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Ab INITIO STUDY OF ACETYL SALICYLIC ACID: NBO & AIM ANALYZE

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ABSTRACT

It is believed that a subset of pharmaceutical agents including acetyl salicylic acid (Aspirin) have low biodegradability in the sewage system. Several approaches that have been applied for the removal of this drug had little or no success. We believe that more detailed crystallographical studies on Aspirin may enhance our knowledge about the properties of this drug and hence may help to create new methods to overcome this problem. Using Density functional theory (DFT), we aimed to understand the crystal morphology of Aspirin from a new perspective. DFT calculations on conformers of aspirin were carried out for geometrical optimization and stability predictions at the B3LYP/6-311G (d,p) and B3LYP/6-311+G (3df,2p) levels of theory. These conformers are related and they differ by only the position of the carboxylic acid proton and they are rotational isomers with respect to the Ph–COOH bond. The aim of this study is to investigate the effect of the carboxylic acid group's orientations on the intra-molecular interactions and the conformational stability of these conformers. The structural parameters of intra-molecular hydrogen bonds were analyzed, while the nature of these bonds was considered using the atoms in molecules (AIM) approach. Natural bond orbital (NBO) analysis was used to determine bond orders and the effective nonbonding interactions. These results showed that there are two

conformers for aspirin which both possess only one intra-molecular hydrogen bond. One of them is more stable in the gas phase, because of stronger intra-molecular hydrogen bond.

Keywords: Aspirin, Density functional theory, Atoms in molecules theory, Natural bond orbital analysis

INTRODUCTION

It has long been known that waste products such as heavy metals or halogenated organic compounds have low biodegradability in the wastewater and therefore are hazardous to the environment [1]. Recently, it has been recognized that a subset of pharmaceutical products such as Ibuprofen, Aspirin (acetyl salicylic acid) or Carbamazepine can also be potentially dangerous to the environment due to their low biodegrading capacity in the water [2]. The two conventional removal methods including Advanced Oxidation Process (AOPs) and active sludge system have been successfully applied on a variety of pharmaceutical products in order to be cleared from the water system. However, it appears that drugs such as anti-inflammatories (i.e acetyl salicylic acid) or anti-virals exhibit resistance to these methods [3]. Therefore, more novel methods should be further developed for these resistant pollutants. To approach this problem reasonably, it is important to better analyze anti-inflammatories (i.e acetyl salicylic acid) from the crystallographical aspect at a deeper level. Understanding the structural properties of these drugs compounds as well as their various configurations will ultimately help in developing efficient removal methods for these compounds. With this respect, numerous analytical methods including X-ray, neutron diffraction and Density Functional Theory (DFT) can be applied on pharmaceutical products to reveal their crystal morphology.

To date, the structure of Aspirin has only been studied in crystals by both X-ray [4] and neutron diffraction methods [5]. DFT is a relatively novel method to study the structure of the crystals. DFT comprises the major part of the quantum mechanical calculations that can be employed on organic crystals in order to analyze their structure or energy state. For example, DFT has been applied on Aspirin crystals to estimate their lattice energies [6]. Moreover, using DFT, the conformational space of anti-inflammatory compounds have been investigated and their preferred site of their electrophilic attacks has been demonstrated [7].

The polymorphism of aspirin is still an enigma despite numerous experimental

studies [8], and its structure in the gas phase is unknown. From a detailed investigation on the energy and intra molecular hydrogen bond at conformers, implications to the biological systems at the structural and functional levels may be understood. In this study we aim to reach this goal, using quantum mechanical methods (DFT).

COMPUTATIONAL METHOD

Three methods were used for the investigation of two conformers, namely DFT, AIM theory and NBO analysis. An efficient and widely used technique to study a molecular structure, DFT, with B3LYP/6-311G (d,p) and B3LYP/6-311+G (3df,2p) levels of calculation, was applied to optimize aspirin molecule in the gas phase. The B3LYP (Beck–Lee–Yang–Parr) version of DFT is the combination of Beck's three parameter non-local hybrid functional of exchange terms with the Lee, Yang and Parr correlation functional [9]. All calculations were performed using the Gaussian 09 software package [10]. Gauss View 5.0 [11] was used to prepare the input file and to visualize the optimized structures. Using the DFT method, the best minimum energy conformations were achieved by full geometrical optimization of each conformer. In order to prove that each of them is located at a stable minimum point of the potential energy surface, frequency calculations were carried out based on these optimized structures, and subsequently their vibration frequencies were obtained. Topological parameters such as electron densities ρ(r); and their Laplacian $\nabla^2\rho$(r) at bond critical point (BCP) were obtained from the Bader theory [12] using the AIM 2000 software [13]. The nature of intra molecular interactions of conformers was investigated using the NBO 3.1 package [14].

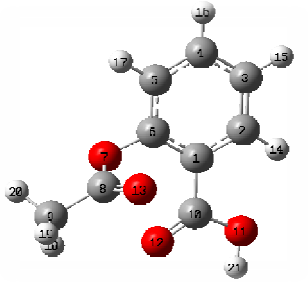
RESULTS AND DISCUSSIONS

3.1 Geometric structures

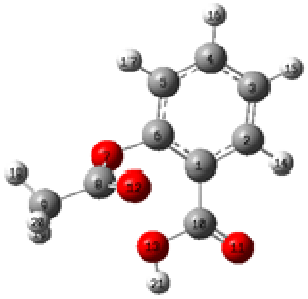
Figure 1 show the optimized structures of conformers of aspirin. As you can see, the difference between these two conformers is mainly the position of the carboxylic acid proton and they are rotational isomers with respect to the Ph–COOH bond. Some selected important distances of conforms of aspirin, at the B3LYP/6-311+G (3df,2p) level of theory are presented in Table 1.

The data in this table shows that the distances between O7–O13 in conformer a are larger than conformer b. So, it can be concluded that the interaction in conformer a is less than the interaction in conformer b.

This subject will be discussed by the results of NBO and AIM in the following sections.



Conformer a



Conformer b

Figure 1: Optimized geometry for the conformers aspirin.

Table 1: The geometrical parameters for conformers aspirin (the bond lengths in Å), at the B3LYP/6-311+G (3df, 2p) by DFT method

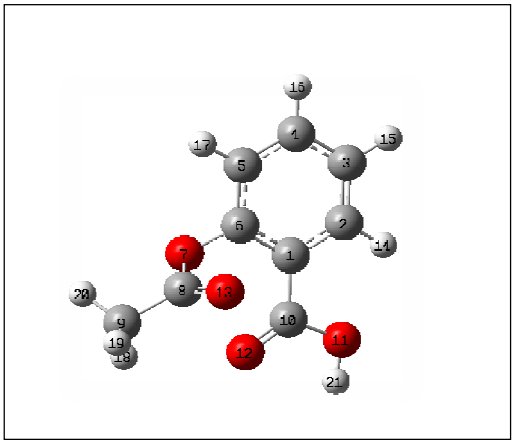
Bond	Conformer a[1]	Conformer b	Exp[2].
O7-O13	2.7518	2.6828	2.6610
O12-O13	3.1791	3.2530	3.3380
C8-O12	1.1955	1.9609	1.1910
C10-O11	1.2065	1.2063	1.2430
O13-H21	0.9671	0.9681	0.8200

[1]For conformer 1, the numbering is as O7-O12, O12-O13, C8-O13, C10-O11, C10-O12, and O11-H21

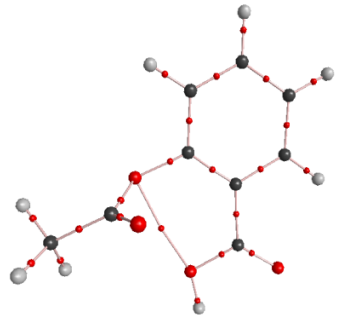
[2]Data taken from X ray

3.2 Atoms in molecules analysis

The AIM theory provides a very useful tool to analyze bond types via parameters, such as electron density, $\rho(r)$; the Laplacian of the electron density, $\nabla^2\rho(r)$ and the ellipticity, ε, which are computed at the BCP [15]. This theory is widely used as a theoretical tool to understand and analyze hydrogen bonds. Generally, for hydrogen bonds, the range of electron density and the Laplacian are 0.002–0.035 and 0.024– 0.139 a.u., respectively [16]. The topological parameters and molecular graphs (indicating critical points and bond paths) of the investigated conformers are exhibited in Table 2.



Conformer a



Conformer b

Figure 2: Molecular graph in conformer a and b. Small red spheres and lines correspond to the bond critical points (BCPs) and the bond paths, respectively.

Table 2: Topological parameters (in a.u.), the electron densities ρ(r); their Laplacians $\nabla^2\rho$(r) and energetic parameters *V(r), G(r)* and *H(r)* (in kcal. mol^{-1}) in conformers at the B3LYP/6-311 G (d,p) level

Conformers studied	HB-length (Å)	ρ(r);	$\nabla^2\rho$(r)	*V(r)*	*G(r)*	*H(r)*	Ellipticity (ε)
a	2.7518	0.01417	0.05567	-0.01799	0.01236	-0.00563	0.76751
b	2.6828	0.01435	0.06018	-0.01115	0.01309	-0.00194	0.03888

It is evident from the table that the value of ρ(r) and $\nabla^2\rho$(r) for these conformers in O7···O13 position are in the range of 0.01417–0.06018 a.u., respectively. These

values of electron densities at BCP imply the presence of hydrogen bonding interaction. For conformers, the molecular graphs represent one intra-molecular hydrogen bond (see Figure 2).

Two topological parameters at BCP are often applied to classify and characterize hydrogen bonds [12]. The Laplacian $\nabla^2\rho(r)$ and the total energy density *H(r)* in all of the above hydrogen bonds are positive and negative, respectively. Therefore, these bonds are classified as medium hydrogen bond and partially covalent–partially electrostatic (Pc–Pe) [17].

Ellipticity is a measure of the bond's stability, i.e. a high ellipticity value indicates an unstable bond [18]. As a result, the hydrogen bond for conformer b in the O7···O13 position is more stable than the ones in the conformer a.

3.3 Natural bond orbital (NBO) analysis

Natural Bond Orbital concept (NBO) was firstly introduced by Foster and Weinhold [14]. In their pioneered work, they used a semi-empirical method (INDO-SCF-MO) to calculate natural hybrid orbitals for a variety of molecules by obtaining one-electron density matrix from which Lewis structures in an a priori manner were constructed [19]. NBO is closely related to the one-center (lone pair) and two-center (localized bond) elements of the Lewis structure picture. NBO fills a gap between quantum) and the bond paths, respectively.

Chemistry calculations with the language of mathematics and well-known concepts in chemistry such as hybridization, conjugation, hyper-conjugation, charge transfer, and orbital interactions. Natural localized orbitals in NBO are categorized into the high occupied orbital (Lewis orbitals) and low unoccupied orbitals (non-Lewis orbitals). Non-Lewis orbitals contain anti-bonds and Rydberg orbitals. Non-zero occupancy of non-Lewis orbitals leads to the small non-covalent corrections to the picture of localized covalent bonds. These corrections which are well known as delocalization are usually so small as to be well approximated by simple second order perturbation expressions [20].

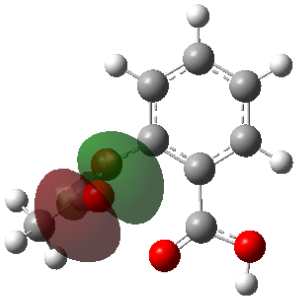
NBO data (Table 3) show that in conformers the highest occupied molecular orbital (HOMO) have same values, but type of orbital is different, and type of LUMO orbital is similar (see Figure 3).

CONCLUSIONS

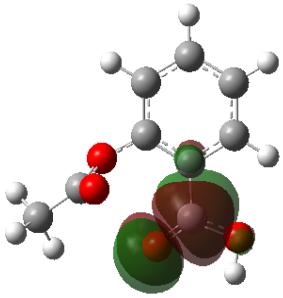
The effects of position of the carboxylic acid proton were investigated using the density functional theory. In this work, bond lengths, electronic properties and the electronic density at the BCP were used to compare the

hydrogen bond strengths in these conformers. The higher energy in conformer a compared to conformer b indicates that is more unstable.

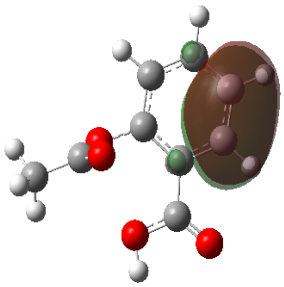
AIM analysis shows that all hydrogen bonds in our investigated conformers in position, O7···O13is partially covalent–partially electrostatic (Pc–Pe) in nature. Moreover, the hydrogen bond in the O7···13 position is in conformer a weaker than that in the conformer b. On the other hand, natural bond orbital analysis confirm that the highest occupied molecular orbital (HOMO) have same values, but type of orbital is different, and type of LUMO orbital is similar.



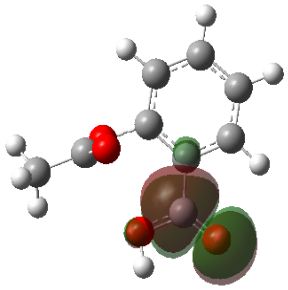
HOMO (Conformer a)



LUMO (Conformer a)



HOMO (Conformer b)



LUMO (Conformer b)
Figure 3: shapes of HOMO and LUMO orbital for conformers
Table 3: HOMO and LUMO of natural bond orbitals of calculated conformers; All orbital energies are in atomic unit (1 au = 627.5095 kcal. mol-1).

Conformer	HOMO		
a	NBO	Energy	Occ.Num1.
b	2LP (2) O13	-0.2632	1.8320
	LUMO		
a	NBO	Energy	Occ.Num1.
b	4BD* (2) C10-O12	0.0001	0.2496

1Occupation number, 2LP is valence lone pair, 3BD: 2-center bonding orbital, 4BD*: 2-center antibonding orbital.

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