Quantum-Mechanical Studies to Investigate the Hydrogen Bonding Interactions of Amino Acids with Molecules of Biological Interest

Hydrogen bonding is one of the most important, widely discussed and highly debated interactions in chemistry due to its central role in all areas of nature from controlling biological activity to directing molecular self-assembly, determining the three-dimensional structures, the chemical reactivity and functions of biological molecules and mediating dynamic processes. In particular, recognition of enzymes by different biomolecules and drugs is known to be largely controlled by hydrogen bonding interactions therefore study of hydrogen bonding in relation to the amino acids which constitute proteins and enzymes is of great importance. With the aim to understand the nature and strength of intermolecular hydrogen bonding interactions of amino acids with molecules of biological interest including H_2O, H_2O_2, amides and THF (tetrahydrofuran), the quantum-mechanical approach has been adopted in the present work. Various computational methodologies such as vibrational frequency analysis, atoms in molecules (AIM) analysis, natural bond orbital (NBO) analysis, molecular electrostatic potential (MEP) analysis and energy decomposition analysis have been employed to investigate 1:1 hydrogen-bonded complexes of amino acids with aforementioned molecules of biological interest. Though the interactions in solution are more complex than the interaction in a complex of a solute molecule with a single solvent molecule, studying such 1:1 complexes will give much information on the molecular interactions. Moreover, such 1:1 complexes can exist in the gas phase and can be isolated and studied experimentally, so the theoretical investigations carried out in the present work may be useful for the analysis of experimental data in future.

The thesis has been divided into five chapters. The introductory chapter of the thesis i.e., chapter 1 presents the discussion on the concept of hydrogen bond along with brief theoretical background followed by the characteristics and importance of hydrogen bonding interactions in biological processes. The chapter also enlightens the importance of amino acids and review of previous reported works on hydrogen bonding interactions of amino acids with molecules of biological interest. This is followed by detailed discussion of theoretical methods employed and computational methodology adopted to analyze the properties of studied molecules with brief introduction to quantum mechanical background.

The next chapter i.e., chapter 2 presents the comparative study of the hydrogen-bonded complexes formed between glycine and THF and between glycine and water involving four lowest-energy glycine conformers. The complexes have been investigated in the gas phase at the *ab initio* molecular orbital theory method MP2 with aug-cc-pVDZ basis set and density functional theory method B3LYP using aug-cc-pVTZ basis set. Bader's theory of atoms in molecules (AIM), natural bond orbital (NBO) and symmetry adapted perturbation theory (SAPT) analyses are employed to elucidate the interaction characteristics in the complexes. The blue- and red-shifts in the hydrogen bond donor X-H (X = O, C, N) stretching frequencies have also been analyzed.

In the chapter 3, the hydrogen bonding of 1:1 complexes formed between alanine and formamide and between alanine and N-methylformamide has been completely investigated using *ab initio* molecular orbital theory method MP2 and density functional theory method B3LYP using aug-cc-pVDZ basis set. Geometry optimization and vibrational frequency calculations have been carried out for isolated and hydrogen-bonded systems. The optimized geometric parameters and stabilization energies for the complexes are estimated and the results are corroborated by natural bond orbital (NBO) analysis, Bader's theory of atoms in molecules (AIM), and molecular electrostatic potential (MEP) studies. The blue- and red-shifts in the stretching frequencies of HB donors X-H (X = O, N, C) have also been analyzed. Finally, the solvent effects are treated via the integral equation formalism-polarizable continuum model.

In the chapter 4, the 1:1 hydrogen-bonded complexes formed between proline and amide (formamide and N-methylformamide) have been investigated completely by the use of computational studies such as atoms in molecules (AIM), natural bond orbitals (NBO) and molecular electrostatic surface potential (MEP). All computations are based on structural models previously generated at wB97XD/aug-cc-pVDZ level. On the basis of vibrational frequency calculations, the red- and blue-shifting of proton donor fragment X-H (X = O, N, C) has also been analyzed. The solvent effect on stabilization energies of complexes is also studied through the integral equation formalism version of polarizable continuum model (IEF-PCM). The second-order delocalization energies and the topological parameters (electron density and laplacian of electron density) have been correlated to the stabilization energies. The correlation graph between change in bond length (Δd) and the corresponding frequency shift ($\Delta \upsilon$) of proton donor group in the complexes has also been plotted.

In the chapter 5, the hydrogen-bonded complexes of serine with water and with H_2O_2 (HP) have been investigated by comprehensive computational studies, using second-order Møller-Plesset perturbation (MP2) theory and density functional theory (DFT). The serine-water and serine-HP complexes have been analyzed in

terms of their equilibrium geometries, harmonic vibrational frequencies, stabilization energies, charge transfer interactions from natural bond orbital study, topological features from quantum theory of atoms in molecules and physical nature of intermolecular hydrogen bonding interactions from symmetry adapted perturbation theory. The second-order delocalization energies and the topological parameters (electron density and laplacian of electron density) have been correlated to the stabilization energies. The correlation has also been established between the change in bond length (Δd) and the corresponding frequency shift ($\Delta \upsilon$) of HB donor group in the complexes.