

FREE ENERGY OF HYDRATION FOR ALANINE ZWITTERION

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ABSTRACT: Molecular Dynamics (MD) simulations in combination with Thermodynamic Integration (TI) method were applied in the calculations of hydration structures and energetic of alanine zwitterion (Alaz) in aqueous solutions ($[Alaz]_{aq}$). The investigations started with construction of the Test-particle model (T-model) potential to describe the interaction between water and Alaz, followed by MD simulations of $[Alaz]_{aq}$ at 298 K. The MD results suggested the hydration free energy profiles as well as the shapes of the potential energy landscapes of the hydrogen bond (H-bond) networks at the charged functional groups of Alaz. The information on the three-dimensional structures and the dynamic behavior of water molecules in the vicinities of the functional groups of Alaz in aqueous solutions was discussed in detail.

KEYWORDS: alanine zwitterion, free energy, thermodynamic integration

1. INTRODUCTION

Information on the relative free energy of hydration (ΔA) is essential in the study of hydration effects on the conformation and stability of amino acid. Theoretical values of ΔA for glycine (Glyz) and alanine (Alaz) zwitterions were presented based on implicit and explicit solvent models [Watanabe *et al.*, 1997; Kikuchi *et al.*, 1997; Truong & Stefanovich, 1995]. It is therefore of interest to gain additional information on the structures and energetic of the H-bond networks in the vicinities of solute molecules. In order to understand the behavior of water molecules, especially in the first hydration shell of solute, Alaz in aqueous solution ($[Alaz]_{aq}$) was chosen as a model system. To investigate the effects of conformation change on the H-bond networks at the charged functional groups of amino acid, two forms of alanine zwitterion in aqueous solutions ($[Alaz]_{aq}$ and $[Alaz-R]_{aq}$) were considered. The structures of Alaz and Alaz-R are included in Fig. 1. Alaz was found in the crystalline state [Lehmann *et al.*, 1972], whereas Alaz-R was reported to be the most stable form in aqueous solution [Kikuchi *et al.*, 1997]. Alaz-R is represented by the COO⁻ plane being 90° with respect to the NC^αC backbone plane. In the present investigation, MD simulations with the TI method were applied in the calculations of ΔA of $[Alaz]_{aq}$. The three-dimensional structures of the H-bond networks were analyzed and displayed using various probability distribution (PD) maps.

2. COMPUTATIONAL DETAILS

2.1 Thermodynamic Integration

The free energy calculations with TI technique were made by performing a series of MD simulations corresponding to discrete values of integration variable or coupling parameter (λ) between the two systems of interest [Cramer, 2002]. Given an initial state A at $\lambda = 0$ and final state B at $\lambda = 1$, ΔA can be approximated by integration over λ using the following expression:

$$\Delta A = \langle A \rangle_B - \langle A \rangle_A = \int_0^1 \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda} d\lambda \approx \sum_{\lambda=0}^1 \left\langle \frac{\partial E}{\partial \lambda} \right\rangle_{\lambda} d\lambda \quad (1)$$

2.2 MD Simulations

NVE-MD simulations were performed on $[\text{Alaz}]_{\text{aq}}$ and $[\text{Alaz-R}]_{\text{aq}}$ at 298 K, based on the T-model [Böhm *et al.*, 1982, 1984]. In each MD run, a rigid solute and 300 water molecules were put in a cubic box subject to periodic boundary conditions. The density of the aqueous solution was maintained at 1.0 g cm^{-3} . The cut-off radius was half of the box length. The long-range Coulomb interaction was taken into account by means of the Ewald summations. The equilibration was made in 100,000 MD steps, with the time step of 0.5 fs. Additional 200,000 MD steps were devoted to property calculations. Structures and energetic of the H-bond networks of water at the NH_3^+ and COO^- groups of $[\text{Alaz}]_{\text{aq}}$ and $[\text{Alaz-R}]_{\text{aq}}$ were analyzed and visualized using the oxygen probability distribution maps, as well as the average solute-solvent and total-average interaction energies probability distribution maps, denoted by PDO, AWPD and AW-WWPD maps, respectively.

3. RESULTS AND DISCUSSION

3.1 Hydration structures of $[\text{Alaz}]_{\text{aq}}$ and $[\text{Alaz-R}]_{\text{aq}}$

Selected PDO, AWPD and AW-WWPD maps of $[\text{Alaz}]_{\text{aq}}$ and $[\text{Alaz-R}]_{\text{aq}}$ are displayed in Fig. 1. The dynamic behavior of specific water molecules in the H-bond networks of NH_3^+ groups of Alaz and Alaz-R was analyzed based on the average potential energy landscapes in Fig. 2.

The PDO maps in Fig. 1 reveal that water molecules form more well defined H-bond networks at the NH_3^+ group compared to the COO^- group. Five well-defined hydration sites, labeled with A, B, C, H and L, were found at the NH_3^+ group, whereas those with D, E, F and J at the COO^- group. L, A and H are located near H2, H3 and H4 of the NH_3^+ group, respectively. Water molecules at A seem to bridge between the NH_3^+ and CH_3 groups. The ones at H and L link between the NH_3^+ and COO^- groups. Fig. 1 shows that the H-bond networks at C link between the NH_3^+ and COO^- groups. This rules out the possibility for the intramolecular H-bond formation between the two charged functional groups. The PDO maps in Fig. 1 also shows that the hydration structures at the NH_3^+ and COO^- groups of $[\text{Alaz}]_{\text{aq}}$ and $[\text{Alaz-R}]_{\text{aq}}$ are not substantially different. However, Alaz-R is slightly more accessible by water. The AWPD and AW-WWPD maps in Fig. 1 indicate that the solute-solvent interaction energies and total interaction energies at the NH_3^+ group of are stronger than at the COO^- group. The shapes of the average potential energy landscapes in Fig. 2 suggest that the motion of water molecules at the NH_3^+ group is confined in shallow and narrow energy valleys. This allows the water exchange within the H-bond networks to take place easier and faster compared to the water exchange with outsides.

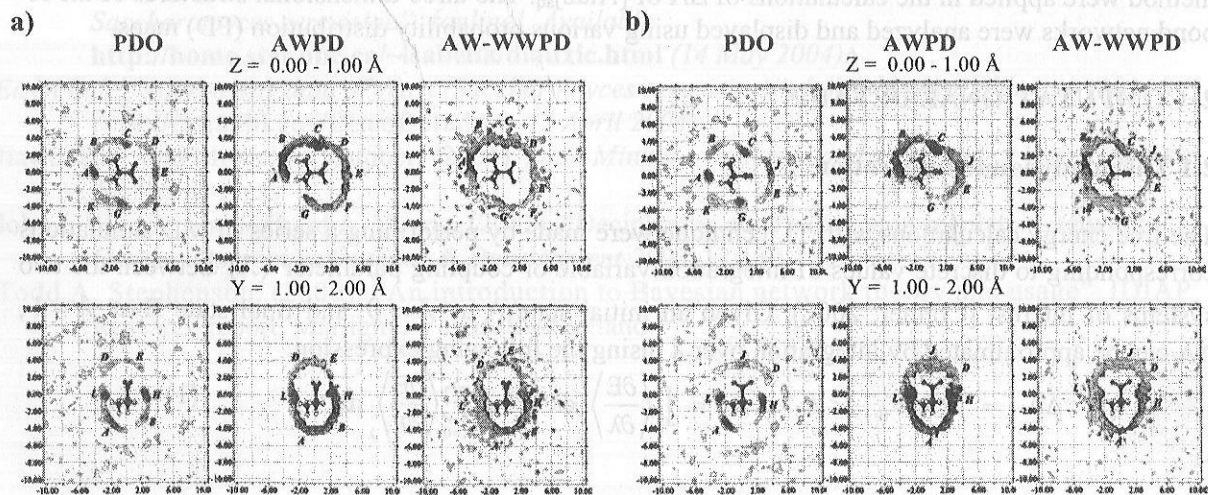


Figure 1. Selected PDO, AWPD and AW-WWPD maps derived from MD simulations.

a) $[\text{Alaz}]_{\text{aq}}$

b) $[\text{Alaz-R}]_{\text{aq}}$

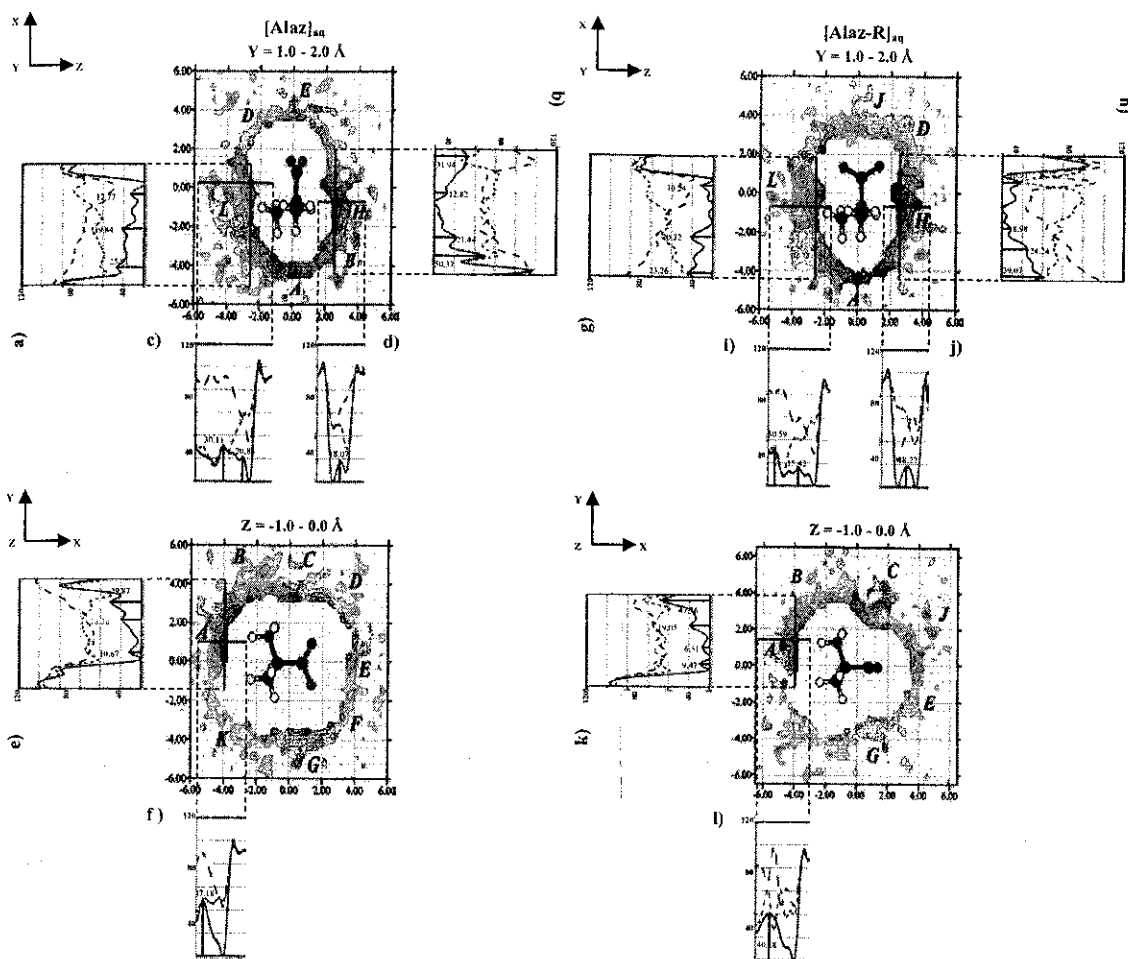


Figure 2. Average potential energy landscape at NH_3^+ group of Alaz and Alaz-R derived from MD simulations.

3.2 Relative Free Energy of Hydration

In the calculations of ΔA , conformation of Alaz was defined by two torsional angles ϕ and ψ , denoted by (ϕ, ψ) . ΔA were estimated from Eq. 1, in which E represents the average solute-solvent interaction energies obtained from MD simulations. The so-called total conformational free energies of hydration (ΔA^T) were also computed by adding the relative gas-phase energy barrier to rotation of the torsion angles to E . The variations of ΔA and ΔA^T with respect to conformation changes are illustrated in Fig. 3a and 3b, respectively. They are regarded as the ΔA and ΔA^T plots, respectively.

Fig. 3a shows at least two well-defined energy minima when ϕ was fixed at 58.30° and ψ varies from -18.66 to 91.34° . The lowest minimum on the ΔA plot is close to conformation **B**, $(58.30, 76.34)$. ΔA of conformations **B** and **A** differ by about 14 kJ mol^{-1} . The situation is different on the ΔA^T plot. Since the rotation of the COO^- groups reduces the partial π character on the $\text{NC}^\alpha\text{CO}$ planar structure, conformation **B** becomes about 13 kJ mol^{-1} less stable than **A**. On average, the rotation of ϕ , when ψ fixed at 76.34° , did not lead to significant effects on the ΔA plot in Fig. 3b. Due to the symmetry of the NH_3^+ group, comparable well-defined energy minima were observed on the ΔA plot. This makes believe that ΔA is not very sensitive to the rotation of the NH_3^+ group. However, since the rotation of the NH_3^+ group brought an H atom of the CH_3 adjacent to an H atom of the NH_3^+ group conformation **C**, with $(23.30, 76.34)$, is about 9 kJ mol^{-1} less stable than **B**, according to the ΔA^T plot.

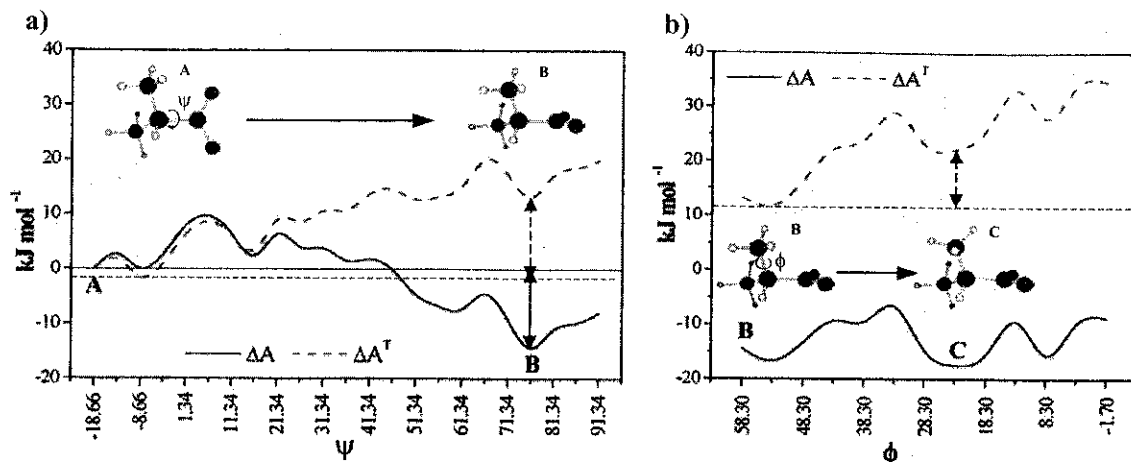


Figure 3. Variations of free energies of hydration with respect to the rotation of torsion angles.

a) ϕ fixed at 58.30° and ψ varied from -18.66 to 91.34° .

b) ψ fixed at 76.34° and ϕ varied from 58.30 to -1.70° .

4. CONCLUSION

In the present work, various theoretical methods were applied in the investigations of structures and energetic of $[\text{Alaz}]_{\text{aq}}$ and $[\text{Alaz-R}]_{\text{aq}}$. The MD results revealed that the three-dimensional structures of the H-bond networks of water in the first hydration shells of Alaz and Alaz-R are quite similar. However, the shapes of the average potential energy landscapes at the charged functional groups are different in details. This implies that the behavior of water molecules, such as the water exchange and residence time, is likely to be sensitive to conformation changes. In order to obtain a better insight into the hydration properties, the present results suggested to include explicitly water molecules in the model systems.

5. REFERENCES

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