Theoretical Study of the Mechanism of Co-Mutagenicity of AminoPhenylNorharman

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INTRODUCTION

The aminofenilnorharman [9- (4'-amino-phenyl)-9H-pyrido[3,4-b]indol], APNH, is a new mutagenic, endogenous and probably carcinogenic *in vivo*, produced by the reaction of co-mutagenic norharman (9H-pyrido [3,4-b]indole), NH, with the aniline in S. typhimutium *TA98* of S9-mix. The mechanisms of appearance of the mutagenicity of APNH[1] were analyzed using abinitio calculations of total energy, HOMO/LUMO energies, bond orders, and atomic charges. The calculations were made for the isolated molecule, and without taking into consideration the complex factors involved in biological activity, or the effect of the solvent. The analyzed molecules were: aniline and NH, and their derivatives produced by enzymatic reactions; APNH; and metabolites N-OH-APNH and NO-PNH.

METHODS

The SPARTAN10 program was used and for all calculations the crystallographic structures of molecules were used as input, and when necessary, the geometries of the molecules were optimized using Hartree-Fock method and 6-31G* basis function. The excitation energies were calculated using the Time-Dependent Density Functional Theory (TD-DFT), using B3LYP functional and 6-31G* basis function.

RESULTS AND DISCUSSION

The optimization of the geometry of APNH showed that the molecule is non-planar; NH was approximately perpendicular to the plane of the aniline. The higher order of aniline binding is (0.931), which corresponds to the C(4)–H(1) bond and that of NH is (0.842), which corresponds to the C(9)–H, bond and these are the atoms that are involved in the formation of APNH. The carcinogenic chemical agents are electrophilic species, their LUMO orbital must have a relatively low energy. Calculations of LUMO energies showed that the NH, APNH, and metabolites are electrophilic species, but that aniline is not. For example, aniline is 0.25 eV; APNH, -089 eV; N-OH-APNH, -0.98; and NO-PNH, -2.85 eV; the latter two species are the most electrophilic. The atomic charges of APNH showed that the charge of N(3), which belonged to aniline, ranges from -0.791 to -0.432 in N-OH-APNH formation, and to -0,060 in NO-HNP formation. So it can be considered that there is formation of free radicals through the removal of the H atom from NH_2, from APNH, and from N-OH-APNH. The total energy of the molecules decreases in the following order: aniline>NH> APNH>N-OH-APNH>NO-NHP indicating that APNH has lower energy than its formers and that the metabolites may be intermediate species of the metabolism of APNH, because they are more stable than APNH.

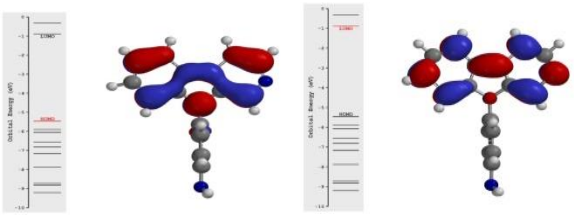

Figure 1. Optimized molecular structure of APNH: Left, HOMO; and Right, LUMO.

CONCLUSIONS

The results showed APNH does not have a planar structure; the electronic transitions are more localized in NH. The formation of the metabolites of APNH occurs in the N of aniline by the removal of H; which was justified by the analysis of the atomic charges, and of the bond orders, which have shown to be more electrophilic than APNH. The mechanism of co-mutagenicity of APNH is related to the enzymatic reaction of its formation and its metabolites.

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[1] R. Nishigaki, et al., Mutat. Res. 562, 19, (2004).