

Thermodynamic and computational study of acidic dissociation constants of glycylglycine in water at different temperatures using Ab initio methods

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Abstract: In this study, acidic dissociation constants of glycylglycine were determined using ab initio and density functional theory (DFT) methods at 25, 30, 35, 40 and 45 °C in aqueous solution. In order to explain the pK_a values obtained, the molecular conformations and solute-solvent interactions of the glycylglycine anions were investigated, using ab initio methods. Several ionization reactions and equilibria in water, which possesses a high hydrogen-bond-donor ability, are proposed. The mentioned reactions and equilibria constituted the necessary theoretical basis to calculate the acidity dissociation constants of glycylglycine. Basis sets at the B3LYP/6-31+G(d) level of theory were used for calculations. Tomasi's method was used to analyze the formation of intermolecular hydrogen bonds between the existent species and water molecules. In this way, it was determined that in alkaline aqueous solutions the cation and neutral specimen of glycylglycine are solvated with one molecule of water. Also, the thermodynamic functions for glycylglycine have been obtained from the pK_a values and their temperature dependence. In this work, there is agreement between the experimentally determined pK_a values for the acid-base reactions proposed by potentiometric with those reported in the literature demonstrates and theoretically calculated pK_a values.

Keyword: Acidity constants, Solvated conformations, Solvation free energy, Ab initio methods, glycylglycine

1. INTRODUCTION

The peptides are an amazing class of compounds. Although they are all constructed from relatively simple building blocks (the amino acids), they exhibit a remarkable range of biological properties: peptides can act as antibiotics, hormones, food additives, poisons or pain-killers and it is primarily because of their medicinal properties that the study of peptides has become one of the most active areas of current research. Glycine is α -amino acid, which means that the amino and carboxylic acid groups are both attached to the same carbon atom. When two amino acids are covalently linked together by amide bonds, the resulting molecules are called dipeptides. With an amino and a carboxylic acid groups being present in these molecules, there are both a basic and an acidic components in them. Both functional groups can be ionized. Although peptides are composed of amino acids, the amide bond itself shows neither the properties of the amino group nor those of the carboxylic acid group. In fact, the properties of the amide group are governed by the conjugation of the nitrogen lone pair with the carbonyl group. This mesomeric effect can be expressed as a resonance between two canonical forms [1].

Different experimental procedures were frequently used for the determination of acidity constants [2-10], but during the last two decades there has been much interest in developing a methodology enabling theoretical prediction of pK_a values, using various quantum theoretical techniques. As pK_a equals

$\Delta G/2.303 RT$, where ΔG is a free energy change of the dissociation reaction either in a gas or solution, acidity of a compound can be determined by the ΔG value [11-13]. Kinds of polarizable continuum models have been applied to calculate free energy differences for cations, neutral compounds and their anions. On the basis of solvation free energies, the pK_a values were obtained for the compounds in question by using thermodynamic equations; involving the combined experimental and calculated data [14].

This paper deals with the influence of factors such as the Self-Consistent Reaction Field (SCRF) model applied, choice of a particular thermodynamic equations, atomic radii used to build a cavity in the solvent (water), optimization of geometry in water, inclusion of electron correlation, and the dimension of the basis set on the solvation free energies and on the calculated pK_a values. pK_a values of glycylglycine were determined in aqueous solution by *ab initio* method at temperatures 25, 30, 35, 40 and 45°C. In order to explain the acidic dissociation constants obtained, we investigated the molecular conformations and solute-solvent interactions of the cation, anion and neutral species of glycylglycine using *ab initio* and density functional theory (DFT) methods.

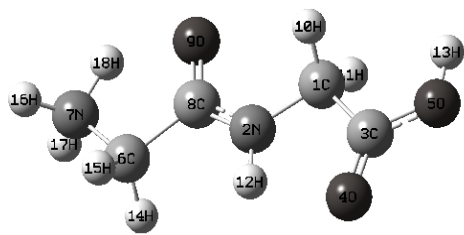


Fig. 1. Optimized structure of glycyglycine cation and practical numbering system adopted for carrying out the calculations.

2. COMPUTATIONAL METHOD

Fig. 1 shows the structure of glycyglycine cation and the practical numbering system adopted for performing the calculations. The initial geometries of the molecules by the semi empirical PM3 method are included in program CS Chem3D version 5.0 [15]. These geometries were optimized with the Gaussian 98 program package using the B3LYP/6-31+G(d) method and the default convergence criteria [16]. To analyze the solvent effects on all the specimens involved in the selected ionization reaction, the polarized continuum model (PCM) of Tomasi et al. was used [17]. Furthermore, to shed light on the experimental pK_a values of glycyglycine in water, the several conformers were tested by the program. Finally, we selected the solvation of the specimen by means of intermolecular hydrogen bonds (IHB) that involves one molecule of the mentioned specimen and some molecules of water. All of the mentioned calculations were accomplished at different temperatures from 25°C to 45°C to calculate thermodynamic parameters of dissociation reactions of glycyglycine.

3. RESULTS AND DISCUSSION

The tendency of a molecule to lose its hydrogen atom as an acidic proton is quantified as pK_a . The acidic dissociation constants of amino acids and dipeptides (pK_{a1} and pK_{a2}) have been extensively studied in different kinds of background electrolytes [18-26]. It is known that, in general, potentiometry and spectroscopic methods are highly sensitive and are suitable for studying chemical equilibria in solutions. These methods involve the direct determinations of the mole ratio of acid-base conjugate pairs in a series of buffered solutions of known pH. If the components involved in the equilibrium can be obtained in pure form, and if their spectral responses do not overlap, the analysis is very simple [27]. The acidic dissociation constants of glycyglycine have been determined using potentiometric technique. The method of determining acidic dissociation constant was previously described and its values are used in this work. These values are compared together with the calculated values using the Tomasi's method at the B3LYP/6-31+G(d) level of theory.

3.1. Solvent-solute interactions

3.1.1. Ionic product of water

It is well-known that all aqueous solutions contain hydrogen

(H^+) and hydroxyl (OH^-) ions. In pure water, these ions are derived completely from the ionization of the water molecules:



Considering that the H^+ ion is hydrated, appearing predominantly as H_3O^+ , the autoprotolysis of water is better represented by the following reaction:



Taking into account that water is only a little dissociated and to simplify the discussion, we shall make the approximations of replacing the activities in acidity constants by the numerical values of the molar concentrations. Consequently,

$$K_w = [H_3O^+][OH^-] \quad (3)$$

At 298.15 K, $K_w = 1.008 \times 10^{-14}$, shows that only a few of the water molecules are ionized [28]. Conventionally, Eqs. (2) and (3) are those more used in studies of acid-base equilibria in aqueous medium. On the other hand, the solvation of anions is effective in protic solvents where hydrogen bonds may be formed between the proton of the solvent and the lone pairs of electrons of the anion [29]. The total energies of the single and solvated OH^- ion have been calculated in water at the B3LYP/6-31+G(d) level of theory, using Tomasi's model. To illustrate, figure 2 shows the structures of the hydroxyl ion solvated with one water and also two water molecules together.

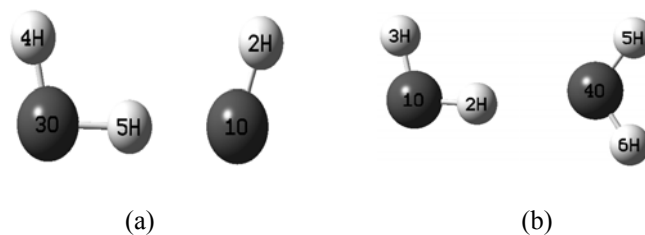
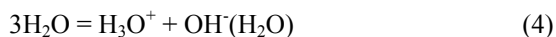


Fig. 2. Optimized Structure of the hydroxyl ion solvated with one water molecule (a) and two water molecules together (b)

It has observed that the distance between the O_1^- atom of hydroxyl group and the H_5 atom of the water (Fig. 2a) is equal to 1.557Å, whereas the bond angle (A_{bond}) that forms the involved atoms ($O_3-H_5-O_1^-$) in the hydrogen-bond donor (IHB) is 177.8°. Furthermore, Fig. 2b shows the distance and bond angle formed by the involved atoms (H_2O_4 , $O_1H_2O_4$) in the IHB are 1.905Å and 171.6°, respectively. The data allows to conclude that the IHBs between the OH^- ion and the water molecules of solvation belong to the class of moderate or strong H bonds [30]. The calculated total energy values show the striking decrease of the total energy of the OH^- ion when its solvation increases. For each solvation water molecule, the OH^- ion decreases its relative energy by 200,414 kJ mol⁻¹ respectively [31].

Considering these facts and in order to provide a more satisfactory representation of the protolysis of water, the reaction has been shown as follows:



The selected reaction considers that both H^+ and OH^- ions are hydrated with one water molecule. Moreover, indicating K_N as the equilibrium constant of the reaction of Eq. (4) and taking into account Eqs. (2) and (3), it is inferred that,

$$K_w = K_N[\text{H}_2\text{O}]$$

where $[\text{H}_2\text{O}]$ is the molar concentration of water. Consequently, at 298.15 K, it was calculated that

$$K_N = \frac{K_w}{[\text{H}_2\text{O}]} = 1.831 \times 10^{-16} \quad (5)$$

Similarly, the total energies of the single and solvated glycylglycine specimen (cationic, neutral and anionic) were calculated in water at the B3LYP/6-31+G(d) level of the theory, using Tomasi's model. Table 1 summarizes the variations of the total energy (kJ mol^{-1}) of the specimen per water molecule as a function of the total number of solvation water molecules at 298.15 K. Fig. 3 and Table 1 show the marked increase of the total energies of ions when those solvation increases. The data show that the water, exerting its hydrogen-bond-donor (HBD) capability, forms IHBs with the glycylglycine anions [32]. These hydrogen bonds have been classified as strong, moderate and weak, according to their lengths, angles and energies [30].

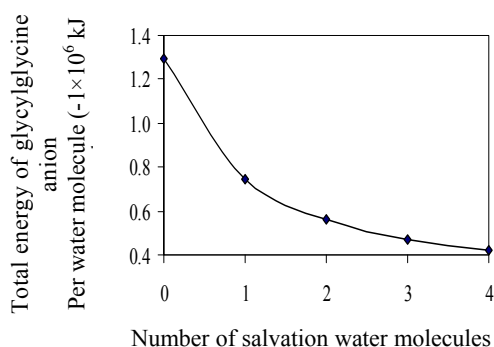


Fig. 3. Plot of the total energy (kJ mol^{-1}) of solvated glycylglycine anion per water molecule against the total number of solvation water molecules at 298.15 K.

Table 1. Calculated total energy using the Tomasi's method at the B3LYP/6-31+G(d) level of theory for cationic, neutral and anionic specimen of glycylglycine at 298.15K.

N	Solvated Specimen	G_{sol}° (Hartree)	G_{sol}° /molecule (kJ mol^{-1})
0	H_2L^+	-4.9294E+02	-1.2942E+06
1	$\text{H}_2\text{L}^+(\text{H}_2\text{O})$	-5.6938E+02	-7.4745E+05
0	HL	-4.9247E+02	-1.2930E+06
1	$\text{HL}(\text{H}_2\text{O})$	-5.6892E+02	-7.4685E+05
2	$\text{HL}(\text{H}_2\text{O})_2$	-6.4536E+02	-5.6480E+05
0	L^-	-4.9205E+02	-1.2919E+06
1	$\text{L}^-(\text{H}_2\text{O})$	-5.6848E+02	-7.4627E+05
2	$\text{L}^-(\text{H}_2\text{O})_2$	-6.4492E+02	-5.6442E+05
3	$\text{L}^-(\text{H}_2\text{O})_3$	-7.2135E+02	-4.7348E+05
4	$\text{L}^-(\text{H}_2\text{O})_4$	-7.9780E+02	-4.1892E+05

N: total number of solvation water molecules; G_{sol}° : total free energy in solution; G_{sol}° /molecule: total energy of solvated specimen per water molecule; H_2L^+ : cation species; HL: neutral; L^- : anion species.

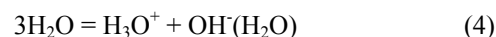
According to Table 1, different acid-base reactions were examined for the studied system. Values of acidic dissociation constants for all of the reactions were calculated using an excel computer program. The results of these calculations which were close to the experimental values were accepted. The accepted model is used to calculate the acidic dissociation constants (pK_{a1} and pK_{a2}). In this paper, the authors proposed the formation of different species including H_2L^+ , $\text{HL}(\text{H}_2\text{O})_2$ and L^- .

3.1.2. First ionization constant of glycylglycine

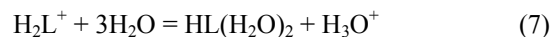
It was selected that in alkaline solutions, glycylglycine suffers a reaction of partial neutralization as follows:



In this reaction H_2L^+ and $\text{HL}(\text{H}_2\text{O})_2$ represents glycylglycine cation and glycylglycine neutral solvated with two water molecules, respectively. The previous reaction is characterized by an equilibrium constant, K_{C1} , which is theoretically determined. Besides the water also takes place:



By combining Eqs. (6) and (4) we obtain the reaction of Eq. (7), which defines the first ionization constant of glycylvaline (K_{a1}), which considers the solvation of the neutral glycylglycine.



It is evident that the constants K_{C1} , K_N and K_{a1} are related by the following equation:

$$K_{a1} = K_{C1} \times K_N \quad (8)$$

The above equation was used to determine theoretically value of the first ionization constant of glycylglycine in water. Table 2 summarizes the optimized values of molecular properties of H_2L^+ cation (Fig. 1), OH^- ion and the $\text{HL}(\text{H}_2\text{O})_2$ neutral molecule (Fig. 4) obtained at the B3LYP/6-31+G(d) level of theory with Tomasi's method in water at 298.15 K.

It must be noted that in the formation of the neutral glycylglycine solvated with two water molecules, the neutral molecules practically do not have the structure that characterizes the glycylglycine cation (Fig. 1 and Table 2). Obviously, the formation of the neutral glycylglycine implies that the electronic density of the N_7 atom increases notably (in absolute value) with respect to the N_7 atom of glycylglycine cation as shown in Table 2. Furthermore, the negative atomic charge of O_4 (q_{O_4}) of the neutral glycylglycine increases (in absolute value). These facts help to explain that the H_{18} atom of NH_3 group ($\text{N}_7\text{-H}_{18}$) group bound to C_6 of glycylglycine cation is more acidic than the

H₁₃ atom of carboxyl (O₅-H₁₃) group bound to C₃ atom of neutral glycylglycine. Also, it should be remarked that the nucleophilic attack the O⁻ atom of the OH⁻(H₂O) ion (see Eq. (6)) on the H₁₈ atom of NH₃ group bound to N₇ of glycylglycine cation produced the neutral glycylglycine solvated with two water molecules as shown in Fig. 4.

This molecule of water originated from the acid-base reaction, together with the hydration water molecule of the OH⁻(H₂O). The two molecules of water that interact with the N₇, O₄ and O₅ of the neutral glycylglycine molecule by means of two IHBs. The distances and angles that characterize these IHBs (Table 2 and Fig. 4) indicate that they belong to the class of weak or moderate IHB [30]. Thus, it is reasonable to observe that the molecular volume of the neutral glycylglycine molecule solvated with two water molecules is approximately the sum of the molecular volumes of the specimen that form it, i.e. glycylglycine cation and OH⁻(H₂O). On the other hand, the pK_{a1} value theoretically obtained (pK_{a1} = 3.39) has a good agreement with the experimental pK_{a1} value (pK_{a1} = 3.07 ± 0.05). We conclude that this fact constitutes a strong support for the reactions and equilibria of ionization here selected.

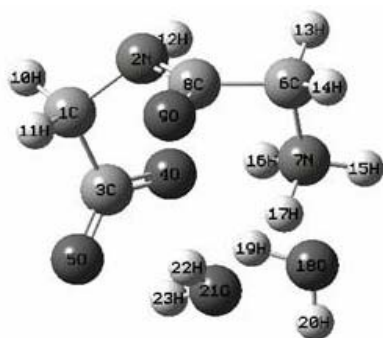


Fig. 4. Optimized structure of neutral glycylglycine solvated with two water molecules, at the B3LYP/6-31+G(d) level of theory and using the Tomasi's method in water at 298.15 K.

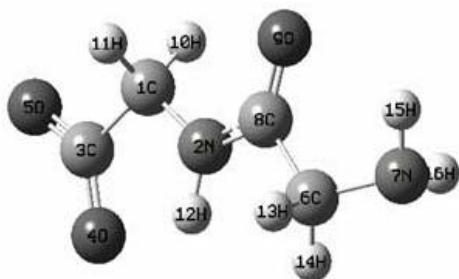
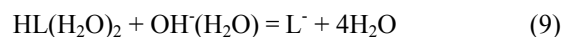


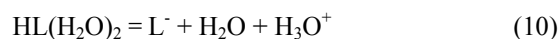
Fig. 5. Optimized structure for the glycylglycine anion at the B3LYP/6-31+G(d) level of theory and using the Tomasi's method in water at 298.15 K.

3.1.3. Second ionization constant of glycylglycine

Here, it is selected that the neutral (H₂O)₂HL suffers a total neutralization process as follows:



In the above reaction, L⁻ represents glycylglycine anion. The reaction described in Eq. (9) is characterized by another equilibrium constant, K_{C2}, which was also theoretically determined. Combining Eqs. (4) and (9), the second ionization reaction of glycylglycine was obtained:



The equilibrium constant K_{a2} that characterizes the above reaction is linked with constants K_{C2} and K_N by Eq. (11):

$$K_{a2} = K_{C2} \times K_N \quad (11)$$

This equation is similar to Eq. (8) and it was used to obtain the value of the second ionization constant of glycylglycine in water. Table 2 gives the values of the molecular parameters and properties calculated for the L⁻ anion, in water at 298.15 K, while Fig. 5 shows the structure of this anion. Thus, the acid-base reactions and solvation of specimen change the structure.

It must be noted that the pK_{a2} value theoretically calculated (pK_{a2} = 8.31) is in reasonable agreement with the experimentally determined pK_a (pK_{a2} = 8.16 ± 0.09) at 298.15 K. In similar investigations, total energies were obtained for glycylglycine systems, using the Tomasi's method at the B3LYP/6-31+G(d) level of theory for the anion, cation and neutral species at temperatures 30, 35, 40 and 45 °C in aqueous solution were shown in Table 2.

Table 2. Calculated total energy using the Tomasi's method at the B3LYP/6-31+G(d) level of theory for cationic, neutral, anionic specimen of glycylglycine and OH⁻ ion hydrated with a water molecule at different temperatures.

T (K)	G_{sol}° (kJ/mol)				K _{C1}	K _{C2}
	H ₂ L ⁺	HL (H ₂ O) ₂	L ⁻	(H ₂ O) OH ⁻		
298	-1.29E+06	-1.69E+06	-1.29E+06	-4E+05	2.19E+12	2.66E+07
303	-1.29E+06	-1.69E+06	-1.29E+06	-4E+05	1.44E+12	1.36E+07
308	-1.29E+06	-1.69E+06	-1.29E+06	-4E+05	9.73E+11	7.10E+06
313	-1.29E+06	-1.69E+06	-1.29E+06	-4E+05	6.62E+11	3.75E+06
318	-1.29E+06	-1.69E+06	-1.29E+06	-4E+05	4.56E+11	2.02E+06

The acid dissociation constants of glycylglycine were determined at different temperatures according to eq. 1 and 2. The calculated values are listed in Table together with the values reported in the literature. The reported values are comparable with those obtained in this work. However, the differences are mostly due to the different techniques, various ionic strengths with different background electrolytes, and different temperatures that were used. Also, the values of dissociation constants in Table 3 reveal that the dissociation constants increase with increasing temperature.

Table 3. Values of the acid dissociation constants of the glycylglycine at different temperatures.

T (K)	-logK _{a1}	-logK _{a2}	ref.
298.15	3.39	8.31	This work
303.15	3.42	8.44	This work
308.15	3.44	8.58	This work
313.15	3.46	8.71	This work
318.15	3.49	8.84	This work
298.15	3.22	8.09	[7]
298.15	3.07	8.16	[8]
298.15	3.10	8.15	[7]
298.15	3.13	8.08	[8]

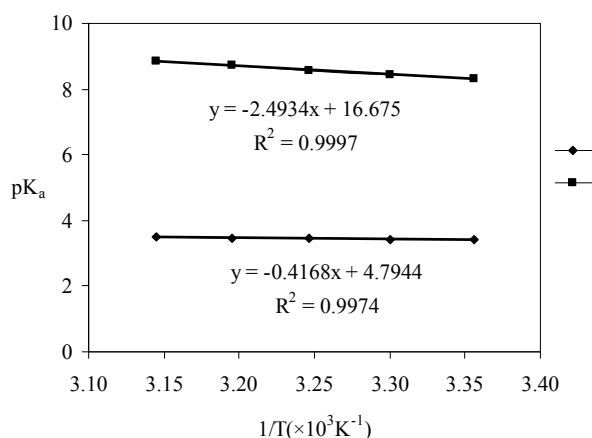


Fig. 2. Curve -logK_a values vs. 1/T for glycylglycine.

Fig. 2 shows the pK_a values of glycylglycine as a function of temperature. Finally, the thermodynamic parameters have been obtained by plotting the left side of Eq. (3) versus 1/T. From the slope and intercept of these plots the value of ΔH and ΔS have been calculate, respectively. The resulting values (ΔH , ΔS and ΔG) are shown in Table 4.

$$-\log K_a = \Delta H/2.303 RT - \Delta S/2.303 R \quad (12)$$

Table 4. Values of the thermodynamic Parameters at 298 K.

equation	ΔH (KJ.mol ⁻¹)	ΔS (J.mol ⁻¹)	ΔG (KJ.mol ⁻¹)
$H_2L^+ + 3H_2O \leftrightarrow HL(H_2O)_2 + H_3O^+$	-7.9708	-91.6828	19.3644
$HL(H_2O)_2 \leftrightarrow L^- + H_2O + H_3O^+$	-47.6810	-318.874	47.3913

4. CONCLUSIONS

In this paper, pK_a values of glycylglycine were determined using *ab initio* and density functional theory (DFT) method in aqueous solution at different temperatures. We have shown that these constants can be calculated with an acceptable degree of accuracy. With this purpose, we selected various acid-base reactions that take into account the solvation of the hydrogen, hydroxyl ions and other cations or anions in protic solvents such as water, which possess a high hydrogen-bond-donor capability. We also observed that the nucleophilic attack on the hydrogen atoms of the COOH and NH₃⁺ groups of glycylglycine to form the corresponding specimen are produced by the OH⁻ ion hydrated with a water molecule. The calculations performed at the B3LYP/6-31+G(d) levels of theory using Tomasi's method allowed to prove that the cations, neutral molecules and anions forms IHBs with some molecules of water. The effect of the temperature on the acid dissociation constants is also investigated and it reveals the complex relations of the acid dissociation constants to temperature. The ionization constants theoretically show an excellent agreement with the acidity constants experimentally determined as shown in Table 4. We conclude that this fact constitutes a strong support for the reactions and equilibria of ionization in aqueous medium selected in this work.

Acknowledgments

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