RESEARCH ARTICLE

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Density Functional Theory Studies on Effects of Additive Hydration on Neutral and Zwitterionic Glycylalanine

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ABSTRACT

The density functional theory computations have been carried out to study the effect of stepwise hydration on the structures of various conformers of the Neutral Glycylalanine...(Water)$_n$ (NGA...(W)$_n$) (n=5-10) and Zwitterionic Glycylalanine...(Water)$_n$ (ZGA...(W)$_n$) (n=5-9) clusters. This indicates that the most stable neural GA conformer is 50.2 kcal/mol lower in energy than its zwitterionic counterpart. The hydrogen bonding interaction energies with BSSE corrections have been analyzed. Starting from complexation with six water molecules, ZGA complexes turn out to be the most stable candidates than their neutral partners. Theories of Bader's Atoms in Molecules (AIM) and Natural Bond Orbital (NBO) are applied to examine the hydrogen bonds in the solvated complexes. In all hydrated complexes, the N-H (amino group)-Ow and O15-H16... Ow bonds are observed to be relatively short and possess comparatively higher values of $\rho(r)$ and $\nabla^2 \rho(r)$. A good correlation between the structural parameters and the properties of charge density is found.

Keywords **:** Glycylalanine, Stepwise hydration, AIM, NBO.

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INTRODUCTION

The interactions between peptide and water are vital to biological activities and they form the free energy background which encompasses the functional roles related with folding [1], structure and conformational stability [2] of proteins. The functional processes mediated by proteins frequently engage specific interactions with individual water molecules [3] by forming the intermolecular hydrogen bonds (H-bonds) [4]. In the hydrated environment, the amino acids and peptides exist in their zwitterionic forms. But in the gas phase, they exist in neutral and unionized forms. The network of H-bonds involving water with both neutral and zwitterionic molecules is crucial in altering their molecular properties [5] and conformations. The various conformations of molecules are well decided by the effect of solvent and additive hydration or microsolvation [6,7]. Microsolvation means a solute molecule is encircled by a specific quantity of water molecules which are connected by H-bonds in definite configuration.

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Glycylalanine (GA), the smallest chiral dipeptide which has methyl (CH_3) hydrophobic group and secondary amide peptide bond in its neutral and zwitterionic forms offers a fertile testing ground to investigate the H-bond interactions which provide valuable information regarding the protein hydration. The crystal configuration of GA has been studied by Wang et al [8]. Cassady [9] performed ab initio Hartree-Fock molecular orbital calculations on

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the neutral and amino N-protonated species of GA. Tulip and Bates [10] examined the structural and electronic properties of solid state GA crystal. Kolev and co-workers [11] have characterized GA dipeptide and glycylalanylalanine tripeptide and their Au(III) complexes using linear-dichroic infrared (IR-LD) spectroscopy.

Liang and Walsh [12] have carried out molecular dynamics simulation studies on the aqueous solvation of GA. Mclain et al [13] determined the structure of GA in aqueous solution. Wright et al [14] have presented ab initio calculations on the neutral and zwitterionic glycylglycine, GA and alanylglycine using a 2s1p Gaussian basis set. Jacob and Fischer [15] reported the FT-IR absorption spectra of GA. Bhate et al [16] studied the structure and hydration of dipeptides with alanine and glycine including GA both experimentally and theoretically by taking ^{13}C and ^{15}N NMR chemical shift values.

Mclain et al [17] determined the bulk water structure around GA and concluded that addition of each of water to dipeptides leads to water-water co-ordination in the surrounding water environment. Hugosson et al [18] have made MM / Car-Parlino calculations on the zwitterionic form of GA considering water as a solvent. Nandini and Sathyanarayana [19] investigated the effect of hydration on the conformation and vibrational spectra of GA zwitterion in solvents. Chaudhuri and Canuto [20] used ab initio methods to examine the structure, energetics and the effect of electron correlation for GA. Kohtani and Jarrold [21] measured the equilibrium constants for the adsorption of the first water molecule on the six protonated dipeptides together with $GA+H^+$ as a function of temperature. Loeffler et al [22] calculated the relative free energies of hydration GA and alanyl-glycine dipeptides in their naturally occurring form both for zwitterionic and protonated species. B.J. Min [23] carried out DFT calculations to study the PES of neutral glycine and its zwitterionic counterpart hydrated by using four water molecules and identified that two water molecules created local minimum for glycine zwitterion. Kasprzhitskii et.al [24] recently studied the inhibitory effect of glycine and alanine dipeptides.

With these backgrounds, since no stepwise hydration of GA in either its neutral or zwitterionic structure has been reported, our present study aims to monitor the influence of stepwise hydration on the conformational characteristics and relative stability of neutral and zwitterionic forms of GA in terms of the number and arrangement of water molecules near the functional group of NGA and ZGA. Our previous studies about additive hydration of glycine [25] and glycylglycine dipeptide [26] and cyclo glycylglycine and glycylalanine dipeptides [27] using water as a solvent endorse this present work. The M05-2X method of DFT is used to study the stepwise hydration of the five most stable conformers of neutral and zwitterionic GA with 5 to 10 and 5 to 9 water molecules respectively. These minimum energy conformers were determined by the potential energy surface (PES) scan studies. Initially it has been tried to build a solvation shell around the five neutral and zwitterionic GA conformers with minimum energy. However, the formation of the hydration shell becomes complicated, as addition of the next water molecule results in a change of the water positions. Hence, it has been restricted to have 10 water molecules in neutral, 9 in zwitterionic cases and the hydration sites are chosen to create more number of GA-water and water-water H-bonding. The effect of hydration with first four water molecules is not that much considerable while trying to construct a complete hydration shell. Hence the study has been started with 5 water molecules. Also the H-bonding capability of neutral and zwitterionic GA conformers by water molecules was studied.

COMPUTATIONAL DETAILS

By using PES scan, the main chain dihedral angles $\psi(N\text{-}C\text{-}C^{\alpha}\text{-}N)$, $\varphi(C\text{-}N\text{-}C^{\alpha}\text{-}C)$ and $\omega(C^{\alpha}\text{-}C\text{-}N\text{-}C^{\alpha})$ of NGA and ZGA are varied by enhancing the step size of 60^o and -30^o respectively to identify their minimum energy conformers. M05-2X level of theory involving simultaneous optimization of exchange and correlation function and kinetic energy density [28] by using 6-311G** basis set has been applied to optimize and study the molecular structures, stability and properties of 5 minimum energy ZGA conformers and their hydrated complexes using 5 to 9 water molecules (ZGA...(W)n n=5-9). The neutral GA complexes have been optimized at Becke's three parameter exact exchange functional (B3) [29] together with the gradient-corrected correlation functional of Lee, Yang and Parr (LYP) [30] of DFT using the same basis set and in order to achieve more rigorous energy complexes for the water interacting neutral complexes, M05-2X/6-311G** and second order Mollar Plesset Perturbation theory (MP2) [31] calculations were carried out for the structures optimized by B3LYP/6-311G** level of theory.

Similarly for zwitterionic complexes, MP2 and B3LYP calculations have been carried out for the geometries optimized at M05-2X/6-311G** level of theory. The H-bond interaction energies for the optimized complexes have been corrected for the basis set superposition errors (BSSE), using the counterpoise method of Boys and Bernardi [32] using the equation

$$E_{int}\,(corr) = E_{AB}(AB) - [E_A(AB) + E_B(AB)] \qquad (1)$$

where, $E_{AB}(AB)$ is the energy of the complex, E_A (AB) and E_B (AB) are the energies of monomers A and B with full complex basis set by setting the appropriate nuclear charge to zero, which is located at the same intermolecular configuration as in the complex. The topological analysis has been carried out at M05-2X/6-311G** level of theory for the water interacting complexes based on the AIM theory of Bader's and co-workers [33]. The Natural Bond Orbital (NBO) second order perturbation stabilization energy $E^{(2)}$ is calculated as

$$E^{(2)} = q_i \frac{F^2(i,j)}{\varepsilon_i - \varepsilon_j} \qquad (2)$$

where, q_i is the orbital occupancy of the ith donor, ε_j, ε_i are diagonal elements (orbital energies) and F(i,j) is off diagonal elements associated with NBO Fock matrix. Gaussian 09W program [34] is used for the entire study.

RESULTS AND DISCUSSION

Structure and Energy

For simplicity, the 5 minimum energy zwitterionic GA complexes are considered as ZGA1, ZGA2, ZGA3, ZGA4, ZGA5 and they are described with strong intramolecular non bonded interactions which are well supported by the previous study [15], the neutral GA conformers are taken as NGA1, NGA2, NGA3, NGA4 and NGA5 and are depicted in Figure 1. This indicates that the most stable neural GA conformer is 50.2 kcal/mol lower in energy than its zwitterionic counterpart. Figs. 2a-2e and Figs. 3a-3f show the optimized and most stable ZGA...(W)n n=5-9 and NGA...(W)n n=5-10 complexes respectively. The optimized zwitterionic structures are given in Figs. S1-S5 and S6-S11 (In supporting information) show the neutral complexes. Table 1 gives the selected geometrical parameters (bond length R (in Å), bond angle θ (in degree) and dihedral angle (in degree)) for ZGA1 and ZGA...$(W)_n$ n=5-9 complexes calculated at M05-2X/6-311G** level of theory along with the previous experimental and theoretical results [8,10,11,19]. The structural parameters of NGA and its most stable hydrated complexes are given in Table S1 in the supporting information.

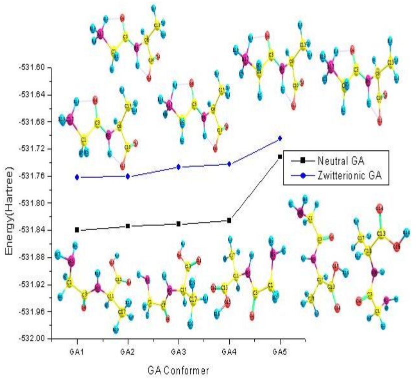


Figure 1: The five minimum energy ZGA and NGA conformers

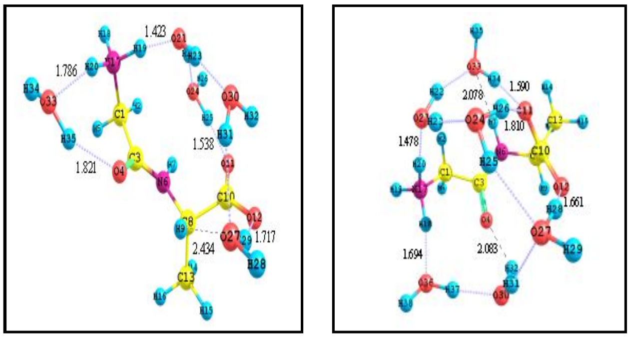


Figure 2a: ZGA3...5W **Figure 2b:** ZGA1...6W

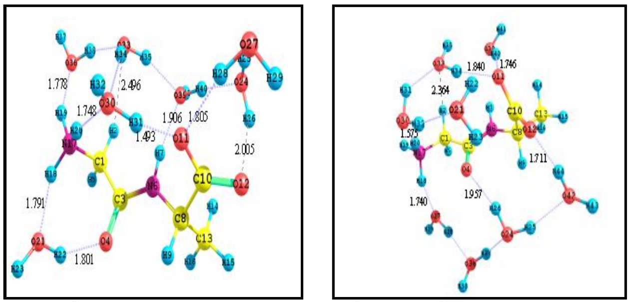


Figure 2c: ZGA4...7W **Figure 2d:** ZGA2...8W

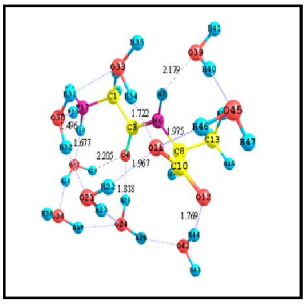


Figure 2e: ZGA2...9W

Figure 2: The optimized structures of the most stable ZGA...(W)n n=5-9 complexes

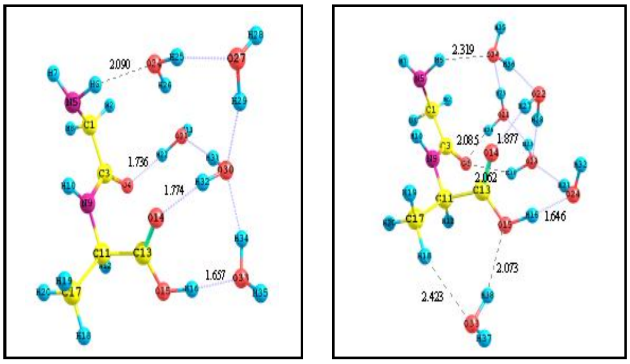


Figure 3a: NGA4...5W **Figure 3b**: NGA4...6W

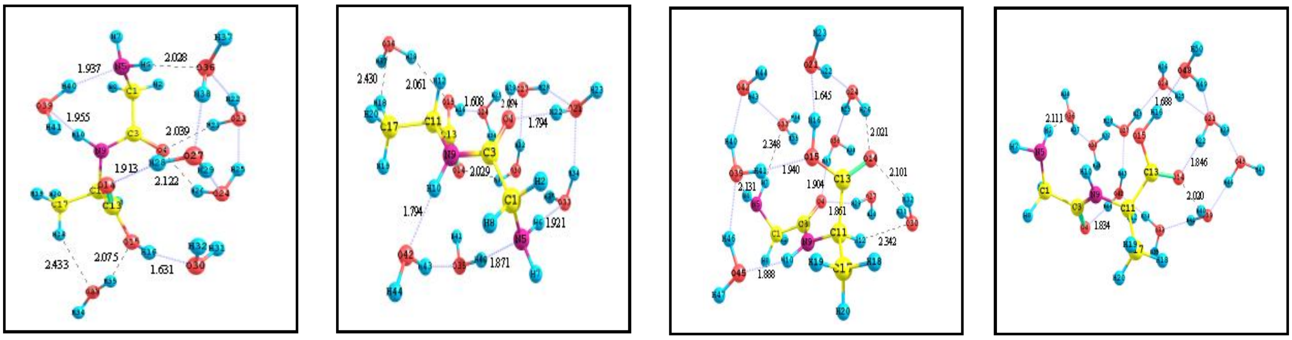


Figure 3c: NGA4...7W **Figure 3d**: NGA4...8W **Figure 3e**: NGA1...9W **Figure 3f**: NGA2...10W

Figure 3:The optimized structures of the most stable NGA...(W)n n=5-10 complexes

Table-1: Selected geometrical parameters (bond length R (in Å), bond angle è (in degree) and dihedral angle (in degree)) for the most stable conformers of bare (ZGA1) and hydrated ZGA...(W)n n=5-9 complexes calculated at M05-2X/6-311G** level of theory. For labeling of atoms refer Figs. 2a-2e.

Parameter	**Bare ZGA**		**Hydrated Complexes**				
	ZGA1		**ZGA....5W**	**ZGA...6W**	**ZGA...7W**	**ZGA...8W**	**ZGA...9W**
	M05-2X	**Observed**	**ZGA3**	**ZGA1**	**ZGA4**	**ZGA2**	**ZGA2**
C1-N17	1.496	1.475[a] 1.475[b]	1.486	1.480	1.489	1.480	1.481
C1-C3	1.544	1.527[a] 1.520[b]	1.526	1.523	1.522	1.518	1.521
C3=O4	1.220	1.223[a] 1.206[b]	1.229	1.218	1.232	1.223	1.234
C3-N6	1.288	1.338[a] 1.343[b]	1.328	1.341	1.325	1.339	1.327
N6-H7	1.016	0.939[a] 1.033[b]	1.010	1.012	1.018	1.013	1.014
N6-C8	1.468	1.445[a] 1.459[b]	1.459	1.464	1.456	1.460	1.455
C8-C10	1.569	1.538[a] 1.538[b]	1.543	1.542	1.545	1.543	1.544
C8-C13	1.522	1.524[a] 1.513[b]	1.526	1.521	1.521	1.521	1.526
C10-O11	1.271	1.256[a] 1.235[b]	1.256	1.267	1.273	1.268	1.263
C10-O12	1.210	1.249[a] 1.242[b]	1.244	1.238	1.232	1.240	1.242

Table 1 Continued.......

Parameter	Bare ZGA		Hydrated Complexes				
	ZGA1		ZGA....5W	ZGA...6W	ZGA...7W	ZGA...8W	ZGA...9W
	M05-2X	Observed	ZGA3	ZGA1	ZGA4	ZGA2	ZGA2
N17-H18	1.036	1.000[a] 1.048[b]	1.014	1.051	1.033	1.039	1.055
N17-H19	1.005	0.861[a] 1.050[b]	1.124	1.014	1.034	1.014	1.014
N17-H20	1.005	0.950[a] 1.051[b]	1.035	1.099	1.040	1.078	1.095
C8-H9	1.084	0.976[a] 1.089[b]	1.087	1.086	1.089	1.086	1.088
C1-H2	1.079	0.984[a] 1.089[b]	1.087	1.088	1.085	1.085	1.086
C1-H5	1.080	1.005[a] 1.089[b]	1.088	1.088	1.088	1.088	1.089
C13-H14	1.087	1.030[a] 1.091[b]	1.091	1.090	1.091	1.090	1.089
C13-H15	1.082	1.067[a] 1.087[b]	1.088	1.088	1.086	1.088	1.086
C13-H16	1.086	1.199[a] 1.088[b]	1.089	1.089	1.089	1.089	1.089
C1-C3-N6	114.9	114.7[a] 115.5[c]	115.6	116.4	115.0	116.6	116.4
N17-C1-C3	104.2	108.3[a] 111.3[c]	107.0	107.2	108.0	106.7	108.1
C1-C3-O4	115.2	121.2[a]	119.3	118.8	120.0	119.3	118.6
N6-C3-O4	129.8	123.7[c]	125.1	124.7	125.2	124.1	125.0
C3-N6-C8	129.1	120.6[a] 122.2[c]	122.6	118.3	123.4	117.2	122.2
N6-C8-C10	104.6	114.1[a]	108.9	108.9	108.8	109.7	110.9
N6-C8-C13	112.8	110.0[a] 110.0[c]	111.8	109.3	111.0	110.7	110.9
C8-C10-O11	112.2	114.3[d]	117.4	115.7	116.3	116.7	118.3
C8-C10-O12	114.5	114.8[d]	116.0	117.7	118.2	117.9	116.0
C3N6C8C13	87.9	76.4[d]	118.0	175.0	117.8	175.6	138.9
N6C8C10O11	-17.2	4.4[d]	-23.50	-51.2	36.5	-38.6	2.6
N6C8C10O12	178.8	176.0[d]	157.7	128.9	-142.9	141.2	-175.6
N17C1C3N6	-180.0	-163.5[a]	-131.5	-137.9	-124.2	-168.1	-141.5
C3N6C8C10	-150.0	-78.36[a]	-120.9	-64.1	-118.2	-61.7	-98.0

[a] Taken from Ref. [8]   [b] Taken from Ref. [10]   [c] Taken from Ref. [11]   [d] Taken from Ref. [19]

The PES yielded the most stable zwitterionic conformer ZGA1 with torsional angles F=-150.0° (Experimental -78.4°), Y = -180.0° (-163.5°) and w = -180.0° (-173.9°) which is closer to the experimentally predicted conformer [8]. Compared to Y and w the deviation is larger for F as previously reported by Nandini and Sathyanarayana [19] which may be due to the existence of ZGA in different phases in experimental (solid) and theoretical gas phase (isolated) calculations.

The difference noticed in the geometrical parameters of the unsolvated and solvated structures shows that the solvation affects them and involves significant conformational changes in both ZGA and NGA complexes as observed in the previous study [20]. In ZGA, the observed bond distance of amine C=O group coincides with the experimental value and the carboxylate C=O bond is slightly stretched by 0.03 Å. But, there is no good agreement has been observed for the bond lengths involving hydrogen atoms as has already been observed before [10] and all are found to be elongated during hydration except the bonds related to $C^{\acute{a}}$ carbon atoms. If the peptide unit $C^{\acute{a}}$-CO-NH-$C^{\acute{a}}$ of ZGA is considered, $C^{\acute{a}}$-N bond lengths are longer than that of the previously observed values and they are found to be shortened in the NGA by 0.02 Å. Compared to unsolvated ZGA, an appreciable lengthening of C3-N6 and shortening of N6-C8 bonds are noticed in the hydrated complexes. The C^{á}-C bonds are observed to be elongated compared with the experimentally calculated values and the creation of solvated complexes describes their contraction. Compared to the earlier reports, a substantial difference is noticed for the bond angles associated with nitrogen atoms of NGA. The lone pair electrons in nitrogen atoms disturb the accurate determination of bond angles.

In NGA, O-H...O interactions involving the carboxylic O-H and O_w are stronger in the solvated NGA structures. This is validated with the H-bond lengths ranging from 1.57 to1.85 Å. The C-H...O interactions are considered to be important in the structure and activity of proteins [35]. Their bond lengths are noticed around 2.149-2.563 Å in the hydrated complexes. The strongest C-H...O bond (2.149 Å) exists in the NGA3...$(W)_6$ complex between C^{á1}-H and O_w. Notably in the NGA3...$(W)_9$ complex, both the alpha carbons of GA participate in the C-H...O_w interactions along with their methyl partner at distances 2.281, 2.517 and 2.385 Å respectively. Considering the NGA...(W)n n=5-10 structures, N-H...O H-bonds are observed varying between 1.985 - 2.09, 1.876 - 2.399, 1.876 - 2.365, 1.858 - 2.363, 1.888 - 2.348, 1.826 - 2.53. Due to complexation, the O-H...N H-bonds from 1.774 till 2.09 Å are observed in the hydrated complexes which are comparatively sturdy than the N-H...O H-bonds.

The N9-H10...N5 intramolecular H-bond is traced for NGA1...$(W)_n$ n=5&6 (2.118 and 2.081 Å), NGA2...$(W)_n$ n=5,6,8-10 (2.101, 2.244, 2.137, 2.111 and 2.154 Å), NGA4...$(W)_n$ n=5&6 (2.184 and 2.204 Å) complexes. In the hydrated NGA3 complexes, the water molecules are inserted between H10 and N5. Consequently, the N9-H10...N5 bond lengths are stretched out with distances about 2.425-2.471 Å. two N-H...O type intramolecular H-bond interactions are recognized. One is between carboxylate oxygen and amide nitrogen atoms (N6-H7...O11) and the other is between one of the amine hydrogens and C=O oxygen atoms (N17-H18...O4). These bonds are significantly stretched as a result of stepwise hydration and their variations are shown in Figs. 4a and 4b respectively for the ZGA...$(W)_n$ n=0, 5-9 complexes.

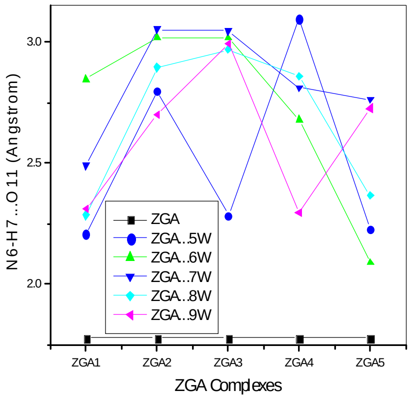


Figure 4a: The N6-H7...O11 intramolecular interactions present in the bare and hydrated ZGA complexes.

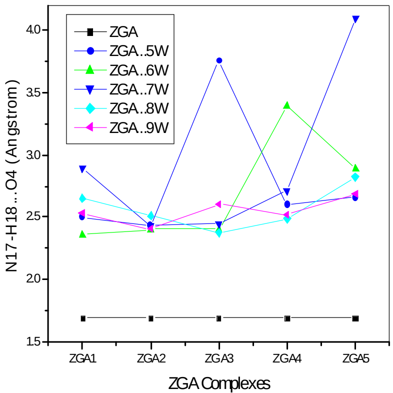


Figure 4b: The N17-H18...O4 intramolecular interactions present in the bare and hydrated ZGA complexes

The value of the torsional angle Φ is considered to be the one of the important factors that determines the conformation of a dipeptide. According to Manoj and Vijayan [36], the dipeptide conformation is considered to be extended if Φ is in between 60 and 180°. Or else, it will be taken as folded structure. In the present study, we have obtained the values for Ö in between 60 and 180° for both bare as well as solvated NGA...$(W)_n$ n=5-10 structures except for NGA2...$(W)_n$ n=5 and 10 showing that they exhibit extended structures. In the case of zwitterions, the Ö values deviate from the previous condition confirms that there are slight folding zwitterions both in isolated and hydrated states.

Tables-2 and 3 list the ΔE (Relative energy), μ_m (Dipole moment), E_{int} (Interaction energy) and Φ and Ψ (Torsional angles) for the solvated ZGA with 5 to 9 water molecules calculated at M05-2X/6-311G** level of theory.

Table-2: Total Energy E_{tot} (in Hartree), Relative Energy ΔE (in kcal/mol), dipole moment μ_m (in debye), Interaction energy E_{int} (in kcal/mol) and torsional angles Φ and Ψ (in degrees) for the hydrated ZGA...$(W)_n$ n=5-9 complexes calculated at M05-2X/6-311G** level of theory.

Complex		ΔE^a			μ_m	$-E_{int}$			Φ	Ψ
		MP2*	M052X	B3LYP@		MP2*	M052X	B3LYP@		
ZGA...5W	**ZGA1**	13.81	13.18	11.92	16.063	79.16	96.91	84.11	-134.99	-142.86
	ZGA2	1.26	1.26	3.77	5.959	88.74	107.59	93.07	-53.26	-149.52
	ZGA3	0.00	0.00	0.00	7.712	92.45	112.67	97.46	-120.90	-131.50
	ZGA4	4.39	5.02	4.39	10.285	93.92	114.07	100.06	-145.81	-133.47
	ZGA5	5.65	5.65	6.28	9.177	83.33	102.43	87.67	-99.74	-124.04
ZGA...6W	**ZGA1**	0.00	0.00	0.00	6.047	115.46	135.47	120.23	-64.09	-137.86
	ZGA2	6.21	6.02	9.41	7.935	108.62	131.99	114.15	-53.74	-164.62
	ZGA3	6.28	5.96	9.54	7.923	108.61	132.00	114.15	-53.80	-164.49
	ZGA4	8.79	6.53	8.16	8.791	112.07	135.57	118.67	-137.98	-101.78
	ZGA5	10.67	9.41	11.92	6.918	97.90	121.45	102.73	-125.1	-107.3
ZGA...7W	**ZGA1**	1.88	3.77	2.51	9.746	116.40	141.63	123.58	-66.36	-152.79
	ZGA2	8.79	9.41	12.55	9.838	112.26	139.37	117.84	-54.19	-165.21
	ZGA3	7.53	8.16	11.29	8.004	114.45	141.50	119.95	-55.29	-166.88
	ZGA4	0.00	0.00	0.00	8.780	122.48	148.78	129.52	-118.25	-124.17
	ZGA5	5.02	5.02	10.04	5.271	117.37	148.62	120.69	-141.61	-56.48
ZGA...8W	**ZGA1**	7.53	6.90	3.14	10.326	120.73	148.09	129.45	-152.29	-108.51
	ZGA2	0.00	0.00	1.51	6.964	121.42	151.42	127.66	-61.68	-168.11
	ZGA3	4.02	4.39	5.65	9.713	118.10	150.08	123.91	-60.23	-155.81
	ZGA4	2.51	1.26	0.00	11.748	121.55	151.86	129.70	-143.31	-159.29
	ZGA5	3.64	3.77	1.26	6.015	122.30	150.79	130.59	-150.35	-86.22
ZGA...9W	**ZGA1**	14.43	13.81	10.04	11.972	130.46	160.39	139.49	-152.54	-116.03
	ZGA2	0.00	0.00	0.00	6.836	129.73	136.92	136.88	-97.99	-141.45
	ZGA3	8.79	7.53	11.92	6.949	129.52	163.09	134.73	-57.97	-171.19
	ZGA4	10.67	9.41	10.67	9.978	123.74	157.00	130.98	-170.5	-137.9
	ZGA5	13.81	14.12	11.30	9.044	115.84	144.77	112.27	-72.5	-152.6

Table-3: Relative Energy ΔE (in kcal/mol), dipole moment μ_m (in debye), Interaction energy E_{int} (in kcal/mol) and torsional angles Φ and Ψ (in degrees) for the hydrated NGA...$(W)_n$ n=5-10 complexes calculated at B3LYP/6-311G** level of theory

Complex		**ΔE[a]**			**μ m**	**-E$_{int}$**			**Φ**	**Ψ**
		MP2*	M052X	B3LYP[@]		MP2*	M052X	B3LYP[@]		
ZGA...5W	**ZGA1**	13.81	13.18	11.92	16.063	79.16	96.91	84.11	-134.99	-142.86
	ZGA2	1.26	1.26	3.77	5.959	88.74	107.59	93.07	-53.26	-149.52
	ZGA3	0.00	0.00	0.00	7.712	92.45	112.67	97.46	-120.90	-131.50
	ZGA4	4.39	5.02	4.39	10.285	93.92	114.07	100.06	-145.81	-133.47
	ZGA5	5.65	5.65	6.28	9.177	83.33	102.43	87.67	-99.74	-124.04
ZGA...6W	**ZGA1**	0.00	0.00	0.00	6.047	115.46	135.47	120.23	-64.09	-137.86
	ZGA2	6.21	6.02	9.41	7.935	108.62	131.99	114.15	-53.74	-164.62
	ZGA3	6.28	5.96	9.54	7.923	108.61	132.00	114.15	-53.80	-164.49
	ZGA4	8.79	6.53	8.16	8.791	112.07	135.57	118.67	-137.98	-101.78
	ZGA5	10.67	9.41	11.92	6.918	97.90	121.45	102.73	-125.1	-107.3
ZGA...7W	**ZGA1**	1.88	3.77	2.51	9.746	116.40	141.63	123.58	-66.36	-152.79
	ZGA2	8.79	9.41	12.55	9.838	112.26	139.37	117.84	-54.19	-165.21
	ZGA3	7.53	8.16	11.29	8.004	114.45	141.50	119.95	-55.29	-166.88
	ZGA4	0.00	0.00	0.00	8.780	122.48	148.78	129.52	-118.25	-124.17
	ZGA5	5.02	5.02	10.04	5.271	117.37	148.62	120.69	-141.61	-56.48
ZGA...8W	**ZGA1**	7.53	6.90	3.14	10.326	120.73	148.09	129.45	-152.29	-108.51
	ZGA2	0.00	0.00	1.51	6.964	121.42	151.42	127.66	-61.68	-168.11
	ZGA3	4.02	4.39	5.65	9.713	118.10	150.08	123.91	-60.23	-155.81
	ZGA4	2.51	1.26	0.00	11.748	121.55	151.86	129.70	-143.31	-159.29
	ZGA5	3.64	3.77	1.26	6.015	122.30	150.79	130.59	-150.35	-86.22
ZGA...9W	**ZGA1**	14.43	13.81	10.04	11.972	130.46	160.39	139.49	-152.54	-116.03
	ZGA2	0.00	0.00	0.00	6.836	129.73	136.92	136.88	-97.99	-141.45
	ZGA3	8.79	7.53	11.92	6.949	129.52	163.09	134.73	-57.97	-171.19
	ZGA4	10.67	9.41	10.67	9.978	123.74	157.00	130.98	-170.5	-137.9
	ZGA5	13.81	14.12	11.30	9.044	115.84	144.77	112.27	-72.5	-152.6

[a] Calculated with respect to the respective most stable complexes

* Calculated at MP2/6-311G**//B3LYP/6-311G**

[@] Calculated at M05-2X/6-311G**//B3LYP/6-311G**

A surprising sensitivity of the energy with increasing degree of hydration is noticed which lead to higher stability of solvated systems. In the five water ZGA complexes, the low lying candidate (ZGA3) with interaction energy -112.67 kcal/mol at M05-2X/6-311G** level has three water molecules creating a chain connected by H-bonds, and this arrangement overpasses the protonated amino and deprotonated carboxylate moieties. The fourth water is inserted between water chain and the carboxylate group via two H-bonds at 1.767 and 1.538 Å distances respectively.

Compared to ZGA3, ZGA4 is having stronger H-bonds from 1.513 to 1.878 Å. The interaction energy difference between these two structures is 1.4, 1.47 and 2.6 kcal/mol at M05-2X, MP2 and B3LYP levels respectively. In the most stable NGA...$(W)_5$ complex (NGA4), four water molecules form a ladder like structure in linking the amino and carboxylic groups of NGA with strong H-bonds (lengths within 2.1 Å). The fifth water binds to two of the first four waters starting a new solvation shell. In NGA3...5W complex, one water molecule acts as a biproton acceptor between N5 and H10 of GA (at distances 1.907 and 1.985 Å), and in NGA1 and NGA5 complexes, it bridges carboxylic group with two H-bonds, one as a donor and other as an acceptor (at distances 1.709, 2.056 and 1.73, 2.012 Å respectively). The most stable zwitterionic five water complex has 10.04 kcal/mol higher energy than its neutral counterpart.

The most stable six water complex (NGA4) (Figure 3b) 5 water molecules involve formation of H-bonding ring. This forms two H-bonds with carboxylic group, two with C=O oxygen and one with amino group of NGA. The sixth bridges the methyl and the carboxylic groups by forming two H-bonds with bond lengths at 2.073 and 2.423 Å. In the most stable ZGA...6W complex (ZGA1), all the water molecules are contained within the two charged groups and it is surprising to note that it becomes energetically more stable than its neutral partner (NGA4) by 4.39, 2.51 and 3.77 kcal/mol at M05-2X, MP2 and B3LYP levels of theory respectively.

In NGA...$(W)_8$ structures, compared to NH_3, water molecules form more H-bonds with -COO group. The oxygen atom of –COOH group is with partially negative charge. This actually reduces the electrostatic potential in the neighborhood of the NH. This prevents it from accepting an incoming proton from the acceptor group. It is noteworthy that at M05-2X/6-311G** level of theory, the neutral and zwitterionic eight water complexes become almost isoenergetic. Even if, being the energetically stable candidate, the zwitterionic complex is only 0.11 kcal/mol lower in energy than the neutral complex. But the other two methods show that the neutral complex is more stable than the zwitterion. In the most stable structure of NGA...$(W)_9$ complex (NGA1), $C^{\alpha 1}$ and $C^{\alpha 2}$ moieties were ignored by the water molecules. In the most stable ZGA...9W complex (ZGA2), two strings containing four water molecules are created which linked the two sides of the charged groups of ZGA separately. The ninth water is acting as a binding partner in connecting the two water strings. The stability of the zwitterionic complexes with nine water molecules is dominating the neutral ones with relative energy of 9.03, 6.93 and 5.88 kcal/mol at M05-2X, MP2 and B3LYP levels of theory respectively. The conformational changes of ZGA and NGA conformers due to hydration with nine water molecules as a function of energy is shown in Figure 5.

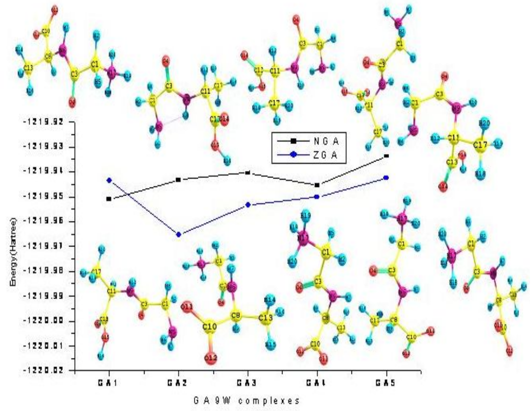


Figure 5: Conformational changes in the ZGA and NGA 9W complexes as a result of hydration. (The water molecules are removed for clarity)

Significant structural rearrangements potentially occurring with increasing degree of hydration is noticed which are reflected by the substantial variation of the torsional angles. Figs. 6a and 6b show the variation of dihedral angles (Φ & Ψ) for ZGA...$(W)_n$ n=5-9 systems. Similar values for NGA...$(W)_n$ n=5-10 structures are given in Figs. 7a and 7b.

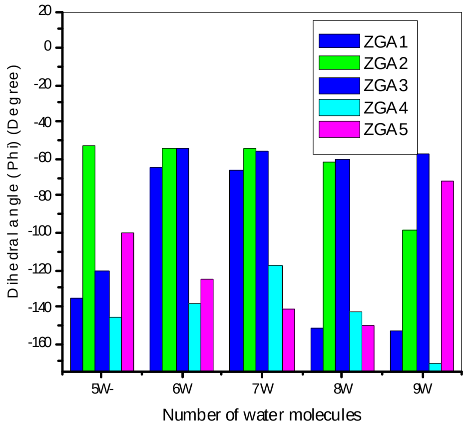


Figure 6a: The variation of Φ for the ZGA...$(W)_n$ n=5-9 complexes

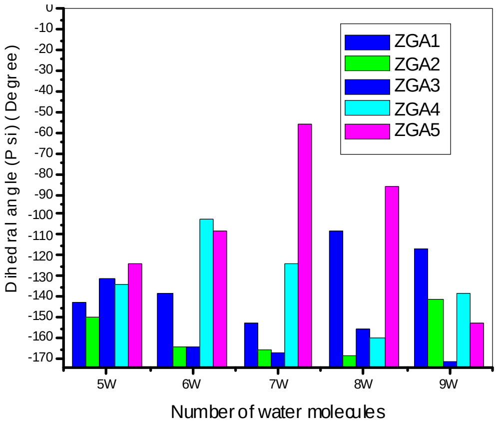


Figure 6b: The variation of Ψ for the ZGA...$(W)_n$ n=5-9 complexes

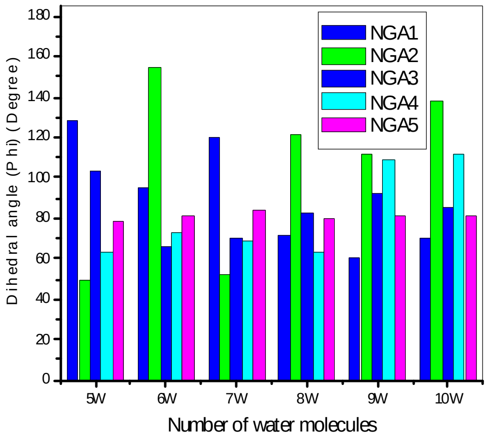


Figure 7a: The variation of Φ for the NGA...$(W)_n$ n=5-10 complexes

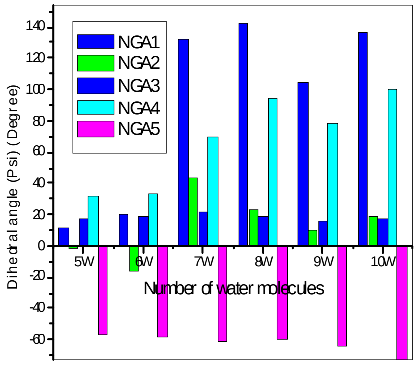
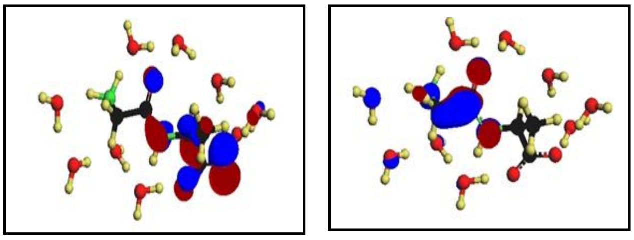


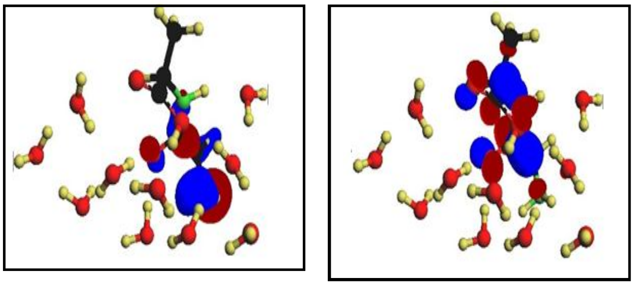
Figure 7b: The variation of Ψ for the NGA...$(W)_n$ n=5-10 complexes

Fig. 8a and Fig. 8b present the HOMO and LUMO for the minimum energy ZGA1....(W)n n=9 and NGA1....(W)n n=10 complexes.



ZGA1...9W HOMO ZGA1...9W LUMO

Figure 8a: HOMO and LUMO for the minimum energy ZGA1....(W)n n=9 complex.



NGA1...10W HOMO NGA1...10W LUMO

Figure 8b HOMO and LUMO for the minimum energy NGA1....(W)n n= 10 complex.

Topological Analysis

The electron density ($\rho(r)$), Laplacian of electron density ($\nabla^2\rho(r)$) and ellipticity (ε) for the most stable complexes calculated at M05-2X/6-311G** for ZGA...$(W)_n$ n=5-9 structures are given in Table-4.

Table S2 lists these values for all the other complexes. The $\rho(r)$, $\nabla^2\rho(r)$ and ε values for the most stable NGA complexes are tabulated in Table 5 and Table S3 lists out these values for the remaining neutral complexes.

Table-4: Hydrogen bond length R (in Å), electron density $\rho(r)$ (in a.u), Laplacian of electron density $\nabla^2\rho$ (in a.u), ellipticity ε and stabilization energies $E^{(2)}$ (in kcal/mol) involved in hydrogen bonds in the most stable conformers of ZGA...$(W)_n$ n=5-9 complexes calculated at M052X/6-311G** level of theory. For labeling of atoms refer Figs. 2a-2e.

Species		Interaction	R(Å)	ρ(r)	$\nabla^2\rho$	ε	$E^{(2)}$
ZGA...5W	**ZGA3**	O27-H29...O12	1.717	0.043	0.141	0.055	0.14
		O8-H9...O27	2.434	0.010	0.038	0.789	15.15
		O33-H35...O4	1.821	0.033	0.124	0.048	8.08
		N17-H20...O33	1.786	0.037	0.128	0.035	18.59
		N17-H19.....O21	1.423	0.096	0.126	0.041	84.87
		O24-H25...O11	1.538	0.065	0.169	0.039	27.94
ZGA...6W	**ZGA1**	O27-H28...O12	1.661	0.051	0.173	0.026	21.16
		O30-H32...O4	2.083	0.018	0.077	0.188	1.42
		N17-H18...O36	1.694	0.048	0.155	0.058	27.64
		N17-H20...O21	1.478	0.082	0.201	0.041	68.53
		O33-H34...O11	1.590	0.060	0.198	0.027	31.44
ZGA...7W	**ZGA4**	O21-H22...O4	1.801	0.035	0.126	0.042	10.69
		N17-H18...O21	1.791	0.036	0.132	0.030	17.01
		N17-H19...O36	1.778	0.037	0.137	0.049	17.25
		N17-H20...O30	1.748	0.040	0.139	0.064	21.69
		C1-H2...O33	2.496	0.011	0.032	0.050	0.54
		O30-H31...O11	1.493	0.074	0.163	0.018	49.65
		N6-H7...O39	1.906	0.028	0.107	0.053	7.49
		O27-H28...O11	1.805	0.035	0.126	0.050	10.15
		O24-H26...O12	2.005	0.022	0.084	0.056	1.25
ZGA...8W	**ZGA2**	O42-H44...O12	1.711	0.045	0.144	0.020	18.15
		O24-H26...O4	1.957	0.024	0.086	0.026	3.37
		N17-H18...O27	1.740	0.042	0.139	0.096	20.69
		N17-H19...O30	1.575	0.065	0.176	0.031	48.71
		C1-H2...O33	2.364	0.015	0.051	0.205	0.88
		O33-H34...O11	1.840	0.033	0.107	0.054	5.83
		O39-H40...O11	1.746	0.042	0.131	0.032	15.37
ZGA...9W	**ZGA2**	N17-H20...O30	1.496	0.081	0.150	0.038	55.08
		N17-H18...O27	1.677	0.051	0.132	0.031	29.25
		O33-H34...O11	1.722	0.042	0.139	0.017	10.75
		O24-H26...O4	1.818	0.032	0.119	0.020	4.98
		O42-H44...O12	1.769	0.037	0.124	0.046	5.25
		C1-H2...O33	2.364	0.014	0.044	0.077	1.35

Table 5. Hydrogen bond length R (in Å), electron density $\rho(r)$ (in a.u), Laplacian of electron density $\nabla^2\rho$ (in a.u), ellipticity ε and stabilization energies $E^{(2)}$ (in kcal/mol) involved in hydrogen bonds in the most stable conformers of NGA...$(W)_n$ n=5-10 complexes. For labeling of atoms refer Figs.3a-3f.

Species		**Interaction**	**R(Å)**	**ρ(r)**	**$\nabla^2\rho$**	**ε**	**$E^{(2)}$**
NGA...5W	**NGA4**	N5-H6...O24	2.090	0.020	0.068	0.053	4.86
		O21-H22...O4	1.736	0.039	0.117	0.029	5.99
		O30-H32...O14	1.744	0.035	0.115	0.022	6.49
		O15-H16...O33	1.657	0.050	0.124	0.032	29.05
NGA...6W	**NGA4**	N5-H6...O36	2.319	0.013	0.042	0.093	1.66
		O27-H28...O14	1.877	0.027	0.099	0.038	4.44
		O24-H26...O4	2.062	0.019	0.066	0.056	1.69
		O15-H16...O30	1.646	0.052	0.125	0.036	30.31
NGA...7W	**NGA4**	O39-H40...N5	1.937	0.032	0.081	0.026	13.72
		N5-H6...O36	2.028	0.021	0.075	0.059	5.99
		N9-H10...O39	1.955	0.028	0.090	0.040	9.66
		O21-O23...O4	2.039	0.021	0.070	0.057	3.34
		O27-H26...O14	1.913	0.025	0.090	0.031	3.45
		C17-H18...O33	2.433	0.011	0.034	0.070	1.96
		O15-H16...O30	1.631	0.054	0.125	0.036	32.12
		O33-H35...O15	2.075	0.018	0.064	0.058	2.54
NGA...8W	**NGA4**	C17-H18-O36	2.430	0.011	0.034	0.094	2.03
		O36-H38...O15	2.061	0.019	0.065	0.050	2.80
		O15-H16...O24	1.608	0.058	0.126	0.037	35.38
		O21-H22...O4	1.794	0.035	0.120	0.016	9.02
		O30-H31...O14	2.029	0.020	0.071	0.064	1.90
		N5-H6...O33	1.921	0.028	0.091	0.064	11.63
		O39-H40...N5	1.871	0.037	0.084	0.013	17.88
		N9-H10...O42	1.794	0.035	0.115	0.029	15.71
NGA...9W	**NGA1**	N9-H10...O45	1.888	0.029	0.097	0.032	11.71
		C11-H22...O30	2.342	0.014	0.042	0.154	2.26
		O30-H32...O14	2.101	0.019	0.062	0.046	2.78
		O24-H26...O14	2.021	0.021	0.073	0.034	1.63
		N5-H6...O39	2.131	0.019	0.066	0.043	2.89
		N5-H7...O33	2.348	0.012	0.040	0.184	1.09
		O15-H16...O21	1.645	0.051	0.128	0.023	29.26
NGA...10W	**NGA2**	O39-H40...O14	2.020	0.020	0.073	0.052	1.76
		O21-H22...O14	1.846	0.030	0.101	0.028	4.77
		O15-H16...O48	1.688	0.045	0.119	0.050	25.42
		O42-H44...O4	1.834	0.031	0.110	0.050	4.05
		N5-H6...O36	2.111	0.018	0.064	0.091	3.99

The electron density at bcp for hydrated ZGA and NGA complexes varies between 0.009-0.102 and 0.007-0.064 a.u. respectively. The $\nabla^2\rho(r)$ ranges from 0.02-0.21 and 0.029-0.156 a.u. for ZGA and NGA complexes respectively.

In all the hydrated complexes, the N-H(amino group)-O_w and O15-H16...O_w bonds are observed to be relatively short and possess comparatively higher values of $\rho(r)$ and $\nabla^2\rho(r)$. The $\rho(r)$ and $\nabla^2\rho(r)$ values for O-H...O interactions in ZGA...$(W)_n$ n=5-9 complexes vary between 0.01-0.079 a.u. and 0.038-0.21 a.u. respectively. The $\rho(r)$ and $\nabla^2\rho(r)$ values for the C-H...O interactions are found to vary in between 0.009-0.032 a.u., 0.026-0.098 a.u. and 0.008-0.018 a.u., 0.025-0.061 a.u. respectively for ZGA and NGA complexes respectively. Figure 9 plots a graph for the prominent N-H...O, O-H...O and C-H...O interactions present in the hydrated ZGA and NGA complexes.

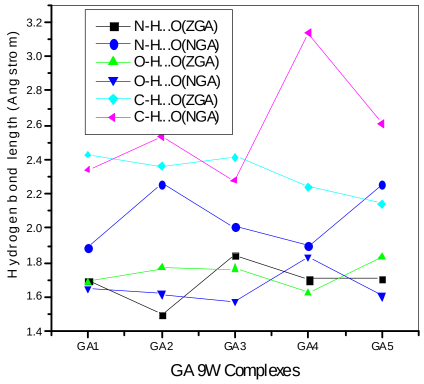


Figure 9: Graph for the prominent N-H...O, O-H...O and C-H...O interactions present in the ZGA...$(W)_n$ n=5-9 and NGA...$(W)_n$ n=5-10 complexes

The changes in ellipticity values are the indication of the higher chance of structural change under external disturbances which can be inferred that the bonds are stretched (å > 0.2) and they grow, at times to å > 1 then disappear [35] due to the conformational change of the entire system.

NBO Analysis

The hydrogen bonds within the NBO framework are interpreted to be formed as a result of charge transfer from the proton acceptor to the proton donor. Tables 4 and 5 give the stabilization energies $E^{(2)}$ of most stable ZGA...$(W)_n$ n=5-9 and NGA...$(W)_n$ n=5-10 complexes worked out at M05-2X/6-311G** respectively. These values for all the other complexes are given in the Tables S2 and S3 (supporting information) respectively. In the most stable ZGA complexes, the interactions where the oxygen of water offers lone pairs to the N-H (amino group) anti bond orbital of ZGA are stronger and $E^{(2)}$ lies within the range of 17.01-84.87 kcal/mol. In the NGA, the interactions where the oxygen of water offers lone pairs to the O15-H16 antibond orbital of NGA are stronger, and the $E^{(2)}$ lies within the range of 25.42-35.38 kcal/mol. The interactions between the oxygen lone pairs of water and C-H antibonding orbital of ZGA and NGA also exist in water interacting complexes with stabilization energies ranging from 0.52-3.16 and 0.44-5.04 kcal/mol respectively.

In all the other complexes, it has been observed that the same type of interactions are stronger and the $E^{(2)}$ lies within the range of 12.05-40.85 kcal/mol with smaller bond lengths (1.57-1.85 Å) compared to the other interactions which indicate that the oxygen of water is accountable to give electrons to GA and the formed hydrogen bonding interactions are strong. The interactions between the oxygen lone pairs of water and C-H antibonding orbital of ZGA and NGA also exist in water interacting complexes with stabilization energies ranging from 0.52-3.16 and 0.44-5.04 kcal/mol respectively.

CONCLUSIONS

Density functional M05-2X and B3LYP/6-311G** employed to analyze the effect of additive solvation of the five stable conformers of ZGA and NGA by using 5 to 9 and 5 to 10 water molecules respectively which owe their importance in developing an archetype to study the solvation of protein molecules. The results presented here illustrate that there is a surprising sensitivity of energy to the each additional water molecule added to both ZGA and NGA. In the bare and 5W complexes, the NGA is found to be energetically favorable than their ZGA counterparts. Starting from complexation with six water molecules, ZGA complexes turn out to be the most stable than their neutral partners. This shows the influence and capability of water clusters in bringing the high energy zwitterionic candidates up to a level with energy lower than the universal most stable neutral species.

The interaction energies have been taken as a tool to investigate the presence of H-bonds and their strength. The information collected from AIM study demonstrates the presence of strong H-bonds with highest electron density and larger structural stability. The NBO study predicts the higher stabilization energies (94.42 and 40.85 kcal/mol) for the N-H...O_w and O-H... O_w interactions in ZGA5...8W and NGA3...9W complexes respectively.

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