Effects of Zinc Binding on the Structure and Stability of Glycylglycine Dipeptide: a Computational Study

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Abstract. Energies and structures of six different isomers resulted of complex between glycylglycine dipeptide and zinc cation were calculated at the BLYP and B3LYP levels of theory with 6-311G** and 6-311++G** basis sets. The energies of the glycylglycine-Zn²⁺ different complexes at the BLYP/6-311++G** obtained more stable than another methods. In this method, the most stable complex was zinc cation bound to the two oxygen sites of the glycylglycine zwitterion and acted as a bidentate ligand. The vibrational frequencies, thermodynamic and electronic properties, HOMO, LUMO, and energy gap for the most stable isomer in different solvents were calculated at the BLYP/6-311++G** level of theory.

Keywords: DFT calculations, Glycylglycine-Zn²⁺, Enthalpy, HOMO, LUMO.

Introduction

Amino acids are one class of interesting and important compounds in life, and have many functions in metabolism¹. One particularly important role is to serve as the building blocks of proteins¹. In recent years, studies of the interaction of a metal cation with amino acids have been the subject of considerable attention²⁻¹⁸ and many investigations have also been done about determining thermodynamical quantities of protein structures¹⁹. Complexation modes between cations and amino acids in cation-peptide systems are important in biological processes such as cellular osmotic equilibrium control or in active transport phenomena²⁰⁻²². Also, metallic cations influence on the three-dimensional structure of nucleic acids²³⁻²⁷. There are different sites of complexation in peptides including the N-terminus nitrogen atom and the carboxylate group at the C-terminus end, and the oxygen or nitrogen atoms which present in the main chain or in the lateral ones. The recognition of the essence of the interactions cation-peptide provides us the important information on the role of important biological molecules²⁸. The coordination modes of cations are very strongly with the sites which they interact. Some metals have a strong relation for specific coordination modes, particularly in metalloenzymes²⁹. Some others may pursue indifferently

several coordination modes³⁰. In this manuscript, we were considered the different formed complexes between the glycylglycine dipeptide and zinc cation (Zn^{2+}). Then, we identified the most stable glycylglycine- Zn^{2+} isomer and calculated the vibrational frequencies, thermodynamic properties and electronic properties it in different solvents.

Computational Methodology

Geometries of various isomers of glycylglycine- Zn^{2+} were fully optimized using the Gaussian 98³¹. The computations were performed within the formalism of the density functional theory (DFT), at the BLYP and B3LYP levels and the 6-311G** and 6-311++G** extended basis sets³⁰. All the structures were obtained without any geometry constraint in order to identify the most stable isomer. The absence of any imaginary vibrational frequency was verified to be sure that each stationary point was a true minimum. We investigated vibrational frequencies, enthalpy, entropy, Gibbs energy, electronic properties, HOMO, LUMO, and energy gap for the most stable isomer in different solvents at the BLYP/6-311++G** level of theory.

Results and Discussion

Structures and relative stability

We fully optimized **I-IV** structures (glycylglycine- Zn^{2+} different complexes) at the BLYP and B3LYP levels with 6-311G** and 6-311++G** basis sets. The obtained results were represented on Fig. 1 and energetic data were collected in Table 1 and Table 2.

Structures and energetic of obtained complexes of glycylglycine dipeptide and zinc cation at the BLYP/6-311++G** method had more stable than another methods. Our computations showed that **V** isomer was the most stable isomer (Table 1). In the most stable complex (**V** isomer), zinc cation was bound by the two oxygen sites of glycylglycine zwitterion and acted as a bidentate ligand (Fig. 1).

Figure 1. Optimized structures of glycylglycine- Zn^{2+} complexes.

Difference of relative energies between structures **II** and **V** was very low (Table 1 and 2). In the BLYP/6-311G** and BLYP/6-311++G** levels, **V** isomer had more stable than **II** isomer about 2.326 and 1.010 kcal/mol, respectively (Table 1). But, at the B3LYP/6-311G** and B3LYP/6-311++G** levels, relative energies of **V** isomer obtained 1.606 and 2.974 kcal/mol higher than **II** isomer, respectively (Table 2).

Table 1. Energies (Hartree) and Relative Energies (kcal/mol) of Optimized Isomers (BLYP/6-311G**, 6-311++G**) of the Isolated Glycylglycine–Zn²⁺ Complexes in Gas Phase.

Isomers	BLYP(6-311G**)	Relative energy	BLYP(6-311++G**)	Relative energy
V	-557.623	0.000	-557.640	0.000
II	-557.619	2.326	-557.638	1.010
III	-557.603	12.538	-557.623	10.617
I	-557.593	18.623	-557.612	17.224
IV	-557.593	18.769	-557.613	16.705
VI	-557.588	21.901	-557.608	19.937

Table 2. Energies (Hartree) and Relative Energies (kcal/mol) of Optimized Isomers (B3LYP/6-311G**, 6-311++G**) of the Isolated Glycylglycine–Zn²⁺ Complexes in Gas Phase.

Isomers	B3LYP(6-311G**)	Relative energy	B3LYP(6-311++G**)	Relative energy
II	-557.424	0.000	-557.444	0.000
V	-557.421	1.606	-557.439	2.974
III	-557.407	10.682	-557.428	9.958
IV	-557.397	16.743	-557.418	15.909
I	-557.391	20.356	-557.411	20.291
VI	-557.386	23.673	-557.407	22.935

Difference energy between these geometries was small enough to anticipate a possible equilibrium between several structures at high temperature. One notices that these results could hardly be extended into another polypeptides or proteins. The energy for the most stable isomer in different solvents was calculated at the BLYP/6-311++G** level of theory (Table 3). The geometry energy was very sensitive to dielectric constants and increased in the high dielectric constants.

Table 3. Energies (Hartree) and Relative Energies (kcal/mol) for **V** Isomer at the BLYP/6-311++G** level in Different Solvents.

Solvent	ϵ	Energies (Hartree)	relative energies (kcal/mol)
H ₂ O	78.390	-2271.282	0
DMSO	46.700	-2271.274	5.090
CH ₃ OH	32.630	-2271.271	6.935
CH ₃ CH ₂ OH	24.550	-2271.265	10.711

Vibrational frequencies

The vibrational frequencies were calculated at the BLYP/6-311++G** level of theory. We scaled the vibrational frequencies for the most stable state (**V** isomer in Fig. 1) and used to

simulate the IR spectra (Fig. 2) in different solvents. The simulated IR spectra could be used as evidence to identify the most stable isomer state (case **V** in Fig. 1). The absence of imaginary vibrational frequency confirmed that the most stable isomer corresponded to true minima.

Figure 2. Simulate the IR spectra for the most stable state (V isomer in Fig. 1) in different solvents. IR spectrum scaled by 1.000000.

Thermodynamic changes

The thermodynamic changes for the most stable isomer (isomer **V** in Fig. 1) were estimated using total energies obtained at the BLYP/6-311++G** method. The thermodynamic properties were calculated from the standard statistical mechanical equations to include the finite-temperature translational, rotational and vibrational energies [32]. For example, the enthalpy (H) was obtained as follows:

$$H = E_{\text{elec}} + E_{\text{vib}}(T=0) + E_{\text{vib}}(T) + E_{\text{rot}}(T) + E_{\text{tra}}(T) + PV \quad (1)$$

where E_{elec} was the total electronic energy at 0 K, $E_{\text{vib}}(T=0)$ was the zero-point vibrational energy which was a linear sum of the basic harmonic frequencies, and $E_{\text{vib}}(T)$, $E_{\text{rot}}(T)$, and $E_{\text{tra}}(T)$ were vibrational, rotational, and translational contributions, respectively. Also, the entropy (S) of molecules could also be calculated from a standard formula:

$$S = S_{\text{elec}} + S_{\text{vib}} + S_{\text{rot}} + S_{\text{tra}} \quad (2)$$

Where S_{elec} , S_{vib} , S_{rot} , and S_{tra} were the electronic, vibrational, rotational, and translational terms. The change in the standard Gibbs free energy was given by

$$\Delta G = \Delta H - T\Delta S \quad (3)$$

The thermodynamic properties for the most stable isomer (case **V** in Fig. 1) in different solvents were calculated. For this isomer, ΔH , ΔS , and ΔG were performed at the BLYP/6-311++G** level of theory (Table 4). Also, $\Delta H < 0$ showed that this process was exothermic.

Table 4. ΔH , ΔS , and ΔG in kcal/mol for V isomer at the BLYP/6-311++G** level in different solvents at 298 k.

solvent	ΔH	ΔS	ΔG
Gas	-289.776	-9.895	-279.881
H ₂ O	-536.844	-10.577	-526.266
DMSO	-532.851	-10.583	-522.268
CH ₃ OH	-531.106	-10.354	-520.751
CH ₃ CH ₂ OH	-527.597	-10.117	-517.480

Electronic properties

Finally, we studied changes on the electronic properties for the most stable isomer state (V isomer) in different solvents and the total densities of states (DOS) of these isomers were shown in Fig.3, where Fermi energy sets to 0 eV. The HOMO, LUMO energies, and their energy gaps were listed in Table 5. The electronic properties were very sensitive to dielectric constants and increased in high dielectric constants. It is clear that the presence of solvents with the high dielectric constants increased their energy gaps and reduced the electrical conductance of the most stable state (V isomer).

Figure 3. Electronic density of states for V isomer at the BLYP/6-311G** level in different solvents.

Table 5. HOMO and LUMO energies and their energy gaps for V isomer at the BLYP/6-311G** level in different solvents.

solvent	HOMO	LUMO	Energy gap (eV)
Gas	-13.86	-12.56	1.30
H ₂ O	-6.23	-2.30	3.93
DMSO	-6.37	-2.44	3.93
CH ₃ OH	-6.41	-2.54	3.87
CH ₃ CH ₂ OH	-6.51	-2.69	3.82

Conclusion

This study performed at a rather good computational level at the BLYP and B3LYP levels; and 6-311G** and 6-311++G** basis sets. Six different glycylglycine-Zn²⁺ isomers were considered. The most stable isomer was zinc cation bound by the two oxygen ends of the zwitterionic dipeptide. The vibrational frequencies for the most stable isomer in different solvents were calculated at the BLYP/6-311++G** level of theory. The absence of imaginary vibrational frequency confirmed V isomer corresponded to true minima. According to obtained results of thermodynamic properties (enthalpy, entropy, and Gibbs energy) of V isomers in different solvents at BLYP/6-311++G**, the process was exothermic. Finally, we studied influence different solvents on electronic properties, HOMO, LUMO, and energy gap of the most stable isomer.

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