

Cite this: *Phys. Chem. Chem. Phys.*, 2012, **14**, 4942–4958

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PAPER

A theoretical investigation of the relative stability of hydrated glycine and methylcarbamic acid—from water clusters to interstellar ices†

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Received 30th November 2011, Accepted 13th February 2012

DOI: 10.1039/c2cp23798a

We have theoretically investigated how the low-energy conformers of the neutral and the zwitterionic forms of glycine as well as methylcarbamic acid are stabilized by the presence water. The MP2/6-311++G(d,p) method was utilized to conduct calculations on glycine and methylcarbamic acid in both isolated clusters and in clusters embedded in the conductor-like polarizable continuum model (C-PCM), where the clusters explicitly contain between one and ten water molecules. The neutral forms of glycine and methylcarbamic acid were found to have similar hydration energies, whereas the neutral methylcarbamic acid was determined to be approximately 32 kJ mol⁻¹ more stable than the neutral glycine in the isolated clusters and 30 kJ mol⁻¹ more stable in the C-PCM embedded clusters. Both the number and strength of the hydrogen bonding interactions between water and the zwitterions drive the stability. This lowers the relative energy of the glycine zwitterion from 50 kJ mol⁻¹ above neutral glycine, when there are two water molecules in the clusters to 11 kJ mol⁻¹ below for the clusters containing ten water molecules. For the methylcarbamic acid clusters with two water molecules, the zwitterion is 51 kJ mol⁻¹ higher in energy than the neutral form, but it remains 13 kJ mol⁻¹ above the neutral methylcarbamic acid in the clusters containing ten water molecules. When the bulk water environment is simulated by the C-PCM calculations, we find both the methylcarbamic acid and glycine zwitterionic forms have similar energies at 20 kJ mol⁻¹ above the neutral methylcarbamic acid energy and 10 kJ mol⁻¹ lower than the neutral glycine energy. Although neither methylcarbamic acid nor glycine have been detected in the interstellar medium yet, our findings indicate that methylcarbamic acid is the more stable product from methylamine and carbon dioxide reactions in a water ice. This suggests that methylcarbamic acid likely plays a role in the intermediate steps if glycine is formed in the interstellar medium.

Introduction

Scientists have been fascinated by the interstellar medium (ISM), a rich reservoir of molecular material, for more than half a century. The origins and the formation of the amino acids in the ISM have received considerable attention because their presence in the ISM may provide crucial information about the delivery of prebiotic molecules to the early Earth and the origins of life on Earth, in addition to the possibility of an Earth-like life elsewhere in the universe.^{1–4} Although the presence of amino acids in the ISM has not been confirmed so far, they were already detected in meteorites, for example by Murchison, Murray, Orgueil, and Ivuna,^{5–9} and also in cometary

samples from Comet 81P/Wild2.^{10,11} Glycine (NH₂CH₂COOH) and the other amino acids that have been identified in these meteorites and cometary samples may have interstellar origins. In a recent study, in order to understand how glycine or methylcarbamic acid might be formed in the ISM we theoretically investigated the interaction between methylamine (CH₃NH₂) and carbon dioxide (CO₂) in the presence of zero to twenty water (H₂O) molecules using B3LYP/6-31G(d) calculations.¹² We found the surprising result that in the presence of just two water molecules, the methylamine and carbon dioxide can directly combine to produce a nitrogen to carbon bond with length 1.70 Å and form the methylcarbamic acid zwitterion (CH₃NH₂⁺CO₂⁻) in a barrier free reaction. Increasing the number of water molecules from two to twenty further stabilizes the methylcarbamic acid zwitterion as indicated by a gradual shortening of the N–C distance in the zwitterion to 1.51 Å. Whereas, when there are no water molecules present in the system, the methylamine and carbon dioxide molecules simply form a weakly bound van der Waals complex with a 2.81 Å N–C separation. The basic structural feature found in the many different optimized local minima of the

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cp23798a

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methylcarbamic acid zwitterion was that some of the water molecules formed hydrogen bonding networks which bridge and connect the hydrogen atoms in the $-\text{NH}_2$ group of methylamine with the oxygen atoms in carbon dioxide. These hydrogen bonding bridges draw the methylamine $-\text{NH}_2$ group closer to carbon dioxide and thereby enable the N–C bond to form. None of the geometry optimized structures we found in the study gave any indications that either zwitterionic or neutral glycine could also be formed by water mediated methylamine and carbon dioxide interactions.¹² One of the many possible explanations for why the methylcarbamic acid zwitterion is formed from methylamine and carbon dioxide, instead of a glycine species, is because the methylcarbamic acid isomer is lower in energy. Consequently in a second study¹³ we partly addressed this question by theoretically computing the relative energies of the different low energy conformers for the neutral forms of isolated glycine ($\text{NH}_2\text{CH}_2\text{COOH}$) and methylcarbamic acid (CH_3NHCOOH) conformers. This second study did confirm that the four lowest energy conformers of neutral methylcarbamic acid are more stable than the lowest energy neutral glycine conformer, where for instance we reported that the lowest energy methylcarbamic acid conformer is 31 and 34 kJ mol^{-1} more stable than glycine at the CCSD(T)/6-311++G(d,p)//MP2/6-311++G(d,p)^{14–23} and MP2/6-311++G(d,p)^{14,24,25} levels of the theory, respectively.¹³

One problem with the calculations performed in our second study is that they only simulate the neutral forms of glycine and methylcarbamic acid which occur in the gas phase. Amino acids are known to mainly exist in the neutral form in the gas phase, while in aqueous solution or in crystalline phase they exist in the zwitterionic form.^{26–29} For instance, glycine, which is the simplest amino acid, has been characterized to be in its neutral form in the gas phase both experimentally and theoretically.^{13,30–34} Calculations on the isolated neutral glycine alone have shown that there are 5 low energy conformers within 11 kJ mol^{-1} of each other, and another 3 conformers with energies less than 28 kJ mol^{-1} above the lowest energy conformer.^{13,31,33,34} On the other hand, the glycine zwitterion is the predominant form in aqueous solution and quantum chemistry calculations do not find a local minimum corresponding to a stable glycine zwitterion structure in the gas phase.^{28,29,35,36} Since our previous two studies suggested that zwitterionic methylcarbamic acid might have lower energy and consequently will be easier to form than glycine species in a water ice similar to that occurring in the ISM, the goal of the present work is to address the following two questions. (1) How many discrete water molecules are needed to solvate glycine and methylcarbamic acid so that the preferred stable form, neutral or zwitterionic, has lowest energy? For glycine the question becomes how many water molecules are needed to make the zwitterion more stable than neutral glycine, whereas for methylcarbamic acid the calculations are intended to help clarify whether the neutral or the zwitterion is the preferred form in bulk water. (2) Clearly from the first question we can answer the more important question: which is the more stable isomer within a water environment: glycine or methylcarbamic acid? This second question amounts to determining which isomer, both with the same number of water molecules, has the lowest energy.

There have been several previous studies which have attempted to determine how many water molecules are needed

to solvate the zwitterionic form of glycine and make it more stable than the neutral form of glycine.^{29,37–45} The calculations are challenging because when glycine interacts with water molecules it can form many different low energy conformers. We refer the reader to recent calculations by Gordon and Aikens⁴⁶ and Bachrach⁴⁷ for a detailed review of these past calculations. In the Aikens and Gordon work,⁴⁶ the solvation of the neutral and zwitterionic forms of glycine was investigated using an incremental microsolvation and the combined microsolvation-continuum approaches. The microsolvation approach simulates the glycine to bulk water interaction by using discrete clusters containing glycine and a finite number of water molecules. To explore the numerous local minima produced when glycine and the water molecules interact, Aikens and Gordon used a Monte Carlo (MC) based basin hopping algorithm⁴⁸ to generate a large number of different local minima so that the global minimum for the glycine water cluster with lowest energy could be identified. For instance, in the clusters containing a glycine and three water molecules, they located 824 distinct local minima containing neutral glycine and 212 local minima with the zwitterion form in the MC step when the energy was evaluated using an effective fragment potential (EFP2).^{49–52} They reduced the number of distinct local minima to 399 for the neutral and to 24 for the zwitterionic clusters by performing geometry optimizations at the RHF/6-31++G(d,p) level. The relative energies of the low energy clusters were further checked by performing single point MP2/6-31++G(d,p) calculations. Aikens and Gordon applied this approach to clusters containing up to eight water molecules. To further estimate water bulk effects combined microsolvation-continuum calculations were performed by applying the conductor-like polarizable continuum model (C-PCM)⁵³ to the optimized lower energy discrete glycine water clusters. Their results from RHF and MP2//RHF level calculations on the discrete clusters suggested that neutral isomers of glycine are more stable than the zwitterionic ones with up to six water molecules. On the other hand, zwitterionic structures with seven and eight discrete water molecules are found to have lower energy at the MP2//RHF level, but not with just the RHF energy. Their results from C-PCM+MP2//RHF calculations showed that the lowest energy zwitterionic glycine structures are more stable than the lowest energy neutral structures by between 15 (glycine and one water) and 37 kJ mol^{-1} (glycine and seven waters), in bulk water.⁴⁶ Bachrach⁴⁷ also studied the microsolvation of the neutral and zwitterionic forms of glycine by using clusters containing up to seven water molecules and the PBE1PBE/6-311++G(d,p) level of theory. He manually built the initial glycine with water clusters using a graphics program, where the structure selection was guided by results obtained from smaller clusters. The initial geometries were fully optimized at the B3LYP/6-31G(d) level, and the structures within 17 kJ mol^{-1} of lowest energy structure were reoptimized with the PBE1PBE/6-311++G(d,p) level of theory. The calculation results suggested that the neutral glycine with zero to six water molecules is more stable than its zwitterionic counterpart, whereas neutral and zwitterionic glycine are found to be isoenergetic in the clusters with seven water molecules.

Although there are already many previously published theoretical studies on the relative stability of glycine conformers

in the gas phase and in the water solution, theoretical studies related to methylcarbamic acid are quite scarce. Lattelais *et al.*⁵⁴ investigated the relative stability of neutral and protonated glycine isomers in the gas phase using B3LYP/6-311G(d,p) calculations and reported that neutral glycine (NH₂CH₂COOH) is less stable than both its amide ester (NH₂COOCH₃) and the methylcarbamic acid (CH₃NHCOOH) isomers by 19 kJ mol⁻¹ and 42 kJ mol⁻¹, respectively. But they did not compare the relative stability of the different conformers belonging to each isomer. Bossa *et al.*⁵⁵ presented the relative energies of the four lowest energy conformers for neutral methylcarbamic acid in the gas phase using B3LYP/6-31G(d) calculations. However, they did not provide a detailed geometrical analysis or a comparison of the methylcarbamic acid relative energies with glycine. As far as we can tell, our recent study of the low energy conformers for both neutral glycine and methylcarbamic acid is the only one which compares the two neutral isomers at the same theoretical level.¹³

The purpose of the present paper is to examine the different structural features and relative energies of the neutral and zwitterionic forms of glycine and methylcarbamic acid in the presence of the same number of water molecules. The relative energies of the different isomers should provide insight into whether glycine or methylcarbamic is preferentially formed in water ices in the ISM. The paper is organized in the following way. The next section describes the computational methods used along with details on how the different initial structures of glycine and methylcarbamic acid clusters in the neutral and zwitterionic form with different number of water molecules were generated. This is followed by the Results and Discussion section, where we present the optimized structures for the low energy conformers and the corresponding relative energies of the glycine and methylcarbamic acid clusters containing one to ten water molecules. We present results for the isolated discrete clusters containing a finite number of water molecules and also results for the different clusters embedded in the polarizable continuum model to simulate bulk water. We also describe in the Results and Discussion section what our results indicate as the preferred forms, neutral or zwitterionic, for both glycine or methylcarbamic acid and the overall relative energies for the two isomers. Concluding remarks are given in the final section of the paper.

Computational method

We investigated the low energy conformers of glycine and its methylcarbamic acid isomer by computing the relative energies of many different structures in the presence of 1 to 10 water molecules at the MP2/6-311++G(d,p) level^{14,16,17,19,20} and B3LYP/6-311++G(d,p) level⁵⁶⁻⁵⁸ of theory. We performed vibrational frequency calculations to verify each of the low energy structures corresponded to a proper local minimum and included the resulting zero point vibrational energy in the conformer relative energy. Throughout the paper we denote the optimized low energy glycine and water clusters as nGlyW_xa (or zGlyW_xa) to nGlyW_xd (or zGlyW_xd) where the n or z stands for the neutral and zwitterionic form, respectively, the W_x indicates the number, *x*, of water molecules present, and a, b, c, d lists their relative energy order where a is the cluster with lowest energy.

The same labeling procedure, nMCAW_xa (or zMCAW_xa), is also used for the optimized neutral and zwitterionic methylcarbamic acid with water clusters.

Since Aikens and Gordon obtained their low energy neutral and zwitterionic glycine structures in clusters containing up to 7 water molecules using a global optimization strategy based on a Monte Carlo (MC) basin hopping strategy,⁴⁸ we took all of the Aikens and Gordon RHF/6-31++G(d,p) optimized structures listed in their Supplementary Information⁴⁶ and reoptimized them using B3LYP/6-311++G(d,p) and then MP2/6-311++G(d,p) to verify whether the previously found lowest energy conformers were still obtained at these two new higher levels of theory. We also reoptimized the PBE1PBE/6-311+G(d,p) level structures reported by Bachrach.⁴⁷

For neutral glycine with eight water molecules, we only reoptimized the 4 structures previously reported by Aikens and Gordon.⁴⁶ Because Aikens and Gordon only reported three zwitterionic glycine complexes with eight water molecules, we prepared 16 additional initial zwitterionic structures. These structures are obtained either by modifying the positions of the water molecules in those three reported structures or by the addition of one and two water molecules to the four lowest energy clusters containing seven and six water molecules which we found in our MP2 calculations. We followed a similar approach to find the low energy conformations of the neutral and zwitterionic glycine clusters containing nine and ten water molecules. That is, we performed the conformational analysis by taking the four lowest energy conformations previously obtained for glycine clusters with six, seven and eight water molecules. To each of these clusters we randomly added more water molecules by placing them in different positions which favored the formation of new hydrogen bond bridges with either glycine or the other water molecules. Additionally, we created some initial structures where 9 or 10 water molecules were randomly arranged around the four lowest energy optimized conformers of isolated glycine.¹³ All of these starting structures were initially geometry optimized using B3LYP/6-311++G(d,p) calculations to produce approximately 30 different true local minima for each of the cluster with *x* water molecules. The half of the clusters with lowest B3LYP/6-311++G(d,p) energy were reoptimized to give the final lowest energy MP2/6-311++G(d,p) structures.

We found the low energy conformers for the neutral methylcarbamic acid with water clusters by following a similar strategy to that used for glycine with 8–10 water molecules. Around 20 initial geometries for the small clusters, with 1 to 4 water molecules, were generated using a molecular geometry editor program.⁵⁹ These initial geometries were first optimized at the B3LYP/6-311++G(d,p) level and then reoptimized at the MP2/6-311++G(d,p) level of theory to refine their structural and energetic results. The production of the larger clusters was guided by the smaller optimized nMCAW_x structures. For example, a water molecule was randomly placed around the four lowest energy optimized nMCAW_x clusters to produce several new nMCAW_(x+1) trial structures. Typically the additional water molecule is randomly placed at a location around the nMCAW_x where some new hydrogen bonds might be formed. The initial trial cluster structures were first optimized using B3LYP/6-311++G(d,p) calculations, and then half of the lowest

energy structures were reoptimized at the MP2/6-311++G(d,p) level. The zwitterionic methylcarbamic acid structures were obtained following a similar approach to that used for the neutral methylcarbamic acid clusters. In addition, we also reoptimized all of the zwitterionic methylcarbamic acid structures containing 1 to 10 water molecules which we had previously obtained at the B3LYP/6-31G(d) level in an earlier study.¹² Again, after initially obtaining several optimized zwitterionic methylcarbamic acid cluster structures at the B3LYP/6-311++G(d,p) level, and half of the clusters with lowest energy were reoptimized using the MP2/6-311++G(d,p) method.

In addition we reoptimized at the MP2/6-311++G(d,p), the lowest energy of the discrete glycine and methylcarbamic acid clusters containing between 1 and 10 water molecules using conductor-like polarizable continuum model (C-PCM)^{60–62} calculations. The C-PCM calculations model solvation based on a continuum approach where the extended bulk water is treated as a polarizable medium. Embedding the discrete glycine or methylcarbamic acid water clusters in the C-PCM simulates both the direct local interactions between water and the solute molecules and the long range bulk water effects on the different cluster geometries.

The GAMESS⁶³ program suite was used for all of the geometry optimizations and frequency calculations performed in this study.

Results and discussion

Previously we have found that the methylcarbamic acid zwitterion forms in a barrier free reaction from methylamine and carbon dioxide in the presence of 2 to 20 water molecules.¹² Since it is still unclear whether glycine or methylcarbamic acid exists in the ISM, we recently performed a study which found isolated methylcarbamic acid to have lower energy than isolated glycine, where in the structure analysis we obtained four low energy conformers for neutral methylcarbamic acid (MCA-1 to MCA-4) and eight for neutral glycine (Gly-1 to Gly-8).¹³ The present work extends the glycine and methylcarbamic acid conformational analysis to structures which include 1 to 10 water molecules so that we simulate both the neutral and zwitterionic forms of the two isomers in a water environment. Clearly, these clusters of either glycine or methylcarbamic acid with the water molecules can form a huge number of stable structures. Consequently, in Fig. 1 to 10 we only show the four lowest energy distinct optimized conformers found for the neutral and zwitterionic forms of glycine and methylcarbamic acid in the presence of 1 to 10 discrete water molecules computed by the MP2/6-311++G(d,p) method. In Table 1, we summarize the relative energies of the four distinct lowest energy conformers of each cluster obtained from the same level calculations. The structural information and energies computed by the B3LYP/6-311++G(d,p) calculations are given in the ESI†. In some of the geometry optimizations we found the two mirror images of the same structure, but we report here only one of the mirror images as the single distinct structure. The energies for two optimized mirror images typically differ by less than 0.2 kJ mol⁻¹, where this energy difference arises from the different starting geometries used in the geometry optimizations and reflects

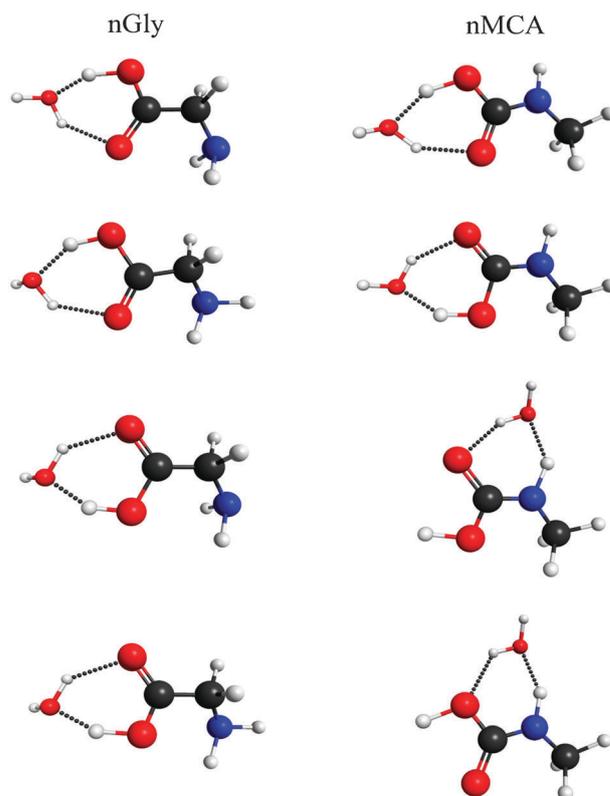


Fig. 1 The four lowest energy neutral glycine and methylcarbamic acid with one water molecule MP2/6-311++G(d,p) local minima. The structures are ordered in increasing relative energy where the lowest energy structures, nGlyW1a and nMCAW1a, are at the top and the nGlyW1d and nMCAW1d structures are in the bottom row.

the accuracy of the relative energy calculations for the different conformers.

Glycine

Many previous workers have tried to determine how many water molecules are needed to make the zwitterionic glycine more stable than the neutral form.^{29,37–45} Although this can be deduced from the energies in Table 1, in Table 2 we list the relative energies for the 4 lowest energy neutral and zwitterionic glycine conformers in the presence of 1 to 10 water molecules where the lowest energy conformer is given the zero reference energy. Below we give more specific details about the clusters containing x water molecules, but first we describe some of the general structural features for the neutral and zwitterionic glycine clusters which are evident from Fig. 1 through 10. Our results are consistent with the structural features found by previous workers, and in the ESI† we document the slight relative energy ordering differences we find as a consequence of using the 6-311++(d,p) basis set. In the neutral nGlyW x structures we find three types of hydrogen bonding. Firstly, the water molecules can form hydrogen bonds with the carboxylic acid group by either accepting or donating protons. Secondly, the water molecules can also hydrogen bond with the amine group, but in all of our optimized structures there is only at most one water molecule which donates a proton to the nitrogen atom. We find no examples of where a water molecule

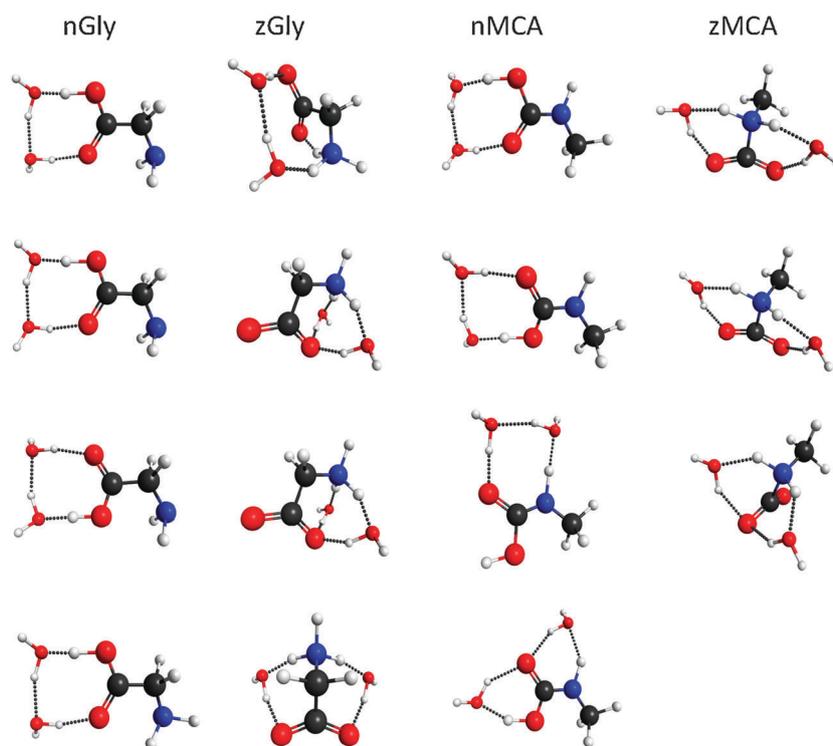


Fig. 2 The four lowest MP2/6-311++G(d,p) energy structures for the neutral and zwitterionic forms of glycine and methylcarbamic acid with two water molecules. The structures are ordered in increasing relative energy with the lowest energy structures, nGlyW2a, zGlyW2a, nMCAW2a and zMCAW2a at the top and nGlyW2d, zGlyW2d, nMCAW2d and zMCAW2c at the bottom. The same relative energy ordering scheme is used in Fig. 3 to 10.

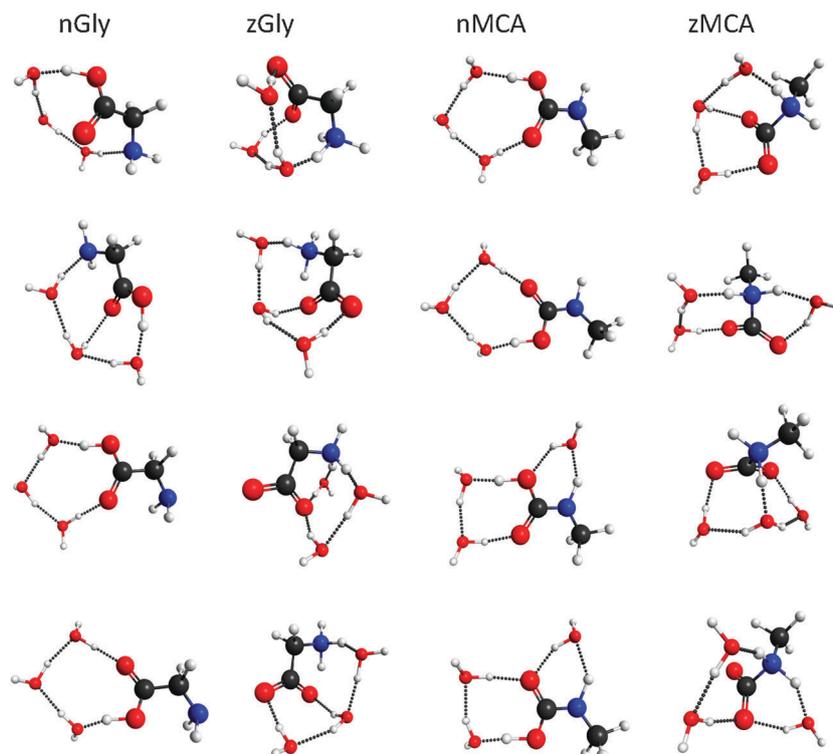


Fig. 3 The four lowest MP2/6-311++G(d,p) energy structures of the neutral and zwitterionic forms of glycine and methylcarbamic acid with 3 water molecules.

accepts a proton from the amine group. Finally, in all clusters the water molecules form networks by hydrogen bonding with

each other. In the nGlyW1 and nGlyW2 low energy structures we only find the water molecules hydrogen bonding with the

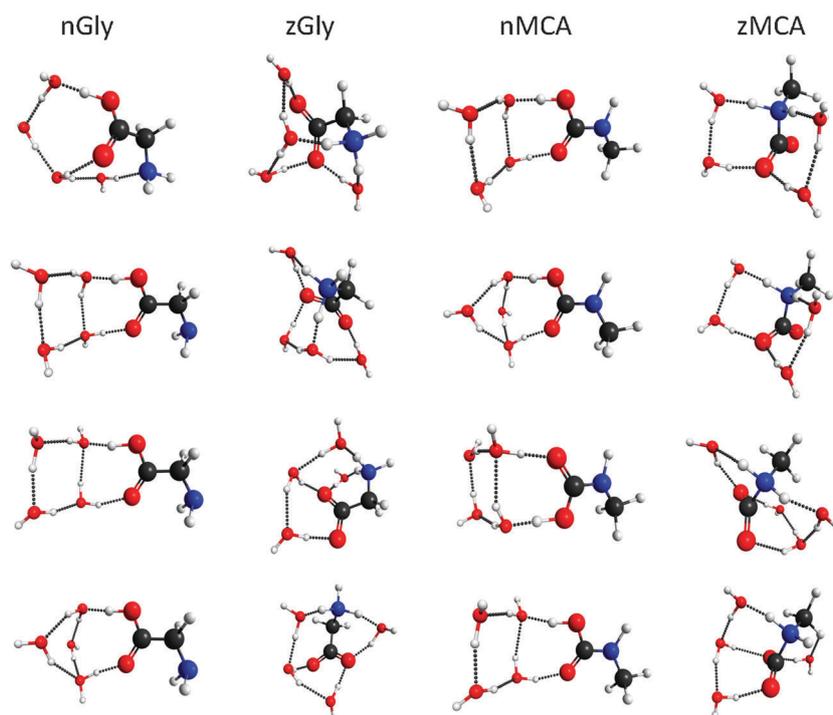


Fig. 4 The four lowest MP2/6-311++G(d,p) energy structures for the neutral and zwitterionic forms of glycine and methylcarbamic acid with 4 water molecules.

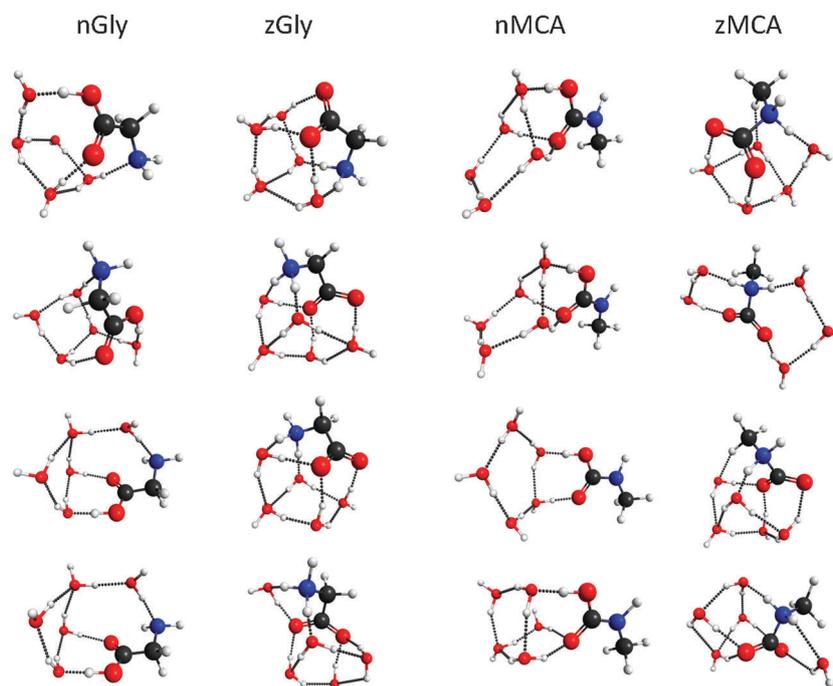


Fig. 5 The four lowest MP2/6-311++G(d,p) energy structures for the neutral and zwitterionic forms of glycine and methylcarbamic acid with 5 water molecules.

carboxylic acid group. Whereas, in the low energy nGlyW_x structures with three or more water molecules, there is always one water molecule which hydrogen bonds with and donates a proton to the amine group. We find this water molecule which hydrogen bonds to the amine group always to be at one end of a network of water molecules, where the other water molecules

either hydrogen bond to each other or to the carboxylic acid group. We also find that some of the low energy nGlyW_x structures, with $x \geq 3$, do not form any hydrogen bonds between water and the amine group, but these structures always have slightly higher energy than the structures with a hydrogen bond between the water to amine group.

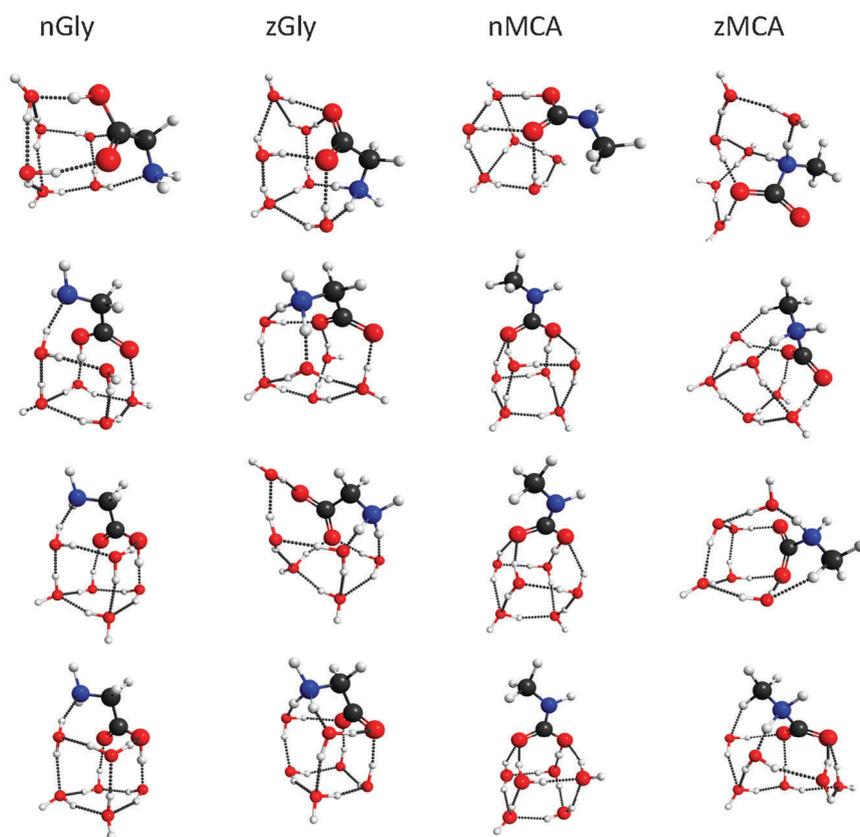


Fig. 6 The four lowest MP2/6-311++G(d,p) energy structures for the neutral and zwitterionic forms of glycine and methylcarbamic acid with 6 water molecules.

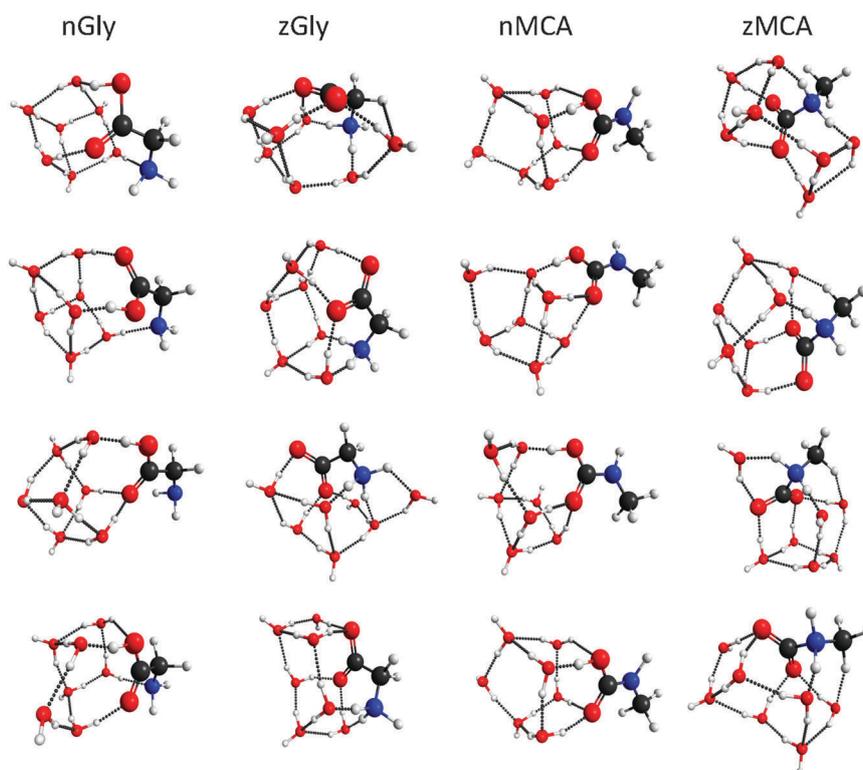


Fig. 7 The four lowest MP2/6-311++G(d,p) energy structures for the neutral and zwitterionic forms of glycine and methylcarbamic acid with 7 water molecules.

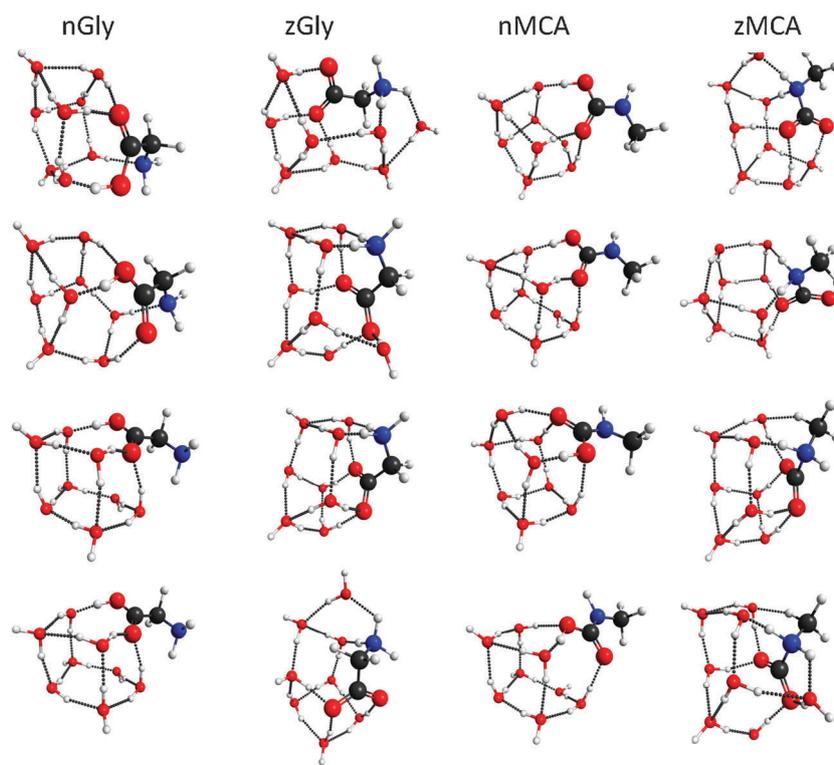


Fig. 8 The four lowest MP2/6-311++G(d,p) energy structures for the neutral and zwitterionic forms of glycine and methylcarbamic acid with 8 water molecules.

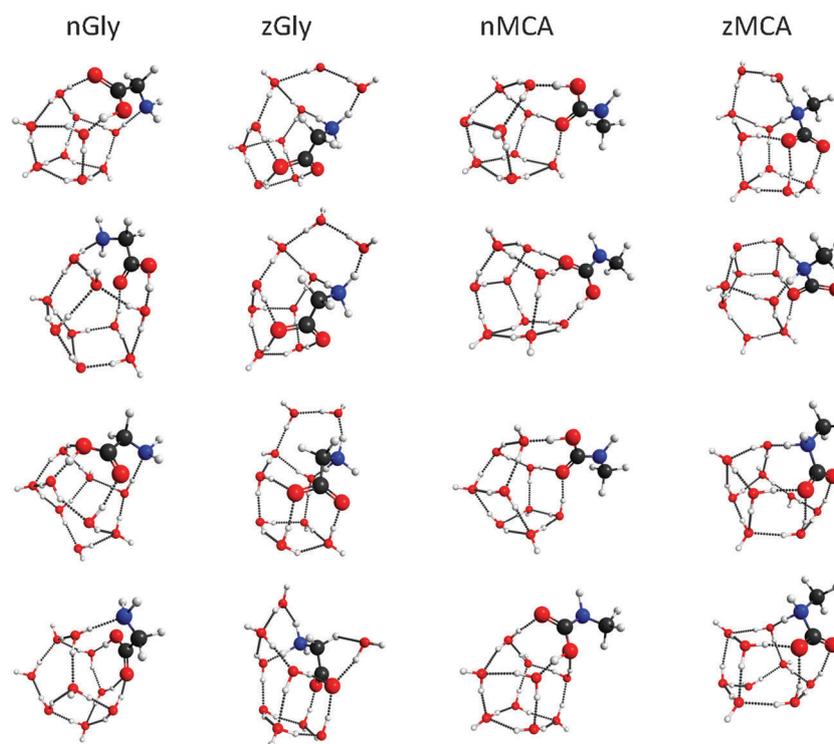


Fig. 9 The four lowest MP2/6-311++G(d,p) energy structures for the neutral and zwitterionic forms of glycine and methylcarbamic acid with 9 water molecules.

The optimized structures found for the zwitterionic glycine clusters, zGlyW x , are consistent with the water molecules being able to form more and stronger hydrogen bonding

interactions with the glycine zwitterion than with the neutral form. As a result, the enhanced hydrogen bonding interactions lowers the energy of the zwitterion relative to the neutral form

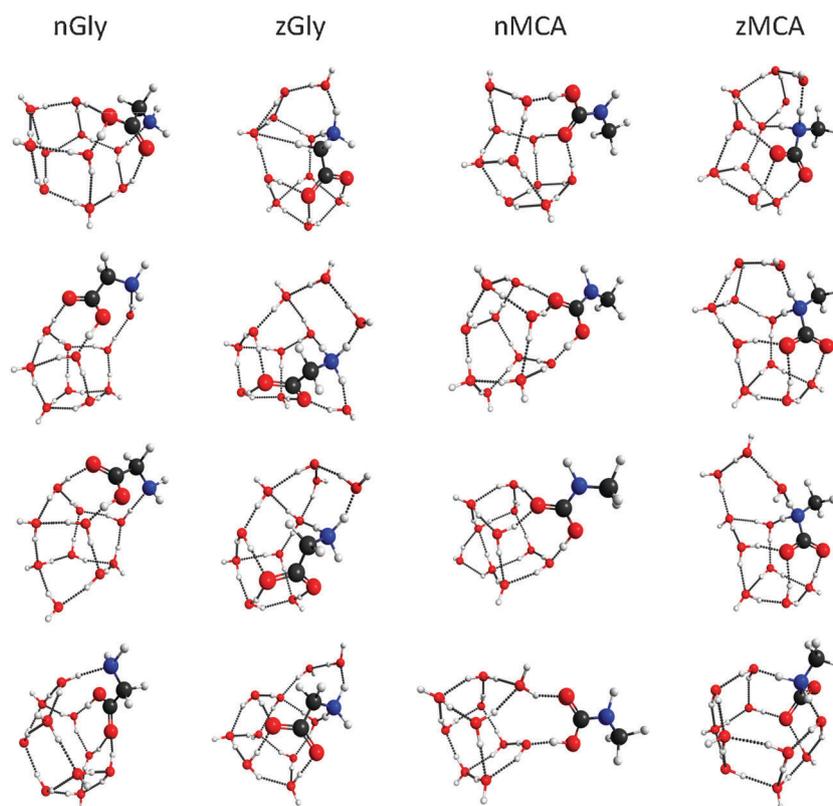


Fig. 10 The four lowest MP2/6-311++G(d,p) energy structures for the neutral and zwitterionic forms of glycine and methylcarbamic acid with 10 water molecules.

Table 1 Relative energies (in kJ mol^{-1}) of the neutral and zwitterionic conformers of glycine and methylcarbamic acid with 1 to 10 water molecules calculated at the MP2/6-311++G(d,p) level of theory

Molecule	Number of water molecules W_x									
	1	2	3	4	5	6	7	8	9	10
nMCA-W _{xa}	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
nMCA-W _{xb}	4.7	4.1	4.1	2.9	0.2	6.0	0.7	2.2	0.7	1.5
nMCA-W _{xc}	10.0	11.7	5.7	3.3	1.6	6.6	1.1	7.3	1.3	2.2
nMCA-W _{xd}	12.7	13.7	6.1	3.8	2.6	12.6	1.5	10.2	5.4	4.4
zMCA-W _{xa}	—	50.9	41.7	32.8	35.9	41.2	24.2	21.9	23.9	13.6
zMCA-W _{xb}	—	51.4	41.9	34.9	39.2	41.8	29.7	40.3	36.7	20.1
zMCA-W _{xc}	—	52.8	42.8	50.8	44.5	45.1	36.7	40.5	43.1	24.8
zMCA-W _{xd}	—	—	44.6	53.4	48.6	47.4	38.5	45.9	44.6	33.6
nGly-W _{xa}	36.2	36.9	35.9	32.2	28.6	29.1	21.4	32.4	33.2	30.9
nGly-W _{xb}	41.5	38.2	37.1	37.7	30.7	31.8	21.8	32.8	39.1	33.1
nGly-W _{xc}	41.6	41.4	37.6	39.7	33.0	33.6	25.3	41.1	41.3	34.1
nGly-W _{xd}	44.1	41.7	41.8	40.7	33.3	34.3	26.8	43.4	42.3	37.1
zGly-W _{xa}	—	86.3	69.8	53.9	44.5	43.4	29.7	33.5	32.3	19.9
zGly-W _{xb}	—	92.5	71.0	54.4	44.6	47.0	30.0	36.2	32.7	21.8
zGly-W _{xc}	—	93.1	71.4	59.6	44.7	47.5	31.2	37.1	40.2	23.0
zGly-W _{xd}	—	95.1	71.8	61.7	45.1	48.4	31.4	49.4	43.4	24.5

as the number of water molecules in the clusters increases. In the present clusters we only find the $-\text{NH}_3^+$ group to form a maximum of two hydrogen bonds by proton donation to two different oxygen atoms which are usually contained in two water molecules. The exceptions to this are for the zGlyW₂ and zGlyW₃ cases, where the $-\text{NH}_3^+$ group directly hydrogen bonds to one of oxygen atoms in the $-\text{CO}_2^-$ group and also forms a hydrogen bond with a water molecule. We anticipate

Table 2 Relative energies (in kJ mol^{-1}) of the neutral and zwitterionic glycine conformers with 1 to 10 water molecules calculated at the MP2/6-311++G(d,p) level of theory

Molecule	Number of water molecules W_x									
	1	2	3	4	5	6	7	8	9	10
nGly-W _{xa}	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.9	11.0
nGly-W _{xb}	5.3	1.3	1.3	5.5	2.1	2.7	0.3	0.3	6.8	13.2
nGly-W _{xc}	5.4	4.5	1.7	7.5	4.5	4.5	3.8	8.7	9.0	14.2
nGly-W _{xd}	7.9	4.9	5.9	8.5	4.7	5.2	5.3	10.9	10.0	17.3
zGly-W _{xa}	—	49.4	33.9	21.7	16.0	14.3	8.3	1.0	0.0	0.0
zGly-W _{xb}	—	55.7	35.2	22.3	16.1	17.9	8.5	3.8	0.4	2.0
zGly-W _{xc}	—	56.3	35.5	27.4	16.1	18.4	9.8	4.7	7.9	3.1
zGly-W _{xd}	—	58.3	35.8	29.5	16.5	19.3	10.0	16.9	11.2	4.7

in larger zGlyW_x clusters, the glycine zwitterion could be further stabilized by the $-\text{NH}_3^+$ group forming a third hydrogen bond with a third water molecule, but so far we have not found this type of structure in the clusters containing up to ten water molecules. We also find the $-\text{CO}_2^-$ group, especially in the larger zGlyW_x clusters, hydrogen bonds with 3 or 4 water molecules. Presumably the zwitterionic zGlyW_x clusters with more than 10 waters could be further stabilized relative to the neutral nGlyW_x clusters if the $-\text{NH}_3^+$ group formed a third hydrogen bond with water, but so far we have not found among the lowest energy structures an optimized cluster structure containing this third $-\text{NH}_3^+$ to the water hydrogen bond. More specific comments on different nGlyW_x and zGlyW_x clusters structures containing x water molecules are given below.

GlyW1. The four lowest energy conformers, nGlyW1a, nGlyW1b, nGlyW1c and nGlyW1d, found for the neutral glycine interacting with a single water molecule, shown in Fig. 1, illustrate how a water molecule can act as both a proton donor to the carbonyl oxygen and a proton acceptor from the hydroxyl group in the carboxylic acid group. The water slightly alters the MP2/6-311++G(d,p) relative energy ordering 0.0, 5.3, 5.4 and 7.9 kJ mol⁻¹ of the 4 lowest energy conformers, although they remain similar to the 0.0, 3.9, 5.4 and 6.7 kJ mol⁻¹ previously computed for the isolated Gly-1 to Gly-4 conformers.¹³ Structures where the water molecule bridges between the carboxylic acid group and the amino group or the saturated carbon are found at least 14 kJ mol⁻¹ higher in energy than the 4 lowest energy conformers and hence they are not included in Fig. 1 and Table 2. We could not locate a local minimum for the zwitterionic form of glycine with single water molecule on the potential energy surface. When we tried to optimize the zwitterionic like initial structures, using both B3LYP/6-311++G(d,p) or MP2/6-311++G(d,p) calculations, a spontaneous intramolecular hydrogen transfer from the amine group to carbon dioxide always took place and optimizations resulted in the formation of the neutral glycine with one water molecule. Similar difficulties in optimizing the glycine zwitterion with one water molecule using DFT and MP2 calculations were also previously reported by Wang *et al.*³⁹ and Bachrach.⁴⁷

GlyW2. Fig. 2 shows the two water molecules in the four neutral conformers, nGlyW2, prefer to form one hydrogen bond with each other and two hydrogen bonds with the carboxylic acid group of glycine. One of the water molecules acts as a proton acceptor from the terminal H, the other water donates a proton to the terminal O on the carboxylic acid group. Although the nGlyW2a and nGlyW2b conformers differ by 1.3 kJ mol⁻¹ in energy, they both contain glycine with the same structure as the lowest energy isolated glycine conformer, Gly-1.¹³ The different energies for the nGlyW2a and nGlyW2b conformers arise from the slightly different orientation of the water molecule closest to terminal O in the carboxylic acid group. The nGlyW2c and nGlyW2d structures correspond to the fourth (Gly-4)¹³ and the third (Gly-3)¹³ lowest energy conformer of the isolated glycine and have relative energy of 4.5 and 4.9 kJ mol⁻¹, respectively. They demonstrate how the various glycine conformers can interact differently with the surrounding water molecules, for instance the two water molecules in nGlyW2c stabilize the isolated Gly-4 conformer by 2.2 kJ mol⁻¹ more than the Gly-1 conformer.

Fig. 2 also shows that in the presence of two waters we were able to locate the zwitterionic form of glycine as a proper local minimum on the potential energy surface. In Table 2, the most stable conformer of zwitterionic glycine with two water molecules, zGlyW2a, is found at 49.4 kJ mol⁻¹ higher in energy than its neutral counterpart, nGlyW2a. Fig. 2 shows that the two water molecules in zGlyW2a hydrogen bond together to a form hydrogen bond bridge between the -NH₃⁺ and one of the oxygen atoms in the -CO₂⁻ group of the glycine zwitterion. The zGlyW2a also has a direct hydrogen bond from the -NH₃⁺ to the other oxygen atom in -CO₂⁻ which is not involved in hydrogen bonding with the water. Whereas, in the slightly higher energy structures zGlyW2b, zGlyW2c, and

zGlyW2d, the two water molecules each form a separate hydrogen bond bridge between both of oxygen atoms in -CO₂⁻ and the -NH₃⁺ groups, and a direct hydrogen bond between the -CO₂⁻ and -NH₃⁺ groups is not formed.

GlyW3. Fig. 3 shows that three water molecules form low energy structures where the water hydrogen bonds with both the amine and carboxylic acid groups on neutral glycine. Structures nGlyW3a and nGlyW3b show the typical hydrogen bond structure for neutral glycine where a water molecule only donates a proton to the amine. It is interesting that the lowest energy nGlyW3a only has one water molecule hydrogen bonding to the carboxylic acid groups while in the next lowest energy structure, nGlyW3b has two different water molecules hydrogen bonding to the carboxylic acid group. Table 2 shows that in the presence of three water molecules, the relative energies for the four lowest energy conformers of the neutral glycine have a 5.9 kJ mol⁻¹ range, while their zwitterionic counterparts have a narrower 1.9 kJ mol⁻¹ spread in energy. Fig. 3 also shows the water molecules in the two lowest nGly structures start to form a network of molecules hydrogen bonding to H atom in the carboxylic group and the N atom in the amine group. Whereas, the water molecules in nGlyW3c and nGlyW3d just hydrogen bond with the carboxylic acid group.

GlyW4. The four water molecules in the lowest energy nGlyW4a structure shown in Fig. 4 form a hydrogen bonding network which bridges both the amine and carboxylic acid groups. Starting at 5.5 kJ mol⁻¹ higher in energy, we find the nGlyW4b, c, and d structures where the four water molecules form a hydrogen bonded ring with each other and two hydrogen bonds with the carboxylic acid group on the glycine. The most stable nGlyW4a structure is found to be 21.7 kJ mol⁻¹ more stable than its zwitterionic counterpart, zGlyW4a. The four lowest energy zwitterions zGlyW4a to zGlyW4d are examples where there is a single water forming a hydrogen bonding bridge directly between the -NH₃⁺ and an oxygen atom from the -CO₂⁻ group. The other three water molecules are linked together by hydrogen bonds, while also hydrogen bonding to the -NH₃⁺ group and the carboxylate ion.

GlyW5. The four different lowest energy neutral glycine nGlyW5 clusters, shown in Fig. 5, now all have one water molecule donating a proton to the amine group and two water molecules hydrogen bonding with the carboxylic acid group. Similarly, in the 4 lowest energy zwitterionic glycine zMCAW5 structures there are two -NH₃⁺ to water hydrogen bonds and three water molecules form hydrogen bonds with the -CO₂⁻ oxygen atoms. Table 2 shows that the lowest energy zwitterion, zGlyW5a, lies 16 kJ mol⁻¹ above the most stable neutral glycine cluster, nGlyW5a.

GlyW6. Fig. 6 shows the six water molecules for both the neutral and zwitterionic glycine clusters adopt a three dimensional cage-like arrangement. The nGlyW6 structures consist of 4 water molecules forming a ring where two of the water molecules hydrogen bond with the carboxylic acid group. The two other waters in the ring each hydrogen bond with the two remaining water molecules, where one of these additional water molecules

hydrogen bonds with the nitrogen atom in the amine group. In the zwitterions, the $-\text{NH}_3^+$ group hydrogen bonds with two water molecules and either 3 or 4 water molecules form hydrogen bonds by donating protons to the carboxylate anion. The lowest energy neutral nGlyW6a conformer is found to be 14.3 kJ mol^{-1} more stable than the lowest energy zwitterionic zGlyW6a structure.

GlyW7. Fig. 7–10 show that the three-dimensional cage like arrangement of the water molecules to expand as the number of water molecules in the clusters increases from seven to ten. Apart from the water cage expansion, the low energy neutral and zwitterionic GlyW x cluster structures appear to have converged to a series of cluster geometries with similar structural features. For the neutral glycine, all the low energy optimized cluster geometries contain two water molecules which form hydrogen bonds with the carboxylic acid group and one other water molecule hydrogen bonding, *via* proton donation, to the amine group. Whereas, the low energy zwitterionic glycine conformers have more hydrogen bonds, with 3 or 4 water molecules hydrogen bonding with the carboxylate anion while two other water molecules form hydrogen bonds, by accepting protons, with the ammonium cation. However, even though both the nGlyW x a and zGlyW x a clusters appear to converge to a representative geometry water cage structure when $x \geq 7$, the energies in Table 2 show that the zwitterion clusters are further stabilized relative to the neutral glycine clusters as the number of water molecules in the cage increases. Hence our calculations on the seven water clusters find the lowest energy neutral glycine conformer, nGlyW7a, is 8.3 kJ mol^{-1} more stable than the zGlyW7a zwitterion cluster.

GlyW8. Table 2 shows that the energy difference between the neutral and zwitterionic glycine conformers is very small, the lowest energy neutral conformer configuration nGlyW8a is found to be 1.0 kJ mol^{-1} more stable than its zwitterionic counterpart, zGlyW8a. Our result is similar to the Aikens and Gordon conclusion that eight discrete water molecules do not appear to completely solvate glycine to make the zwitterion the more stable form.⁴⁶ However Table 2 shows the three lowest energy zwitterionic conformers and two neutral glycine conformers all within a 5 kJ mol^{-1} energy range. This suggests that both the neutral and zwitterion forms should be present in an equilibrium distribution of clusters composed glycine with 8 water molecules. Thus at the MP2/6-311++G(d,p) level the preferential form of glycine starts to switch from the neutral to zwitterionic form when there are eight water molecules present. However, this result is dependent on the computational method being used. For instance the B3LYP/6-311++G(d,p) results given in Table S2 (ESI[†]) find the structures nGlyW8a (0.0 kJ mol^{-1}), nGlyW8b (2.0 kJ mol^{-1}) and zGlyW8c (5.0 kJ mol^{-1}) as the three lowest energy eight waters clusters.

GlyW9. These structures were obtained by reoptimization at the MP2 level of the 15 lowest energy structures initially obtained by B3LYP calculations. For the first time in this study, the MP2 calculations give two low energy glycine zwitterionic structures, zGlyW9a and zGlyW9b, which are 0.9 and 0.5 kJ mol^{-1} , respectively, lower in energy than the lowest energy neutral nGlyW9a conformer. Again this result is

method dependent, since Table S2 (ESI[†]) shows the preliminary B3LYP/6-311++G(d,p) calculations still find the lowest energy neutral cluster nGlyW9a to be 3.5 kJ mol^{-1} more stable than the lowest energy zwitterionic cluster zGlyW9a. Although we only found 2 zwitterionic conformers more stable than the lowest energy neutral glycine complex at the MP2 level there are clearly many different neutral and zwitterionic conformers all close in energy to the zGlyW9a structure. For instance, we found 4 zwitterion and 6 neutral structures within 11.2 kJ mol^{-1} of the zGlyW9a cluster.

GlyW10. For the glycine clusters containing ten discrete water molecules, we found a total of six different zwitterionic glycine conformers which are more stable than the lowest energy neutral cluster, nGlyW10a. In addition to the structures shown in Fig. 10, the six lowest energy zwitterionic glycine conformers are shown in Fig. S2 in the ESI[†]. These six zwitterionic structures are found to be 11.0 , 9.0 , 7.9 , 6.3 , 5.9 and 4.1 kJ mol^{-1} more stable than the lowest energy neutral nGlyW10a conformer at the MP2/6-311++G(d,p) level. The B3LYP/6-311++G(d,p) calculations also find 5 zwitterionic conformers to be more stable than the lowest energy neutral cluster, although B3LYP found the zGlyW10b and nGlyW10b structures to be the lowest energy zwitterionic and neutral. Both our MP2 and B3LYP calculations give very similar optimized structures and both methods find the zwitterionic form of glycine is more stable than the neutral form when the glycine water cluster contains at least ten water molecules.

Relative stability of neutral and zwitterionic glycine

Fig. 11(a) summarizes how the relative stability ΔE of the zwitterionic to neutral form of glycine varies with the number of discrete water molecules included in the system for the different levels of theory. We compute ΔE as the energy difference between the lowest energy zwitterion conformer and the lowest energy neutral glycine conformer and ΔE is negative when the zwitterion is the more stable form of glycine. The MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) curves are from the calculations described in this paper. The EFP1/HF with RHF/6-31++G(d,p), RHF/6-31++G(d,p), and MP2/6-31++G(d,p)//RHF/6-31++G(d,p) curves summarize the data given by Aikens and Gordon.⁴⁶ The PBE1PBE/6-311++G(d,p) curve is obtained by using the data reported by Bachrach.⁴⁷ Fig. 11(a) illustrates that for all levels of theory the zwitterionic form of the glycine is stabilized more relative to the neutral form as the number of discrete water molecules contained in the different clusters increases. However, the number of water molecules required to fully solvate glycine and make the zwitterion the more stable form of glycine varies with the computational method used. The HF based methods must provide less zwitterion stabilization to give the larger ΔE values. From their MP2 calculations, Aikens and Gordon previously concluded that electron correlation stabilizes the low energy zwitterion structures more than the low energy neutral glycine structures.⁴⁶ Fairly similar zwitterion relative stability ΔE curves are obtained with our MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) calculations and by the Bachrach⁴⁷ PBE1PBE/6-311++G(d,p) calculations. The largest differences between Bachrach's and our calculations occur for the clusters containing

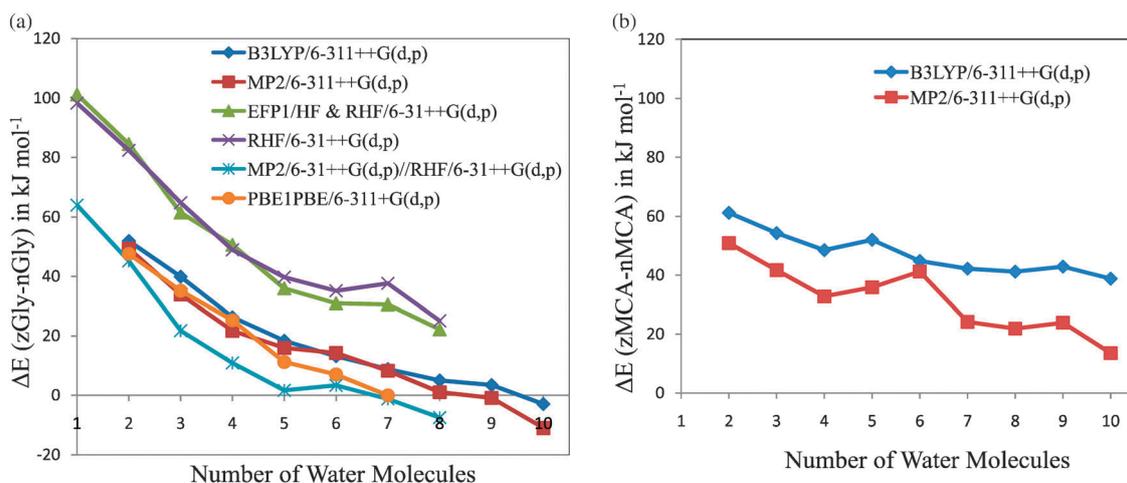


Fig. 11 Variation of the energy differences between the lowest energy zwitterionic and neutral structures with the number of water molecules for (a) glycine and (b) methylcarbamic acid obtained at the B3LYP/6-311++G(d,p), MP2/6-311++G(d,p) and other levels of theory.

seven water molecules, and as we noted above this difference can be traced to Bachrach not finding some of the additional lower energy neutral glycine conformers. Use of a slightly smaller basis set and only evaluating the single point MP2 energy in the Aikens and Gordon MP2/6-31++G(d,p)/RHF/6-31++G(d,p) calculations might be causing an overestimation of the glycine zwitterion stability to give the somewhat smaller ΔE values than we obtain in our calculations. The results of our MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) calculations show ΔE values close to zero in Fig. 11(a) in clusters containing eight or nine water molecules suggesting that both zwitterionic and neutral forms of glycine could be present in these clusters. The more negative ΔE value obtained for the low energy clusters with ten water molecules indicate that glycine should be predominantly in the zwitterionic form.

Methylcarbamic acid

Similar to what we found for the glycine water clusters, the neutral and zwitterionic forms of methylcarbamic acid in water clusters, shown in Fig. 1 through 10, exhibit several general structural trends. The first general structural feature to notice for the neutral nMCAW $_x$ clusters is that the carboxylic acid group is often in the same plane as the neighboring N–H bond. This probably arises because the C=O bond in the carboxylic acid group can form a peptide like bond with the N–H bond. Secondly, although we might expect some of the water molecules in the nMCAW $_x$ structures to form a hydrogen bond bridge between the –NH and the carboxylic acid groups, we have only found examples of these water molecule bridges being present in the small clusters containing one to three water molecules. While we do expect these –NH to carboxylic acid water bridges to form in the larger clusters with four or more water molecules, we did not find them amongst the 4 lowest energy nMCAW $_x$ conformers we describe in this paper. It is interesting that in the smaller nMCAW $_x$ clusters, the water bridge is formed by the –NH donating a proton when hydrogen bonding with water rather than accepting a proton like we found for the –NH $_2$ group in the nGlyW $_x$ clusters. In all the nMCAW $_x$ clusters, the lower

energy conformers are obtained with the OH part of the carboxylic group hydrogen bonding to an oxygen atom on one water molecule, and the carboxylic group oxygen atom hydrogen bonds to two protons from two other water molecules, while the remainder of the water molecules hydrogen bond to each other. Consequently the nMCAW $_x$ structures, as x gets larger, are only slightly more stabilized by increasing the number of water molecules in the cluster, since these extra water molecules do not produce any other additional interactions between the methylcarbamic acid and water. Instead we find all the different low energy nMCAW $_x$ cluster with x water molecules have between two to four of the water molecules in the hydrogen bonding with the carboxylic acid group in a manner similar to what we found for the neutral nGlyW $_x$ clusters.

Analogous to what we found for the glycine zwitterion, there is a greater tendency in the zwitterionic zMCAW $_x$ clusters to form networks of water molecules which hydrogen bond between the –NH $_2^+$ and –CO $_2^-$ groups. In our calculations we find the –NH $_2^+$ group in the zMCAW $_x$ clusters readily forms its maximum number of two hydrogen bonds by donating both protons to two water molecules, while the –CO $_2^-$ group, especially in the larger clusters, hydrogen bonds with 3 or 4 water molecules. This extra hydrogen bonding appears to stabilize the zwitterion relative to the neutral nMCAW $_x$ structure. However, our earlier calculations suggested that the hydrogen bonding in water bridges between carbon dioxide and methylamine is what facilitates the C–N bond formation of the methylcarbamic acid zwitterion in a barrier free reaction.¹² Consequently, the C–N bond formation between carbon dioxide and methylamine reduces the zMCAW $_x$ stability relative to the neutral nMCAW $_x$ structure.

MCAW1. The optimized structures for the four lowest energy clusters containing neutral methylcarbamic acid and one water molecule are shown in Fig. 1 and their relative energies are given in Table 1. We find methylcarbamic acid adopts the same conformer in the nMCAW1a and nMCAW1d clusters, where this conformer has the same geometry as the lowest energy isolated methylcarbamic acid structure, MCA-1, that we previously reported.¹³ These nMCAW1a and nMCAW1d

conformers differ in energy by 12.7 kJ mol^{-1} , and illustrate how a water molecule hydrogen bonding with just the carboxylic acid group is energetically more favorable than water forming a hydrogen bonding bridge between the $-\text{NH}$ and the carboxylic acid group. The nMCAW1b and nMCAW1c structures contain the second lowest energy MCA-2 conformer of the isolated methylcarbamic acid.¹³ Water hydrogen bonding to the oxygen atom instead of the OH side of the carboxylic acid group causes the nMCAW1c structure to be slightly lower in energy than nMCAW1d. Similar to the glycine zwitterion case, we could not locate a stable geometry corresponding to the zwitterionic form of methylcarbamic acid with one water molecule. We only obtained a van der Waals bound complex between methylamine and carbon dioxide, where the water molecule bridges between the amino group and carbon dioxide to produce a structure with a N–C distance of around 2.7 \AA . We have described this complex previously,¹² and do not discuss it further here. Table 1 shows that at the MP2/6-311++G(d,p) level we find lowest energy neutral methylcarbamic acid nMCAW1a conformer to be 36.2 kJ mol^{-1} more stable than the lowest energy neutral glycine nGlyW1a structure.

MCAW2. The optimized geometries for the four and three lowest energy methylcarbamic acid neutral and zwitterionic forms, respectively, with two water molecules are shown in Fig. 2. The two lowest energy neutral conformers nMCAW2a and nMCAW2b are close in energy owing to just two of the water molecules hydrogen bonding with the carboxylic acid group. Table 1 shows there is a 7.5 kJ mol^{-1} jump in energy for the nMCAW2c and nMCAW2d conformers when one of the water molecules hydrogen bond with the $-\text{NH}$ group. At the MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) levels of theory, we could only locate 3 local minima for zwitterionic methylcarbamic acid with two water molecules on the potential energy surface. We tried several attempts to obtain more minima, but these always resulted in the geometry optimization calculation producing either one of the zMCAW2a, zMCAW2b and zMCAW2c conformers or the methylamine and carbon dioxide breaking apart. In the zMCAW2a and zMCAW2b structures the two water molecules separately form hydrogen bond bridges between the different oxygen atoms in carbon dioxide and the amine group hydrogen atoms, whereas in structure zMCAW2c the two water molecules form hydrogen bonds with only one of the oxygen atoms in carbon dioxide and the amine hydrogen atoms. All three conformers have energies which are separated by less than 2.0 kJ mol^{-1} .

Recently we suggested that the zwitterionic form of methylcarbamic acid can be formed directly from methylamine and carbon dioxide when there are at least 2 discrete water molecules present. Using the B3LYP/6-31G(d) level of theory we obtained the methylcarbamic acid zwitterion with a N–C bond length of 1.700 \AA between the carbon dioxide carbon atom and the methylamine nitrogen atom.¹² In this study we find the MP2/6-311++G(d,p) calculations agree very well with our previous results and we obtain a methylcarbamic zwitterion with a 1.706 \AA N–C bond length for the lowest energy zMCAW2a conformer. Table 1 shows that the zMCAW2a conformer is calculated to be 50.9 kJ mol^{-1} less stable than the lowest energy neutral structure nMCAW2a. Our calculations also

find the glycine isomers nGlyW2a (36.9 kJ mol^{-1}) and zGlyW2a (86.3 kJ mol^{-1}) are less stable than nMCAW2a.

MCAW3. The two lowest energy neutral methylcarbamic acid conformers shown in Fig. 3 have the 3 water molecules hydrogen bonding with the carboxylic acid group. The nMCAW3c and nMCAW3d conformers are the last two nMCAWx clusters where we find a water molecule hydrogen bonding with the $-\text{NH}$ group. The lowest energy zwitterion structure, zMCAW3a, has only one water molecule forming a hydrogen bond with one of the hydrogen atoms on the $-\text{NH}_2^+$ group, but this structure is only 0.2 kJ mol^{-1} lower in energy than the zMCAW3b which has two water molecules to $-\text{NH}_2^+$ hydrogen bonds. Previously, using B3LYP/6-31G(d) level calculations, we found zMCAW3b to be the lowest energy conformer,¹² and in Table S1 (ESI[†]) we note that zMCAW3b is still more stable than zMCAW3a by 0.4 kJ mol^{-1} at the B3LYP/6-311++G(d,p) level of theory. With the 3 water molecules we find the lowest energy neutral nMCAW3a conformer is 41.7 kJ mol^{-1} more stable than its zwitterionic counterpart zMCAW3a.

MCAW4. Fig. 4 illustrates the typical structural features found in all of the neutral methylcarbamic acid clusters containing 4 or more water molecules. Essentially we find all the water molecules hydrogen bond together and just two or three water molecules hydrogen bond with the carboxylic acid group. For the four water molecules case, Fig. 4 shows the water molecules combine to form a ring and then two of waters from the ring also form hydrogen bonds with the hydrogen and the oxygen ends of the carboxylic acid group in the neutral methylcarbamic acid. The four lowest energy zwitterion structures shown in Fig. 4 have more hydrogen bond interactions between the water molecules and methylcarbamic acid than found for the neutral structures. The structures of the two lowest energy conformers zMCAW4a and zMCAW4b are very similar to each other and fairly close in energy. They both involve two water molecules hydrogen bonding to the same oxygen atom in the carboxylate anion. The zMCAW4c conformer has separate water molecules which hydrogen bond to each of the two oxygen atoms in the carboxylate anion and is 16 kJ mol^{-1} higher in energy than zMCAW4b. The zMCAW4d structure shown in Fig. 4 is interesting because it is an example of an optimized structure where we find one of the water molecules forms a hydrogen bonding bridge between the carboxylate anion and the methyl group of the methylamine. However, as expected hydrogen bonding between a water molecule and a methyl group does not strongly stabilize the zwitterion and we find the zMCAW4d structure is at 21.6 kJ mol^{-1} higher energy than the lowest energy zMCAW4a cluster. The optimized MP2 and B3LYP methylcarbamic zwitterion structures reported here are in good agreement with our previous B3LYP/6-31G(d) results¹² and all of the calculations find zMCAW4a to be the lowest energy zwitterionic conformer. We compute the zMCAW4a zwitterion conformer at 32.8 kJ mol^{-1} higher energy than the neutral nMCAW4a methylcarbamic conformer with MP2/6-311++G(d,p) theory.

MCAW5. Fig. 5 shows the five water molecules also hydrogen bond together to form a ring in the lowest energy neutral methylcarbamic acid conformers and then three or two of the waters hydrogen bond with the carboxylic acid group. Three of the waters in the two lowest energy nMCAW5a and nMCAW5b conformers essentially have the same interactions with the carboxylic acid group while the orientations of the two other water molecules are slightly different resulting in the two different conformers being very close in energy. Only two of the water molecules in nMCAW5c hydrogen bond with the carboxylic acid, and Table 1 shows that the energy for nMCAW5c is only 1.6 kJ mol^{-1} higher than the lowest energy neutral nMCAW5a conformer. The nMCAW5d conformer is the precursor structure found in the clusters with more water molecules. The nMCAW5d conformer consists of a three dimensional cage of water molecules which also hydrogen bonds with the neutral methylcarbamic acid and it is similar to the water cage structures we found for the large neutral glycine clusters. Table S1 in the ESI† indicates that nMCAW5c structure is the lowest energy conformer at the B3LYP/6-311++G(d,p) level but it is only 3 kJ mol^{-1} more stable than nMCAW5a. The methylcarbamic acid zwitterion conformers shown in Fig. 5 exhibit the same structural features as described above. However, the lowest energy zMCAW5a and the zMCAW5c conformers are interesting because we find a hydrogen bond between the methyl group and a water molecule.

MCAW6-10. Fig. 6 to 10 show the low energy optimized structures we have obtained for the neutral and zwitterion forms of methylcarbamic acid with six to ten water molecules. Generally we obtained similar structures from the MP2 and B3LYP calculations, although we found MP2 and B3LYP calculations to switch the ordering of the two lowest energy clusters containing 9 and 10 water molecules. In the neutral methylcarbamic acid clusters, the six to ten water molecules hydrogen bond together to form a three-dimensional cage and only two or three of these water molecules hydrogen bond with the carboxylic acid group. The six to ten water molecules in the clusters with the zwitterionic form of methylcarbamic acid also start to form three-dimensional networks of water molecules, but the water molecules hydrogen bond with both the carboxylate anion and the $-\text{NH}_2^+$ cation. We also find some more examples of water hydrogen bonding with the methyl group in the higher energy zMCAW6, zMCAW7 and zMCAW8 clusters.

Relative stability of neutral and zwitterionic methylcarbamic acid

Fig. 11(b) shows how the relative energy difference ΔE between the lowest energy conformers of the zwitterionic and the neutral forms of the methylcarbamic acid varies with the number of discrete water molecules in the clusters. The energy difference ΔE was calculated using the MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) relative energies given in Table 1 and Table S1 (ESI†). Since the water molecules can form more hydrogen bonds with the zwitterion than with the neutral methylcarbamic acid, Fig. 11(b) illustrates how these extra hydrogen bonds stabilize the zwitterion relative to the neutral form as more

water molecules are included in the clusters. We noted above for Fig. 11(a) that the ΔE values obtained by the MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) calculations agree well with each other and differ by less than 10 kJ mol^{-1} for a specific number of water molecules. Both the MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) sets of calculations give results in Fig. 11(a) which are consistent with the zwitterion being the preferred form of glycine when it is solvated by ten water molecules. Fig. 11(b) shows the MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) calculations give much larger differences in the two ΔE curves than found in Fig. 11(a) and we can only conclude that clusters containing ten water molecules are not large enough to make the zwitterion more stable than neutral methylcarbamic acid. One plausible reason why the methylcarbamic acid zwitterion does not appear to be as strongly stabilized as in the glycine case is because some of the water interactions with the zwitterion are used to aid in binding the CH_3NH_2^+ and CO_2^- together and form the C–N bond.

Relative stability of the glycine and methylcarbamic acid isomers

Fig. 12 compares the relative stabilities of the lowest energy clusters containing the neutral and zwitterion forms of glycine against the methylcarbamic acid neutral and zwitterion forms in the presence of one to ten water molecules using the MP2/6-311++G(d,p) relative energies given in Table 1. The energy difference ΔE between the neutral glycine and neutral methylcarbamic acid is relatively constant with an average value of 31.9 kJ mol^{-1} with a maximum value of 36.9 kJ mol^{-1} for the 2 water clusters and a minimum value of 21.4 kJ mol^{-1} with the 7 water clusters. Previously we found the difference in lowest energy of the neutral conformers of isolated methylcarbamic acid to be 34.0 kJ mol^{-1} lower in energy than isolated glycine.¹³ These results suggest that the neutral forms of both glycine and methylcarbamic acid have very similar hydration energies arising from similar hydrogen bonding interactions with the neighboring water molecules in the different sized clusters. The B3LYP/6-311++G(d,p) results in Table S1 (ESI†) show a similar constant ΔE variation where the average value is higher at 41.7 kJ mol^{-1} , but this is still very close to the 41.2 kJ mol^{-1} difference computed by the same level of theory for the isolated glycine and methylcarbamic acid.¹³ This 7.7 kJ mol^{-1} difference in the ΔE value obtained with the MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) calculations partly explains why there is a relatively large difference in the MP2 and B3LYP relative stabilities computed for the zwitterion to neutral forms of methylcarbamic acid shown in Fig. 11(b).

The glycine zwitterion is more strongly stabilized by interactions with water and as expected, Fig. 12(a) shows the relative energy difference of the lowest energy glycine zwitterion conformer to the neutral form of methylcarbamic acid decreases from 86.3 to 19.9 kJ mol^{-1} in the clusters containing between two and ten water molecules. This is consistent with Fig. 11(a) which shows the energy difference ΔE at the MP2/6-311++G(d,p) (B3LYP/6-311++G(d,p)) level for glycine changed by 60.4 kJ mol^{-1} (65.1 kJ mol^{-1}) on going from

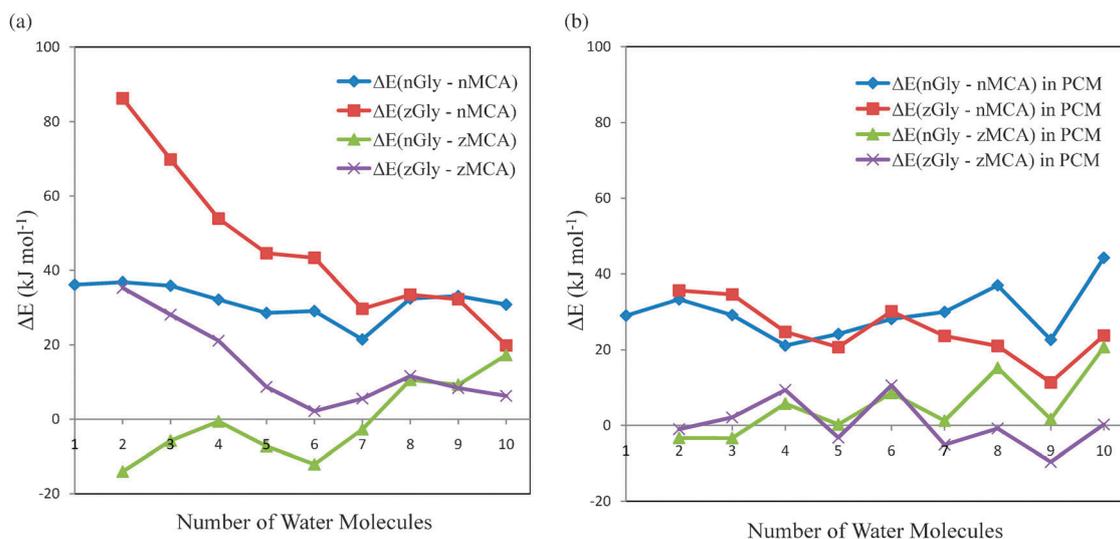


Fig. 12 Variation of the energy differences between the lowest energy structures of the neutral and zwitterionic forms of glycine and methylcarbamic acid with the number of water molecules obtained with MP2/6-311++G(d,p) calculations for (a) the explicit water cluster and (b) the water clusters embedded in the polarizable continuum (C-PCM).

2 to 10 water molecules, whereas Fig. 11(b) indicates a much smaller 37.3 kJ mol^{-1} (22.4 kJ mol^{-1}) change in ΔE for methylcarbamic acid with 2 to 10 water molecules. Thus, the results in Fig. 11(b) suggest that the neutral form will be the predominant form of methylcarbamic acid in bulk water. Interestingly, Fig. 12 shows the relative energy separation between the glycine zwitterion and the methylcarbamic acid zwitterion are much smaller and decrease from 35.4 kJ mol^{-1} with two water molecules to 6.3 kJ mol^{-1} with ten suggesting that both zwitterions might have comparable energies in bulk water. We also include a plot of the neutral glycine to zwitterionic methylcarbamic acid relative energies in Fig. 12(a) and find as expected that zwitterionic methylcarbamic acid becomes the more stable form in the clusters containing more than 7 water molecules.

In summary, our calculations on glycine and methylcarbamic acid clusters containing between one to ten discrete water molecules always find the clusters containing the neutral form of methylcarbamic acid to be the lowest in energy. Fig. 11(a) and 12(a) also show the zwitterion forms of glycine and methylcarbamic acid are more favorable over neutral glycine when there are 8 or more water molecules in the cluster. However, our calculations also suggest that the zwitterionic forms of glycine and methylcarbamic acid may have comparable energies in larger clusters and bulk water.

Polarizable continuum model

To simulate the effects of the bulk water on the stability of the different forms of glycine and methylcarbamic acid, we performed calculations using the conductor-like polarizable continuum model (C-PCM).⁵³ In this approach, a solute is embedded into a cavity of a solvent, which is modeled as a continuum of uniform dielectric constant. The geometries of the MP2/6-311++G(d,p) lowest energy clusters of glycine and methylcarbamic acid in their neutral and zwitterionic forms with 2 to 10 explicit water molecules were reoptimized using

the C-PCM procedure at the MP2/6-311++G(d,p) level used to simulate bulk water. Fig. 12(b) compares the relative stabilities ΔE of the two glycine forms against the two methylcarbamic acid forms obtained by the C-PCM method and is analogous to the finite cluster results given in Fig. 12(a).

Fig. 13 shows the energy differences ΔE between the zwitterion and neutral forms for both glycine and methylcarbamic acid. For glycine, the C-PCM method causes the MP2/6-311++G(d,p) ΔE shown in Fig. 11(a) to be shifted approximately 20 kJ mol^{-1} to lower energy making the zwitterion $10\text{--}20 \text{ kJ mol}^{-1}$ more stable than neutral glycine in bulk water. Thus, the C-PCM result is consistent with the zwitterion being the predominant of glycine in bulk water and compares reasonably well with the Aikens and Gordon estimate that the zwitterion is 15 to 37 kJ mol^{-1} more stable than neutral glycine obtained from their C-PCM + MP2 single point calculations. For methylcarbamic acid, Fig. 13 shows that the C-PCM lowers the ΔE values in Fig. 11(b) for the smaller clusters with up to 7 water molecules but ΔE shift becomes negligible in the larger clusters. Consequently, the C-PCM calculations suggest that the neutral form of methylcarbamic acid is the major form in bulk water with the methylcarbamic acid zwitterion being about 20 kJ mol^{-1} higher in energy. Fig. 12(b) shows that the C-PCM ΔE energies exhibit a relatively large oscillatory behavior in the larger clusters, and we note that these oscillations are less evident in Fig. 13 when the relative energies of the zwitterion or neutral form of either glycine or methylcarbamic acid are compared. Similar to the results obtained with the finite sized clusters, the energy difference ΔE in Fig. 12(b) shows that neutral methylcarbamic acid is approximately 30 kJ mol^{-1} more stable than neutral glycine. This again suggests that the two neutral isomers have similar hydration energies in bulk water. Since the C-PCM calculations find the zwitterion being the preferred form of glycine, the $\Delta E(\text{zGly} - \text{nMCA})$ curve crosses the $\Delta E(\text{nGly} - \text{nMCA})$ curve with both glycine and methylcarbamic acid being in their neutral forms. The C-PCM energy difference

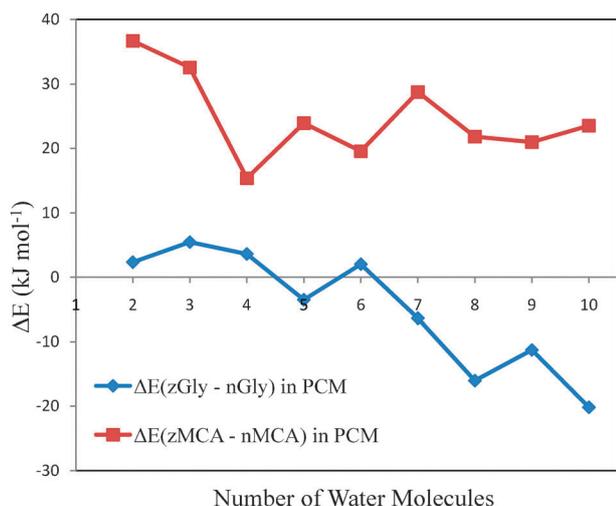


Fig. 13 Variation of energy difference between the lowest energy structures of the neutral and zwitterionic forms with the number of water molecules for (a) glycine and (b) methylcarbamic acid obtained with MP2/6-311++G(d,p) in the polarizable continuum (C-PCM).

$\Delta E(\text{zGly}-\text{zMCA})$ for the two zwitterions tends to zero in the larger clusters and is consistent with the finite cluster result that the zwitterionic forms of glycine and methylcarbamic acid have similar energies in bulk water. Moreover, the C-PCM ΔE values suggest that the glycine and methylcarbamic acid zwitterions are both around 20 kJ mol⁻¹ higher in energy than neutral methylcarbamic acid and 10 kJ mol⁻¹ lower in energy than neutral glycine when the two molecules are in a bulk water environment.

Conclusions

There is considerable interest in whether glycine, the simplest amino acid, can be formed and is present in icy grains of dense molecular clouds present in the ISM. Previously we have found that methylamine and carbon dioxide in the presence of just two water molecules can combine in a barrier free reaction to form the methylcarbamic acid zwitterion which then might serve as a precursor to glycine formation. However, in calculations on the isolated neutral forms of the molecules we found the methylcarbamic acid to be between 31 and 37 kJ mol⁻¹ more stable than glycine. Clearly the relative stabilities of glycine and methylcarbamic acid in an ice should be different and in the present study we have theoretically investigated how the low energy conformers of the neutral and the zwitterionic forms of glycine and methylcarbamic acid are stabilized by the presence water. The role of water was evaluated by performing MP2/6-311++G(d,p) level calculations on both isolated clusters and C-PCM embedded clusters containing 1 to 10 explicit water molecules. In a bulk water environment the glycine zwitterion is the established preferred form, but it is less certain what is the preferred for the methylcarbamic acid.

Our calculations show that the neutral forms of glycine and methylcarbamic acid have similar hydration energies because of their similar hydrogen bonding interactions taking place between water and the two neutral molecules. The calculations on the different finite sized clusters find the neutral methylcarbamic acid

to be approximately 32 kJ mol⁻¹ lower in energy than for neutral glycine, while the C-PCM embedded clusters lower this difference to 30 kJ mol⁻¹, where both energies are very similar to the energy differences we previously calculated for from the lowest energy isolated methylcarbamic acid and glycine conformers. The optimized cluster structures obtained for the glycine and methylcarbamic acid zwitterions show that these molecules are able to form more and stronger hydrogen bonding interactions with water than the neutral molecules. These stronger interactions lower the relative energy of the glycine zwitterion from 50 kJ mol⁻¹ above neutral glycine when there are two water molecules in the cluster to 11 kJ mol⁻¹ below for the cluster with ten water molecules, where the switch to the zwitterion being the more stable form occurs when there are 8 or 9 water molecules in the clusters. The methylcarbamic acid zwitterion cluster is not stabilized as strongly when more water is added to the cluster, possibly because some of the stabilization provided by the water molecules is used to bind the CH₃NH₂⁺ and CO₂⁻ together. For the methylcarbamic acid cluster with two water molecules, the zwitterion is 51 kJ mol⁻¹ higher in energy than the neutral form and remains 13 kJ mol⁻¹ above the neutral methylcarbamic acid in the cluster with ten water molecules. The C-PCM calculations give similar energies for both the methylcarbamic acid and glycine zwitterionic forms at 20 kJ mol⁻¹ above the neutral methylcarbamic acid energy and 10 kJ mol⁻¹ lower than the neutral glycine energy.

In a recent study we found that the neutral form of the isolated methylcarbamic acid is more stable than isolated glycine. The present study finds that neutral methylcarbamic acid is still more stable than neutral and zwitterionic glycine even within a water environment. Although neither methylcarbamic acid nor glycine have been detected in the ISM yet, our findings suggest, based on the species with lowest energy, that methylcarbamic acid is the most likely product from methylamine and carbon dioxide reactions in a water ice and that methylcarbamic acid must play a role in the intermediate steps towards glycine formation.

Acknowledgements

This project is supported by the W. M. Keck Foundation. The authors are also grateful for the generous computing resources provided by TeraGrid under grant no. TG-CHE100092 and the Hawaii Open Supercomputing Center.

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