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Calculation 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. To explain the pK_a values obtained, the molecular conformations and solute–solvent interactions of the anions, cations, and neutrals molecules of glycylglycine were investigated. Several ionization reactions and equilibria in water, which possess a high hydrogen-band-donor ability were 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 also used to analyze the formation of intermolecular hydrogen bonds between the existent species and water molecules. It was concluded that in alkaline aqueous solutions, the neutral, anion and cation species of glycylglycine are solvated with some molecules of water. The thermodynamic parameters have been obtained for dissociation reactions of glycylglycine from the pK_a values and their temperature dependence. There is a good agreement between the experimentally determined pK_a values for the acid-base reactions obtained by potentiometric with those calculated theoretically.

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 [1]. 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.

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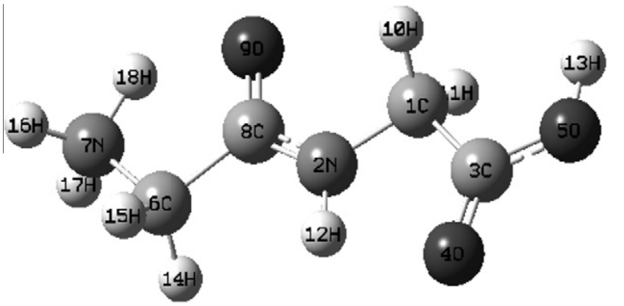

Fig. 1. Optimized structure of glycylglycine cation and practical numbering system adopted for carrying out the calculations.

2. Computational method

Fig. 1 shows the structure of glycylglycine 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 glycylglycine 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 glycylglicine.

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 glycylglycine have been determined using potentiometric technique. The method of determining acidic dissociation constant was previously described [2,10] 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:

$$H_2O \leftrightarrows H^+ + OH^- \tag{1}$$

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

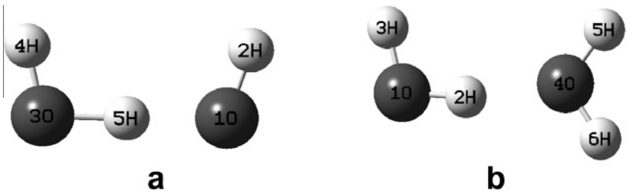

Fig. 2. Optimized Structure of the hydroxyl ion solvated with one water molecule (a) and two water molecules together (b).

$$2H_2O \leftrightarrows H_3O^+ + OH^- \tag{2}$$

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,

$$K_w = [H_3O^+][OH^-] \tag{3}$$

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, Fig. 2 shows the structures of the hydroxyl ion solvated with one water and also two water molecules together.

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 1.557 Å, 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 1.905 Å 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:

$$3H_2O \leftrightarrows H_3O^+ + OH^-(H_2O) \tag{4}$$

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,

$$K_w = K_N[H_2O]$$

where $[H_2O]$ is the molar concentration of water. Consequently, at 298.15 K, it was calculated that

$$K_N = \frac{K_w}{[H_2O]} = 1.831 \times 10^{-16} \tag{5}$$

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,