



Investigation of quantum-chemical properties of paracetamol

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ABSTRACT

Paracetamol is a widely used drug in medical practice. We have studied the quantum-chemical properties of paracetamol, which are vital for understanding of mechanisms of biological and pharmacological activity at a molecular level. The geometry optimization for paracetamol molecule was performed by PM3 method, Polak-Ribiere algorithm. We have determined the distance between atoms, total charge density, characteristics of molecular orbitals (HOMO, LUMO) of paracetamol molecule.

Key words: paracetamol, spatial structure, quantum-chemical properties.

INTRODUCTION

Paracetamol belongs to the NSAID (non-steroid anti-inflammatory drugs), the class of drug known as “aniline analgesics”, which is commonly employed in medical practice [1, 2].

Paracetamol is a medicine that is commonly used as over-the-counter drug in medical practice with low peripheral adverse effects. It is available in many forms: single ingredient (78%) or multi-ingredient combination (84%), with codeine for example. Annual consumption of this medication reaches 24 milliard capsules in USA and Europe. More than 300 medications containing paracetamol as active ingredient are permitted for medical use in Ukraine.

Paracetamol possesses analgesics, antipyretic and weak anti-inflammatory properties. It is considered to be a weak inhibitor of prostaglandins (PGs) synthesis and it also affects the thermoregulatory center of hypothalamus. The analgesic and antipyretic action of paracetamol is due to inhibition of a central COX isoform, derived from the same gene as COX-1 and referred to as COX-3 [4, 5]. Paracetamol does not have anti-inflammatory properties and does not cause gastric lesions. This characteristic is explained by the fact that paracetamol preferentially inhibits COX-3 present in the central nervous system, where it penetrates.

The major advantages of paracetamol are its low toxicity and relatively low ability to cause methemoglobin formation. It does not cause the development of Reye's syndrome in contrast to aspirin; it has no gastrointestinal toxicity and does not cause thrombocyte aggregation. At the same time, the adverse effects of paracetamol are usually associated with the long time use or overdose. Paracetamol nephrotoxicity is due to the accumulation of its metabolites in renal papillae and glutathione depletion leads to an acute hepatic failure [6, 7]. The nephrotoxicity of paracetamol is a dose dependent action [8, 9]. However, paracetamol is considered as a safe analgesic, recommended for children treatment and approved by WHO and FDA.

EXPERIMENTAL SECTION

Research of quantum chemical and pharmacological properties of paracetamol was conducted by the method of molecular mechanic MM+ and semi empirical method PM3 [10-14].

All calculations were carried out using the Polak – Ribiere conjugate gradient algorithm.

During the research, the following parameters were studied: interatomic distance (E), the angles between the bonds ($^{\circ}$), atomic charges (a.u./eV), distribution of electron density of outer-shell electrons, the total strain energy (kcal/mol), bonding energy (kcal/mol), electronic energy (kcal/mol), inter-nucleus interaction energy (kcal/mol), heat of formation (kcal/mol), localization and energy of highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals (eV) and absolute hardness (η , eV) [15].

The global hardness corresponds to the gap between the HOMO and LUMO orbitals. The larger the HOMO-LUMO energy gap, the harder the molecule is. Absolute hardness of the paracetamol molecule was determined by the equation 1.

$$\eta = \frac{1}{2} (E_{\text{LUMO}} - E_{\text{HOMO}}) \quad (1)$$

Paracetamol is a para-aminophenol derivative of acetanilide. The chemical formula is N-(4-hydroxyphenyl) acetamide.

RESULTS AND DISCUSSION

Molecular model of paracetamol molecule was calculated based on geometrical optimization depicted in Figure 1; atoms numeration used in calculation of quantum chemical parameters is depicted in Figure 2.

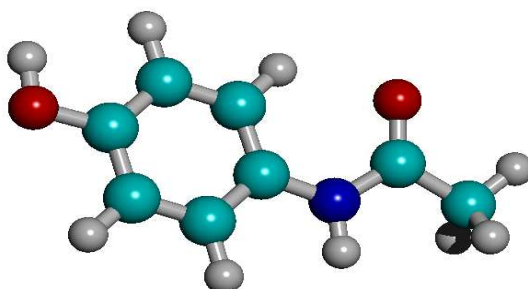


Figure 1. Structure of paracetamol molecule – green color corresponds to carbon atoms, red - oxygen, blue – nitrogen, grey - hydrogen

Calculated charges for each atom in the paracetamol molecule are presented in Figure 3. The regions of high electron density reside on oxygen atom of phenyl and oxogroups (-0,253; -0,358 a.u.) as well as on nitrogen atom (-0,324 a.u.). The electron density on the carbon atom of methyl group is equal to -0,242 a.u. The electron density on C₂, C₃, C₄ atoms of benzene ring are -0,187, -0,117 and -0,152 respectively. The electron deficient area are observed on carbon atoms of phenol ring directly bonded to oxygen and nitrogen atoms (0,051, 0,043 a.u.). Positive charges are located on hydrogen atoms (from 0,227 to 0,087 a.u.).

Dipole moment of a molecule represents a sum of dipole moments of each chemical bond and having the directionality from the center of negative charges to the center of positive charges. It characterizes the asymmetry of charge distribution in electroneutral system. Dipole moment quantitatively determines a static polarization of particle. Its value is a measure that defines the activity of chemical interaction.

The total dipole moment of paracetamol molecule is 2,624 D. The distances at axes are X = 1,147 D, Y = - 2,358 D, Z = 0,102D. The low value of the dipole moment denotes the low solubility of paracetamol.

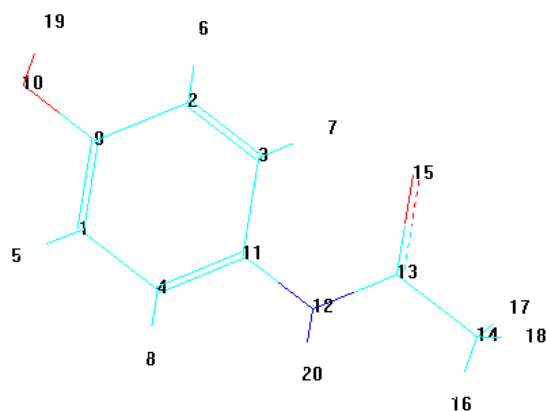


Figure 2. Atom numeration of paracetamol molecule used in calculation of quantum chemical parameters

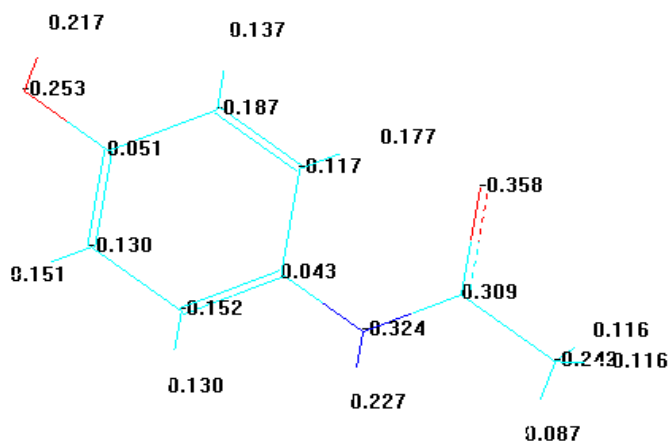


Figure 3. Atom charges in paracetamol molecule

The distribution of electron density of outer valence electrons of the paracetamol is shown in Figure 4. The highest electron density is observed on oxygen, nitrogen, C₂, C₄, C₁₁ atoms. Phenol hydroxide potentially can react with nucleophilic centers of other molecules. Hydrogen atoms directly bonded to oxygen and nitrogen are capable to form hydrogen bonds with electro neutral atoms of other molecules.

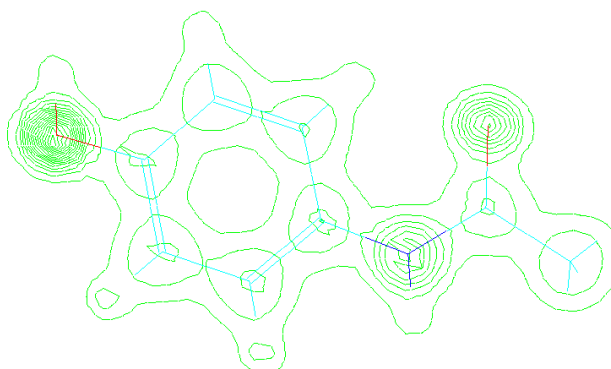


Figure 4. Distribution of electron density of outer valence electrons in the paracetamol molecule

The reactivity of the molecule is characterized by the localization of HOMO LUMO (H. Fukui theory) [16]. Table 1 shows some electro-optical parameters of the paracetamol molecule. Localization of electron density of HOMO LUMO depicted in Fig. 5 (a, b).

Table 1: Electro-optical properties of paracetamol

Property	Value
Total energy (E) (kcal/mol)	- 46028,7
Binding energy (kcal/mol)	- 2127,463
Heat of formation (kcal/mol)	-59,307
Electronic energy (kcal/mol)	- 211958,224
Nuclear energy (kcal/mol)	165929,535
Polarizability (A)	16,18
Hydration energy (kcal/mol)	-10,71
Log P	1,96
Dipole moment (Debyes)	2,624
HOMO (eV)	0,254533
LUMO (eV)	- 8,475318
Hardness (η) (eV)	4,364926

HOMO characterizes the molecule ability to interact with electron acceptors, LUMO – with electron donors. According to the Koopmans' theorem, energies of boundaries surfaces correspond to the ionization energy (HOMO energy) and electron affinity (LUMO energy). The frontier orbitals are delocalized in the paracetamol molecule.

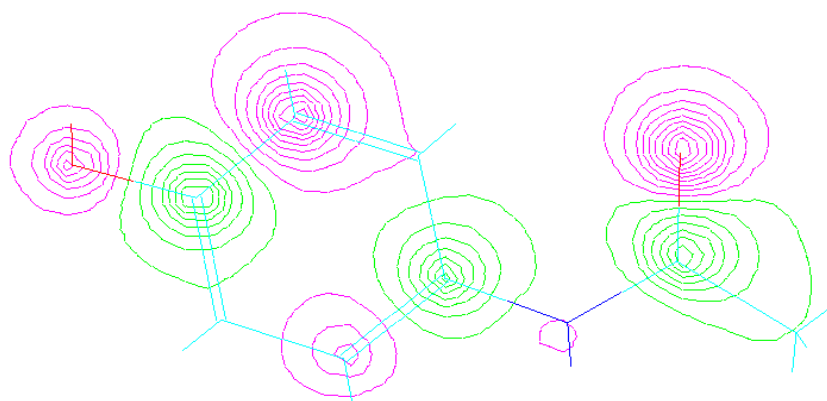


Figure 5a. Localization of HOMO in the molecule

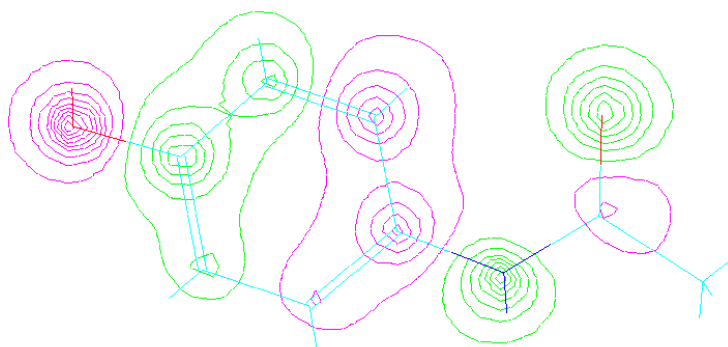


Figure 5b. Localization of LUMO in the molecule

Molecular parameters such as hardness can be computed using data from Table 1. Based on the values obtained for HOMO and LUMO, the hardness is equal to 4,364926 ($\eta = \frac{1}{2} E_{\text{LUMO}} - E_{\text{HOMO}}$).

By the comparison of hardness value (η) of hard molecules (BF_3 – 7,8 eV, HCL – 8,0 eV) and soft molecules (CH_3I – 4,7 eV, C_6H_6 – 5,2 eV) we can conclude that the studied molecule can be considered as a soft reagent. Thus, paracetamol most actively will react with soft reagents comprising cysteine residues in proteins and glutathione [16, 17].

CONCLUSION

Main geometrical and energetic parameters were established for paracetamol molecule. It was shown that paracetamol is a soft reagent. In general, theoretical results are in complete agreement with observed experimental reactivity.

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