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Conformational preference and spectroscopical characteristics of the active pharmaceutical ingredient Levetiracetam

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ABSTRACT

The analysis of the possible conformers and the conformational change between solid and liquid states of a particular drug molecule are mandatory for describing reliably its spectroscopical properties, but also for understanding the interaction with the receptor and its mechanism of action. Therefore, here we investigated the free energy conformational landscape of levetiracetam (LEV) in gas-phase as well as in water and ethanol, aiming to describe the three-dimensional structure and energetic stability of its conformers. Twenty-two unique conformers were identified and their energetic stability was determined at DFT B3LYP/6-31G+(2d,2p) level of theory. The six most stable monomers in water, within a relative free energy window of 0.71 kcal·mol^{-1} and clearly separated in energy from the remaining subset of 16 conformers, as well as the three most stable dimers were then used to compute the Boltzmann populations-averaged UV-Vis and NMR spectra of LEV.

The conformational landscape in solution is distinctly different from that corresponding to gas-phase, particularly due to the relative orientations of the butanamide group.

Aiming to clarify the stability of the possible dimers of LEV, we also investigated computationally the structure of a set of eleven non-hydrated and hydrated homo-chiral hydrogen bonded LEV dimers.

Keywords: Levetiracetam; conformational analysis; hydrogen-bonded dimers; NMR; UV-Vis; DFT.

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