM1, suggest that the DFTB structure is more stable than the OPLS-AA structure. For the case of n = 7, the PM3 and HF/aug-cc-pVTZ calculations favor the DFTB structure, while others the OPLS-AA structure.

With the exception of HF, all quantum chemical methods predict an oscillation in the hydration energy when going from $n = 6$ to $n = 8$, with a decrease from $n = 6$-7 and an increase from $n = 7$-8 (Table 1). This oscillation may indicate that the binding energy of these clusters is the result of a delicate balance between the number of hydrogen bonds (as well as the number of donor-acceptor interactions in these hydrogen bonds) and steric effects.

d. Computational advantages of the tight-binding method

Computational efficiency is the most important advantage of tight-binding over more accurate correlated *ab initio* quantum chemical methodologies. For example, for $n = 8$, a DFTB+ single energy calculation takes less than 10 seconds using one CPU (2.8

GHz Opteron) in the NIH Biowulf cluster, while a similar calculation using the highly correlated CBS-QB3 method requires ~144,000 seconds of CPU time on the same hardware, a factor of 14,400! Considering the greater computational demand involved in the corresponding gradient calculations, it is clear that the use of *ab initio* methods such as CBS-QB3 (or even more efficient methods such as DFT) for conducting Monte Carlo conformational searches and molecular dynamics simulations of $NH_4^+(H2O)_n$ clusters is prohibitive from a computational point of view. In addition, despite the fact that the computational efficiency of conventional semi-empirical methods such as AM1 and PM3 is comparable to DFTB, the results obtained in this work seem to indicate that these methods tend to underestimate the binding energies of the clusters. In principle, it may be possible to re-parameterize these efficient Hamiltonians to improve their accuracy and reliability. However, this is a task that is beyond the scope of the present study.

e. Charge densities

Figure 3 depicts a plot of the charges on NH_4^+ and on the H_2O molecules in $NH_4^+(H_2O)_n$ clusters as a function of n computed with DFTB (using the Huckel approach), as well as with HF and PBE (using the Natural Bond Orbital approach). The results show that despite the difference in the actual values, the DFTB, HF and PBE charges follow essentially the same trend: the net electron density transfer from the H_2O molecules to the NH_4^+ ion increases steadily from zero at $n = 0$ until it reaches a value of ~ 0.20 $\bar{e}$ for $n \geq 4$. As can be observed by the inset in Figure 3, in the case of $n > 4$, the electron-deficiency on the water molecules placed in the second cluster shell seems to be significant, suggesting an important net electron density transfer from outer shells in

these types of clusters. In fact, as observed in Figure 2, the electron density transfer from water molecules forming ring structures that are directly hydrogen-bonded to ammonium is smaller than the corresponding electron density transfer from the H_2O molecules either external to the rings or forming water rings that are not directly hydrogen-bonded to the ammonium ion. Thus, larger positive charges seem to accumulate in outer water shells located further from the ammonium ion, minimizing Coulombic repulsions.
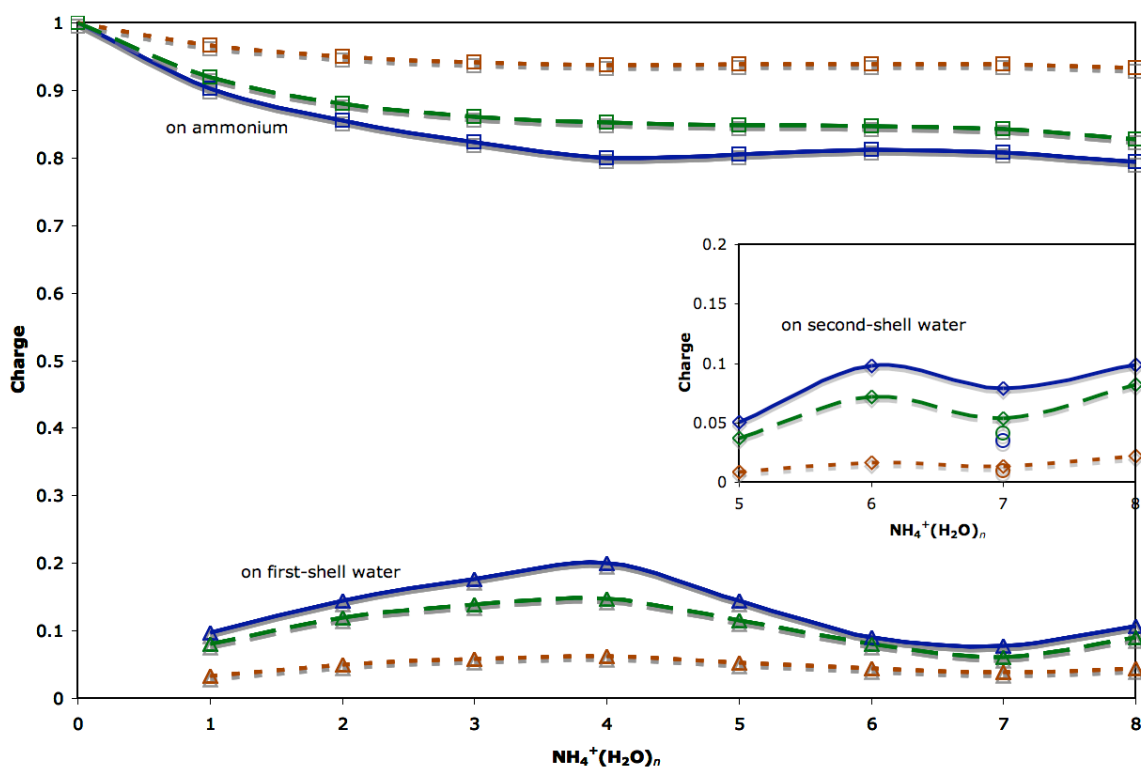

Figure 3. Calculated charges in $NH_4^+(H_2O)_n$ clusters as a function of the total number of water molecules in the clusters, using DFTB (solid blue), PBE (dashed green), and HF (dotted brown) calculations. Charges remaining on the NH_4^+ core ion are shown on the top plots (squares). The total charge on the H_2O molecules directly attached to the ammonium ion in clusters $n = 1 - 8$ are shown in the plots starting from n = 1 (triangles).

Charges on the second water shell (for $n = 5 - 8$, diamonds) are shown in the insert (charges on the third shell are marked as open circles).

Conclusions:

In this work, we present a computationally efficient procedure to identify low-energy isomers in solvated ionic systems. The method makes use of Monte Carlo conformational searches using the OPLS-AA force field combined with tight-binding calculations, and allows extending conformational searches to an ion (NH_4^+) solvated by up to eight water molecules. This approach reproduced well both the experimental and highly correlated *ab initio* quantum chemistry stepwise hydration energies of these clusters. It also identified ring and cage structures observed in other analogous systems. In contrast, computationally efficient models such as the MM3 force field that use fixed point charges and bond dipoles fail to reproduce the stepwise hydration energies of ammonium-water ionic hydrogen bonded systems. The ability to properly describe the charge density fluctuations is particularly critical in the study of ionic hydrogen bonds in moderate-size systems, since large electronic density changes can occur with various conformations[59,60]. Consequently, it is not surprising that MM3 fails in predicting the stepwise hydration energies of the NH_4^+-$(H_2O)_n$ clusters.

The reasonably good agreement between the DFTB stepwise hydration energies and the experimental data as well as with results computed with accurate and significantly more computational demanding quantum chemistry methodologies such as

CBSs and G2/G3 is very encouraging and suggests the possibility of using this methodology to explore the potential energy surfaces of larger clusters.

Contrary to the tight-binding results, the PBE and MP2 calculations overestimate the binding energies of the ionic hydrogen bonds. Although not shown in this work, a similar overestimation of the binding energies was obtained with other DFT exchange-correlation functionals such as the three-parameter hybrid B3LYP. It is rather surprising that the DFT-based tight-binding method performs better than DFT. It is quite possible that this might be the result of a systematic cancellation of errors. Although encouraging, more work leading to a systematic validation of DFTB in treating other ionic systems is needed.

In summary, the calculated DFTB binding energies for the NH_4^+-$(H_2O)_n$ clusters (n = 1-8) are in very good agreement with experimental results. The calculated low-energy structures and their charge densities vary considerably with cluster size, and show migration of the positive charge from the ammonium ion to outer sites, in agreement with electrostatic arguments.

The results obtained in this work are encouraging and suggest the possibility of using the computationally efficient DFTB approach for simulating relatively large ion/solvent systems.

Acknowledgement

completely. In no case does such identifications imply recommendation or endorsement by the National Institute of Standards and Technology, nor does it imply that the material or equipment identified is necessarily the best available for the purpose.

References:

(1)   Meot-Ner (Mautner), M. *Chemical Reviews* **2005**, *105*, 213.
(2)   Scheiner, S. *Hydrogen bonding : a theoretical perspective*; Oxford University Press: New York, 1997.
(3)   Desiraju, G. R.; Steiner, T. *The weak hydrogen bond : in structural chemistry and biology*; Oxford University Press: Oxford ; New York, 1999.
(4)   Perrin, C. L.; Nielson, J. B. *Annual Review of Physical Chemistry* **1997**, *48*, 511.
(5)   Tobias, D. J.; Hemminger, J. C. *Science* **2008**, *319*, 1197.
(6)   Visek, W. J. *Journal of Dairy Science* **1984**, *67*, 481.
(7)   Aue, D. H.; Webb, H. M.; Bowers, M. T. *Journal of the American Chemical Society* **1976**, *98*, 318.
(8)   Taft, R. W. *Progress in Physical Organic Chemistry* **1983**, *14*, 247.
(9)   Meot-Ner (Mautner), M. N. *Journal of Physical Chemistry* **1987**, *91*, 417.
(10)   Meot-Ner (Mautner), M. *Accounts of Chemical Research* **1984**, *17*, 186.
(11)   Payzant, J. D.; J., C. A.; Kebarle, P. *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **1973**, *51*, 3242.
(12)   Meot-Ner (Mautner), M. *Journal of the American Chemical Society* **1984**, *106*, 1265.
(13)   Meot-Ner (Mautner), M.; Speller, C. V. *Journal of Physical Chemistry* **1986**, *90*, 6616.
(14)   Cox, J. D.; Wagman, D. D.; Medvedev, V. A. *CODATA key values for thermodynamics*; Hemisphere Pub. Corp.: New York, 1989.
(15)   Shi, Z.; Ford, J. V.; Wei, S.; Castleman, A. W. *Journal of Chemical Physics* **1993**, *99*, 8009.
(16)   Wang, Y. S.; Chang, H. C.; Jiang, J. C.; Lin, S. H.; Lee, Y. T.; Chang, H. C. *Journal of the American Chemical Society* **1998**, *120*, 8777.
(17)   Jiang, J. C.; Chang, H. C.; Lee, Y. T.; Lin, S. H. *Journal of Physical Chemistry A* **1999**, *103*, 3123.
(18)   Bruge, F.; Bernasconi, M.; Parrinello, M. *Journal of Chemical Physics* **1999**, *110*, 4734.
(19)   Kassab, E.; Evleth, E. M.; Hamoutahra, Z. D. *Journal of the American Chemical Society* **1990**, *112*, 103.
(20)   Jorgensen, W. L.; GAO, J. *Journal of Physical Chemistry* **1986**, *90*, 2174.
(21)   Perrin, C. L.; Gipe, R. K. *Science* **1987**, *238*, 1393.
(22)   Bruge, F.; Bernasconi, M.; Parrinello, M. *Journal of the American Chemical Society* **1999**, *121*, 10883.
(23)   Palinkas, G.; Radnai, T.; Szasz, G. I.; Heinzinger, K. *Journal of Chemical Physics* **1981**, *74*, 3522.

(24)	Liebman, J. F.; Romm, M. J.; Meotner, M.; Cybulski, S. M.; Scheiner, S. *Journal of Physical Chemistry* **1991**, *95*, 1112.

(25)	Vedani, A. *Journal of Computational Chemistry* **1988**, *9*, 269.

(26)	Goodford, P. J. *Journal of Medicinal Chemistry* **1985**, *28*, 849.

(27)	Halgren, T. A. *Journal of Computational Chemistry* **1996**, *17*, 490.

(28)	Lii, J. H.; Allinger, N. L. *Journal of Computational Chemistry* **1998**, *19*, 1001.

(29)	Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *Journal of Chemical Physics* **1983**, *79*, 926.

(30)	Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Hermans, J. *Intermolecular forces : proceedings of the Fourteenth Jerusalem Symposium on Quantum Chemistry and Biochemistry held in Jerusalem, Israel, April 13-16, 1981*; Dordrecht Reidel, 1981.

(31)	Patel, S.; Brooks, C. L. *Journal of Computational Chemistry* **2004**, *25*, 1.

(32)	Patel, S.; Mackerell, A. D.; Brooks, C. L. *Journal of Computational Chemistry* **2004**, *25*, 1504.

(33)	Maple, J. R.; Cao, Y. X.; Damm, W. G.; Halgren, T. A.; Kaminski, G. A.; Zhang, L. Y.; Friesner, R. A. *Journal of Chemical Theory and Computation* **2005**, *1*, 694.

(34)	Friesner, R. A. *Peptide Solvation and H-Bonds* **2006**, *72*, 79.

(35)	Elstner, M.; Porezag, D.; Jungnickel, G.; Elsner, J.; Haugk, M.; Frauenheim, T.; Suhai, S.; Seifert, G. *Physical Review B* **1998**, *58*, 7260.

(36)	Aradi, B.; Hourahine, B.; Frauenheim, T. *Journal of Physical Chemistry A* **2007**, *111*, 5678.

(37)	James, T.; Wales, D. J. *Journal of Chemical Physics* **2005**, *122*.

(38)	Frenkel, D.; Smit, B. *Understanding molecular simulation : from algorithms to applications*, 2nd ed.; Academic Press: San Diego, 2002.

(39)	Rapaport, D. C. *The art of molecular dynamics simulation*, 2nd ed.; Cambridge University Press: Cambridge, UK ; New York, NY, 2004.

(40)	Vesely, F. J. *Journal of Computational Physics* **1982**, *47*, 291.

(41)	Metropolis, N.; Rosenbluth, A. W.; Rosenbluth, M. N.; Teller, A. H.; Teller, E. *Journal of Chemical Physics* **1953**, *21*, 1087.

(42)	Ren, P. Y.; Ponder, J. W. *Journal of Physical Chemistry B* **2003**, *107*, 5933.

(43)	Pappu, R. V.; Hart, R. K.; Ponder, J. W. *Journal of Physical Chemistry B* **1998**, *102*, 9725.

(44)	Ponder, J. W.; Richards, F. M. *Journal of Computational Chemistry* **1987**, *8*, 1016.

(45)	Kruger, T.; Elstner, M.; Schiffels, P.; Frauenheim, T. *Journal of Chemical Physics* **2005**, *122*.

(46)	Elstner, M.; Hobza, P.; Frauenheim, T.; Suhai, S.; Kaxiras, E. *Journal of Chemical Physics* **2001**, *114*, 5149.

(47)	Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *Journal of the American Chemical Society* **1993**, *115*, 5348.

(48)	Stewart, J. J. P. *Journal of Molecular Modeling* **2004**, *10*, 155.

(49)	Perdew, J. P.; Burke, K.; Ernzerhof, M. *Physical Review Letters* **1996**, *77*, 3865.

(50)   Headgordon, M.; Pople, J. A.; Frisch, M. J. *Chemical Physics Letters* **1988**, *153*, 503.

(51)   Montgomery, J. A.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *Journal of Chemical Physics* **1999**, *110*, 2822.

(52)   Curtiss, L. A.; Raghavachari, K.; Trucks, G. W.; Pople, J. A. *Journal of Chemical Physics* **1991**, *94*, 7221.

(53)   Curtiss, L. A.; Raghavachari, K.; Redfern, P. C.; Rassolov, V.; Pople, J. A. *Journal of Chemical Physics* **1998**, *109*, 7764.

(54)   Kendall, R. A.; Dunning, T. H.; Harrison, R. J. *Journal of Chemical Physics* **1992**, *96*, 6796.

(55)   Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision C.02; Gaussian, Inc: Wallingford CT, 2004.

(56)   Carpenter, J. E.; Weinhold, F. *Journal of the American Chemical Society* **1988**, *110*, 368.

(57)   Meot-Ner (Mautner), M. M. and Lias, S. G. "Binding Energies Between Ions and Molecules, and The Thermochemistry of Cluster Ions" in NIST Chemistry WebBook, NIST Standard Reference Database Number 69, Eds. P.J. Linstrom and W.G. Mallard, June 2005, National Institute of Standards and Technology, Gaithersburg MD, 20899 (http://webbook.nist.gov).

(58)   Chang, H. C.; Wang, Y. S.; Lee, Y. T.; Chang, H. C. *International Journal of Mass Spectrometry* **1998**, *180*, 91.

(59)   Wu, Y. D.; Zhao, Y. L. *Journal of the American Chemical Society* **2001**, *123*, 5313.

(60)   Zhao, Y. L.; Wu, Y. D. *Journal of the American Chemical Society* **2002**, *124*, 1570.