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Molecular structure activity on pharmaceutical applications of Phenacetin using spectroscopic investigation

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ABSTRACT

The pharmaceutical compound; Phenacetin was investigated by analyzing FT-IR, FT-Raman and ^{1}H & ^{13}C NMR spectra. The hybrid efficient computational calculations performed for computing physical and chemical parameters. The cause of pharmaceutical activity due to the substitutions; carboxylic, methyl and amine groups in appropriate positions on the pedestal compound was deeply investigated. Moreover, ^{13}C NMR and ^{1}H NMR chemical shifts correlated with TMS standard to explain the truth of compositional ratio of base and ligand groups. The bathochromic shift due to chromophores over the energy levels in UV–Visible region was strongly emphasized the Anti-inflammatory chemical properties. The chemical stability was pronounced by the strong kubo gap which showed the occurring of charge transformation within the molecule. The occurrence of the chemical reaction was feasibly interpreted by Gibbs free energy profile. The standard vibrational analysis stressed the active participation of composed ligand groups for the existence of the analgesic as well as antipyretic properties of the Phenacetin compound. The strong dipole interaction energy utilization for the transition among non-vanishing donor and acceptor for composition of the molecular structure was interpreted.

1. Introduction

Phenacetin or 4-Ethoxyacetanilide is white crystalline powder, odorless fine white crystalline solid with a lightly bitter taste. Acetanilide was the first aniline derivative found to possess analgesic as well as antipyretic properties and was quickly introduced into medical practice under the name of Antifebrin [1]. Its aniline derivatives such as Phenacetin [2] have less toxic effect and have rich analgesic and antipyretic properties [3,4]. The consecutive connection of amine-carbonyl and methyl group made a chemical and physical attraction between atoms and created another hexagonal ring. When the amide group is conjugated between nitrogen lone-pair electrons and the carbonyl π-bond, the Anti-inflammatory chemical properties have been induced in the chemical product [5,6].

Acetaminophen phenetidine is organic synthesis raw materials and it acts as pharmaceutical intermediates [7]. It is an antipyretic analgesic non steroidal anti-inflammatory drug. Analgesic, antipyretic analgesics for the treatment of fever, headache, neuralgia, etc., [8]. Phenacetin is reasonably anticipated to be a human carcinogen; analgesic mixtures containing Phenacetin are listed as known human carcinogens. Phenacetin reacts with oxidizing agents, iodine and nitrating agents. 4-ethaxyacetanilide with amine is also used as a chemical intermediate for the production of azo dyes for synthetic textiles, especially polyesters, but also polyamide, polyvinyl, and polyacrylonitrile fibers. The general pharmacological effects are Adjuvants, Anesthesia, Analgesics, Anti-inflammatory Agents, Non-Steroidal, Carcinogens, EnzymeInhibitors, Hypnotics and Sedatives, Insecticides.

After go through the available sources, it is well known that, the Phenacetin is pharmaceutically active. In order to explore the rest of other properties related to pharmaceutical action of the compound, the theoretical and experimental investigation is to be carried out. In this attempt, the vibrational and NMR and UV–Visible spectroscopic analyses have been performed to screen the physical and chemical properties of the present compound using computational calculations. The docking studies have been carried out to explain the binding mechanism with the human protein.

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2. Experimental details

- The FT-IR spectrum of the compound was recorded using a Bruker IFS 66 V spectrometer.
- The FT-Raman spectrum of the same compound was also recorded using the same instrument with an FRA 106 Raman module equipped with aNd:YAG laser source operating at 1.064 μm line widths with 200 mW power.
- The high resolution ^{1}HNMR and ^{13}CNMR spectra were recorded using 300 MHz and 75 MHz NMR spectrometer respectively.
- The UV–Vis spectra were recorded in liquid phase dissolved in ethanol in the range of 200 nm–800 nm, with the scanning interval of 0.2 nm, using the UV-1700 series instrument.

3. Computational profile

In order to obtain the calculated data, the entire computational calculations have been performed using the Gaussian 09 D. 01 version software program in core i7 computer [9]. The fundamental frequency and geometrical parameters were computed using B3LYP and B3PW91 methods in combination with 6–31++G(d, p) and 6-311++G(d,p) basis sets. The electronic spectra and related data, such as NBO and energy levels of frontier molecular orbitals were calculated using time-dependent SCF method with same basis set. Similarly the ^{1}H and ^{13}CNMR chemical shifts calculated by GIAO interface method using B3LYP/6-311++G(2d,p) basis set. The Mullikan charge level distribution among atoms was mapped and the asymmetric accumulation of charges was profoundly analyzed for the cause of pharmaceutical action of the compound. The first order and polarizability and the first order hyper polarizability of the compound were also computed and ECD-VCD spectra were simulated using B3LYP method with the 6-311++G (d,p) basis set.

4. Results and discussion

4.1. Conformational analysis

The molecular geometry scan was performed and the optimized geometry of the compound is identified by the zero point vibrational energy. The conformational analysis was performed by varying the torsion angle C_1–N_{11}–C_{13}–O_{14} at ±120° to find out the conformational structure. From the scan, it was found that, two conformational structures such as C1 and C2 with energies of 136.39 and 135.987 and was displayed in Fig. 1. There was no huge energy difference observed between two conformers and thereby it was confirmed that, no change in fundamental physical and chemical properties.

4.2. Structural deformation analysis

In this molecule, the amine, carbonyl and methyl group were substituted in ortho position in left moiety whereas ethoxy and methyl group were replaced the hydrogen in meta position. Both the substitutions were symmetrically replaced the hydrogen in the benzene ring. The highly enlarged bonds (C1–C2 and C3–C4) were found at the substitutional place which was due to the hold up the two ligands on both sides. The bond length C2–C3 was compressed much due to the strain generated due to the loading of both ligands and it was observed on one side of the ring. The outward stretching of atoms C1 and C4 showed the asymmetrical distortion of the hexagonal frame of the ring. Though, the carbonyl group on C13 and dual insertion of hydrogens on C20, the bond lengths C13–C15 and C20–C23 were observed same (1.516 Å). From the deformation of the ring due to the symmetrical substitutions, it was observed that, the ring was the main bridge for the link of two substitutions and thereby the final physical and chemical property of the present compound would be on par with the ligands. Usually, the semi circle ring is formed with 120° in the hexagonal ring; whereas in this case, the top semicircle (121.15°) was 0.76° stretched out than bottom semicircle (120.39°). It said that, the amine and carbonyl group made intensive loading in the ring and the part creates adverse effect than rest part of the substitution (see Table 1).

4.3. Mulliken charge population analysis

The entire construction of compound is stabilized by electrostatic attraction and repulsion between various parts of the

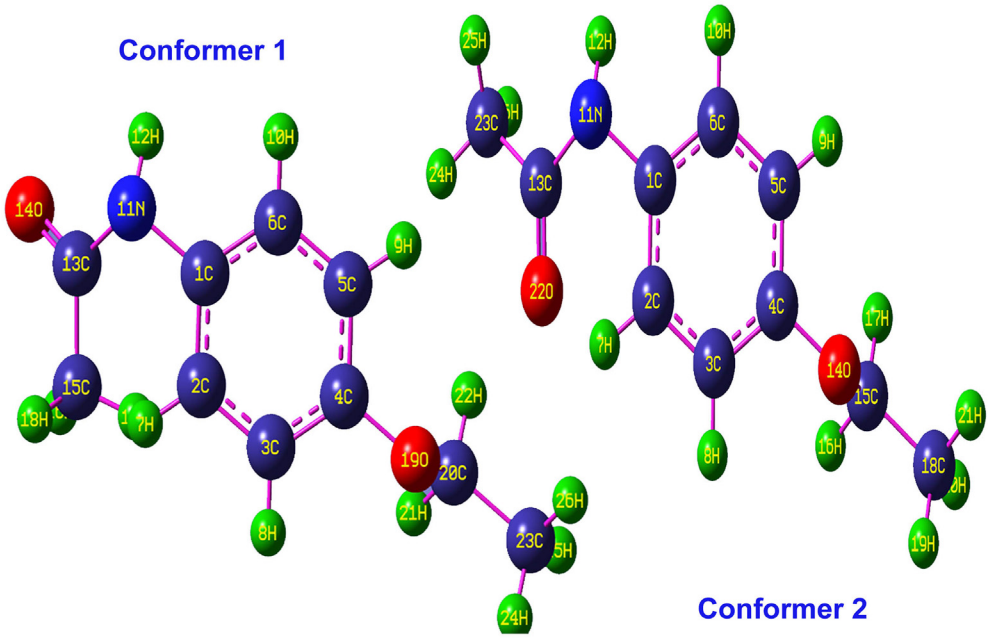

Fig. 1. Molecular structure of Phenacetin.