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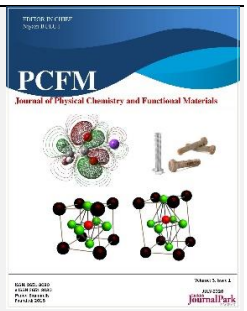

Computational Study on Paracetamol Drug

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ABSTRACT

Paracetamol is a drug used to relieve pain and fever. It is also known as acetaminophen and APAP. It's typically used to relieve mild to moderate pain. Gaussian software programs 09 conducted a theoretical study to find Paracetamol reactivity. Density Functional Theory (DFT) on the best set 6-31++G using to determine geometrical structure and energy bandgap. Frontier molecular orbitals estimated to find the properties of the molecule. Atomic charge distribution has conformed the charge on each atom in the molecular structure. Molecular electrostatic potential evolution for the paracetamol structure and show that structures with high electronegativity.

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1. Introduction

Two official names of the same chemical compound derived from its chemical name are paracetamol (an international name used in Europe) and acetaminophen (an international name used in the USA): N-acetyl-para-aminophenol [1]. Paracetamol (acetaminophen) has one of the most commonly used non-prescription medications in the world, from cradle to grave. It's available and it's cheap. Paracetamol is tolerated better than non-steroidal anti-inflammatory drugs (NSAIDs), but it may be less effective. A decrease in aspirin use during the 1980's because of its connection with Reye's syndrome and allowed used paracetamol for children, to become the antipyretic and analgesic [2] and it's also the antipyretic and analgesic quality to all age categories. While a safe and effective drug, paracetamol doses are uncomfortably high and a maximum dose of 4 g a day allows a large number of tablets to be taken [3]. Paracetamol is a drug which is small in molecular mass Figure 1. It is a weak acid (pKa 9.7), and is therefore essentially unionized at pH values [4]. Paracetamol is marginal to be bound to plasma proteins [5] and with a delivery capacity of around 50 L following intravenous dosing. It is assumed that paracetamol is transmitted without binding to tissues in the body [6]. This lack of binding means that the concentrations of paracetamol in in vitro studies can be directly compared with them in vivo concentrations without tissue absorption or protein binding corrections. Chemically, paracetamol is a phenol, which is readily oxidized like other phenols. Usage paracetamol for rheumatic conditions Paracetamol lacks anti-inflammatory action. It's less toxic than aspirin, moreover, and does not cause anemia and liver harm, often caused by continuous use acetanilide and acetphenetidines. Paracetamol is used to treat fever reduction, muscle and joint recovery & pain

relief, symptoms of cold and flu relief, common headache relief [7]. Paracetamol potentiates the effects of acenocoumarol and warfarin on anticoagulants, with increased risk of bleeding. The possible processes are inhibition of oral anticoagulant metabolism; however, more recent data have not confirmed such hypotheses [7, 8].

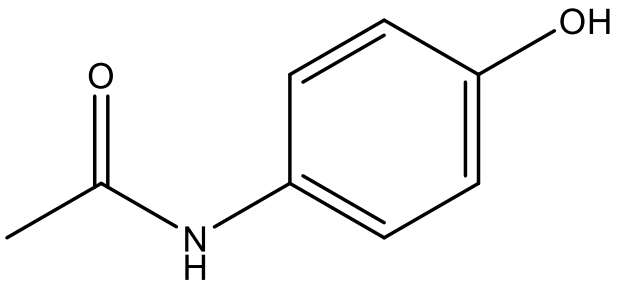

Figure 1. N-(4-hydroxyphenyl) acetamide (Paracetamol)

2. Computational methods

All other computations analysis was carried out using GAUSSIAN 09W [9] and with a personal computer. Hartree-Fock and Hybrid approach; B3LYP is implemented using the 6-31++G base set. Becke's three parameter hybrid model with the Lee-Yang-Parr correlation model (B3LYP) combined in DFT methods [10, 11]. Becke's three exact exchange-function parameters (B3) Combined with Lee, Yang and Parr (LYP) gradient-corrected correlation functional, predicted the most advantageous effects for slightly more detailed molecules on molecular dynamics and vibrational frequencies. The B3LYP (DFT) method at 6-31++G basis set has been chosen for the study Paracetamol molecule.

3. Result and Discussion

3.1. Energy band gaps

The first phase of computational research is to use Gaussian software 09 to find the optimized molecular structure. DFT on the base set 6-31++G was used for optimized Paracetamol molecular structure with atomic numbering and orientation of the molecule was determined in Figure 2. Certain geometrical parameters for the molecular were shown in a table 1. The bond length for C-C in a ring equal to 1.3819 Å and for the C=C in the ring equal to 1.4336 Å, but the bond length for C-C in a chine equal to 1.5084 Å. Moreover, the bond length for C-H in a plane equal to 1.0870 Å, and for out of the plane (CH_3) equal to 1.0965 Å but for O-H equal to 0.9770 Å. The bond length for C-N, C-O and C=O equal to 1.3558, 1.3839 and 1.2586 Å respectively. The angle between the atoms of paracetamol structure was very high this is conformed the molecule is highly reactive.

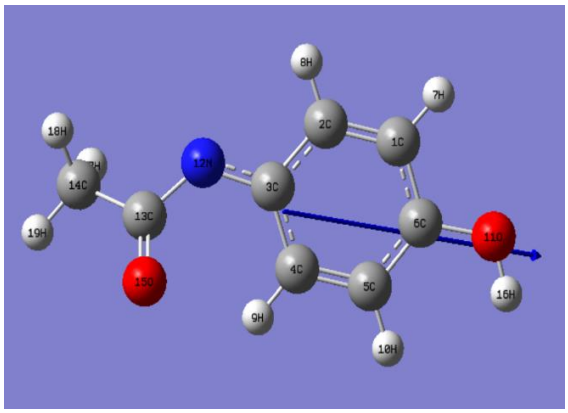

Figure 2. Paracetamol structure with energy bandgap

Table 1. Some geometrical parameters for paracetamol drug.

Sy.	NA	NB	NC	Bond	Angle (Å)	Dihedral
C1						
C2	1			1.381973		
C3	2	1		1.433679	121.2945	
C4	3	2	1	1.435722	117.9936	-0.23941
C5	4	3	2	1.385728	120.4384	0.199876
C6	1	2	3	1.408956	119.3596	0.123036
H7	1	2	3	1.083558	121.8296	-179.793
H8	2	1	6	1.083924	121.2857	-179.977
H9	4	3	2	1.082444	119.2227	178.6958
H10	5	4	3	1.087071	120.0119	179.6904
O11	6	1	2	1.383965	116.5244	-179.979
N12	3	2	1	1.355847	116.9778	-178.382
C13	12	3	2	1.391021	124.9064	-169.814
C14	13	12	3	1.508425	114.3045	-148.014

3.1. Frontier molecular orbitals

Frontier Molecular Orbitals (FMOs) have been used to determine most reactive site in the conjugated system, and to identify other types of reactions [12]. Reactivity of the molecule is measured by the energy values of the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) and its energy

difference (ΔE) [13]. Figure 3. Show HOMO and LOMO were calculated using level B3LYP/6-31++G (d, p) for paracetamol drugs. The energy bandgap (HOMO – LUMO) reflects the lowest electronic energy prerequisite for moving electron from π–π *. For paracetamol molecule the average electronic energy (HOMO) expressed at 39th is measured at -0.24846 eV and lowest electronic energy (LOMO) shown at 40th is measured as -0.22348 eV. The energy bandgaps that were determined by the difference between HOMO and LOMO energy levels for present structure emerged after being fully optimized and finding from MOs which is equal to -0.02455 eV. The result of energy bandgap shows that paracetamol has lower energy bandgap, it is more reactive structures. Chemical hardness, electronegativity, electronic chemical potential and electro-philicity index were calculated, all data show in a Table 2. and calculated using DFT at the basis set 6-31++G.

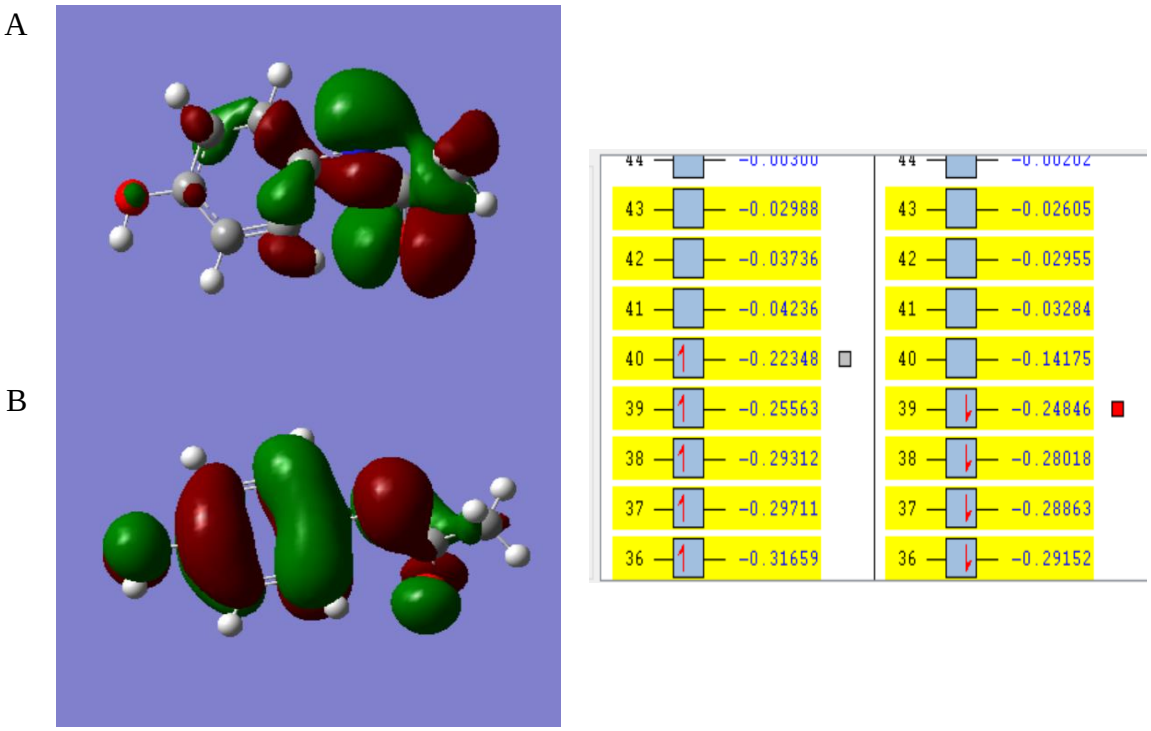

Figure 3. Frontier surfaces for Pracetmol A) HOMO and B) LUMO computed by B3LYP/6-31++G(d,p) level.

Table 2. Calculated energies, dipole moments (D), frontier orbital energies and description of chemical reactivity of the compound.

In a Basis Set B3LYP/6-31++G(d,p)	Equations	Result of Paracetamol
E_{Total}	-514.70464803	-514.70464803
E_{HOMO}	-0.24846	-0.24846
E_{LOMO}	-0.22348	-0.22348
Energy bandgaps	HOMO - LOMO	-0.02455
Chemical hardness (η)	$\eta = (E_{LUMO} - E_{HOMO})/2$	0.01249
Electronegativity (χ)	$\chi = -(E_{HOMO} + E_{LUMO})/2$	0.23417
Chemical potential (μ)	$\mu = (E_{HOMO} + E_{LUMO})/2$	-0.23597
Electro-philicity index	$\omega = \mu^2/2\eta$	356.92307
Dipole moment	3.6449	3.6449

3.1. Mulliken charge distribution

Table 3. demonstrates atomic charges distribution which was calculated by Mulliken theory. The calculations were carefully developed on the DFT methods and 6-31++G basis set. In paracetamol molecule these values of the atomic charges distribution on the oxygen atoms indicate that the structural component has potentially interacted with weak electronic molecules. While nitrogen atoms have interacted with a more electrophilic species such radicals. Paracetamol contain two oxygen have higher negative charge and effected on the neighbor's carbon

atoms, whereas only have one nitrogen atoms. According to the Mulliken paracetamol is more electrophilic and react with more nucleophilic species.

Table 3. Mulliken atomic charges distribution

Atom	Charge (Coulomb)
C1	0.130781
C2	-0.18917
C3	-0.8307
C4	0.476433
C5	0.088883
C6	-0.46809
H7	0.258555
H8	0.263639
H9	0.269918
H10	0.219188
O11	-0.57297
N12	-0.02286
C13	0.365378
C14	-0.69745
O15	-0.44489
H16	0.443492
H17	0.237654
H18	0.253053
H19	0.219153

3.2. Molecular Electrostatic Potential (MEP)

Electrostatic potential map surface shows the charge distribution on the atoms in a molecule. The graph diagram allows us to imagine a molecular surface with variable charged particle zones. The advantages of the electrostatic potential map are to show how the chemical interaction occurs in a molecule, and how the chemical bond between atoms was formed. We can infer how the molecules interact with other molecules using the charging distribution on the molecular surface. In the electrostatic map the molecule can be identified by the color scale. The red color demonstrated higher electronic density, and the distribution of electrons in this zone is very high, the color down to orange and green then to blue. The color blue demonstrates the lower density of the electron and the electro negativity is lower. The large electronegativity was distributed in the range red color then down in a blue color. In a paracetamol molecule Figure 4. the electronegativity was distributed in range oxygen number fifteen and crabon number fourteen. The blue zone in the paracetamol molecule was distributed in a range of hydrogen number sixteen. The overall result for electrostatic potential map surface is paracteoml molecule was more ionized because it has more electronegativity range.

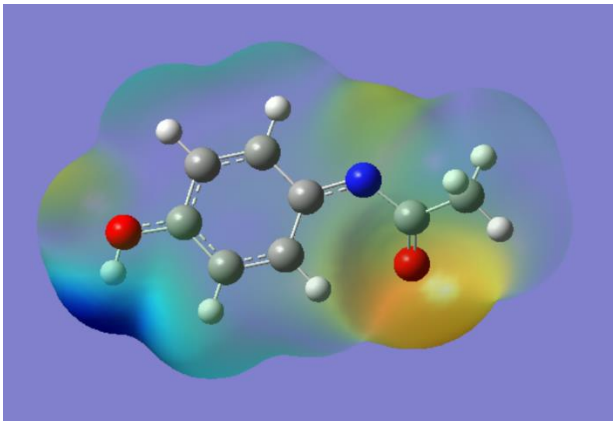

Figure 4. Electrostatic Potential Map

4. Conclusion

DFT methods at B3LYP/6-31++G basis set was used for study of paracetamol and to determine the reactivity of the molecule. The geometrical structure for paracetamol is reactive with higher bond length. The bond angle and bond length of the structure was show very reactivity of the molecule. Calculating the energy, dipole moments and frontier energy were denoted the molecule's properties including the reactivity. The distribution of atomic charges and the molecular electrostatic potential (MEP) is determined to look at the areas of higher electron density as possible sites of interaction, such as nitrogen and oxygen. The collectivity data indicated that the paracetamol structure was very reactive.

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