EFFECTS OF METHYLATION ON ZEBULARINE STUDIED BY DENSITY FUNCTIONAL THEORY

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1-(β-D-ribofuranosyl)-2-pyrimidone (zebularine or zeb) and 1-(β-D-ribofuranosyl)-5-methyl-2-pyrimidinone (d5) are effective inhibitors of cytidine deaminases (CDA). Methyl modification of zeb at the C(5) position in the base moiety produces d5. A density functional theory (DFT) study reveals the impact of the methyl group on the electronic structures and spectra of the nucleoside pair. It is found that the addition of methyl group has little effect on the geometry of the nucleosides as well as their sugar puckering, but affects anisotropic properties such as dihedral angles, condensed Fukui functions and charge distribution can be seen in their molecular electrostatic potentials (MEPs). Electron spectra serve as the fingerprint for the methyl group. The valence spectra clearly indicate that the molecular pair is related in the inner valence space of IP $> 20eV$, whereas the outer valence space reveals the methyl associated electronic structural modifications of the molecular pair. In the present study, the molecular orbitals (MO) such as MO8, MO18 and MO37 (HOMO as MO1) are identified as the fingerprint MOs for methyl, whereas other MOs marked in the figure are secondary methyl related MOs. Chemical shift in the inner shell and their spectra are also calculated. It reveals the similarities and differences of methyl effect to large nucleosides and small amino acids such as L-alanine.