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Research Article

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Geometry optimization and stability of solvated glycine dipeptide: EFP study

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ABSTRACT

The effective fragment potential (EFP) method is an efficient ab initio based polarizable model that describes the explicit solvent effects, is applied to glycine dipeptide solvated in water. The structures of neutral and zwitterionic glycine dipeptide immersed in water layers of 5.0 and 6.0 Å are investigated by performing RHF/EFP geometry optimizations at the RHF/cc-pVDZ level of theory. Using the optimized geometries, the stability of the hydrated zwitterionic and neutral structures is discussed structurally and in terms of energetics at the second-order Møller–Plesset theory (MP2)/cc-pVDZ level.

Key words: EFP; RHF; MP2; Glycine; cc-pVDZ

INTRODUCTION

The most biological processes occur in solution, solvent effects must also be considered. The biologically relevant form of amino acids is the zwitterionic form and are essentially always in this form at neutral pH [1,2]. Zwitterionic species of amino acids have both a negatively charged carboxylate group (COO-) and a positively charged ammonium group (NH3+). They are the dominant form in aqueous solution over a wide range of pH. In contrast, in the gas phase, where interactions with environment are not present, amino acids are mostly in their neutral nonionic form [3-6]. Fact that the amino acids are zwitterions in the water phase implies that interactions with the water molecules are a key determinant of the stable zwitterionic structure. Glycine dipeptide is the simplest peptide with the chemical name 2-[(2-Aminoacetyl)amino]acetic acid. Because of its low toxicity, it is useful as a buffer for biological systems with effective ranges between pH 2.5-3.8 and 7.5-8.9 [7], however, it is only moderately stable for storage once dissolved. It is used in the synthesis of more complex peptides [8].

To study the effect of hydration, an explicit solvent treatment can be performed directly with the polarizable continuum model (PCM) [9,10]. The effective fragment potential (EFP) method [11,12] is a model potential derived from first principles quantum chemistry. In the effective fragment molecular orbital method [13], all fragments are treated on the same footing, with the mutual polarization treated in the EFP fashion. Intensive studies have been performed on solvated alanine by many researchers [14,15]. Jensen and Gordon [16] reported that a zwitterionic glycine molecule with two water molecules is a local minimum, based on correlated *ab initio* calculations with polarization basis functions. However, with two water molecules, the neutral isomer is still lower in energy. Aikens and Gordon [17] discussed the importance of bulk water for the stability of zwitterionic glycine by applying the QM method for the important water molecules that are directly interacting with glycine and PCM for bulk water. Yamabe *et al*. [18] indicated that a water chain consisting of several water molecules enhances the proton transfer of glycine.

Within the scope of this work, the attempt is to determine the structure and properties of the hydration layers around glycine dipeptide and describe the neutral and zwitterion minimum energy structures and their stability in a polar water environment. The motivation for this study arose for several reasons. It is now well-established that the effect

of solvation has to be included in simulations to achieve physical meaningful results [19], especially for vibrational spectra [19-25]. Nevertheless, the zwitterionic form of dipeptides in aqueous solution still remains poorly studied. Hetch *et al.* observed correlations between solute-induced perturbations of the solvent structure and amino acid hydrophobicity [26]. Later, Ide *et al*. concluded, also on the basis of Raman spectroscopy, that the structure of water in solutions of various amino acids at neutral pH does not depend on the nature of the amino acid side chains [27]. UN Dash *et al* experimentally studied the molecular interaction between amino acids and the solvents, and concluded that the intermolecular interactions of peptides depend on nature of amino acid and structure of the solvent [28]. OP Chimankar *et al* experimentally studied the importance of interionic association of glycylglycine with aqueous electrolyte solutions [29]. The lack of a first-principles study, which would fully cover the aspects of the dynamics of hydrated amino acids, can be explained by the computational complexity of *ab initio* methods required to simulate systems with large numbers of atoms (Ehrenfest, Car-Parrinello, or first principles Born-Oppenheimer MD simulations). An analysis of the conformational dynamics of an alanine dipeptide analogue in the gas phase [30], Car-Parrinello molecular dynamics study of the effect of protonation in a hydrated glycine molecule [31] and stability of tetraglycine [32] have been reported.

In this work, minimum energy structure and stability of neutral and zwitterionic solvated glycine dipeptide molecule is performed. The use of the EFP based QM/MM method allows one to consider explicitly to study interaction energy between solvent and solute molecules.

2. Computational details

Glycine dipeptide molecules in both neutral and zwitterionic form were modeled using molecular modeling software Avogadro [33]. The molecular modeling software VEGA [34] was used to construct water layers of 5.0 and 6.0 Å from glycine dipeptide molecule, defined as the closest atom-atom distance from the solute to the solvent. The RHF/EFP geometry optimization calculations were then carried out at the RHF/cc-pVDZ level of theory [35] implemented in the GAMESS-US software suit [36,37]. To obtain the energies of the zwitterionic form of hydrated glycine dipeptide relative to those of the neutral form, the numbers of water molecules must be the same for each water layer but a slightly different number is generated by VEGA. To avoid this problem, a few water molecules were removed; for example, at the 5.0 Å water layer consisting of 52 and 50 water molecules for the neutral and zwitterion, respectively, two water molecules in the neutral system, which is far away from the solute, was removed. The energies of hydrated molecule, free solute and solvent (EFP) for the neutral and zwitterionic forms was carried out at the MP2/cc-pVDZ level of theory.

To study the relative stabilities of hydrated zwitterionic glycine dipeptide systems by comparing their energies with those of the hydrated neutral systems, the relative energy ΔE^{tot} is estimated by subtracting the total energy E^{neu} of the hydrated neutral system from that of the corresponding hydrated zwitterionic system E^{zwit}, i.e.,

$$E^{tot} = E^{zwit} - E^{neu} \tag{1}$$

The optimized geometry for solvated glycine dipeptide is used to compute the energy of the free solute (solu), $E^{solu,zwit}$ and $E^{solu,neu}$, by removing solvent molecules from the system. Similarly, removing the solute allows one to compute the energy of the free solvent (solv) $E^{solv,zwit}$ and $E^{solv,neu}$. Then, the solvent–solute interaction energies are

$$E^{\text{solu-solv,zwit}} = E^{zwit} - (E^{solu,zwit} + E^{solv,zwit}) \tag{2}$$

$$E^{\text{solu-solv,neu}} = E^{neu} - (E^{solu,neu} + E^{solv,neu}) \tag{3}$$

And the relative energy can be decomposed as

$$\Delta E^{tot} = \Delta E^{solu} + \Delta E^{solv} + \Delta E^{solu-solv} \tag{4}$$

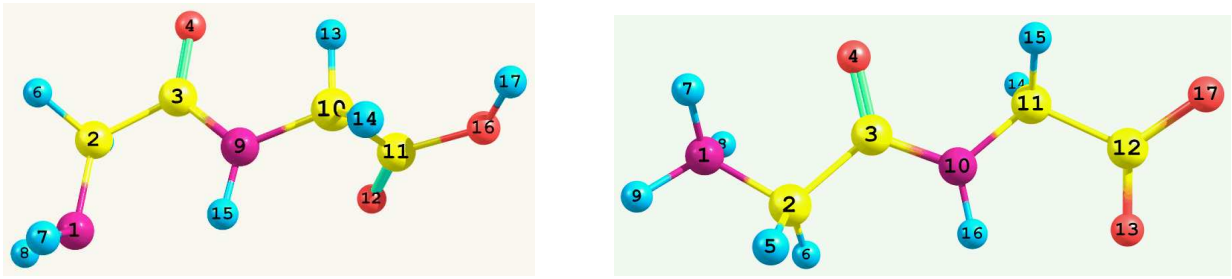
where $\Delta E^{solu} = \Delta E^{solu,zwit} - \Delta E^{solu,neu}$ describes the relative stability of two forms of glycine dipeptide without solvent, $\Delta E^{solv} = \Delta E^{solv,zwit} - \Delta E^{solv,neu}$ describes the stability of solvent in the two hydrated forms of glycine dipeptide and $\Delta E^{solu-solv} = \Delta E^{solu-solv,zwit} - \Delta E^{solu-solv,neu}$ is the relative value of the solute–solvent interactions in the two forms of glycine dipeptide.

RESULTS AND DISCUSSION

Fig. 1 depicts the optimized solute structure of the neutral and zwitterionic glycine dipeptide in solvent phase. Fig. 2 displays the hydrated neutral and zwitterionic glycine dipeptide in the water layer of thickness 6.0 Å. In zwitterionic system, the N1-C2 and C12-O13 bond lengths increased by 0.018 and 0.055 Å, respectively, C12-O17 bond length decreased by 0.067 Å, N1-C2-C3 bond angle increased by 6.8°, C11-C12-O13 bond angle decreased by 5.5° and no change in C11-C12-O17 bond angle. Table 1 presents the total relative energy with the EFP water layers. The negative sign in the relative energies ΔE^{tot} means that the zwitterionic system is more stable, as may be seen in Eqs. (2) and (3). The relative energy contributions within the solute molecules, ΔE^{solu} in the second column (the standalone solute energies) do not change very much with the increase in the thickness of water layer. The zwitterionic system always gains stability relative to the neutral system.

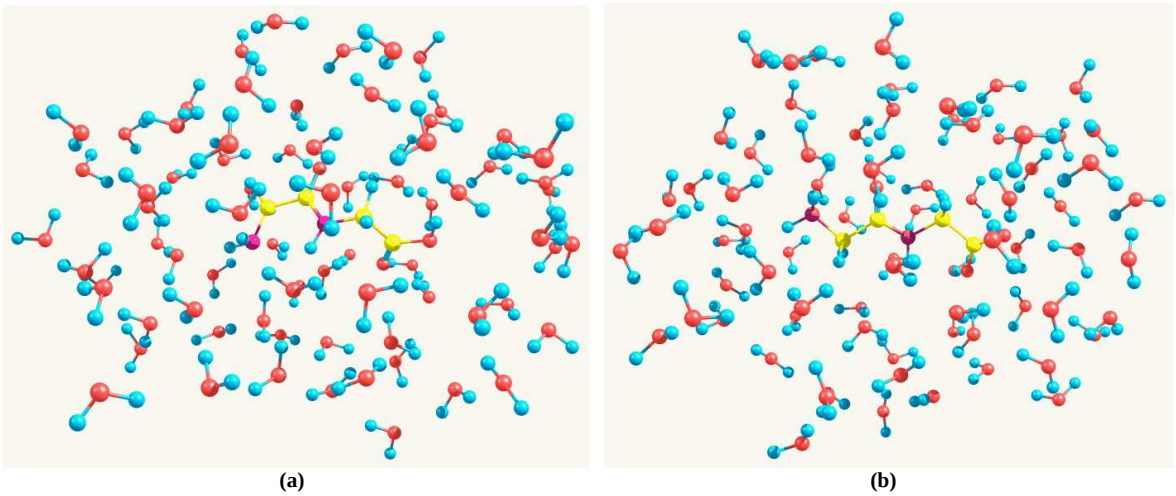
Table 1. Relative energy contributions (kJ/mol) for RHF/EFP (solvent by EFP) for hydrated zwitterionic glycine dipeptide relative to the neutral form: the internal solute ΔE^{solu} and solvent ΔE^{solv} energies, as well as the solute–solvent interaction energy $\Delta E^{solu-solv}$. The cc-pVDZ basis set is used. The number of water molecules is shown in parentheses.

Water layer (Å)	ΔE^{solu}	ΔE^{solv}	$\Delta E^{solu-solv}$	ΔE^{tot}
5.0 (50)	280.51	103.31	-472.97	-89.14
6.0 (74)	255.57	221.75	-559.10	-81.77



(a) **(b)**

Fig. 1. Optimized solute structures of glycine dipeptide (a) neutral and (b) zwitterionic form in solvent (water) phase. (Red-O, Magenta-N, Yellow-C and Cyan-H)



(a) **(b)**

Fig. 2. Optimized structures of hydrated (water layer of 6.0 Å) glycine dipeptide (a) neutral and (b) zwitterionic form. (Red-O, Magenta - N, Yellow-C and Cyan-H)

The solvent internal energies, ΔE^{solv} (third column in Table 1), increase with the thickness of water layer. This implies that the hydrogen bond networks of the water clusters under the influence of neutral glycine dipeptide are always more strongly bound. In contrast, the fourth column of Table 1 (the solute–solvent interaction energy: $\Delta E^{solu-solv}$) shows that the solute–solvent relative energies are more negative (more strongly bound) for the zwitterionic systems than for the neutral systems, with strong interactions between the charged groups within the zwitterion and weaker hydrogen bond networks within the water cluster (given by ΔE^{solv}). The values of ΔE^{solv} and $\Delta E^{solu-solv}$ are strongly correlated. The strong interaction between a charged group and a water cluster in the hydrated zwitterion

weakens the water hydrogen bond networks, leading to large positive ΔE^{solv} values. The opposite tendency is found for the neutral systems. The total relative energies, ΔE^{tot} in the fifth column of Table 1 are negative for the water layers of thickness 5.0 and 6.0 Å . This means that there is no qualitative change in the relative neutral-zwitterion stabilities as the number of water molecules increases; the hydrated zwitterionic systems are always more stable.

CONCLUSION

In this study the geometry optimization of hydrated neutral and zwitterionic glycine dipeptide in water layers of 5.0 and 6.0 Å is carried out via RHF/EFP model. The solute–solvent relative energies are more negative (more strongly bound) for the zwitterionic systems than for the neutral systems, with strong interactions between the charged groups within the zwitterion and weaker hydrogen bond networks within the water cluster. The hydrated zwitterionic glycine dipeptide is more stable than the neutral form.

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