STRUCTURES AND ENERGETIC OF THE H-BOND NETWORKS IN AQUEOUS SOLUTION OF ALANINE

Kritsana Sagarik and Natthiya Deeying

School of Chemistry, Institute of Science, Suranaree University of Technology, Nakhon Ratchasima 30000, Thailand

ABSTRACT: Structures and energetic of the hydrogen bond (H-bond) networks in aqueous solutions of alanine (Ala) were investigated using various computational techniques. The test-particle model (T-model) was applied in the calculations of the intermolecular potential between Ala and water. Various conformations of Ala were considered in Molecular Dynamics (MD) simulations and hydration free energy calculations. In the present work, the Thermodynamic Integration (TI) method was proven to be the most suitable approach for the hydration free energy calculations. The behavior of water molecules in the H-bond networks at the functional groups of Ala was analyzed and discussed based on Probability Distribution (PD) maps and potential energy landscapes. The preferential conformation of Ala in aqueous solution inferred from the hydration free energy profile is to be ϕ = 180 and ψ = 200 degree.

KEYWORDS: H-bond, alanine, T-model, molecular dynamics simulations, hydration free energy

1. INTRODUCTION

Interactions between water and functional groups of proteins are of primary important in determining the conformational stability of proteins (Gregory 1994). In general, in order to study the most stable conformations of proteins in aqueous solution, simple low molecular weight compounds, such as amino acids and peptides, have been selected as model molecules in theoretical and experimental investigations. In the past decades, attempts have been made to discover basic principles behind protein-folding pathway, *e.g.* in terms of solute-solvent and solvent-solvent interactions. Although various models have be proposed, it has been generally accepted that the information on solvent effects on conformational equilibrium, inferred from statistical mechanical methods such as Monte Carlo (MC) and Molecular Dynamics (MD) simulations, are the most accurate (Leach 1996). This has been accomplished through the hydration free energy calculations. In the present study, solvent effects on the conformation of amino acids were investigated using alanine (Ala) as a model molecule. Since the three-dimensional structures of the hydrogen bond (H-bond) networks at the functional groups of Ala were also of interest, an explicit water model was adopted (Leach 1996). The T-model potential was constructed to describe the interaction between Ala and water. It was applied in MD simulations of the hydration structures and energies of Ala in aqueous solutions ($[Ala]_{aq}$). In the present theoretical treatment, hydration free energy calculations were made using MD simulations in combinations with the Thermodynamic Integration (TI) method. The results were analyzed and discussed in comparison with available theoretical and experimental data of the same as well as similar systems.

2. COMPUTATIONAL METHODS

2.1 MD simulations

The derivation of the T-model was presented in detail elsewhere (Böhm 1984). In MD simulations, an Ala molecule and three hundred water molecules were put in a cubic box subject to periodic boundary conditions. In the course of MD simulation, the density and temperature of $[Ala]_{aq}$ were maintained at 1.0 g/cm^3 and 298 K, respectively. About fifty thousand MD steps were devoted to the

equilibration and fifty thousand steps to property calculations. Each MD step was equal to 0.0005 ps. The three-dimensional structures of the H-bond networks in the first hydration shells of Ala were visualized and analyzed based on the oxygen probability distribution (PDO) maps. The same approaches were applied in the calculations of the average solute-solvent (AWPD) and solvent-solvent interaction energy probability distribution (WWPD) maps. The average potential energy landscapes of the H-bond networks were constructed from the total average interaction energy distribution (AW-WWPD) maps. The average geometries of the H-bonds and the behavior of water molecules in the first hydration shells were anticipated from the average H-bond distances ($< R_{A-H..B} >$) and angles ($< \theta_{A-H..B} >$) and the H-bond lifetimes ($< t_{A-H..B} >$), respectively.

2.2 Hydration free energy calculations

The conformation of Ala was described by two torsion angles, ϕ and ψ. They are show in Figure 1.

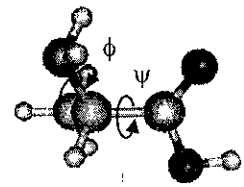


Figure 1. Geometry of Ala with torsional angle ϕ and ψ.

The hydration free energy profiles for $[Ala]_{aq}$ were derived from MD using the TI method (Mezei 1986), with double-wide sampling scheme. The hydration free energy difference (ΔA) was computed from simple numerical integration formula,

$$\Delta A = \frac{1}{N}\sum_{i=1}^{N}[V(1)-V(0)]_i \qquad (1)$$

where N is the number of MD steps and $[V(1)-V(0)]_i$ is the difference between the potential energy of $[Ala]_{aq}$ at MD step i and step i -1.

3. RESULTS AND DISCUSSION

3.1 Hydration structures of $[Ala]_{aq}$

The PDO maps in Figure 2 show well defined H-bond networks at the O-H and N-H groups. The important ones are labeled with **A**, **D**, **E** and **S**, respectively. Water molecules at **A** act as proton acceptor towards the OH group, whereas the ones at **D** acts simultaneously as proton acceptor and donor, towards the N-H group and O atom, respectively. Water molecules at **S** are above the NH_2 group. According to the probability densities on the PDO maps, the degree of hydration decreases in the order of **A** > **E** > **S** > **D**. However, the information from the AWPD maps indicates that the stability order based on the solute-solvent interaction energies is written as **A** > **S** > **D** > **E**. When the solvent-solvent interactions were taken into account in the AW-WWPD maps, the stability order changes to **S** > **A** > **D** > **E**. The discrepancy between the degree of hydration obtained from PDO maps and the stability order derived from the AW-WWPD maps, as well as the behavior of water molecules in the H-bond networks can be explained using the shapes of the average potential energy landscapes displayed in Figure 3 and the H-bond lifetimes in Table 1. Although the water molecules at **A** do not possess the lowest total average interaction energy in the stability order, the average potential energy landscapes of the H-bond network at **A** are rather narrow and shallow. This seems to restrict the motions of water molecules at **A**, compared to the others, leading to a long H-bond lifetime, $< t_{O\text{-}H..Ow} >$ of about 83 %.

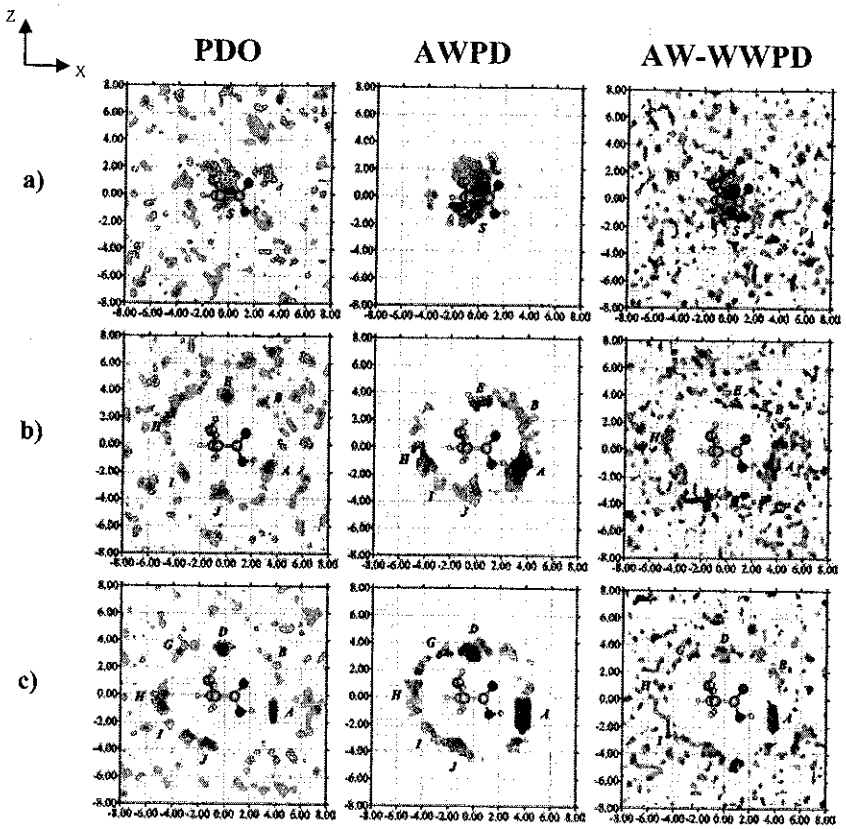
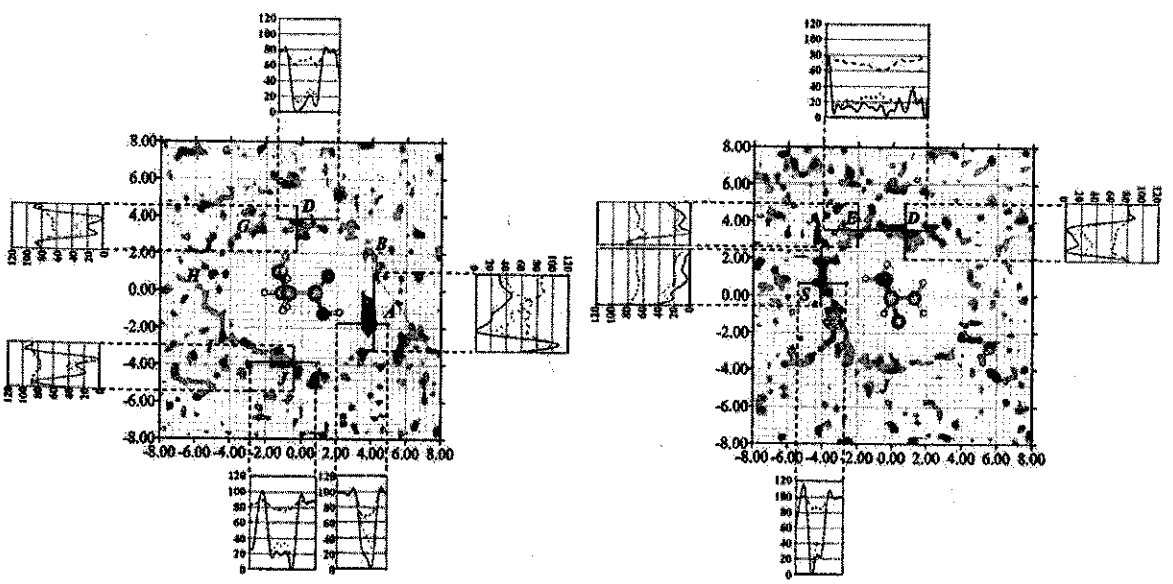


Figure 2. The PDO, AWPD and AW-WWPD of $[Ala]_{aq}$ derived from MD, a) Y = 3.0 to 4.0 Å, b) Y = 1.0 to 2.0 Å and c) Y = -1.0 to 0.0 Å.



a) Y = -1.0 to 0.0 Å **b) X = -1.0 to 0.0 Å**

Figure 3. The average potential energy landscapes of the H-bond networks.

Table 1. Some average H-bond distances (< $R_{A\text{-}H..B}$ >) and angles (< $\theta_{A\text{-}H..B}$ > as well as the H-bond lifetimes (< $t_{A\text{-}H..B}$ >) derived from MD simulations.
SD = Standard Deviation.
A-H..B = H-bond donor-acceptor pair between molecules A and B.
Distance and angle are in Å and degree, respectively.

H-bond			SD	H-bond			SD
N-H1..Ow	$< R_{N\text{-}H1..Ow} >$	3.30	0.26		$< R_{O\text{-}H..Ow} >$	2.93	0.24
	$< \theta_{N\text{-}H1..Ow} >$	14.99	8.65		$< \theta_{O\text{-}H..Ow} >$	21.22	11.48
	$< t_{N\text{-}H1..Ow} >$	64.68	-		$< t_{O\text{-}H..Ow} >$	83.18	-
N-H2..Ow	$< R_{N\text{-}H2..Ow} >$	3.27	0.29	Ow-Hw..O-H	$< R_{Ow\text{-}Hw..O\text{-}H} >$	3.22	0.30
	$< \theta_{N\text{-}H2..Ow} >$	29.78	11.91		$< \theta_{Ow\text{-}Hw..O\text{-}H} >$	40.00	12.39
	$< t_{N\text{-}H2..Ow} >$	46.48	-		$< t_{Ow\text{-}Hw..O\text{-}H} >$	8.00	-

3.2 Hydration free energies of $[Ala]_{aq}$

The hydration free energy profiles in Figure 4 suggest that the most preferential hydration of Ala in aqueous solution is represented by ϕ = 180 and ψ = 200 degree.

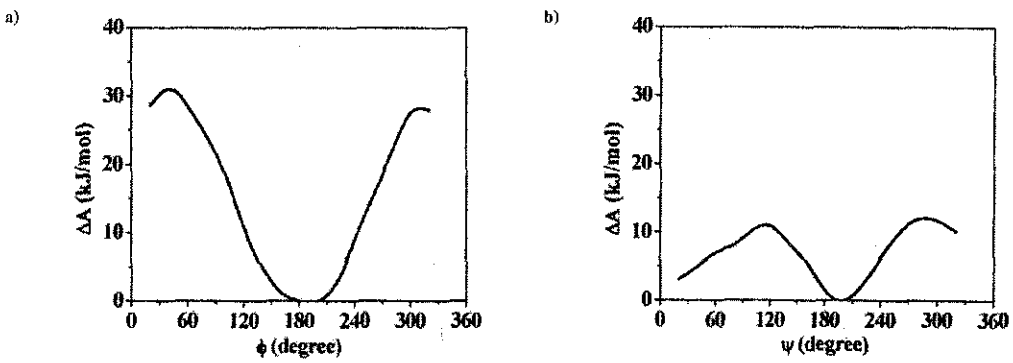


Figure 4. Hydration free energy profiles for the $[Ala]_{aq}$,
a) ϕ varies from 0 to 360 degree
b) ψ varies from 0 to 360 degree (with ϕ = 180 degree).

4. REFERENCES

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