STRUCTURES AND STABILITY OF MODEL SALT-BRIDGE INTERACTION IN AQUEOUS SOLUTION

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ABSTRACT: Structures and stability of model salt-bridge interaction in aqueous solution were investigated using complex formed from guanidinium (GN) and formate (FM) ions. The intermolecular potentials to describe the GN-H_2O, FM-H_2O and GN-FM interactions were constructed using the Test-particle model (T-model) and applied in Molecular Dynamics (MD) simulations of the aqueous solutions at 298 K. Although the charged hydrogen bonds (H-bonds) between GN and FM are quite strong, the hydration free-energy calculations showed the possibility for the solvent-separated structure in the aqueous solutions. The structures and energetic of the H-bond networks in the vicinities of the GN-FM complex were visualized and discussed based on probability distribution (PD) maps and the average potential energy landscapes.

KEYWORDS: T-model, guanidinium, formate, salt bridge, aqueous solution

1. INTRODUCTION

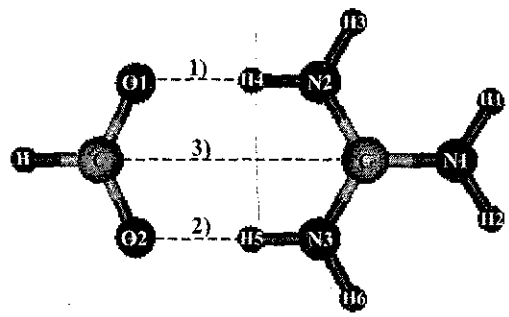
Structures and interaction energies of ion-pairs in proteins have been of interest since on average one-third of the charged residues in proteins involved in ion-pairs and 76 % of these are concerned with stabilizing the protein tertiary structures (Barlow 1983). Interaction among water, formate (FM), and guanidinium (GN) ions has been selected as model system in the study of salt-bridge interactions (Zheng 1996). In the present study, structures and energetic of the aqueous solutions of FM, GN and GN-FM complexes were investigated using MD simulations. The structures of the H-bond networks at the functional groups were displayed using various PD maps. The stability of the GN-FM complex in aqueous solution was anticipated from the free energy profile for hydration, inferred from the MD simulations.

2. COMPUTATIONAL METHODS

The T-model potentials to describe the GN-H_2O, FM-H_2O and GN-FM interactions were applied in NVE-MD simulations of the GN-FM complex in aqueous solution ($[(GN\text{-}FM)]_{aq}$) at 298 K. A GN-FM complex and 500 water molecules were put in a cubic box subject to periodic boundary conditions. The GN-FM complex was positioned at the center of the simulation box. The density of the aqueous solution was kept constant at 1 g ml^{-1}. Fifty thousand MD steps of 0.0005 ps were devoted to equilibration and another one hundred thousand steps to property calculation. Based on specified conditions, three series of MD simulations were performed on $[(GN\text{-}FM)]_{aq}$. The calculation of free energy of hydration was made using MD simulations in combination with the Thermodynamic Integration (TI) method (Meizei 1986). In order to ensure the reversible path in the free energy calculation, the distance between the center of mass of FM and GN was varied from 3 Å to 9 Å.

3. RESULTS AND DISCUSSION

The gas-phase equilibrium structure and interaction energy of the GN-FM complex, obtained from the T-model (Böhm 1984) are shown in Figure 1. The oxygen probability distribution (PDO) maps in Figure 2a show well defined H-bond networks in the vicinities of GN compared to FM. They are labeled with **G**, **D**, **A** and **C**, respectively. The shapes of the average potential energy landscapes in Figure 3 reveal that the motions of water molecules are confined in long and narrow energy valleys, spanning from O1 to H4 to H3 as well as from O2 to H5 to H6. This suggests that water molecules could move or exchange easier within the H-bond networks, compared to the water exchange between the first hydration shell and outside. The AWPD and AW-WWPD maps show that the GN-FM complex is quite stable in aqueous solutions. In the course of MD simulations, the H-bond lifetime ($< t_{N\text{-}H\ldots O} >$) in Table 1 amounts on average to 88 %. The relative free energy profile in Figure 4 shows two possible thermodynamic states which correspond to the ion-pair and solvent-separated structures. The solvent-separated structure is about 73 kJ mol^{-1} more stable than the ion-pair structure. The free energy barrier to the conversion from the ion-pair to solvent-separated structures is about 5 kJ mol^{-1}, whereas from the solvent-separated to ion-pair is about 78 kJ mol^{-1}.



$\Delta E^{T\text{-model}}$ = **-480.765 kJ mol^{-1}**

1) H4...O1 = 1.73 Å 2) H5...O2 = 1.73 Å
N2...O1 = 2.74 Å N3..,O2 = 2.74 Å
N2-H4...O1 = 177.67° N3-H5...O2 = 177.86°
3) C...C = 3.93 Å

Figure 1. Equilibrium geometry of GN-FM computed from T-model potential.

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

H-bond			SD	H-bond			SD
N2-H4...O1	$< R_{N2\text{-}H4\ldots O1} >$	3.02	0.32	N3-H5...O1	$< R_{N3\text{-}H5\ldots O1} >$	3.20	0.38
	$< \theta_{N2\text{-}H4\ldots O1} >$	23.27	11.90		$< \theta_{N3\text{-}H5\ldots O1} >$	30.02	11.61
	$< t_{N2\text{-}H4\ldots O1} >$	93.45	-		$< t_{N3\text{-}H5\ldots O1} >$	87.16	-
N2-H4...O2	$< R_{N2\text{-}H4\ldots O2} >$	3.24	0.41	N3-H5...O2	$< R_{N3\text{-}H5\ldots O2} >$	3.06	0.34
	$< \theta_{N2\text{-}H4\ldots O2} >$	30.69	13.00		$< \theta_{N3\text{-}H5\ldots O2} >$	23.17	12.03
	$< t_{N2\text{-}H4\ldots O2} >$	80.94	-		$< t_{N3\text{-}H5\ldots O2} >$	88.64	-

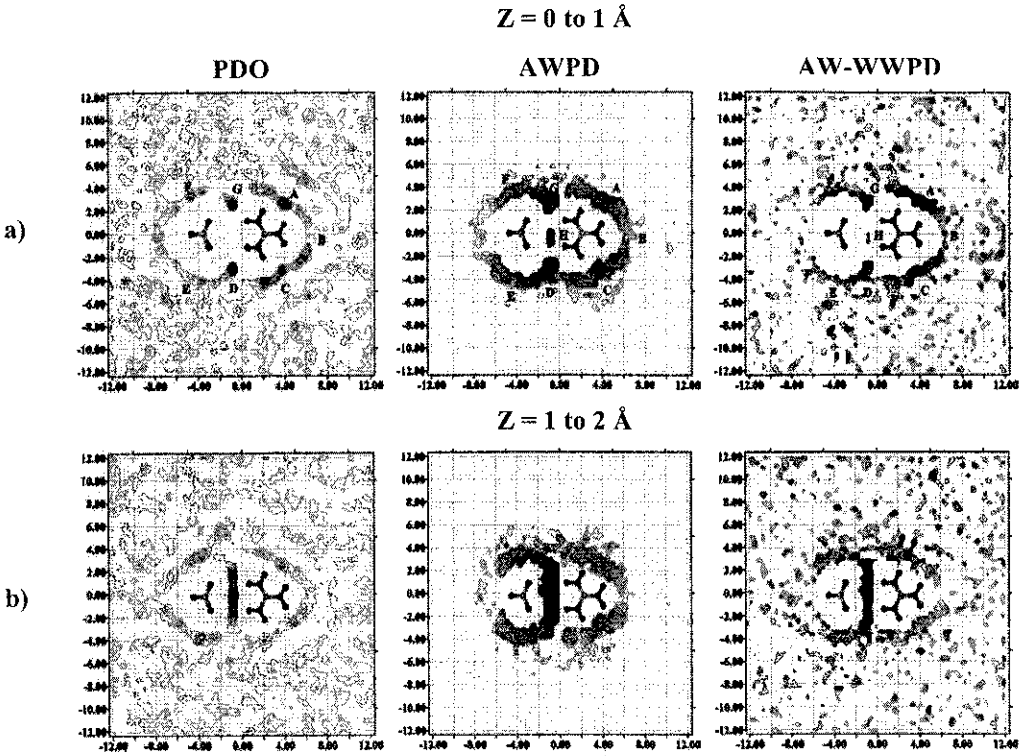


Figure 2. PDO, AWPD and AW-WWPD derived from MD simulations.
PDO = the oxygen probability distribution map.
AWPD = the average solute-solvent interaction energy probability distribution map.
AW-WWPD = total-average interaction energy probability distribution map.

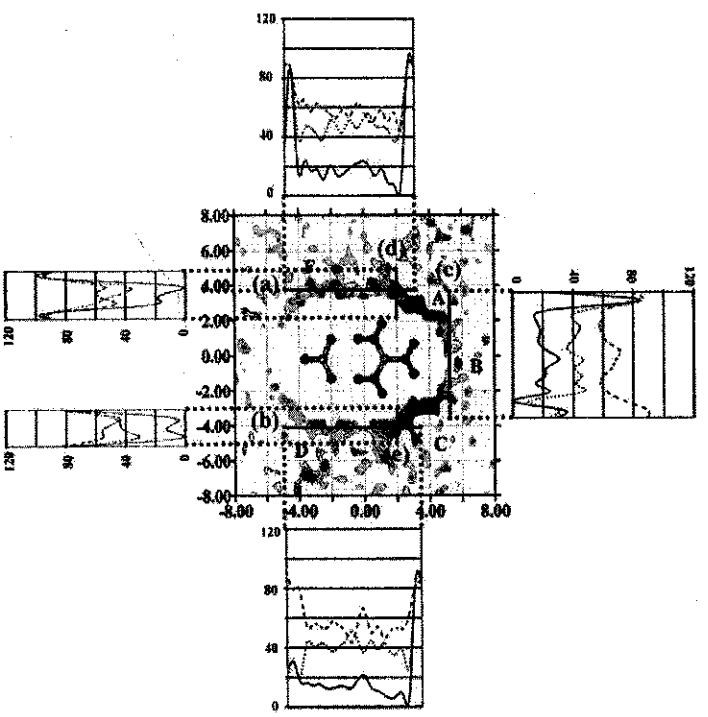


Figure 3. Average potential energy landscapes derived from MD simulations.

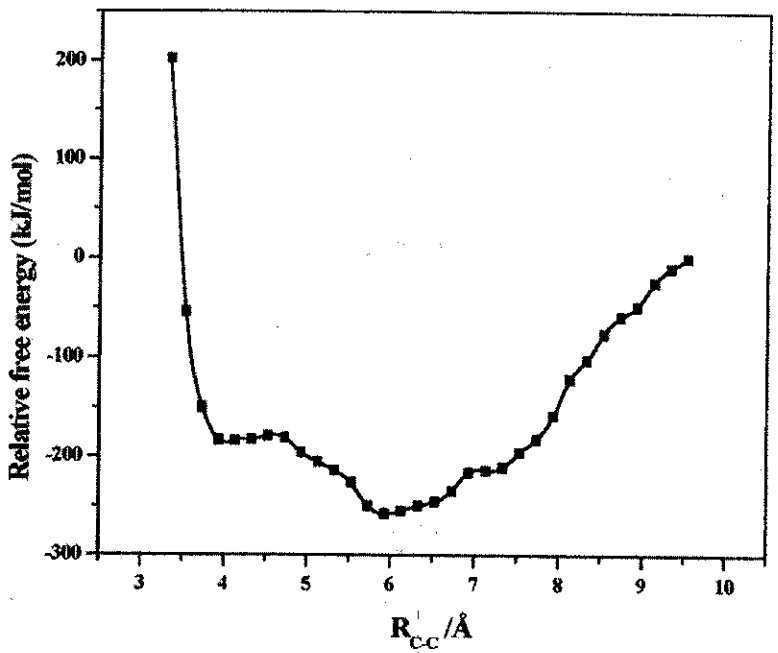


Figure 4. Free energy profile for $[(GN\text{-}FM)]_{aq}$.

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