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Structural Basis for the Enhanced Stability of Protein Model Compounds and Peptide Backbone Unit in Ammonium Ionic Liquids

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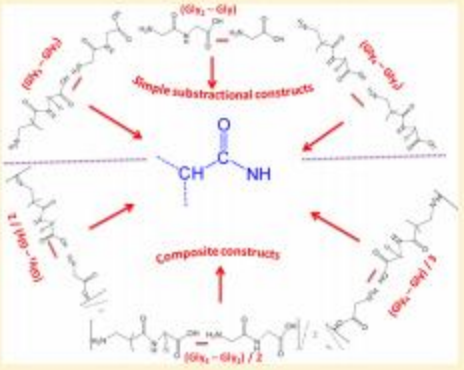
Supporting Information

ABSTRACT: Protein folding/unfolding is a fascinating study in the presence of cosolvents, which protect/disrupt the native structure of protein, respectively. The structure and stability of proteins and their functional groups may be modulated by the addition of cosolvents. Ionic liquids (ILs) are finding a vast array of applications as novel cosolvents for a wide variety of biochemical processes that include protein folding. Here, the systematic and quantitative apparent transfer free energies ($\Delta G'_{tr}$) of protein model compounds from water to ILs through solubility measurements as a function of IL concentration at 25 °C have been exploited to quantify and interpret biomolecular interactions between model compounds of glycine peptides (GPs) with ammonium based ILs. The investigated aqueous systems consist of zwitterionic glycine peptides: glycine (Gly), diglycine (Gly_2), triglycine (Gly_3), tetraglycine (Gly_4), and cyclic glycylglycine (c(GG)) in the presence of six ILs such as diethylammonium acetate (DEAA), diethylammonium hydrogen sulfate (DEAS), triethylammonium acetate (TEAA), triethylammonium hydrogen sulfate (TEAS), triethylammonium dihydrogen phosphate (TEAP), and trimethylammonium acetate (TMAA). We have observed positive values of $\Delta G'_{tr}$ for GPs from water to ILs, indicating that interactions between ILs and GPs are unfavorable, which leads to stabilization of the structure of model protein compounds. Moreover, our experimental data $\Delta G'_{tr}$ is used to obtain transfer free energies ($\Delta g'_{tr}$) of the peptide backbone unit (or glycyl unit) (—CH_2C═ONH—), which is the most numerous group in globular proteins, from water to IL solutions. To obtain the mechanism events of the ILs' role in enhancing the stability of the model compounds, we have further obtained *m*-values for GPs from solubility limits. These results explicitly elucidate that all alkyl ammonium ILs act as stabilizers for model compounds through the exclusion of ILs from model compounds of proteins and also reflect the effect of alkyl chain on the stability of protein model compounds.



1. INTRODUCTION

The ability of amino acids to form a three-dimensional protein structure is significantly interesting and fascinating that combines the aspects of biophysical properties, structural features, and the conformation of certain functional groups of biomolecules. Proteins are virtually unique in being linear macromolecules with a nonrepetitive, specific covalent structure with the capability of adopting a relatively three-dimensional structure/conformation.[1−4] The three-dimensional structure arises particularly because of sequences in amino acids of the polypeptide chains that fold to generate compact domains. The nature and the arrangement of the amino acid side-chain along with the protein backbone are responsible for the individual characteristics of the macromolecule, and it has been recognized that all the information pertaining to protein is implicit in the amino acid sequence.[5,6] Basically, these bonds/backbones are influenced by the aqueous solutions; hence, it is very much important to have a clear idea on the solubility, stability, and thermodynamic properties of these amino acids/backbone in aqueous solution. Although protein model compounds containing amino acids of zwitterionic glycine peptides (GPs) are the simplest and highly interesting molecules that are of fundamental importance in science and are currently under active research.

Most proteins found in nature must adopt a specific conformation, called the folded or native state, to function properly. Under physiological conditions, protein of amino acid residues can undergo a reversible disorder ↔ order transition called protein folding.[7−9] Protein folding plays a central and vital role in the properties of biomolecules in solution and poses remarkable challenges in both modern biophysical and pharmaceutical contexts.

The solubility and stability of biomolecules under cosolvent conditions are dependent on the nature of the cosolvent, which can alter protein's properties and structural effects through biomolecular interactions between its functional groups and the cosolvent molecules.[10−15] For ions containing charged groups, the role of ion−ion interactions is predominant for protein stability.[16,17] The stability of protein is essentially and marginally stable against environmental stress, such as temperature, pressure, or cosolvent. Various studies have been made in

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