

Microsolvation of Glycine: A DFT Study

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PBE1PBE/6-311+G(d,p) computations exploring the microsolvation of neutral and zwitterionic glycine are reported. A broad configuration search was performed to identify the lowest energy clusters of glycine with one to seven water molecules. The structures of the clusters are analyzed on the basis of the hydrogen-bonding network established between the water molecules and between water and glycine. Neutral glycine is favored when associated with zero to six water molecules, but with seven water molecules the two structures are isoenergetic.

Introduction

The gas-phase structure of glycine is of the neutral form, $\text{NH}_2\text{-CH}_2\text{CO}_2\text{H}$, confirmed by both experiment^{1–3} and ab initio computation;^{4,5} the zwitterion tautomer, $^+\text{NH}_3\text{CH}_2\text{CO}_2^-$, is not a local minimum in the gas phase.⁶ In aqueous solution, glycine is predominantly found as the zwitterion tautomer.^{7,8} One can imagine taking neutral glycine and sequentially associating additional water molecules until one has (zwitterionic or neutral) glycine in bulk aqueous solution.

In 1995, Jensen and Gordon⁹ posed two questions related to this sequential solvation of glycine. First, how many water molecules are necessary to stabilize the zwitterion tautomer? Second, how many water molecules are needed to make the neutral and zwitterion glycine tautomers isoenergetic? They tackled the first of these questions using MP2/DZP+//HF/DZP computations. Though a minimum is found for the glycine zwitterion:one water complex, it sits in a shallow well (also shown by Ding and Krogh-Jespersen¹⁰). The zwitterion:two water complex was found to be stable, and so they concluded that two water molecules were needed to stabilize the zwitterion tautomer of glycine.

Wang and co-workers re-examined the glycine:one water complex with a variety of basis sets and also examined the role of electron correlation.¹¹ At the HF level, the zwitterion:one water complex is a local minimum. Both B3LYP and MP2 with a basis set lacking polarization functions (particularly those basis sets without polarization functions on hydrogen) predict a stable zwitterion:one water complex. However, with any large basis set and either B3LYP or MP2, the zwitterion:one water complex is not a local minimum; instead, optimization invariably leads to the proton transferring from the nitrogen to the oxygen, forming the neutral glycine tautomer. This study points out the need for both polarized basis sets and electron correlation in order to properly assess the potential energy surface of the glycine:water complex. They also note that optimized geometries differ minimally when a counterpoise correction scheme is applied to reduce basis set superposition error.

The glycine:one water complex was recently identified in the gas phase with a laser ablation-molecular beam Fourier-transform microwave spectroscopy experiment.¹² Only a single species was detected, and in conjunction with MP2/6-311++G-

(d,p) computations, it was identified as composed of the neutral glycine tautomer.

Only limited computational studies of glycine with three water molecules have been reported. Kassab et al. examined the intramolecular proton transfer of glycine; however, as we will show, neither their neutral nor their zwitterion cluster is the minimum energy structure.¹³ Chaudhari, Sahu, and Lee optimized five zwitterion:three water structures at B3LYP/6-311++G* but did not compare them to clusters of the neutral tautomer.¹⁴

The microsolvation of tyrosine has been examined both by computations and experiment (IR and IR ion dip spectroscopy). Snoek and Simons¹⁵ report that tyrosine zwitterion complexed with one or two water molecules lies more than 7 kcal mol⁻¹ above the neutral tyrosine clusters. However, the tyrosine zwitterion:three water cluster is only 1.6 kcal mol⁻¹ higher than its neutral analogue at MP2/aug-cc-pVDZ//B3LYP/6-31+G(d). A subsequent study by Paizs and Oomens examined the clusters of tyrosine complexed with up to six water molecules.¹⁶ They performed a large search of the configuration space at B3LYP/6-31+G** and then corrected for BSSE and evaluated single-point energies with MP2. They find that the neutral form of tyrosine is always lower in energy than the zwitterion, regardless of the number of associated water molecules. However, the energy gap between the two decreases with each added water molecule, starting at 11.86 kcal mol⁻¹ with one water and diminishing to 1.16 kcal mol⁻¹ with six water molecules. They also note evidence of the zwitterion in the IR spectra when five or more water molecules are associated with tyrosine.

We present here DFT computations on the sequential solvation of glycine in its neutral and zwitterion forms with water. We have extensively searched the configuration spaces of these clusters with one to seven water molecules, looking expressly for the point at which the neutral and zwitterion become isoenergetic.

Computational Methods

We examined the clusters formed from glycine, in either its neutral or zwitterionic form, with one to seven water molecules. The clusters are labeled as **N***x*-*y* or **Z***x*-*y*, where **N** or **Z** indicates the neutral or zwitterion form of glycine, respectively, *x* designates the number of water molecules in the cluster, and *y* indexes the different configurations. Initial geometries of the

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glycine:water clusters were built using GaussView 3.09,¹⁷ guided by the results of the clusters with fewer water molecules. Water molecules were placed in a variety of locations to sample the various arrays of hydrogen-bonding networks available between glycine and water and between water molecules (discussed below). In addition, some initial configurations were created using a locally modified version of Saunders' "kick" strategy.¹⁸

These initial configurations were first fully optimized at B3LYP/6-31G(d)^{19–22} followed by computation of the analytical frequencies. These calculations provide a relatively quick screen of the configurations (up to 61 configurations were sampled for some clusters). However, B3LYP often provides inaccurate hydrogen bond energies²³ (especially with biologically relevant molecules²⁴), and the small 6-31G(d) basis set does not provide sufficient flexibility. The configurations with B3LYP/6-31G(d) energies within 4 kcal mol⁻¹ of the minimum energy structure were then re-examined at PBE1PBE/6-311+G(d,p).²⁵ Some higher energy configurations were also re-examined in some cases. The geometries were fully reoptimized at this level, and analytical frequencies were computed to evaluate the zero-point vibrational energy (ZPVE) and confirm that each configuration was a local energy minimum. The PBE1PBE functional has been shown to perform well with hydrogen-bonded systems,²³ and use of this nearly triple- ζ basis set, augmented with both diffuse functions and polarization functions, should provide adequate flexibility. Nonetheless, we benchmarked the PBE1PBE/6-311+G(d,p) energies against those computed at CCSD(T)/6-311+G(2d,p) for four different configurations involving glycine and two water molecules.

We report the electronic energies corrected for zero-point vibrational energy, computed also at PBE1PBE/6-311+G(d,p). The ZPVEs were used without any scaling. This energy will be appropriate for comparison to jet-expansion experiments, which are at very low temperatures, that might be performed in the future. While some investigations of amino acid:water clusters have used the counterpoise correction for basis set superposition error, we do not employ it here because (a) it overestimates BSSE, (b) geometries are typically not reoptimized with the counterpoise correction²⁶ nor are the ZPVEs adjusted accordingly, and (c) the large number of configurations examined make this calculation prohibitively time-consuming. All computations were performed using the Gaussian-03 suite.²⁷

Results

Benchmarking the Computations. B3LYP/6-31G(d) is one of the most widely utilized computational methods over the past decade. Recently, however, many reports of its failings have appeared.^{28–31} This functional also has difficulty in adequately treating hydrogen bonding.^{23,24} Nonetheless, we chose to survey the configurations using this method because of its widespread use among computational organic chemists. The resultant optimized configurations of all of the glycine:water clusters are shown in Supporting Information along with their relative energies. Low-energy configurations were reoptimized at PBE1PBE/6-311+G(d,p). This functional performs much better in predicting hydrogen bond energies.^{23,24}

To confirm that PBE1PBE/6-311+G(d,p) is adequate for describing the configurations of the water:glycine clusters, we compare structural and energetic results provided by this method with larger computations. First, we look at the structure and energies of glycine conformers. Kasalova et al. have recently reported CCSD(T)/cc-pVTZ structures of the two lowest energy conformers of glycine, **N0-a** and **N0-b**.⁵ The corresponding PBE1PBE structures are shown in Figure 1. The bond distances

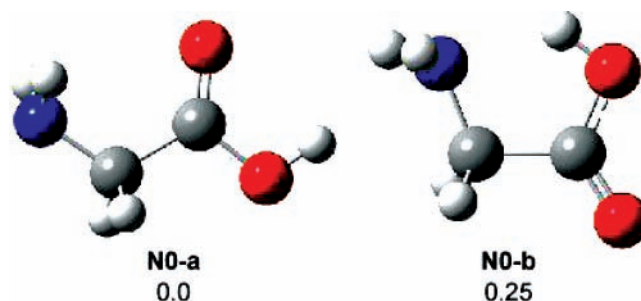


Figure 1. PBE1PBE optimized structures of **N0-a** and **N0-b**. Relative energies in kcal mol⁻¹.

TABLE 1: Relative Energies (kcal mol⁻¹) of N2 Configurations at CCSD(T) and PBE1PBE

	PBE1PBE ^a	B3LYP ^b	CCSD(T) ^c
N2-a	0.0	0.0	0.0
N2-b	0.99	1.00	1.14
Z2-a	11.63	12.25	12.51
Z2-c	13.39	13.81	13.36

^a Computed at PBE1PBE/6-311+G(d,p). ^b Computed at B3LYP/6-311+G(d,p)//PBE1PBE/6-311+G(d,p). ^c Computed at CCSD(T)/6-311+G(2d,p)//PBE1PBE/6-311+G(d,p).

computed with the two methods differ by less than 0.007 Å, and the angles are within 0.6° (see Table S1, Supporting Information). Both CCSD(T)/6-311+G**//MP2/6-311+G** and MP2 with a basis set that is effectively TZP+(3d2f,2p1d) predict that **N0-a** is the more stable isomer, by 0.86 and 0.44 kcal mol⁻¹, respectively.⁴ PBE1PBE predicts that the two isomers are essentially isoenergetic, though **N0-a** is 0.25 kcal mol⁻¹ below **N0-b** when ZPVE is included.

Alonso et al. optimized the structures of two low-energy configurations of the glycine:one water cluster, **N1-a** and **N1-b**, at MP2/6-311+G(d,p).¹² We have reproduced their computations (including also the next two low-energy configurations **N1-c** and **N1-d**) and compared their MP2 and PBE1PBE structures, with results in Table S2, Supporting Information. Again the geometries are in generally excellent agreement. The only significant differences between the MP2 and the PBE1PBE structures are for the length of the hydrogen bonds; MP2 predicts these distances are from 0.05 to 0.1 Å longer than what PBE1PBE predicts. This, however, does not manifest in any significant energetic consequence. The energetic ordering of these four isomers is identical with both methods, and the energy differences of the lowest three isomers are nearly identical. PBE1PBE predicts that **N1-c** is 0.6 kcal mol⁻¹ less stable than what MP2 predicts. We conclude that PBE1PBE provides reasonable structures.

To assess the ability of PBE1PBE to provide reasonable energies of the clusters, we have computed the energy of two configurations of **N-2** and two of **Z-2** using CCSD(T)/6-311+G(2d,p)//PBE1PBE/6-311+G(d,p). We also compare the energies computed at B3LYP/6-311+G(d,p)//PBE1PBE/6-311+G(d,p). These relative energies are listed in Table 1. The relative energetic ordering of these four clusters is identical with the three methods. More assuring is that the relative energies themselves are in quite close agreement. The largest error is in the relative energy of **Z2-a**, where PBE1PBE underestimates its energy by 0.92 kcal mol⁻¹. However, the relative energies of the other clusters differ by less than 0.15 kcal mol⁻¹. B3LYP seems to do perhaps a slightly better job in predicting these relative energies than PBE1PBE. It seems that PBE1PBE is properly accounting for the energetic consequences of tautomer

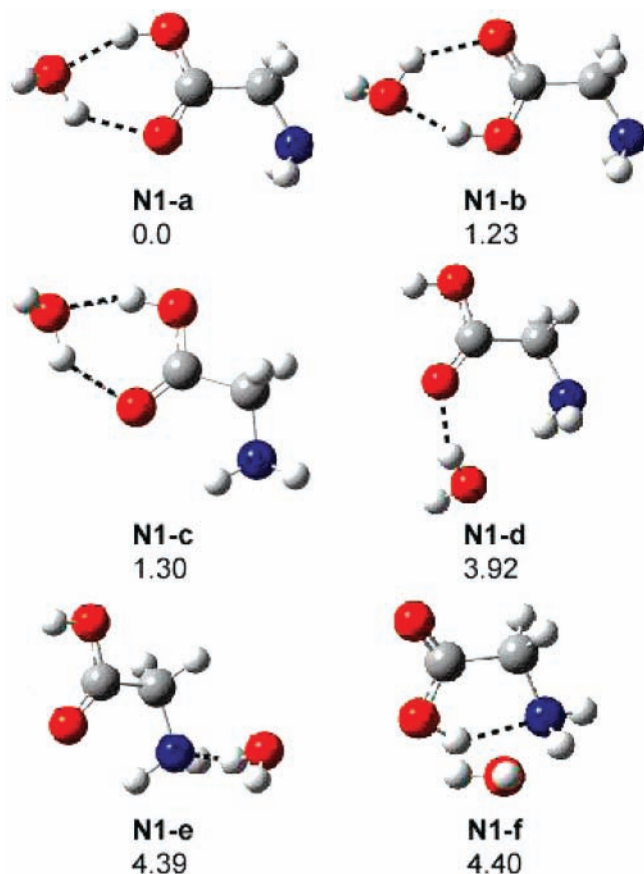


Figure 2. PBE1PBE optimized structures of **N1-a** through **N1-f**. Relative energies in kcal mol⁻¹. Dashed lines indicate hydrogen bonds of distances less than 2.0 Å.

and conformation differences and hydrogen bonding in differing environments.

Glycine:Water Clusters: Structures and Energies. *Glycine:1 Water.* We optimized 10 configurations of the cluster formed of neutral glycine and 1 water molecule at both B3LYP/6-31G* and PBE1PBE/6-311+G(d,p). These included the two configurations (**N1-a** and **N1-b**) examined by Alonso and the seven structures identified by Jensen and Gordon.⁹ The six lowest energy configurations are shown in Figure 2, along with their relative energies.

The three lowest energy configurations of **N1** all involve the water interacting with the carboxylic acid group through two hydrogen bonds, donating a proton to the carbonyl oxygen and accepting the proton from the hydroxyl group. The configurations differ in the conformation of the glycine, and **N1-a** reflects the most favorable conformation of the bare glycine. Water can bridge across the carboxylic acid and amine groups in a number of different ways; the most favorable is in **N1-d**, but this configuration is much less stable than **N1-a**. **N1-e** exhibits only one hydrogen bond where the water donates a hydrogen to the amine. Last, **N1-f** is the most favorable configuration that has the hydroxyl hydrogen anti to the carbonyl group. Even though this hydrogen can hydrogen bond to the amine, the configuration is not competitive with the lowest energy configurations.

Though a single configuration of the glycine zwitterion with one water molecule was located using B3LYP/6-31G*, the proton migrated back to oxygen upon reoptimization at PBE1PBE/6-311+G(d,p). Despite repeated attempts, no stable **Z1** structure could be located with this method. This result is consistent with Wang's study¹¹ in finding that **Z1** does not exist once diffuse functions are added to the basis set.

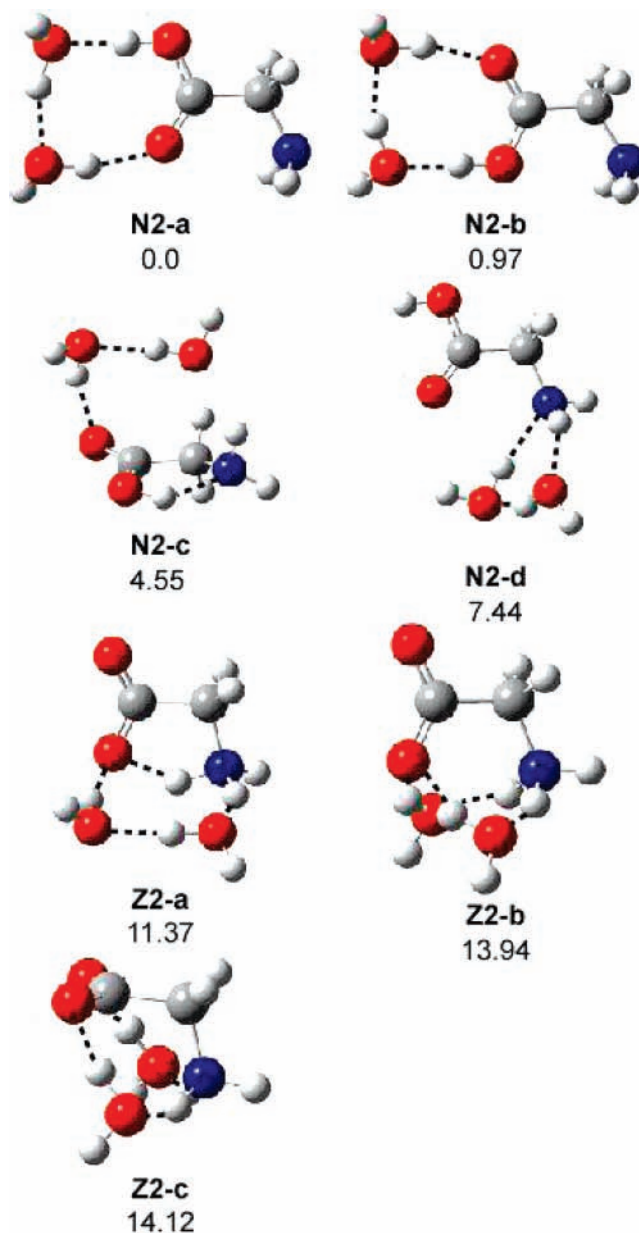


Figure 3. Lowest energy optimized structures of **N2** and **Z2**. See Figure 2 for details.

Glycine:2 Waters. Fifteen configurations of **N2** were located on the B3LYP/6-31G* potential energy surface (PES). There are two low-lying configurations, and the others are at least 6 kcal mol⁻¹ higher in energy. The four lowest energy configurations were reoptimized at PBE1PBE, and these structures are shown in Figure 3. **N2-a** and **N2-b** differ in the conformation of glycine. Just as with **N1**, the lowest energy configuration of the cluster has the amine hydrogens pointed toward the carbonyl oxygen, reflecting the stability of bare glycine. The next higher energy cluster, **N2-c**, contains a water–water hydrogen bond like **N2-a** and **N2-b** but has the unfavorable anti arrangement of the hydroxyl hydrogen. All of the higher lying configurations lack the water–water hydrogen bond. (**N2-g** has a water–water hydrogen bond but again has the anti hydroxyl hydrogen arrangement) This is the first hint that water–water hydrogen bonding is an important determinant of cluster geometries.

Using B3LYP, we located six configurations of the cluster formed of glycine zwitterion and two water molecules. These include the three configurations examined by Jensen and Gordon,⁹ **Z2-a**, **Z2-b**, and **Z2-c**, which are the three lowest

energy structures. These three structures were reoptimized at PBE1PBE, and the resulting geometries are drawn in Figure 3. The lowest energy configuration involving the zwitterion, **Z2-a**, has an intramolecular hydrogen bond between the ammonium and the carboxylate groups, along with a water–water hydrogen bond. **Z2-b** and **Z2-c** lack both of these types of hydrogen bonds; instead, each water bridges the two charged functional groups of the zwitterion.

These results confirm Jensen and Gordon's⁹ claim that two water molecules are necessary to stabilize the glycine zwitterion structure so that it can exist as a true minimum on the PES. However, the dihydrated zwitterion is noncompetitive with the neutral cluster; the most stable configuration **Z2-a** lies more than 11 kcal mol⁻¹ above **N2-a**.

Glycine:3 Waters. Fifteen configurations of **N3** were located at B3LYP. The seven lowest energy configurations were then reoptimized at PBE1PBE, but only six unique configurations were obtained, as shown in Figure 4. Again, in the lowest energy configuration **N3-a**, glycine adopts its most favorable conformation, and the water molecules form a hydrogen-bonding chain that bridges the two oxygen atoms of the carboxylic acid group. The second lowest configuration **N3-b** has the same water chain but a different glycine conformation where the amine hydrogens interact with the alcohol oxygen instead of the carbonyl oxygen. Water interaction with the amine group results in either fewer hydrogen bonds between water molecules or fewer water–carboxylic acid interactions, and these losses apparently outweigh the gains made through amine–water hydrogen bonds, as seen by the higher energies of the other configurations of **N3**. The structure of glycine:3 water molecules proposed by Kassab et al. corresponds to **N3-f**.¹³

We located fourteen unique configurations of **Z3** at B3LYP. The four lowest energy configurations were then reoptimized at PBE1PBE, and their structures are drawn in Figure 4. These four configurations have two water molecules hydrogen bonded to the ammonium group. All configurations containing only one water molecule hydrogen bonded to the ammonium group are much higher in energy. The two lowest energy configurations (**Z3-a** and **Z3-b**) have an intramolecular hydrogen bond between an ammonium hydrogen and oxygen, along with two hydrogen bonds between the three water molecules. The other two configurations lack both of these features. Kassab's structure corresponds with **Z3-d**.¹³ While the glycine zwitterion is a stable tautomer when surrounded by three water molecules, it is still much higher in energy than its neutral glycine tautomer.

Glycine:4 Waters. We located 27 configurations of **N4** on the B3LYP potential energy surface. The 10 lowest configurations were reoptimized at PBE1PBE, and we show the four lowest energy configurations in Figure 5. (All 10 configurations are presented in Figure S5, Supporting Information.) These lowest four configurations can be thought of as formed from a ring of the four water molecules interacting through four hydrogen bonds, and this ring is then hydrogen bonded to the carboxylic acid group. They differ in the orientation of the hydrogen bonds in the ring and the dangling O–H bonds of the waters. All attempts to fashion a configuration where the four water molecules form a hydrogen-bonded chain that bridges the ends of the carboxylic acid result in the formation of water rings. The structures that possess a three water chain bridging the carboxylic acid (like in **N3-a**) are higher in energy. **N4-a** through **N4-d** demonstrate the advantage of forming rings of the water molecules, a pattern we will see in the larger clusters. Water–water hydrogen bonding is clearly preferred over water–amine hydrogen bonds.

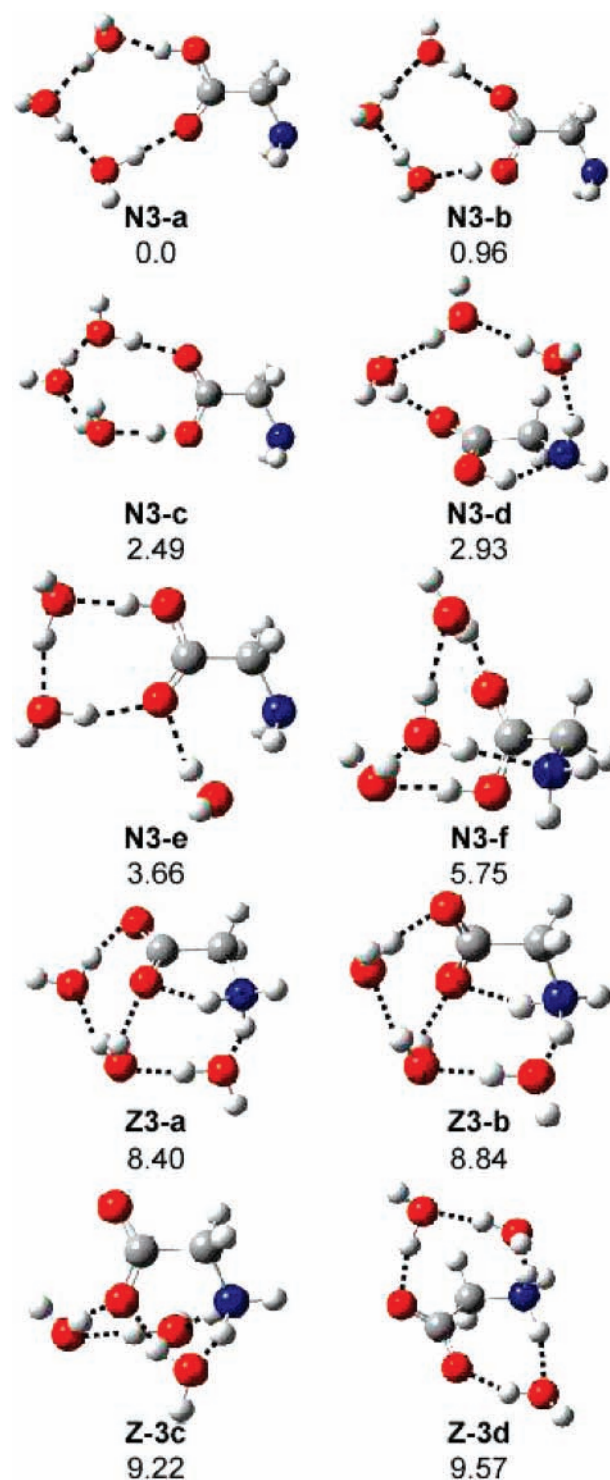


Figure 4. Lowest energy optimized structures of **N3** and **Z3**. See Figure 2 for details.

We found 18 configurations of **Z4** at B3LYP and reoptimized the structure of the lowest seven with PBE1PBE. The resulting five lowest energy configurations are shown in Figure 5. All of these low-energy configurations have two water molecules accepting protons from the ammonium group. Additionally, they attempt to maximize the number of water–water hydrogen bonds by forming rings or chains. These trends continue with the higher clusters.

The most stable zwitterion cluster (**Z4-a**) lies 6.04 kcal mol⁻¹ above the most stable neutral form, **N4-a**. It is important to note, however, that the use of a smaller basis set gives erroneous

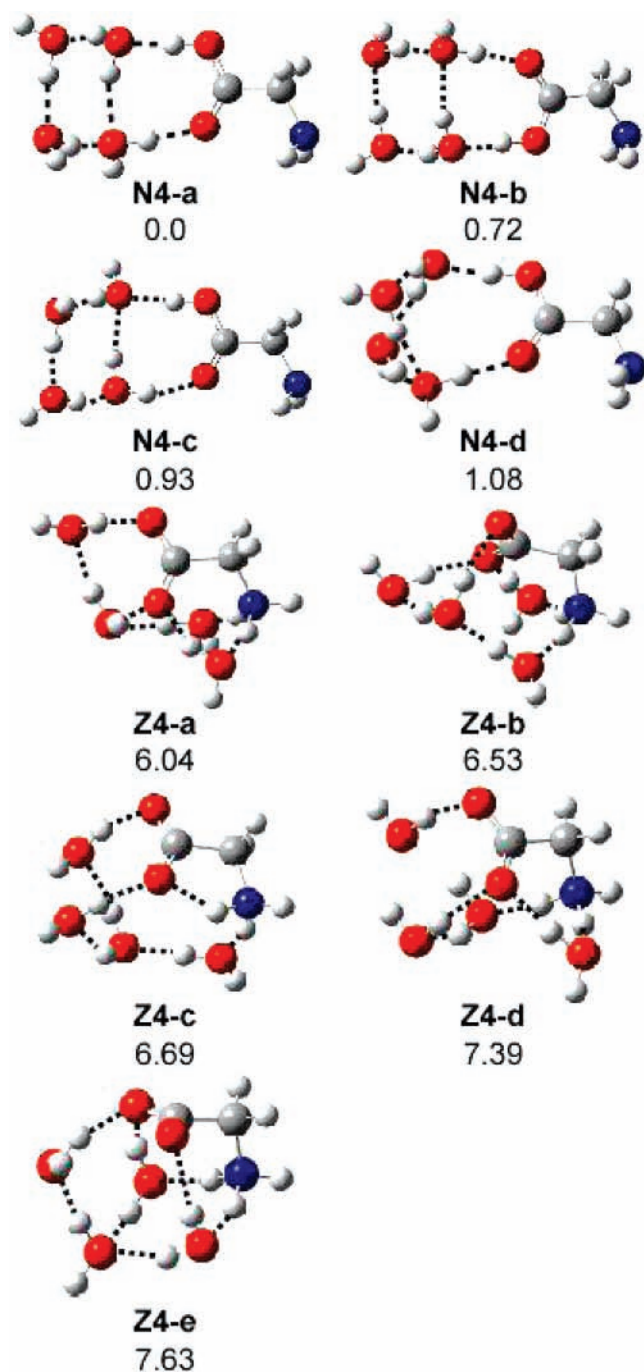


Figure 5. Lowest energy optimized structures of **N4** and **Z4**. See Figure 2 for details.

predictions. At B3LYP/6-31G(d), **N4-a** is the global minimum, but **Z4-a** is only 0.24 kcal mol⁻¹ higher in energy. When using this same small basis set, PBE1PBE predicts that **Z4-a** is actually lower in energy than **N4-a**. Small basis sets should therefore be used with great caution when computing clusters with extensive hydrogen bonding.

Glycine:5 Waters. Thirty-seven configurations of **N5** were optimized on the B3LYP surface. The 19 lowest energy configurations were reoptimized at PBE1PBE, and the 4 lowest structures are shown in Figure 6. (All 19 **N5** structures are drawn in Figure S5.) The lowest energy structure **N5-a** follows the trend of the smaller clusters in having a (five-member) ring of water molecules hydrogen bonded to the carboxylic acid group. In fact, four of the six lowest energy configurations have this arrangement. **N5-b** and **N5-c** have a four-member ring of water

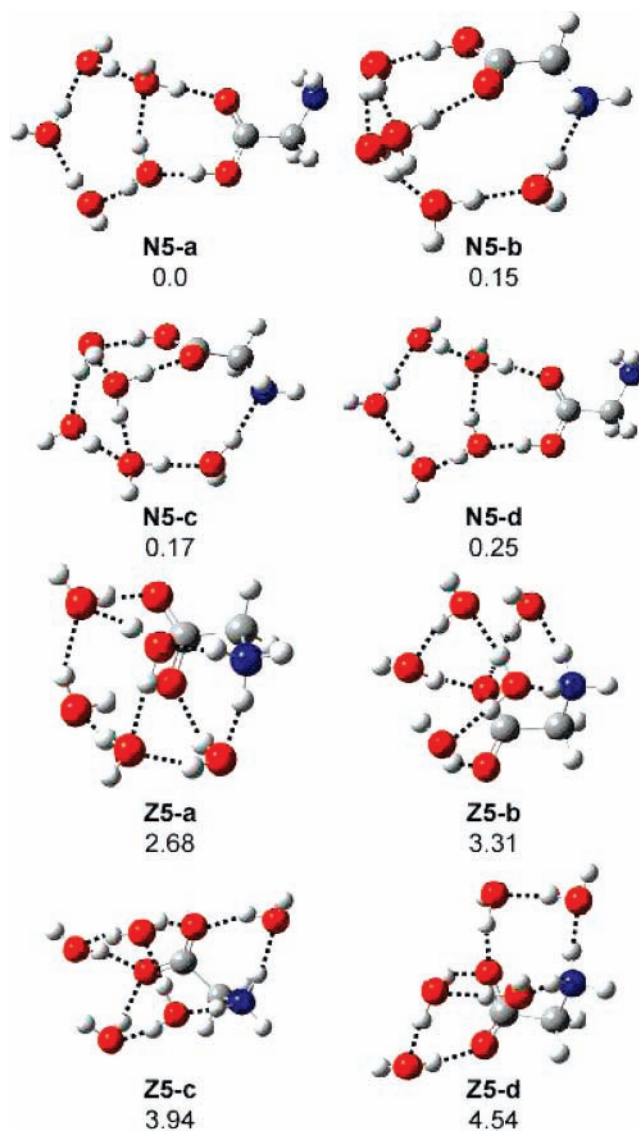


Figure 6. Lowest energy optimized structures of **N5** and **Z5**. See Figure 2 for details.

molecules hydrogen bonded to the carboxylic acid group with the last water forming a bridge between the water ring and the amine group. It is with five water molecules that hydrogen bonding to the amine group becomes energetically competitive with water–water hydrogen bonding. We anticipate that low-energy clusters of neutral glycine with six or seven water molecules will involve water–amine hydrogen bonding.

Forty-eight configurations of **Z5** were optimized at B3LYP. Of these, 12 were reoptimized with PBE1PBE, and the 4 lowest energy structures are displayed in Figure 6. (All 12 **Z5** structures are drawn in Figure S5.) These low-energy configurations all have two water–amine hydrogen bonds and a significant number of water–water hydrogen bonds.

The neutral glycine-five water clusters **N5** are lower in energy than the zwitterion-five water clusters, but the energy difference is only 2.68 kcal mol⁻¹. Actually, **Z5-a** is lower than **N5-a** in terms of electronic energy; it is with the inclusion of the zero-point vibrational energy that their relative order reverses.

Glycine:6 Waters. We located 29 different configurations of **N6** on the B3LYP PES. Eighteen of these structures were reoptimized at PBE1PBE, and the four lowest energy configurations are shown in Figure 7. Three of these low-energy configurations (**N6-a**, **N6-b**, and **N6-d**) form a cube-like

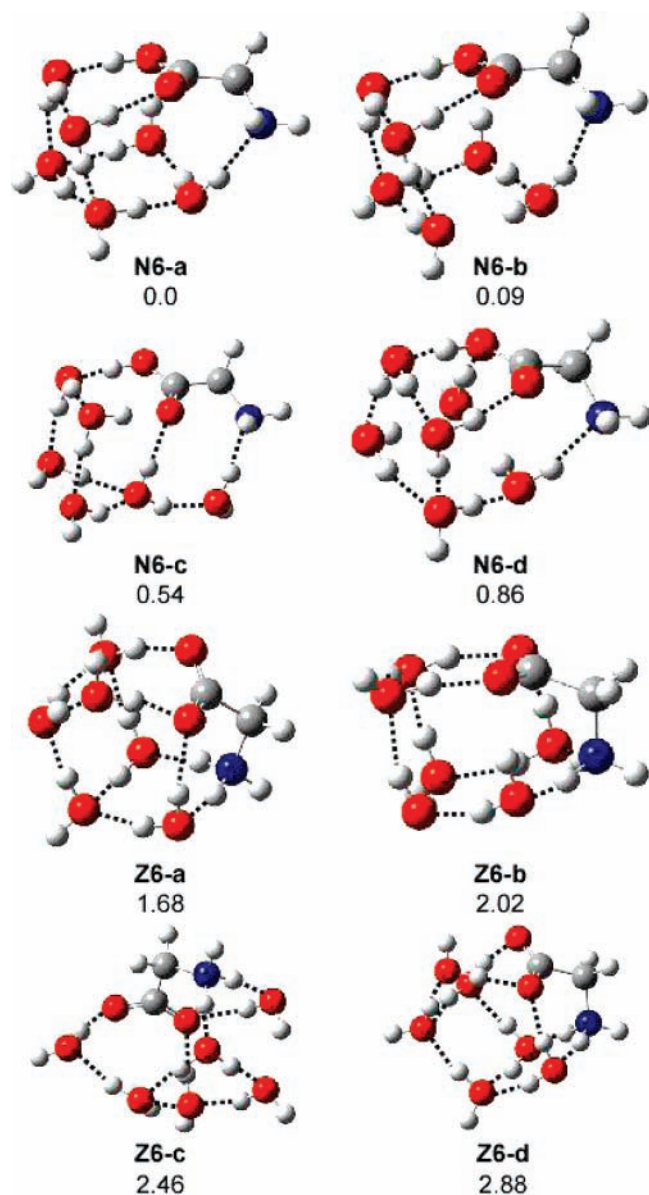


Figure 7. Lowest energy optimized structures of **N6** and **Z6**. See Figure 2 for details.

structure, where the corners are occupied by oxygen atoms, two from the carboxylic acid and the remaining six from the water molecules. The hydrogen-bonding network does not complete the cube structure; two of the H \cdots O distances are always over 2 Å. The third structure **N6-c** has one water molecule that participates in four hydrogen bonds. In all of these low-lying configurations, a hydrogen bond is established between a water molecule that donates a hydrogen to the amine group. Attempts to form a hydrogen bond where the amine donates the proton results in higher energy structures (see Figure S7, Supporting Information). Clusters involving a large water ring (having either five or six water molecules) that hydrogen bonds to the carboxylic acid group are also higher in energy than these cube-like structures. **N6-a** through **N6-d** offer the opportunity to have multiple hydrogen bonds between the water molecules, between the water molecules and the carboxylic acid group, and to have one hydrogen bond to the amine. This extensive hydrogen-bonding network results in more stabilization than what occurs with a large water ring interacting with glycine.

Structure **N6-e** presents an interesting structure. The optimization began with the neutral structure of glycine, but during

the optimization, the carboxylic acid proton transferred to the neighboring water molecule, generating a cluster between the conjugate base of glycine and a hydronium ion associated with five water molecules. A couple of other such configurations were also located, though higher in energy (see Supporting Information). The six water molecules provide sufficient polarization to stabilize the glycine conjugate base. This suggests that there may now be sufficient neighboring water to also stabilize a glycine zwitterion.

We were able to locate 53 unique configurations of **Z6** at B3LYP/6-31G(d). We then reoptimized 13 of these structures at PBE1PBE, which resulted in 11 unique configurations. The 4 lowest energy configurations of **Z6** are drawn in Figure 7, while all 13 are shown in Figure S7. The low-energy configurations all have the ammonium group involved in two hydrogen bonds to the waters. **Z6-a** features two loops formed of water chains, a chain of three hydrogen-bonded water molecules that bridge the oxygens of the carboxylate group and a second chain of three waters that bridge two hydrogens of the ammonium group. These loops connect through two hydrogen bonds. **Z6-b** also features two loops: a chain of two water molecules bridging the oxygens and a second chain of four waters bridging the ammonium hydrogens. Again, these two chains connect with two hydrogen bonds. Both of these structures have extensive hydrogen bonding between the water molecules, along with four hydrogen bonds between the waters and the zwitterion.

Despite the tantalizing hint that six waters might significantly stabilize the zwitterion provided by **N6-e** (the conjugate base: hydronium structure), the neutral form remains lower in energy than the zwitterion form. **N6-a** is the lowest energy configuration on the glycine:6 water surface. In fact, there are four **N6** configurations lower in energy than the lowest zwitterion form, **Z6-a**, which lies 1.68 kcal mol $^{-1}$ above **N6a**.

Glycine:7 Waters. Thirty-five different configurations of **N7** were optimized at B3LYP, and of these, 20 were reoptimized at PBE1PBE. These 20 structures are also drawn in Figure S8, and the 4 lowest energy structures are also reproduced in Figure 8. These low-energy configurations all involve two water molecules directly hydrogen bonded to the carboxylic acid group while one water molecule acts as a hydrogen donor to the amine group of glycine. The other waters are involved in creating an extensive water–water hydrogen-bonding network. For example, the lowest energy structure **N7-a** can be viewed as a chain of two waters bridging the carboxylic acid oxygen atoms while the other five-water molecules form a ring, positioned below the chain in such a way as to hydrogen bond to the chain and the amine. **N7-c** also has the five-water ring structure as in **N7-a**, but it hydrogen bonds in a different pattern with the two-water chain above it. Similarly, **N7-c** has a three-water chain across the carboxylic acid oxygens with a four-water molecule ring below. Searches initiated with the amine group donating a hydrogen atom to water led invariably to high-energy structures where no such hydrogen bond exists (see **N7-o** and **N7-q**). Unlike with **N6** where a glycine conjugate base:hydronium cluster was of low energy, by using PBE1PBE, the proton never transferred off of the carboxylic acid group in any of the optimizations of **N7** configurations, though in **N7-i** the O–H distance is rather long: 1.10 Å.

Sixty-one different configurations of **Z7** were located with B3LYP. We then reoptimized the geometry of 30 of these structures with PBE1PBE. The structures are all drawn in Figure S8, and the 4 lowest energy structures are shown in Figure 8. The lowest energy structure **Z7-a** can be thought of as built from the **Z6-b**, where the seventh water molecule bridges a

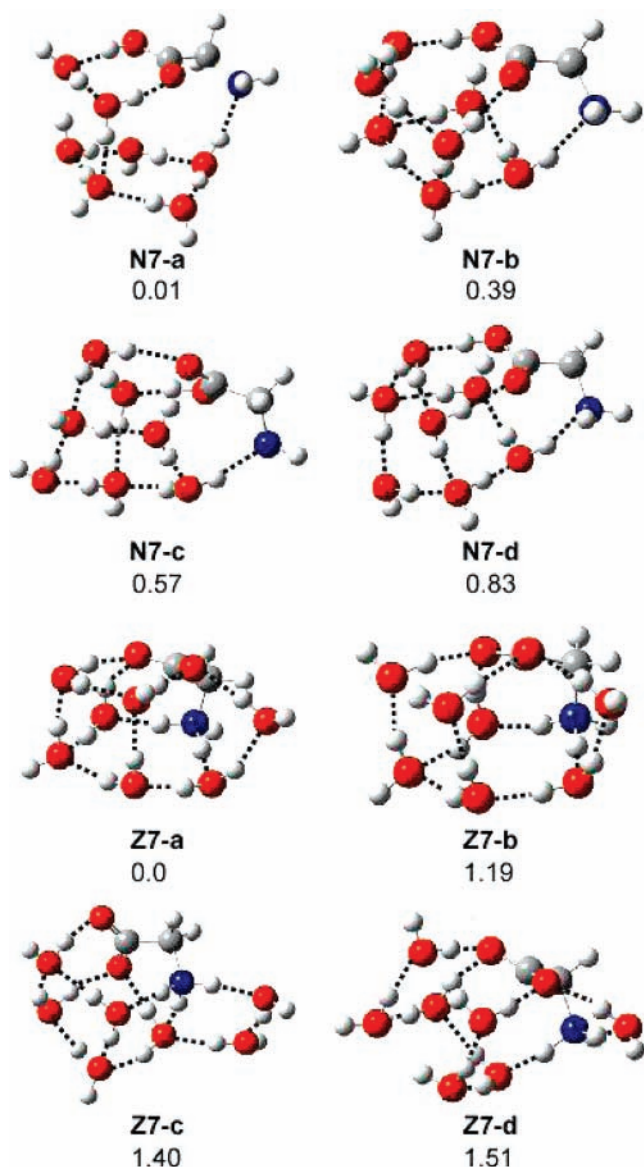


Figure 8. Lowest energy optimized structures of N7 and Z7. See Figure 2 for details.

water that hydrogen bonds to the ammonium group and a carbonyl oxygen. **Z7-b** has a similar hydrogen-bonding network as in **Z7-a**, but with the hydrogen bond in the two-water chain across the carboxylate group oriented in a different direction. **Z7-c** can be thought of as built off of the **Z5-a** core, which involves hydrogen bonds to two of the ammonium hydrogen atoms, supplemented with a two water chain that bridges the water cluster to the third hydrogen of the ammonium group. The ammonium cation is therefore stabilized by three hydrogen bonds. **Z7-d** has a six-water cluster that hydrogen bonds to the oxygens and to one hydrogen of the ammonium group. The seventh water molecule accepts a hydrogen from the ammonium group and donates a hydrogen to a carboxylate oxygen. What is unusual of the **Z7** clusters is that the third most stable configuration has three hydrogen bonds involving the ammonium group. The smaller water clusters favor two hydrogen bonds to the ammonium group, and the other **Z7** clusters with three hydrogen bonds to the ammonium are at least 4 kcal mol⁻¹ higher in energy than **Z7-c**.

Unlike all of the smaller clusters, the zwitterionic glycine cluster has reached energetic parity with the neutral cluster when seven water molecules are present. **Z7-a** and **N7-a** are essentially

identical in energy. Of the 10 lowest energy glycine:7 water clusters, half are of the zwitterionic form and half of the neutral form. Clearly, with seven water molecules, the zwitterionic glycine form has become competitive with its neutral isomer! However, there are four **N7** structures lower in energy than the second lowest **Z7** structure. Thus, at low temperatures, the population of neutral structures will still be favored over the zwitterion structures.

Discussion

A number of trends concerning the geometries of the glycine:water clusters become evident through this study. First, when associating with neutral glycine, the first two waters will establish hydrogen bonds to the carboxylic acid group. Additional waters will then form a ring of hydrogen-bonded water molecules. It is not until the sixth water molecule is added that the lowest energy cluster exhibits a hydrogen bond to the amine group. Invariably, this water-amine interaction is always with the water donating a hydrogen to the amine.

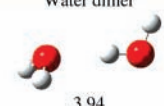
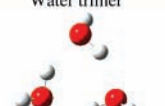
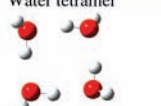
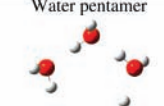
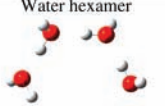
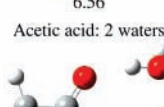
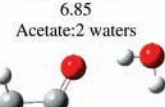
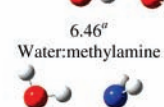
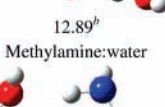
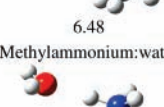
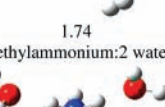
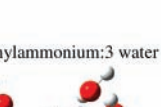
In the formation of the water clusters of zwitterionic glycine, a different pattern emerges. In the absence of water, optimization of the zwitterion structure leads to proton transfer from the ammonium group to the carboxylate group. Even one water is insufficient to keep the “extra” proton bonded to nitrogen. The ammonium group needs to be stabilized by hydrogen bonding with water, and two such hydrogen bonds are needed. (In **Z2-a**, the second hydrogen bond is made to the carbonyl group.) Additional water molecules then hydrogen bond to the carbonyl oxygens and create water–water hydrogen bond networks. Even with seven water molecules, forming a third hydrogen bond to the ammonium group is not competitive with the alternative hydrogen-bonding opportunities.

These trends are understandable in terms of the strength of the various types of hydrogen bonds that can be formed in these clusters. Table 2 presents a variety of model systems aimed at gauging the strength of the hydrogen bonds. We computed the water clusters involving two to six water molecules at PBE1PBE/6-311+G(d,p). The average hydrogen bond strength is computed as the difference between the energy of the cluster and that of the isolated waters, divided by the number of hydrogen bonds. The strength of the hydrogen bond increases with the size of the cluster and is worth over 6 kcal mol⁻¹ in rings involving at least 4 water molecules, thus the propensity for these larger rings in the glycine:water clusters.

The average hydrogen bond strength between water and acetic acid or acetate was determined in the following way. The cluster of acetic acid or acetate with two water molecules was optimized (and shown in Table 2). The complexation energy was then reduced by the average value of a water–water hydrogen bond (6.50 kcal mol⁻¹) and then divided by two to give the average value of the remaining two hydrogen bonds, 6.46 kcal mol⁻¹. These hydrogen bonds in the acetic acid cluster are essentially identical in strength to the water–water hydrogen bond. Not surprisingly, the hydrogen bond strength between acetate and water (12.89 kcal mol⁻¹) is much higher than for the hydrogen bond between acetic acid and water or between water molecules, reflecting the negative charge on the acceptor oxygen atoms.

To model the water–amine hydrogen bond, we optimized two structures, water donating a hydrogen to methylamine and methylamine donating a hydrogen to water. The former is much more favorable, with a hydrogen bond energy of 6.48 kcal mol⁻¹, comparable with the other hydrogen bonds involving neutral species evaluated in Table 2. However, amine is a poor hydrogen bond donor; the bond energy is only 1.74 kcal mol⁻¹.

TABLE 2: Average Hydrogen Bond Energies (kcal mol⁻¹) in Model Clusters at PBE1PBE/6-311+G(d,p)

Water dimer  3.94	Water trimer  4.30	Water tetramer  6.08
Water pentamer  6.56	Water hexamer  6.85	
Acetic acid: 2 waters  6.46 ^a	Acetate: 2 waters  12.89 ^b	
Water:methylamine  6.48	Methylamine:water  1.74	
Methylammonium:water  18.70	Methylammonium:2 water  17.11	Methylammonium:3 water  15.84

^a Average energy for the hydrogen bonds between acetic acid and water. ^b Average energy for the hydrogen bonds between acetate and water.

This explains the paucity of clusters where amine donates a hydrogen to water.

Last, we examined the hydrogen bond between water and ammonium by optimizing the structure of methyl ammonium associated with one, two, or three water molecules. The average hydrogen bond strength decreases with each subsequent hydrogen bond: 18.7, 17.1, and 15.8 kcal mol⁻¹. The strong hydrogen bond between water and ammonium explains why the first two waters will associate with the ammonium of the zwitterion. However, the third hydrogen bond to ammonium is much weaker (only 13.3 kcal mol⁻¹). The third water hydrogen bonded to ammonium would be directed away from all other waters in clusters involving a small number of water molecules, unable to make any further interactions. In the larger clusters, a typical water molecule is involved with three hydrogen bonds, each worth about 6.5 kcal mol⁻¹, for a total of about 19 kcal mol⁻¹ of stabilization energy, more than the stabilization afforded by bonding only to the third hydrogen of ammonium. This explains why the most favorable clusters have two and only two waters associated with the ammonium. The third water will only attach to ammonium when there are enough other water molecules available to construct a hydrogen-bonding network back to the other side of the ammonium group.

The cluster geometries reflect these simple model hydrogen bond strengths. In the neutral clusters, the waters will first associate with the carboxylic acid group, then start building a network of water–water hydrogen bonds, before finally bridging over to the amine group, with the water donating to the amine. In the zwitterion clusters, waters first associate with the ammonium group and then also to the carboxylate, building water–water hydrogen bonds to span these separated groups.

TABLE 3: Energy Difference (kcal mol⁻¹) between the Lowest Energy Neutral Cluster and the Lowest Energy Zwitterion Cluster

number of water molecules	$\Delta E(Z-N)$
1	
2	7.44
3	8.40
4	6.04
5	2.68
6	1.68
7	-0.01

In these small clusters, there are insufficient waters to create a network that can span to the third hydrogen of ammonium, leading to these clusters having only two waters associated with the ammonium group.

In Table 3, we summarize the energy difference between the neutral and the zwitterionic forms of glycine in the water clusters. The zwitterionic form does not exist in the gas phase either bare or with one water molecule associated with it. These calculations are consistent with experiment, especially the recent report¹² of the glycine:one water cluster. It is only with two water molecules that zwitterionic glycine is stable. This zwitterion cluster is, however, much higher in energy than the neutral isomer with two waters. The gap is actually a bit larger with three water molecules but then shrinks with every additional water molecule to the cluster. With seven water molecules, the clusters formed from two glycine isomers are isoenergetic.

Seven neighboring waters provide sufficient stabilization of the zwitterion form to make it competitive with the neutral form. The ammonium group is stabilized by donating two hydrogens to two different water molecules. The carboxylate group accepts hydrogens from three different water molecules. The remaining water molecules develop a hydrogen-bonding network that spans the waters at the two functional groups.

We anticipate that additional water molecules will create clusters that further benefit the zwitterion over the neutral glycine tautomer.

Conclusions

This study provides an answer to Jensen and Gordon's⁹ long-ago posed question of how many water molecules are required to make the glycine neutral and zwitterion structures isoelectronic. In the gas phase, isolated glycine exists as the neutral structure. A single water molecule is insufficient to stabilize the zwitterion structure, and it does not exist on the potential energy surface. Further sequential addition of water molecules does produce a stable zwitterion structure. In fact, added water molecules favor the zwitterion over the neutral structure, because of the stronger hydrogen bonds to the charged fragments (carboxylate and ammonium) over their neutral counterparts (carboxylic acid and amine). With the addition of seven water molecules, the zwitterion and neutral clusters are isoenergetic. We are extending this work to microsolvation studies of other amino acids, which we will report in the near future.

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Supporting Information Available: Complete citation of Reference 27, Tables S1 and S2, relative energies and drawings

of all structures computed at B3LYP/6-31G(d) and coordinates, energies and drawings of all structures computed at PBE1PBE/6-311+G(d,p). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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