

Polarization of Methylene Blue in aqueous solutions: impact over the Hydrogen Bonds

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Abstract: Photodynamic Therapy (PDT) is a well known treatment for neoplastic diseases that requires a combined action of a photosensitizer (PS), light-sensitive chemical compound, and a light source. When irradiated, a photosensitizer can be promoted to excited states and induce the formation of reactive oxygen species (ROS) such as singlet oxygen (¹O₂) [1]. ROS has a cytotoxic action over neighboring biomolecules of PS fostering cell death [2]. It's well established that the ROS generation is strongly affected by aggregation of PS, a common phenomena that occurs in homogeneous media and membranes, decreasing the efficacy of PDT treatment. Dimer and higher aggregates formation have been widely discussed in literature, but a molecular picture of this mechanism is still missing. In this work, we studied the dimer formation of a well-known phenothiazine dve, the Methylene Blue (MB) because of the its high quantum yield, very low dark toxicity and other desirable properties for PS. We performed Molecular Dynamics (MD) simulations combined with Density Functional Theory (DFT) to understand the formation of hydrogen bonds (HB) between solutesolvent and its impact over the thermodynamic stability of dimer configuration. Since MB is a cationic dye, solvent effects can induce a charge polarization in this solute, affecting hydrogen bond formation. We developed a protocol to estimate converged average solute-solvent potential and to obtain the polarized charge distribution of MB in solution. Cubic cells were modeled with 4000 SPC water molecules in a NPT ensemble using GROMOS 53a6 force field. Running-lengths of 20 ns in MD simulations were adopted to extract representative configurations inputs to study polarization and its effects over the hydrogen bond formation by means of DFT calculations. Solvent induced polarization produces a negative charge localization in central ring N atom which results in stronger hydrogen bonds with solvent molecules. We extended the geometric criteria of HB formation and analyzed the angular distribution of Donor – H – Acceptor from 0 to 180° obtained from MD. One hundred selected configurations were analyzed considering a weight chosen according to the number of times that a specific configuration is accessed in the sampling. In polarized MB, the set of configurations sampled presented to a pattern similar to that of the whole simulation, a bimodal angular distribution with two well defined peaks around 9.5 and 108.5 degrees. Second peak is not expected in conventional hydrogen bond formation, but it represents a strong electrostatic character of this type of bond. Molecular dynamics calculations were



performed using GROMACS 4.5 package. All the DFT calculations were done using the Orca 3.0.3 code. The functional B3LYP and def2-PVTZ basis set were used throughout.

Key-words: Methylene Blue, Molecular Dynamics, Density Functional Theory, Polarization, Hydrogen Bond.

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