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DFT STUDIES OF VIBRATIONAL FREQUENCIES OF ASPIRIN, PARACETAMOL AND PHENACETIN

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ABSTRACT

Density functional theory DFT (B3LYP)/6-31G (d) has been applied to compute the geometry optimization, dipole moment and vibrational frequencies of aspirin, paracetamol and phenacetin. From the comparison of vibrational frequencies, it is observed that the value of O-H stretching in aspirin is lower as compared to paracetamol shows its greater tendency to form cation whereas paracetamol has least tendency to form cation as the O-H stretching in paracetamol is at greater frequency even than that of phenacetin, which explains that why there is displacement of –COOH by –OH group in aspirin i.e. (aspirin) acetyl-salicylic acid readily converts into salicylic acid, which is responsible for most of its actions. The greater values of O-H and C-H stretching of paracetamol than aspirin and phenacetin explains its selective behavior to inhibit cyclooxynase-2 (COX-2) and poor inhibitor of the synthesis of prostaglandins, which is responsible for pain headache and infection. On comparison of dipole moment of it is also observed that the order is Aspirin > Paracetamol > Phenacetin and from our earlier ADMP studies of total energy curve vs time in trajectory curve of aspirin, paracetamol and pehnacetin at DFT/6-31G(d) it is found that the energy required to release Hydrogen from these drugs are in the order Paracetamol > Phenacetin > Aspirin, therefore from infrared spectra, dipole moment and ADMP studies of aspirin, paracetamol and phenacetin it is concluded that aspirin is most reactive which explains that why it inhibit the synthesis of prostaglandins responsible for pain, headache and fever; restricts the blood supply to the tumor in effect-not allowing it to grow than a pea and paracetamol is a poor inhibitor of prostaglandins synthesis, does not have antiinflammatory action; phenacetin shows more reactive sites than paracetamol but less than aspirin, which give the evidence that why it is being replaced aspirin.

Key words: Quantum chemical calculations, DFT, HF, Vibrational frequencies, IR, Dipole moment, Polarizability, Aspirin, Paracetamol, Phenacetin.

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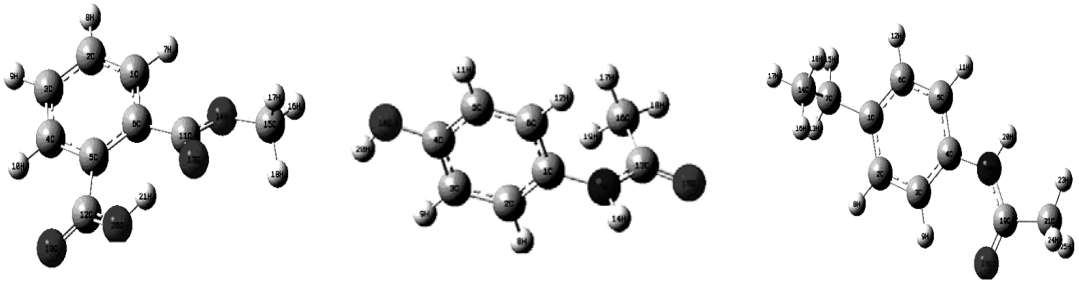
INTRODUCTION

Analysis of vibrational spectra of organic molecules has played an important role for a long time determining their molecular structures, intramolecular and intermolecular forces. The frequencies calculated by the Restricted Hartree-Fock method are, however consistently higher[1] than the experimental wavenumbers of fundamentals by 10 because of the neglect of electron correlation and anharmonicity effects. Therefore, we have applied density functional theory[2-5] as an alternate to Restricted HF method, which includes electron correlation, having affording opportunities of performing vibrational analysis of aspirin, phenacetin and paracetamol.

In order to handle dreadful diseases like aids, cancer, alzheimer's etc, there is a need for new research in the field of medicine, concerning drug-DNA interactions. Many physcio chemical techniques as well as quantum mechanical approaches are in vogue in studying these techniques, as action mechanism of drugs at molecular level is still unclear. An attempt is made by Murthy and his co-workers[6-10] to correlate electron ionization cross section with drug dosage and its toxic effects. The present study is an effort to understand the mechanism and other aspects of medically important systems of some common drugs (aspirin, paracetamol and phenacetin), through the determination of vibrational frequencies, dipole moment and comparision of these properties with the earlier computed ADMP[11-14]. The drug-DNA interactions are mainly based on electron transfer and electronic polarizability, and the process of transferring or gaining electron. These interactions can better be explained by exploring the concept of interaction of drugs towards protons and electrons. Measurement of these fundamental chemical properties of drugs now being possible with modern mass spectrometric techniques such as fast atom bombardment (FAB)[15,16], secondary ion mass spectrometry(SIMS)[17] and the soft ion techniques, elecetrospray ionization (ESI) and matrix assisted laser desorption ionization (MALDI)[18-21], high pressure mass spectrometry[22], fourier transform ion cyclotron resonance (FTIR) mass spectrometry[20] and kinetic methods[15,21-28] have been used in evaluating the chemical behavior in gas phase. Undoubtly an accurate experimental determination is the ultimate choice for obtaining chemical properties even then sophisticated high level ab-initio calculations have become attractive alternative when the experimental determination is difficult or ambiguous. Aspirin (acetyl-salicylic acid) is an organic acid and stable in dry air.

It is known for its analgesic, antipyretic actions and helps even in curing the disease like cancer, but still it is unclear that which one among the three drugs taken for the present study has better pain relieving effect i.e., which one stop the synthesis of prostaglandins responsible for pain, headache and fever without any or minor side effect. Regular aspirin

intake may reduce the risk of colorectal cancer by 50% however,the mechanism of this chemopreventive effect is not known. Efforts have been made here by studying the molecular properties of these drugs, to explain above mechanism at molecular level.



1 **2** **3**

Fig. 1-3: The optimized structures of aspirin, paracetamol and phenacetin, respectively calculated at DFT (B3LYP)/6-31(d)

The availability of quantum mechanical programs G-03W and GAUSS view 4.1 Version[29], which include all electron of the systems and in which all integrals are evaluated without approximation, promoted us to use quantum mechanical programs to explore the finer details of aspirin, paracetamol and phenacetin to provide information on the infrared spectra of aspirin, phenacetin and paracetamol taken for the present study and on comparison with the experimental findings and our earlier studies to see upto which extend these calculated results authenticate the adequacy and the reliability of the ab-initio method.

Computational details

The neutral gas phase of aspirin, paracetamol and phenacetin were fully optimized by employing HF/6-31G(d) and DFT(B3LYP)/6-31G(d) and then this optimized structure is started as initial geometry for calculation of vibrational frequencies of aspirin, paracetamol, phenacetin with RHF/6-31G(d), DFT(B3LYP)/6-31G(d) at ab-initio level. Fig. 1-3 are the optimized structures of aspirin, paracetamol and phenacetin, respectively calculated at DFT (B3LYP)/6-31G(d). All calculations in the present work were carried out on Intel Core-i3 using G-03W and GAUSS VIEW 4.1 VERSION[24] of ab-initio quantum mechanical program out in the Department of Physics, MMEC, MMU, Mullana, Ambala.

RESULTS AND DISCUSSION

The mid infrared region ranging from 4000 cm^{-1} to 3200 cm^{-1} is the O-H and N-H region. In case of aspirin, paracetamol and phenacetin, the peaks obtained in this region in

the calculated IR Fig. 5 at DFT(B3LYP)/6-31G(d) are 3217.01 cm^{-1} in aspirin corresponds to O_{20}-H_{21} stretching and the experimental Fig. 4 IR of Aspirin[30] (Chemistry M01B Laboratory Manual) is also in the region 3200-2500 cm^{-1}, 3601.58 cm^{-1} and 3429.78 cm^{-1} in Paracetamol corresponds to O_{10}-H_{20} stretching and N_7-H_{14} stretching respectively, 3475.63 cm^{-1} in phenacetin is assigned as N_{10}-H_{20} stretching, respectively. All these assignments are as expected to general conventions.

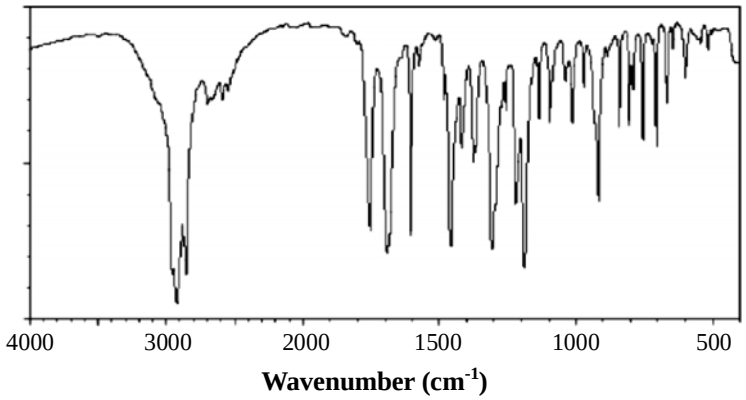


Fig. 4

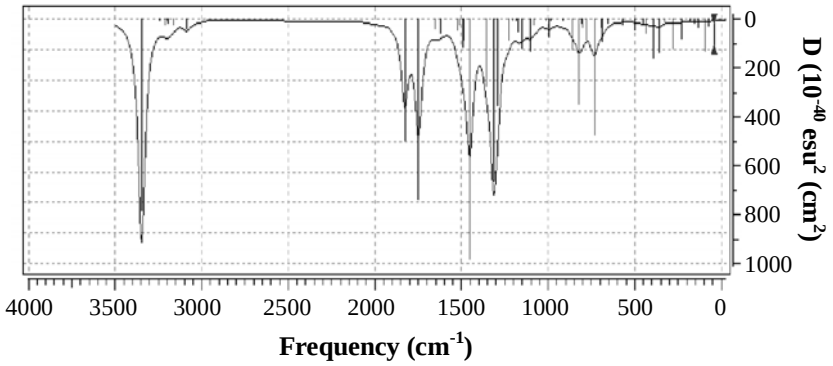


Fig. 5: Aspirin

Fig. 4 and 5: The experimental IR aspirin and calculated IR at DFT (B3LYP)/6-31G (d)

As C-H in-plane bending in between 1300-1000 cm^{-1}, C-H out of plane bending in between 900-675 cm^{-1} and skeleton vibration in between 1600-1585 cm^{-1} are the most important characteristic bands in the spectra of aromatic compounds. In case of aspirin the calculated IR peaks are obtained at 1261.31 cm^{-1}, 1239.85 cm^{-1} corresponds to C-H in plane bending.

946.61 cm^{-1}, 878.55 cm^{-1}, 777.16 cm^{-1}, 750.56 cm^{-1} and 704.315 cm^{-1}, all these are assigned as out of plane bending and 1588.86 cm^{-1} corresponds to skeleton vibration or ring distortion gives the evidence of aromatic hydrocarbons and the experimentally observed IR is in the region 1600-1400 cm^{-1} corresponds to skeleton vibration.

Similarly, the calculated IR frequencies in the region 1300-1000 cm^{-1} of paracetamol Fig. 1.3 and phenacetin Fig. 1.4 are 1275.13 cm^{-1}, 1149.35 cm^{-1}, 1083.04 cm^{-1}, 1023.16 cm^{-1}, and 1299.43 cm^{-1}, 1242.24 cm^{-1}, 1169.27 cm^{-1}, 1112.81 cm^{-1}, are assigned as C-H in plane bending. In the region 900-675 cm^{-1}, the calculated IR are 909.53 cm^{-1}, 820.35 cm^{-1}, 787.01 cm^{-1}, 690.18 cm^{-1}, and 946.17 cm^{-1}, 905.31 cm^{-1}, 798.03 cm^{-1} are C-H out of plane bending. 1580 cm^{-1}, 1504 cm^{-1} and 1609.783 cm^{-1} are assigned as $C_4 = C_3$, $C_1 = C_2$ and $C_3 = C_2$, $C_5 = C_6$ stretching or skeleton vibrations.

The most important characteristic vibrations of COOR (ester) and COOH is C=O stretching, the observed IR peak of C=O stretching in aspirin is in the region 1750-1730 cm^{-1} and 1725-1700 cm^{-1} for ester and carboxylic, respectively and the corresponding calculated IR is at 1756.30 cm^{-1} and 1680.85 cm^{-1}, respectively.

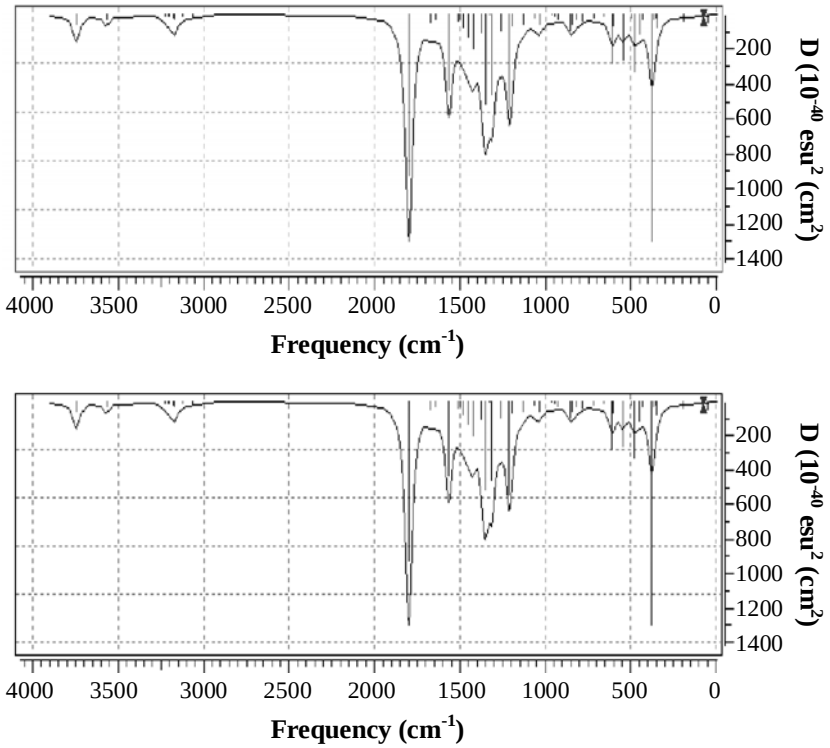


Fig. 6: Paracetamol

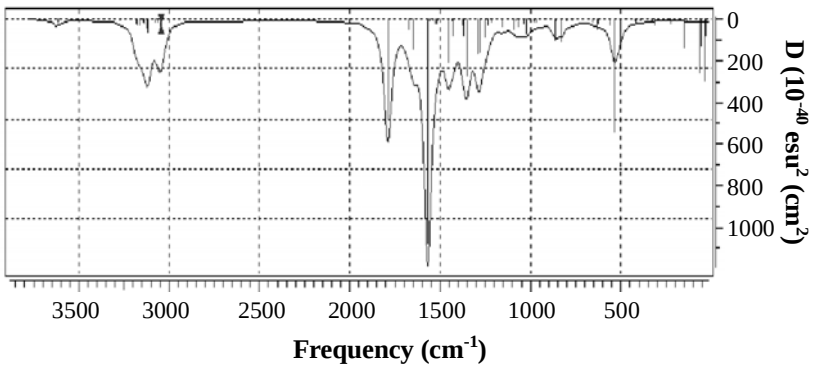


Fig. 7: Phenacetin

Fig. 6-7: IR spectra of paracetamol and phenacetin calculated IR at DFT (B3LYP)/6-31G(d)

The calculated IR 1264.51 cm^{-1} is attributed to C_{11}-O_{14} stretching and the observed peak is in the region 1300-1000 cm^{-1}. However, the C=O stretching in the calculated IR of paracetamol and phenacetin are at 1729.45 cm^{-1} and 1720.22 cm^{-1}, respectively, which are at lower frequencies than the C=O of ester stretching in aspirin, it is because resonance strengthen the C=O bond in aspirin, as a result absorption take place at higher frequency then that of aldehyde, ketone and alcohol.

From the comparison of vibrational frequencies with the earlier observed IR frequencies, we conclude that the calculated vibrational frequencies at DFT level are at par with the experimental values. However, if we use 0.8929 scaling factor for Hartree-Fock method with different split-valence basis sets then we get the vibrational frequencies approximately nearer to the experimental values. We have calculated vibrational frequencies of aspirin, paracetamol and phenacetin with DFT (B3LYP) and 6-31G(d) basis set, and given assignments to all the frequencies of the molecules, which explains, how the aspects of molecular structure of aspirin, paracetamol and phenacetin serve as a powerful tool in explaining their involvement in medicine e.g. The lower value of O-H stretching in aspirin as compared to paracetamol shows its greater tendency to form cation whereas paracetamol has the least tendency as the O-H stretching in paracetamol is at greater frequency even than that of phenacetin, which explains that why there is displacement of –COOH by –OH group in aspirin i.e. (aspirin) acetyl-salicylic acid readily converts into salicylic acid, which is responsible for most of its actions e.g. inhibition of prostaglandins, its anticoagulation behavior, analgesic, antipyretic and antiinflammatory effects, which favors the experimental pharmacokinetic studies of aspirin on humans. The greater values of O-H and C-H stretching

of paracetamol than aspirin and phenacetin explains its selective behavior to inhibit cyclooxynase-2 (COX-2) and poor inhibitor of the synthesis of prostaglandins which is responsible for pain headache and infection. Meanwhile, paracetamol is standard antipyretic but has poor analgesic and anti-inflammatory actions. The present work on vibrational frequencies opens a new approach to the study of drug interactions inside the body besides the other physico-chemical methods that are available today. It explains all possible aspects of molecular structure of all these drugs involved in drug designs and these aspects alone are sufficient to give an insight into medical activity of the drugs inside the body without using the highly expensive physico-chemical method.

Table 1: Dipole moment (in units of Debye) of asp calculated at HF and DFT methods with different basis sets

Methods / Basis sets	Aspirin	Paracetamol	Phenacetin
HF/6-31G(d)	6.38852	4.5069	3.5875
HF/6-31G(d,p)	6.9161	4.5253	3.5882
HF/6-31+G(d,p)	7.0790	4.7136	3.7110
HF/6-31++G(d,p)	7.0767	4.7152	3.7094
HF/6-311G	7.9885	4.7766	3.9994
HF/6-311G(d)	6.8951	4.5279	3.5897
HF/6-311G(d,p)	6.8789	4.4916	3.5515
HF/6-311+G(d,p)	6.9501	4.6286	3.6439
HF/6-311++G(d,p)	6.9497	4.6285	3.6444
DFT(B3LYP)/6-31G(d)	6.6536	4.5116	3.2752

On comparison of dipole moment of aspirin, paracetamol and phenacetin (Table 1), it is observed that the order is Aspirin > Paracetamol > Phenacetin. This observation shows that aspirin is more asymmetric as compared to Paracetamol and Phenacetin. It is found that dipole moment depends on the substituents being in the order –COOH > R-COOR$^{'}$ > -OH > -NHCOCH$_3$ > -C$_2$H$_5$. In other words, the order of dipole moment is the order of their reactivities. It is in accordance to their behavior in medical activities i.e. rapid conversion of (Aspirin)acetyl–salicylic acid into salicylic acid, which is responsible for most of its actions e.g. its anticoagulation behavior, analgesic, antipyretic and anti-inflammatory effects.

From our earlier ADMP[14] calculations of total energy curve vs time in trajectory curve of aspirin, paracetamol and pehnacetin at DFT/6-31G(d), it is found that the energy required to release hydrogen from these drugs are in the order Paracetamol > Phenacetin > Aspirin and therefore, Aspirin is most reactive, which explains that why it inhibit the synthesis of prostaglandins responsible for pain, headache and fever; restricts the blood supply to the tumor in effect- not allowing it to grow than a pea and paracetamol is a poor inhibitor of prostaglandins synthesis, does not have antiinflammatory action; phenacetin shows more reactive sites than paracetamol but less than aspirin, which give the evidence that why it is being replaced aspirin. Therefore, it is concluded that aspirin is more reactive as compared to others drugs under consideration.

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