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Structural analysis, solvent effects and intramolecular interactions in Rilpivirine: a new non-nucleoside reverse transcriptase inhibitor for HIV treatment

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Abstract

The intramolecular hydrogen bonding in rilpivirine has been evaluated by density functional theory (DFT) calculations. All possible conformers of the corresponding compound were fully optimized at B3LYP/6-311++G(d,p) level using the Gaussian 09 program package. From 22 different obtained conformers, the most stable one were R5 and R8 in the gas phase and aqueous solution, respectively. Those could be stabilized by steric and electronic effects and the intramolecular hydrogen bonding. The solvent effects on the electronic and structural properties were investigated using the Tomasi's polarized continuum model. The conceptual DFT based reactivity and stability descriptors, chemical potential, hardness, electrophilicity index, energy gap and also total energies and dipole moments were calculated. The topological properties of the electron density distributions for C-H...N and C-H...C intramolecular hydrogen bond bridges were analyzed in terms of electron density (ρ) and its Laplacian ($\nabla^2\rho$) at the bond and ring critical points from Bader's quantum theory of atoms in molecules. Results show that the C-H...N and C-H...C bonds show low electron density and non-covalent characteristics ($\nabla^2\rho(\text{BCP}) > 0$) while C-H and C-O have covalent character ($\nabla^2\rho(\text{BCP}) < 0$). Charge density distributions and chemical reactive sites of studied conformers have been obtained by molecular electrostatic potential surface. The theoretical calculations for rilpivirine conformers in aqueous solution were also performed at the same level of theory. Calculated data indicate that the order of stability of rilpivirine conformers in water is different to their stability order in the gas phase.

Keywords: rilpivirine; conformer; solvent effect; intramolecular hydrogen bonding; DFT.

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