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Geometry optimization and stability of solvated dialanine: 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 alanine dipeptide solvated in water. The structures of neutral and zwitterionic dialanine immersed in water layers of 3.0, 3.5, 4.0, 4.5 and 5.0 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; Dialanine; cc-pVDZ.

1. 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 The fact that amino acids are zwitterionic structure. Alanine is the smallest chiral R-amino acid, with a nonreactive methyl (-CH3) group as the side chain. It is one of the aliphatic amino acids that has the important property of not interacting favorably with water. It is considered to be hydrophobic and is normally placed on the hydrophobicity scale after glycine, leucine, isoleucine, and valine.⁷⁻⁸

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 Gordon¹⁶ 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 Gordon¹⁷ 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 dialanine 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 dialanine zwitterion 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 The lack of a first-principles study, which would fully cover the aspects of the dynamics of hydrated alanine 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 phase²⁸, Car-Parrinello molecular dynamics study of the effect of protonation in a hydrated glycine molecule²⁹ and stability of tetraglycine³⁰ have been reported.

In this work, minimum energy structure and stability of neutral and zwitterionic solvated dialanine 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

Dialanine molecule in both neutral and zwitterionic form were modeled using molecular modeling software Avogadro.³¹ The molecular modeling software VEGA³² was used to construct water layers of 3.0, 3.5, 4.0, 4.5 and 5.0 Å from dialanine, 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 theory³³ implemented in the GAMESS-US software suit.^{34,35} To obtain the energies of the zwitterionic form of hydrated dialanine 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 3.0 Å water layer consisting of 15 and 14 water molecules for the neutral and zwitterion, respectively, one water molecule in the neutral system, which is far away from the solute, was removed. The energies of hydrated dialanine, free solute and solvent (EFP) for the neutral and zwitterionic forms were carried out at the MP2/cc-pVDZ level of theory.



Fig. 1. Optimized structures of dialanine in (a) neutral and (b) zwitterionic form. (Red-O, Blue-N Gray-C and Gray small size-H)









(e) Fig. 2. Optimized structures of hydrated neutral systems in different water layers of (a) 3.0 (b) 3.5 (c) 4.0 (d) 4.5 and (e) 5.0 Å







Fig. 3. Optimized structures of hydrated zwitterionic systems in different water layers of (a) 3.0 (b) 3.5 (c) 4.0 (d) 4.5 and (e) 5.0 Å

3. Results and Discussion

Figure 1 depicts the optimized solute structure of the neutral and zwitterionic dialanine. Figure 2 and Figure 3 display **the** hydrated neutral and zwitterionic dialanine, respectively in different water layers. To study the relative stabilities of hydrated zwitterionic dialanine systems by comparing their energies with those of the

hydrated neutral systems, the relative energy E^{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 dialanine 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

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

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

and the relative energy can be decomposed as

$$E^{tot} = E^{solu} + E^{solv} + E^{solu-solv}$$
(4)

where $E^{solu} = E^{solu, zwit} - E^{solu, neu}$ describes the relative stability of two forms of dialanine without solvent, $E^{solv} = E^{solv,zwit} - E^{solv,neu}$ describes the stability of solvent in the two hydrated forms of dialanine, and $E^{solu-solv} = E^{solu-solv,zwit} - E^{solu-solv,neu}$ is the relative value of the solute-solvent interactions in the two forms of dialanine. Table 1 presents the total relative energy with the incremental thickness of EFP water layers. The plus sign in the relative energies means that the neutral system is more stable, as may be seen in Eqs. (2) and (3). The relative energy contributions within the solute molecules, E^{solu} in the second column (the standalone solute energies) do not change very much with the increase in the number of water layers. The neutral system always gains stability relative to the zwitterion. The solvent internal energies, E^{solv} (third column in Table 1), increase with the number of water layers but not monotonically. This implies that the hydrogen bond networks of the water clusters under the influence of neutral dialanine are always more strongly bound. In contrast, the fourth column of Table 1 (the solute–solvent interaction energy: $E^{solu-solv}$) 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 E^{solv}). The values of E^{solv} and $E^{solu-solv}$ 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 E^{solv} values. The opposite tendency is found for the neutral systems. The total relative energies, E^{tot} in the fifth column of Table 1 are positive for the water layers of thickness 3.0, 3.5 4.5 and 5.0 Å. This means that there is no qualitative change in the relative neutral-zwitterion stabilities as the number of water molecules increases; the hydrated neutral systems are always more stable. For the 3.0 and 3.5 Å water layer system, the relative energy is nearly zero and for 4.0 Å water layer system, the relative energy is negative. Even though the neutral system gains relative stability in water layers of 3.0, 3.5 4.5 and 5.0 Å, the zwitterionic system dramatically gains the relative stability at the 4.0 Å water layer. The interaction between the COO- and NH3+ groups of zwitterionic dialanine and nearby water molecules strongly contributes to the stability of the zwitterion. According to the optimized geometries of zwitterionic dialanine with 3.0, 3.5, 4.0, 4.5 and 5.0 Å water layers, 3, 5, 5, 4, 3 water molecules directly interact with the COO- group and 2, 3, 3, 2, 3 water molecules interacting with the NH3+ group, respectively.

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

Water layer (Å)	E^{solu}	E solv	$E^{solu-solv}$	E ^{tot}
3.0 (14)	202.35	83.89	-284.79	1.46
3.5 (19)	221.94	112.16	-333.70	0.40
4.0 (31)	240.75	174.23	-430.69	-15.70
4.5 (43)	260.07	218.82	-469.39	9.50
5.0 (58)	226.02	239.21	-444.08	21.15

Tables 2 and 3 list the interaction energies of the COO– and NH3+ groups with water molecules forming hydrogen bonds with these groups as a function of the incremental water layers and the corresponding optimized hydrogen bond lengths, respectively. The interaction energies are obtained as follows: the solute and the number of interacting water molecules forming hydrogen bonds directly with the carboxyl group are extracted from the fully solvated system. Then, the interaction energies between the solute and these water molecules are computed by infinitely separating the solute and this small water cluster. This is a very important test of the performance of the EFP method because it describes a very strong interaction between ionic (COO-nad NH3+) groups and water molecules, which appears to be difficult for continuum models such as PCM.³⁶

It is interesting that the interaction energies E^{int} between ionic groups of zwitterionic system and interacting water molecules shown in Table 2 reach more than 50% of the total solute–solvent interaction energies. It can be seen in Table 2 that more number of water molecules in the 3.5 and 4.0 Å layer interact more strongly with the ionic group than do the nearest neighbor waters in the 3.0, 4.5 or 4.5 Å layers. This may be because the larger clusters have only six direct solute–solvent hydrogen bonds, while the 3.5 and 4.0 Å clusters has eight direct hydrogen bonds.

Table 2. Interaction energy E^{int} (kJ/mol) between the zwitterionic dialanine and water molecules forming hydrogen bonds with the COO– and NH3+ groups with the cc-pVDZ basis set (extracted from the large fully optimized structures with the thickness of water layers given in angstrom).

Water layer (Å)	No. of water molecul	es forming H-bonds with	$E^{ m int}$	
	COO- group	NH3+ group		
3.0	2	3	-320.33	
3.5	3	5	-398.66	
4.0	3	5	-377.19	
4.5	2	4	-297.19	
5.0	3	3	-278.09	

Table 3. Hydrogen bond lengths (angstrom) between the COO– and NH3+ groups of the hydrated zwitterionic dialanine and EFP water molecules (optimized with cc-pVDZ). The numbers of water molecules are given in parentheses

Water layer (Å)	Hydrog	en bond le	ngths with	1				
	COO- group				NH3+ group			
3.0 (3, 2)	1.86	1.914	1.918	-	-	1.662	1.823	-
3.5 (5, 3)	1.888	1.959	1.893	1.759	1.952	1.96	1.807	1.873
4.0 (5, 3)	1.978	1.868	1.845	1.926	1.833	1.839	1.714	1.978
4.5 (4, 2)	1.971	1.821	1.877	1.831	-	1.841	1.86	-
5.0 (3, 3)	1.98	1.829	1.902	-	-	1.814	1.777	1.934

4. Conclusion

In this study the geometry optimization of hydrated neutral and zwitterionic dialanine in water layers of 3.0, 3.5, 4.0, 4.5 and 5.0 Å is carried out via RHF/EFP model. The hydrated neutral dialanine is more stable than the zwitterionic form. An interesting finding is that the stabilities do not increase monotonically with the water cluster size.

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