THESIS

THEORETICAL MULTINUCLEAR NMR AND IR STUDIES USING COMBINED QUANTUM MECHANICS/MOLECULAR DYNAMICS SIMULATIONS OF SOLVATED NEVIRAPINE STRUCTURE

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Conformational analysis of the HIV-1 reverse transcriptase inhibitor nevirapine, 11-cyclopropyl-5,-11-dihydro-4-methyl-6H-dipyrido[3,2-b:2′,3′-e][1,4]diazepin-6-one, was undertaken using *ab initio* and density functional theory calculations. In particular, fully optimized structures and rotational potential energies of the nitrogen and carbon bonds in the cyclopropyl ring (C15-N11-C17-C19, α) were examined in detail in gas phase calculations. Optimized geometries obtained from all applied calculations showed similarities to the complexed structure with HIV-1 reverse transcriptase. For additional structural information, conformational minima of nevirapine, with optimized geometries at B3LYP/6-31G** level, were used to predict the ^{1}H, ^{13}C and ^{15}N-NMR chemical shifts at B3LYP/6-311++G** level using the GIAO approach for DMSO and chloroform IEF-PCM solvation models. The calculated chemical shifts agreed well with experimental data indicating that the geometry of nevirapine in solution is practically the same as that of the molecule in the inhibition complex. Solvation free energies (ΔG_{sol}) of nevirapine in DMSO and chloroform were also obtained and showed that ΔG_{sol} varies with the alpha angle. A combination of Molecular Dynamics simulations and the ONIOM2 method was used to simulate a nevirapine molecule in these solutions and hence to calculate ^{1}H-NMR chemical shifts with greater accuracy than previous simple gas and solvation model calculations. This approach was able to accurately predict all shifts, including that of the acidic proton which has its de-shielding greatly influenced by hydrogen bonding effects of a polar solvent such as DMSO. The IR absorption calculations confirmed that this acidic proton, via hydrogen bonding, forms a significant structure between nevirapine and a DMSO molecule, and this is different to the loosely bound structure in chloroform. Thus this combined MD-ONIOM2 method can be useful and efficient for systems where solvents significantly influence the electronic environment of a solute and to simulate properties such as NMR chemical shifts and IR spectra.

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