

Abstract

Propofol or 2,6-diisopropylphenol is a popular intravenous anaesthetic that is known to manifest anaesthetic properties by docking onto the tryptophan and the tyrosine residues of the GABAA receptor. Several x-ray crystallography studies have indicated that the docking mechanism involves hydrogen bonding interactions, exhibited between the hydroxyl groups in propofol and the amino acids involved in the interactions. Moreover, the molecule exhibits several conformations due to the rotational degree of freedom of the isopropyl group with respect to the phenyl ring. The conformational analysis and the study of weak interactions of this biologically significant molecule has been one of the aspects of this study. Matrix isolation infrared spectroscopy, which has been shown to be a powerful tool to study weak interactions and conformers has been used in the present study together with *ab initio* computations. In this matrix isolation technique, molecules of interest are trapped in an inert host matrix at cryogenic temperatures at high dilutions to ensure isolation. The technique results in spectra that have sharp features enabling one to resolve features due to conformers and complexes formed due to weak hydrogen bonded interactions. In order to corroborate experimental data, computations were also performed. Geometry optimization algorithms, harmonic analysis and frequency calculations are critical to the understanding of experimental data. Calculations employing various levels of theory such as the B3LYP, M06-2X and MP2 together with 6-311++g(d,p) and the aug-cc-pVDZ basis sets were performed. AIM analysis, LMOEDA and NBO analysis were also performed to understand the nature of interactions that were under consideration. Conformational analysis yielded five stable conformers computationally, while three were identified in experiments. Earlier work in the literature had not clearly resolved the conformers and our work is, to the best of our knowledge, the first report of conformer resolution in propofol. Fourteen 1:1 hydrogen bonded complexes of propofol with H₂O were obtained computationally, of which the global minimum structure was identified in the matrix. Evidence for the hydrogen bonded complex was obtained from the shifts in the stretching frequency of the O-H group of phenol in propofol. The experimental results were corroborated by computations. Propofol interaction with water presented a rich and diverse landscape of hydrogen bonded isomers, and the work is clearly important as it sheds light on the non-covalent interactions that leads to its biological activity.