

Investigation of the Structure, Stability, and Solubility of Psilocybin in Water and Pure Organic Solvents: A Molecular Simulation Study

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Background: Psilocybin, derived from magic mushrooms, has versatile medicinal potential, including neuro-protection and mental health benefits. FDA approval for clinical research suggests promise in treating anxiety, depression, and addiction. Nevertheless, clinical application is hindered by solubility issues and neurotoxicity. This study utilizes computational simulations to explore psilocybin's behavior in organic solvents, offering insights into its stability, structure, and solubility challenges, especially in contrast to its solubility in water.

Methodology: This study involves investigating psilocybin's characteristics in different solvents, including water and 35 common organic solvents. This is done through free energy calculations and detailed structural analysis. The solvation-free energy (ΔG_{solv}) is used to assess the interaction between psilocybin and the solvent, with a negative value indicating a preference for being in solution. The comparison between psilocybin forms A and B involves electronic structure calculations to establish their ideal gas reference states and interconversion energy. The research aims to relate these findings to the relative concentration of psilocybin forms in solution.

Results: The study validates the existence of two Psilocybin forms, A and B, with form B being thermodynamically more stable through free energy and DFT analysis. Hydrogen bonding significantly influences the solvation of Psilocybin form B, while aliphatic and non-hydrogen-containing solvents have minimal coulombic contributions. Alcohols and water exhibit different solvation behaviors, likely due to their unique properties. These results enhance our understanding of Psilocybin's stability and solvation in diverse solvent environments.

Conclusion: Findings suggest the thermodynamic stability of Psilocybin form B compared to A. Further studies are proposed to investigate different forms of solvents like ionic liquids

Keywords: Psilocybin; Solvents; Solubility; Stability; Free energy

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