Molecular Criteria for Mutagenesis by Methylation of DNA: Some Computational Elucidations

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Alkylation of critical DNA base sites plays a key role in the mutagenic and carcinogenic activity of alkylating agents and N-nitroso compounds. N7-guanine alkylation is not linked to mutagenesis and carcinogenesis, while alkylation at the O6-guanine and O4-thymine sites is of mutagenic and carcinogenic significance. Criteria for mutagenicity of an alkylated DNA base include (a) loss of the N1-proton of guanines and the N3-proton of thymines, (b) rotation of the alkyl group away from the H-bonding zone, (c) base pair configuration approaching the Watson-Crick type.

These criteria are applied to three methylated DNA bases – N7-methylguanine, O6-methylguanine and O4-methylthymine – using the MPW1K/6-31+G** and MP2/cc-pVDZ methods in gas phase and simulated aqueous phase. Proton loss is predicted more feasible for O6-methylguanine and O4-methylthymine than for N7-methylguanine in good accord with their pKa values. Rotation of the O-methyl group of O6-methylguanine and O4-methylthymine away from the H-bonding zone involves a barrier which is smaller for the former than for the latter. The three methylated bases in cationic and neutral N-deprotonated forms are H-bonded with normal DNA bases leading to various modified base pairs. All but one are predicted to be stable, but only those pairs without the N1-G or N3-T protons and displaying Watson-Crick type configuration would be mutagenic. Application of the three proposed criteria successfully differentiates the non-mutagenic N7-methylguanine from the mutagenic O6-methylguanine and O4-methylthymine in accord with experimental results.