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Biophysical Chemistry 117 (2005) 119 – 140

Biophysical Chemistry

http://www.elsevier.com/locate/biophyschem

Structures and stability of salt-bridge in aqueous solution

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Received 16 February 2005; accepted 21 April 2005

Abstract

Structures and stability of salt-bridges in aqueous solutions were investigated using a complex formed from the guanidinium (Gdm^+) and formate (FmO^-) ions as a model system. The Test-particle model (T-model) potentials to describe the interactions in the $Gdm^+–H_2O$, $FmO^-–H_2O$ and $Gdm^+–FmO^-$ complexes were constructed, tested and applied in molecular dynamics (MD) simulations of the aqueous solutions at 298 K. The three-dimensional structures and energetic of the hydrogen bond (H-bond) networks of water in the first hydration shells of the Gdm^+ and FmO^- ions, as well as the $Gdm^+–FmO^-$ complex, were visualized and analyzed using various probability distribution (PD) maps. The structures of the average potential energy landscapes at the H-bond networks were employed to characterize the stability and dynamic behavior of water molecules in the first hydration shells of the solutes. It was observed that water molecules in the first hydration shell of the close-contact $Gdm^+–FmO^-$ complex form associated H-bond networks, which introduce a net stabilization effect to the ion-pair, whereas those in the interstitial H-bond network destabilize and break the solvent-separated $Gdm^+–FmO^-$ complex. The present results showed that, in order to provide complete insights into the structures and stability of ion-pairs in aqueous solutions, explicit water molecules have to be included in the model calculations.

Keywords: Guanidinium; Formate; Salt-bridge; Ion-pair; Hydration

1. Introduction

Salt-bridges or ion-pairs have been of interest since, on average, one-third of the charged residues in proteins are involved in ion-pairs, and about 76% of these play important roles in stabilization of the protein secondary and tertiary structures [1,2]. Due to strong electrostatic interaction, salt-bridges have also been recognized to possess other specific functions to perform, especially in globular proteins [2]. They were suggested, for example, to act as active mediator for molecular recognition in enzymes and proteins [3–5]. About 40% of ion-pairs within proteins involve arginine–carboxylate (Arg–COO^-) interactions [2,6], e.g., the arginine–glutamate (Arg–Glu) and arginine–aspartate (Arg–Asp) side-chain interactions. Therefore, the guanidinium (Gdm^+) and formate (FmO^-) ions [7,8], as well as the methylguanidinium ($MGdm^+$) and acetate (AcO^-) ions [9,10], have been frequently chosen as model systems in the studies of ion-pair interactions between side-chains of proteins. It was pointed out based on 37 high-resolution protein structures that the most preferential structure for the Arg–COO^- interaction is represented by a planar structure, in which a single N–H···O–C hydrogen bond (H-bond) is the most common type of interaction; whereas double N–H···O–C H-bonds are also frequently found [6]. By extracting orientation information from protein coordinate data, in comparison with the results of electrostatic modeling of the $MGdm^+–AcO^-$ complex, the authors in Ref. [11] concluded that, due to the electrostatic domination, the so-called "side-on" and "end-on" doubly N–H···O–C H–bond configurations are the most favorable, with the side-on being slightly lower in energy. Additionally, the analysis of protein crystal structure data

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doi:10.1016/j.bpc.2005.04.012

[11] showed that the end-on structure is more preferential for the intermolecular interactions and the side-on for the intramolecular ones. According to a systematic geometric analysis of the Brookhaven Protein Data Bank (PDB), the stereochemistry of the side-chain H-bonds of proteins was pointed out to be characterized by at least three factors: (a) the electronic configuration of the H-bond acceptor atoms; (b) the steric accessibility of the H-bond donor atoms and; (c) the conformation of amino acid side-chains [12].

Several theoretical investigations were made on model salt-bridges in the gas phase, aqueous and non-aqueous solutions, using both continuum [8,9] and explicit solvent models [13,14]. When a continuum model with the self-consistent reaction field (SCRF) method was applied in the investigation of the $\mathrm{MGdm^+–AcO^-}$ complex in aqueous solutions ($[\mathrm{MGdm^+–AcO^-}]_{aq}$) [9], the solvent induced destabilization of the salt-bridge interaction was observed. It was also illustrated that the preference of the ion-pairs over the neutral complexes in polar solvents is considerably reduced or even reversed in very low dielectric media, such as chloroform [9] and $\mathrm{CCl_4}$ [8]. The authors in Ref. [9] stressed the effects of environment on the H-bonds in the ion-pairs. Through an explicit water model, molecular dynamics (MD) free energy calculations were performed on $[\mathrm{MGdm^+–AcO^-}]_{aq}$, using various approaches to take into account long-range electrostatic interaction [14]. The potential of mean force (PMF) for the doubly N–H···O–C H-bond configuration showed minima which are the characteristic of both close-contact and solvent-separated ion-pairs [14]. However, the free energy profiles of the $\mathrm{Gdm^+–AcO^-}$ and methylammonium–$\mathrm{AcO^-}$ ($\mathrm{MAm^+–AcO^-}$) complexes, computed from Monte Carlo (MC) simulations, displayed only a single shallow free energy minimum at the distance corresponding to the close-contact ion-pairs [13]. The shallow free energy minimum suggested that the association between the ions in aqueous solutions is not particularly strong. The authors in Ref. [13] described the existence of double minima on the free energy profile as a result of the constraint imposed on the relative orientation of the ions in the PMF calculations.

Although in principle, ab initio calculations with continuum model such as the SCRF method could provide useful information on molecular association in continuum solvent characterized by a dielectric constant, more and more theoretical and experimental evidences showed the necessity to include the details of solvent molecules in model calculations, especially for H-bond systems [15]. This is due to the fact that continuum models neglect specific short-range solute–solvent interaction, as well as the behavior and structures of solvent molecules in the first solvation shell of solute. Continuum models were pointed out to be suitable only for the systems, in which solvents act only as perturbation on the gas-phase property of the system [15].

According to the literature survey, at least four remarks could be made in the field of salt-bridge interactions in solutions: (a) previous theoretical and experimental investigations tend to focus attention only on the effects of solute–solute and solute–solvent interactions; (b) the detail information on the solvent structures especially in the first solvation shell of solute has been neglected in many investigations; (c) due to the limitation of computer resources, there has been an increasing number of theoretical studies made based on continuum models; (d) there were few theoretical and experimental investigations which combine structural and energetic effects, as well as the dynamic behavior of solvent molecules in the first solvation shell of solute, in the study of ion-pairs in solutions, etc. These remarks partly formed the basis of our previous theoretical investigations on alanine zwitterion in aqueous solutions ($[\mathrm{Alaz}]_{aq}$) [16], in which the detail structures and energetic of the H-bond networks of water in the first hydration shell of Alaz were derived from MD simulations. In Ref. [16], the three-dimensional structures of the H-bond networks of water were analyzed and visualized using various probability distribution (PD) maps, such as the oxygen (PDO) and hydrogen probability distribution (PDH) maps, as well as the average solute–solvent (AWPD) and solvent–solvent interaction energy probability distribution (WWPD) maps. The structures of the average potential energy landscapes were employed to describe the dynamic behavior of water molecules in the first hydration shell of the functional groups of Alaz. They were computed from the total-average interaction energy probability distribution (AW-WWPD) maps. The probabilities for the water exchange, both within the H-bond networks and between the H-bond networks and the outsides, were anticipated from these pieces of information. It was concluded in Ref. [16] that a complete picture of molecular hydration could be obtained only when explicit water molecules, together with their hydration dynamics in the first hydration shell, are considered in the model calculations.

In the present work, the structures and energetic of a model salt-bridge formed from $\mathrm{Gdm^+}$ and $\mathrm{FmO^-}$ were studied, both in the gas phase and aqueous solutions. The present theoretical investigation started with construction of intermolecular potentials to describe the interactions in the $\mathrm{Gdm^+–H_2O}$, $\mathrm{FmO^-–H_2O}$ and $\mathrm{Gdm^+–FmO^-}$ complexes, using the Test-particle model (T-model) [17–20]. The T-model potentials were applied in the calculations of the equilibrium structures and interaction energies of the $\mathrm{Gdm^+–H_2O}$, $\mathrm{FmO^-–H_2O}$ and $\mathrm{Gdm^+–FmO^-}$ complexes in the gas phase. Some lowest-lying minimum energy geometries of these H-bond complexes were tested using ab initio calculations at the MP2 level of theory. The computed T-model potentials were applied in MD simulations of $[\mathrm{Gdm^+}]_{aq}$, $[\mathrm{FmO^-}]_{aq}$ and $[\mathrm{Gdm^+–FmO^-}]_{aq}$ at 298 K. In order to obtain information on the three-dimensional structures and the stability of the H-bond networks in the first hydration shells of solutes, the MD results were