Microsolvation effect on alanine: a many-body interaction study using ab initio method

Ajay Chaudhari, Prabhat K. Sahu, Shyi-Long Lee*

Department of Chemistry and Biochemistry, National Chung-Cheng University, Ming-Hsiung, ChiaYi 62104, Taiwan

Received 11 November 2003; accepted 24 June 2004
Available online 7 August 2004

Abstract

The interaction between alanine and three water molecules is studied using ab initio method and 6-311+G* basis set. Various structures for alanine–(water)3 complex are investigated. Four different lowest energy structures are reported. Many-body analysis is also carried out to obtain relaxation energy and many-body energies (two, three and four-body). Out of the four conformers, the most stable conformer has basis set superposition error corrected total energy \( K_{550.0962701} \) hartree and binding energy \( -38.04 \) kcal/mol. Many-body analysis shows that two and three-body interaction energies have significant contribution to the binding energies, whereas four-body interaction energies are negligible as compared to two and three-body interaction energies.

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Keywords: Many-body interaction; Ab initio method; Alanine–water complex

1. Introduction

Amino acids are the basic structural units of proteins. All peptides and polypeptides are polymers of alpha-amino acids. Since amino acids have the capability of reacting with both acid and base, they naturally act as buffers. Amino acids are always in ionic form in aqueous solutions. The simplest member of this group is glycine, where the saturated carbon atom is un-substituted, rendering it optically inactive. Alanine is the next simplest amino acid having distinct enantiomeric structures and is involved in the metabolism of tryptophan and the vitamin pyridoxine. It is one of the simplest amino acids with respect to molecular structure and is one of the most widely used in protein construction, averaging about 9% of average protein composition on a per-mole basis when compared with the other amino acids.

The amino acids are known to exist in solution and in crystalline phase as zwitterions [1–3]. Knowledge of interaction of water with amino acid is important for the ultimate understanding of protein hydration and the role of water in biological systems. There are various investigations reporting structure, stability and solvent effect on amino acid [4–19]. Most of these studies are on the simplest amino acid, the glycine. In these studies, it has been shown that the zwitterionic form of amino acid is stabilized by the aqueous media. Recently, it has been shown that [20] one water molecule does not stabilize the zwitterionic form of glycine. In microscopic solvent effect on the solute structure, few water molecules are attached to the appropriate site of a solute molecule through hydrogen bonding. It has been shown that both, bulk and microscopic solvent effect, changes the molecular properties in the same way [21,22], but in microscopic solvent effect we get additional information on how different many-body interaction energies contribute to the binding energy and also on hydrogen bonding. To the best of our knowledge, there is no study that reports how many-body interaction energies (1,2,…,n body) contribute to the binding energy in alanine–water complex.

The aim of this article is to study alanine–(water)3 complex at HF/6-311+G* level of theory. Many-body
analysis [23–28] is applied to obtain two, three and four-body interaction energies. The chemical hardness and chemical potential is also calculated. The letter is structured as follows. The computational details are given in Section 2. Section 3 gives the brief summary of the energy decomposition scheme including correction for basis set superposition error (BSSE) by using counterpoise method and generalized counterpoise method [29–31]. Results are presented in Section 4. Finally, the conclusions are inferred in Section 5.

2. Computational details

Different conformers of alanine–(water)₃ were investigated and four optimized conformers are reported in this study at HF/6-311 + G* level. The optimized geometries are shown in Fig. 1. The alanine considered here is in zwitterionic form as the aqueous media stabilize the zwitterionic form of amino acids. For hydrogen bonded systems, it is expected that both diffuse and polarization function may be necessary in the basis set. The calculations are performed using GAUSSIAN 98W program [32].

3. Energy decomposition

Many-body energies (two, three and four-body interaction energies) are calculated as follows. The decomposition of the total energy of the complex can be written as

\[
\Delta E = E(1234) - \{E_A + 3E_W\}
\]

\[
= \sum_{i=1}^{4} E(i) - \{E_A + 3E_W\} \quad \text{(relaxation energy)}
\]

\[+ \sum_{i=1}^{3} \sum_{j=1}^{4} \Delta^2 E(ij) \quad \text{(two-body energy)}\]

\[+ \sum_{i=1}^{2} \sum_{j=1}^{3} \sum_{k=1}^{4} \Delta^3 E(ijk) \quad \text{(three-body energy)}\]

\[+ \Delta^4 E(1234) \quad \text{(four-body energy)} \quad (1)\]

where \(E(i), E(ij), E(ijk), E(1234)\) are the energies of the various monomers, dimers, trimers, and tetramer in the complex and \(E_A, E_W\) are the energies of isolated alanine and water molecules, respectively. The pairwise two-body interaction energies and higher three and four-body interaction energies are defined as the following equations.

\[
\Delta^2 E(ij) = E(ij) - \{E(i) + E(j)\} \quad (2)
\]

\[
\Delta^3 E(ijk) = E(ijk) - \{E(i) + E(j) + E(k)\}
\]

\[= \{\Delta^2 E(ij) + \Delta^2 E(ik) + \Delta^2 E(jk)\}, \quad (3)\]

Fig. 1. Four conformers of alanine–(water)₃ complex.

The BSSE corrected energy of a subsystem (ijkl) is evaluated in the full basis of a larger system (1234), and denoted by the term $E(ijk|1234)$. Accordingly, the $n$-body terms are substituted with the BSSE corrected ones:

\[
\Delta^3 E_{C}(ijkl) = E(ijk|1234) - \{E(i|1234) + E(j|1234) + E(k|1234) + E(l|1234)\}
\]

\[
\Delta^3 E_{C}(ijklk) = E(ijk|1234) - \{E(i|1234) + E(j|1234) + E(k|1234)\} - \{E(l|1234) + E(2|1234)\} - \{E(3|1234) + E(4|1234)\} - \{\Delta^2 E(12|1234) + \Delta^2 E(13|1234) + \Delta^2 E(14|1234) + \Delta^2 E(23|1234) + \Delta^2 E(24|1234) + \Delta^2 E(34|1234)\} - \{\Delta^3 E(123|1234) + \Delta^3 E(124|1234) + \Delta^3 E(134|1234) + \Delta^3 E(234|1234)\} (7)

The sum of relaxation energy, two-body energy, three-body energy and four-body energy gives the total binding energy of the complex. The BSSE corrected total energy is calculated as suggested by Valiron and Mayer [30].

### 4. Result and discussions

The four optimized structures for alanine–(water)$_3$ complexes are shown in Fig. 1. In structures I, II and III, the three water molecules are attached to the amino group of the alanine and in structure IV those are attached to the carboxylic group of alanine. Selected optimized geometries for these complexes are listed in Table 1. The BSSE corrected total energies for these four structures are given in Table 2. It can be seen from Table 2 that the conformers I and II have the lowest and highest BSSE corrected total energy, respectively, indicating that conformer I is the most stable.
stable and conformer II is the most unstable structure among the four. On comparing the hydrogen bonding distances $H_2$–$O_{14}$ and $H_{12}$–$O_{17}$ in conformer I and II, it is observed that these distances are longer in conformer I than those in conformer II. The BSSE corrected total energies of these four conformers differ within 8 kcal/mol. The total energies of conformer I and IV differ only by 1.25 kcal/mol.

In order to calculate the many-body interaction energies, the alanine–(water)$_3$ complex is divided into two, three and four-body terms, relaxation energy of the monomers, i.e. alanine and three water monomers in a complex. There are four monomers, six dimers, four trimers and one tetramer in a complex. The calculated values of BSSE corrected many-body interaction energies using Eqs. (5)–(7) are listed in Table 3. The most stable conformer I has the highest binding energy ($-38.04$ kcal/mol). From the two-body interaction energies, it can be seen that the interaction between alanine and water (A–W$_1$, A–W$_2$ and A–W$_3$) is attractive for all the four conformers. W$_1$–W$_2$ interaction is repulsive for all the four conformers. W$_1$–W$_3$ conformer is repulsive for conformer I and attractive for all other conformers whereas W$_2$–W$_3$ interaction is repulsive for conformer I and II and is attractive for III and IV. The highest two-body interaction energy ($-18.44$ kcal/mol) is found for A–W$_1$ in conformer I among all the two-body interaction. It is also observed that alanine–water interaction has more contribution to total two-body energies than water–water interaction for all the conformers. The W$_1$–W$_2$ has little contribution to total two-body energy than W$_1$–W$_3$ and W$_2$–W$_3$. It can also be seen that W$_1$–W$_3$ has significant contribution to total two-body energies for conformers II, III and IV whereas W$_2$–W$_3$ has more contribution for conformer IV only since there is direct interaction in W$_2$ and W$_3$ for this conformer. From the values of total two-body energies, it can be concluded that the two-body interaction has significant contribution to binding energy. The two-body interaction is attractive for all the conformers and is highest for conformer I and lowest for conformer III. The total two-body interaction energy for conformer I is largest among the four since in conformer I, there is direct hydrogen bonding interaction of alanine and three water molecules without any bonding interaction among the three water molecules which results in large values of two-body interaction energies. The two-body interaction energy is always larger when there is direct hydrogen bonding between the two molecules than when there is indirect interaction.

From three-body interaction energies, it can be seen that A–W$_1$–W$_2$ interaction is repulsive for all the conformers. A–W$_1$–W$_3$ and A–W$_2$–W$_3$ interaction is attractive for conformer I only and repulsive for all others. In contrast, W$_1$–W$_2$–W$_3$ interaction is repulsive for conformer I and attractive for rest of the three. The highest three-body interaction is found for conformer III ($-3.81$ kcal/mol) in A–W$_1$–W$_3$. The total three-body interaction energy values indicate that the three-body interaction is repulsive for conformer I and is attractive for other three. The highest total three-body contribution is found in conformer IV ($-4.17$ kcal/mol). The most stable conformer I has little three-body contribution since in this conformer there is no direct interaction between the water molecules.

As compared to the two and three-body interaction energies, the four-body interaction energy is very small and has very little contribution to the binding energy as can be seen from Table 3. The relaxation energy, which is a measure of the degree of strain that drive the structural distortion of individual molecule in the complex, is highest (5.52 kcal/mol) for the alanine. It indicates larger geometrical changes when three water molecules formed three hydrogen bonds with the three hydrogen atoms of amino group of alanine, without any bonding among the water molecules.

The chemical hardness ($\eta$) and chemical potential ($\mu$) [33] are two important quantities, which are of great use in characterizing the chemical system. These are calculated as

$$\eta = (I - A)/2 \quad \text{and} \quad \mu = -(I + A)/2$$
where $I = -E_{\text{HOMO}}$ and $A = -E_{\text{LUMO}}$. $I$ and $A$ are the ionization potential and electron affinity of the molecules.

Table 4 gives the values of $\eta$ and $\mu$. The stability of the conformer I is confirmed by the values of $\eta$ and $\mu$. It can be concluded that the conformer I is found to be most stable among the four conformers studied, according to Maximum Hardness Principle (MHP) [33,34].

5. Conclusions

Four conformers of alanine–(water)$_3$ complex using HF/6-311+G* method are reported. We have applied many-body analysis to obtain the two, three and four-body interaction energies. It has been shown that two and three-body interaction energies have significant contribution to the total binding energy whereas four-body interaction energies are negligible. The stability of the conformer with lowest BSSE corrected total energy is confirmed by the chemical hardness and chemical potential values.

Acknowledgements

The financial support from the National Science Council, Taiwan is gratefully acknowledged.

References