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EXPERIMENTAL CUM THEORETICAL EVALUATION OF MOLECULAR STRUCTURE, VIBRATIONAL SPECTRA, NBO, UV, NMR, OF A BIOACTIVE COMPOUND – PHENOXYACETOHYDRAZIDE

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Abstract:
Hydrazide-Hydrazone compounds are key species for a range of bioactivities. The first complete density functional theoretical study of Phenoxyacetohydrazide (PAH) is reported. The normal mode frequencies, intensities and the corresponding vibrational assignments were calculated using the GAUSSIAN 09W set of quantum chemistry codes at the DFT/B3LYP levels of theory using the 6-311++G** basis set. Stability of the molecule arising from hyperconjugative interactions has been probed using NBO analysis. 1H and 13C NMR spectra have been analysed and the chemical shifts were calculated using the gauge independent atomic orbital (GIAO) method. The theoretical UV-Vis spectrum and the electronic properties, such as HOMO (Highest occupied molecular orbital) and LUMO (Lowest unoccupied molecular orbital) were performed by time dependent density functional theory (TD-DFT) approach.

Keywords:
Phenoxyacetohydrazide, NBO, UV, NMR, Vibrational analysis, DFT.

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1. INTRODUCTION

The role of acid hydrazides as active intermediates in synthetic and pharmaceutical chemistry [1–6] has prompt the investigation of the stability and structure of acetohydrazide [7]. A range of bioactivities are reported for hydrazide-hydrazone compounds, such as antibacterial, anticonvulsant, antimalarial, analgesic, anti-inflammatory, antiplatelet, antifungal, antituberculosis,and anticancer activities [8–13]. A variety of semicarbazones, thiosemicarbazones and guanylhydrazonesare found to be key compounds for drug design [14], for metal complexes [15],organocatalysis [16],and are used for the preparation of heterocyclic rings [17]. Some evidence proposes a pharmacophoric character for the hydrazone moiety present in phenyl hydrazone derivatives in the inhibition of cyclooxygenase [18]. Antioxidant [19–22],antiglycation [23–26] and antileishmanial [27] activity have recently been reported, as well as applications in mass spectrometry [28]. The present work aimed to investigate the structural stability and vibrational assignment of Phenoxyacetohydrazide(PAH). Quantum chemical computations are the newly emerging techniques in resolving the structural chemical

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behaviour of the bio-chemicals [29]. Density functional theory (DFT) computation, which incorporates the electron correlation, has recently become an efficient tool in the prediction of molecular structure, harmonic frequencies and IR and Raman activities of biological compounds [30-32]. The vibrational spectroscopy has proved to be a powerful tool for probing the occurrence of the hydrogen bonds. C–H· · ·O hydrogen bonds are currently one of the main fields of hydrogen bonding research both experimentally and theoretically [33], and these types of hydrogen bonds are the key interaction in structure and activity of biological systems [34-37]. The present work deals with the FT-IR and FTRaman spectral investigations of Phenoxyacetohydraide [PAH] to understand the structural and bonding features, electron delocalization, steric effect and the intramolecular charge transfer interactions. Theoretically computed vibrational wavenumbers were compared with experimental values. These calculations were expected to provide new insight into the vibrational spectrum and molecular parameters. The natural bond orbital analysis (NBO) and the distribution of electric charges on atoms of free molecules of PAH compounds were investigated by using the DFT computation with B3LYP/6-311++G** basis set. The time dependent density functional theory (TD-DFT) calculation of NLO properties and dipole moments were performed and discussed with theoretical values of β. The molecular electrostatic potential (MEP) was investigated using B3LYP method. The electrostatic potential is the energy of interaction of a point positive charge (an electrophilic) with the nuclei and electrons of a molecule. Negative electrostatic potentials indicate areas that are prone to electrophilic attack. The electrostatic potential can be mapped onto the electron density by using colour to represent the value of the potential [38]. For further application, the energy difference between highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), the HOMO/ LUMO gap, has also been calculated. In addition, the hydrogen bond donors and receptors were predicted based on the theoretical calculations. Considering the industrial and biological importance of this compound, extensive experimental and theoretical quantum chemical studies were carried out on PAH to obtain a complete reliable vibrational assignments, structural characteristics and electronic properties of the compound.

2. EXPERIMENTAL DETAILS

The fine polycrystalline sample of PAH was obtained from Sigma Aldrich, UK, and used as such for the spectral measurements. The room temperature FTIR spectrum of the compound was measured in the region 4000–400 cm^{-1} at a resolution of ±1 cm^{-1}, using a BRUKER IFS-66V vacuum Fourier transform spectrometer equipped with a mercurycadmiumtelluride (MCT) detector, a KBr beam splitter and globar source. The FT-Raman spectrum of 2MQ was recorded on a BRUKER RFS 100/S FT-Ramanspectrometer. The spectrum was recorded in 4000–100 cm^{-1} Stokes region using 1064 nm line of an Nd:YAG laser for excitation, operating at 200mW power. The reported wavenumbers are expected to be accurate within ±1 cm^{-1}. 1H and 13C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker HC400 instrument (400 MHz; DMSO). Chemical shifts for protons are reported in parts per million scales (delta scale) downfield from tetramethylsilane.

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3. COMPUTATIONAL DETAILS

The quantum chemical calculation of PAH has been performed using the B3LYP supplemented with the standard 6-311++G** basis set, using the Gaussian 09 program [39].The optimized structural parameters have been evaluated for the calculations of vibrational frequencies by assuming C_1 point group symmetry. At the optimized geometry for the title molecule no imaginary frequency modes were obtained, so there is a true minimum on the potential energy surface was found. As a result, the unscaled calculated frequencies, reduced masses, force constants, infrared intensities, and Raman activities were obtained. In order to fit the theoretical wave numbers to the experimental, the scaling factors have been introduced by using a least square optimization of the computed to the experimental data.The symmetry of the molecule is also helpful in making vibrational assignments. By combining the results of the Gauss view program [40] with symmetry considerations, vibrational frequency assignments were made with a high degree of confidence. There is always some ambiguity in defining the internal coordinates. However, the defined coordinates form a complete set and matches quite well with the motions observed using the Gauss view program.The natural bonding orbital (NBO) calculations were performed using NBO 3.1 program, implemented in the Gaussian 09 package at the DFT/B3LYP level. NBO helps to understand various second order interactions between the filled orbitals of one subsystem and the vacant orbitals of another subsystem, which is a measure of the intermolecular delocalization and hyper conjugation. The electronic absorption spectra for optimized molecule calculated with the time dependent DFT.

4. RESULTS AND DISCUSSION

4.1.MOLECULAR GEOMETRY

In this work, a detailed study about the structure of the molecule is obtained by the computational DFT/B3LYP method. The crystal structure is controlled by the strong intermolecular forces, whereas the theoretical data represent an isolated molecule controlled by intramolecular interactions. The main objective of the study is to describe the theoretically predicted structural and electronic properties that best represents the gaseous molecule. The optimized structure of the title molecule is shown in Figure 1.

The calculated geometrical parameters form a basic in calculating the other parameters. The C-C bond length on benzene ring ranges from 1.3881 to 1.4002 A^0, which is longer than C = C bond length but shorter than C – C bond length 1.3899 ^{0} .This is due to the steric repulsion caused by the substitution of acetyl and amide group. Considering the C9 - C12 bond length, whose value is increased to 1.5266 A^0, is due to the presence of the electronegative nitrogen and oxygen atoms nearby. The C12 – O13 with the value 1.2175A^0 in the acetyl group depicts the double bond character and C2 – O8 with the value 1.368 A^0 depicts the single bond character.

The substitution of the highly electronegative oxygen atom in the ring has slightly distorted the hexagonal symmetry and it is revealed in the bond angles C1-C2-C3, C2-C1-C6 and C2-C3-C4.

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The planar geometry of the molecule is slightly deviated by the oxy group substitution and the corresponding dihedral angle is C1-C2-O8-C9 = -179.55^0.

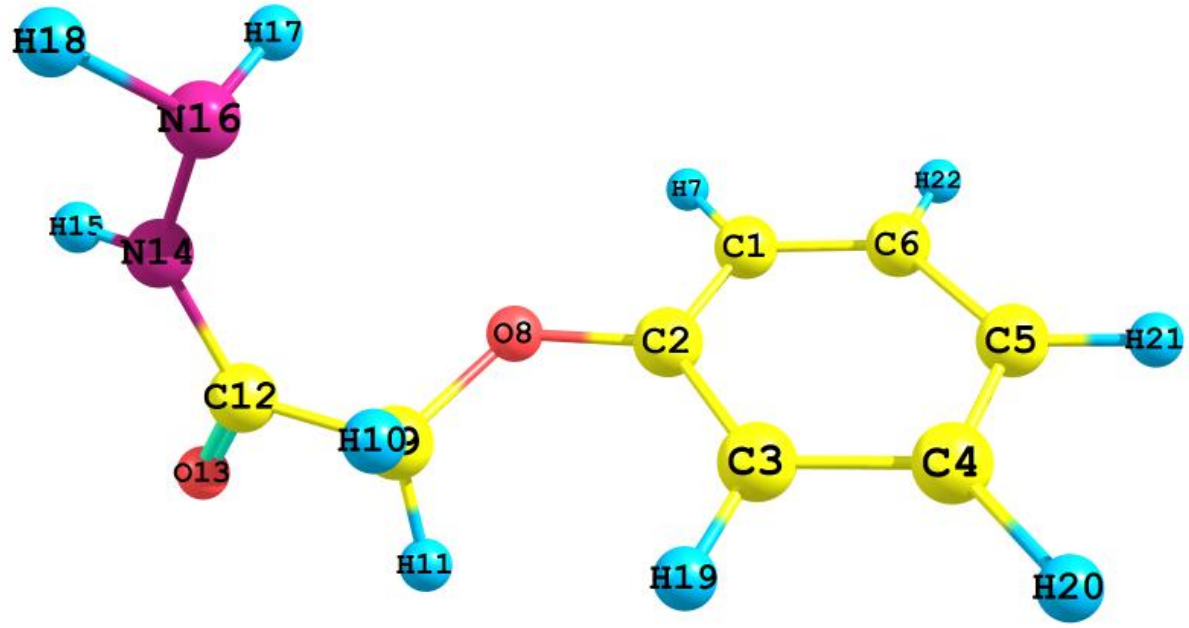

Figure 1: Optimized structure of phenoxyacetohydrazide (pah) with atom numbering scheme

4.2.NBO ANALYSIS

NBO theory is a complementary method in studying the energetic and structural data of the molecules. The computational DFT method helps to investigate the second order interaction between the filled orbitals of one subsystem and vacant orbitals of another subsystem. The hyper conjugative interaction energy was deduced from the second – order perturbation approach as:

$$E(2) = -n_\sigma \frac{\langle \sigma | F | \sigma \rangle}{\varepsilon_{\sigma^*} - \varepsilon_\sigma} = -n_\sigma \frac{F_{ij}^2}{\Delta E}$$

where$\langle \sigma | F | \sigma \rangle^2$, or F_{ij} is the Fock matrix element between i and j NBO orbitals, ε_σ and $\varepsilon_{\sigma^*}$are the energies of σ and σ* NBO's, and n_σ is the population of the donor σ orbital. The larger E (2) values indicates the more intense the interactions between electron donors and electron acceptors and they are summarised in Table 1.

The most important interaction (n-σ*) and (n-π*) energies, related to the resonance in the molecules, are electron donation from the LP (1)N atom of electron donating group to the anti-bonding acceptor π*(C-O) is shown by LP(1)N14→π*(C12-O13) = 58.09 KJ/mol. The larger energy shows the hyper conjugation between the electron donating nitrogen and the carboxyl group. The intramolecular hyper conjugative interactions are formed by the orbital overlap between π(C-C) and π*(C-C) bond orbitals which results in ICT (intramolecular charge transfer) causing stabilization of the system. These interactions are observed as increase in ED in C-C antibonding orbital that weakens their respective bonds [41].

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Table 1: The second-order perturbation energies e(2) (kcal/mol) corresponding to the most important charge transfer interactions(donor-acceptor) in pah by b3lyp/6-311++g** method

Donor(I)	Types Of Bond	Occupancy	Acceptor(J)	Types of Bond	Occupancy	E(2) Kcal/Mol	E(i)-E(j)a.u	F(i,j)
C1-C6	π	1.70434	C2-C3	π*	0.38668	21.97	0.28	0.071
C1-C6	π	1.70434	C4-C5	π*	0.33510	17.47	0.29	0.064
C4-C5	π	1.68896	C1-C6	π*	0.32254	21.70	0.28	0.070
C4-C5	π	1.68896	C2-C3	π*	1.66605	17.29	0.27	0.063
LP(2) O8		1.84995	C2-C3	π*	1.66605	28.68	0.34	0.094
LP(2) O13		1.86508	C9-C12	σ*	0.06667	19.54	0.62	0.100
LP(2)O13		1.86508	C12-N14	σ*	0.07863	24.67	0.71	0.0120
LP(1) N14		1.72639	C12-O13	π*	0.26292	58.09	0.29	0.117

The energy of σ*(C12-N14) anti-bonding orbital (0.07863 a.u) is higher than the energy of σ*(C9-C12) anti-bonding orbital (0.06667 a.u) which supports the possibility of delocalization of ED from C-N to the C-C region. The transfer of charges from the lone-pair $n_2(O_8)$ to the anti-bonding orbital π*(C2-C3) increase the population at π*(C2-C3) accounting for the stabilization of 28.68 KJ/mol which provides the elongation and weakening of the respective bond. The interaction between the lone-pair n_2 (O_{13}) and the anti-bonding orbitals σ and σ* are amounted to be 19.54 and 24.67 KJ/mol respectively.

4.3.NMR ANALYSIS

The prediction of molecular geometries is essential for calculating the magnetic properties. Therefore the titled compound is optimized fully by using B3LYP/6-311++G** method. Then, Gauge-including atomic orbital (GIAO) ^{1}H and ^{13}C chemical shift calculations have been made by same method. It is a superior procedure that exhibits a faster convergence of the calculated properties of the extension of the basis set used. On account of the economical factor and effectiveness of calculation this method seems to be preferable. The H and C NMR chemical shifts are calculated and tabulated in Table 2.

From the Table 2, it is clear that the C NMR chemical shifts of the title molecule falls in the range of the typical organic molecule (>100) [42]. The presence of CH_2 group has decreased the chemical shift of C9 to 68.32ppm. The H atom which is the smallest of all the atoms, are mostly localized on the periphery of the molecules. This enables their chemical shift for intermolecular hydrogen bonding. Hydrogen attached to nearby electron withdrawing atom or group can decrease shielding and move the resonance of attached proton towards a higher frequency. In contrast, electron donating atom or group increase shielding and moves towards a lower

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frequency. Here the proton attached to N tom is quite low compared to other H atoms. All the values are < 8ppm due to shielding effect [43].

Table 2: Experimental and theoretical chemical shifts of pah

C Atoms	Experimental values (ppm)	Theoretical values(ppm)	H Atoms	Experimental values(ppm)	Theoretical values(ppm)
12-C	168.66	175.62	20-H	7.31	7.38
2-C	157.16	165.99	22-H	7.31	7.36
6-C	129.82	134.14	7-H	6.88	7.06
4-C	129.82	134.05	21-H	7.00	7.01
5-C	122.25	124.24	19-H	6.88	6.68
1-C	114.58	121.49	15-H	8.02	5.90
3-C	114.58	112.11	10-H	4.551	4.89
9-C	66.99	68.32	11-H	4.551	3.86
			17-H	3.86	3.42
			18-H	3.86	3.14

4.4.HOMO-LUMO GAP

The HOMO-LUMO energy gap helps in determining the significant degree of electric excitation and charge transfer. The electron donating ability is characterized by the HOMO energy and electron accepting ability is characterized by LUMO energy. The gap between HOMO and LUMO characterizes the molecular chemical stability [44] and prove the bioactivity from ICT [45,46]. A molecule with small energy gap is highly polarizable and associated with a high chemical reactivity.
HOMO energy = -0.22970 eV.
LUMO energy = -0.01661 eV.
HOMO-LUMO energy gap = 0.21309eV.

This value explains the eventual charge transfer within the molecule and the bioactivity of the molecule.

4.5.VIBRATIONAL ANALYSIS

The title molecule PAH consists of 22 atoms and it comes under C_1 point group symmetry. This undergoes 60 normal modes of vibrations. The aim of vibrational analysis is to find the vibrational modes connected with specific molecular structures of calculated compound. Using DFT/B3LYP (6-311++G**) method the vibrational frequencies, IR intensities, Raman activity and normal mode (descriptions characterized by PED) of the title compound are obtained. Figure

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2 represents the experimental and calculated IR spectrum and Figure 3 represents the experimental and calculated RAMAN spectrum.

Carbonyl Group Vibrations

The C = O stretching vibrations are identified from the IR and Raman spectra because of the increase in the degree of conjugation of strength and polarization. The carbonyl stretching vibrations in amine group are expected in the region 1715 – 1680 cm^{-1}. The carbonyl stretching vibration is assigned to the very intense band at 1667 cm^{-1} and the theoretically calculated wavenumber takes the frequency a 1689cm^{-1}. The C-O stretching vibrations are very strong due to the C-C interaction vibrations and lies in the range 1300-1100cm^{-1}. The peak observed at 1208 cm^{-1} in the calculated frequencies is assigned for C-O stretching.

Amine Group Vibrations

Primary aliphatic amines absorb in the region 3450–3250 cm^{-1}in solids or liquids and they are broad and of medium intensity. In solid and liquid phases, a band of medium intensity is observed at 3400–3000 cm^{-1} for secondary aromatic amines. In general the vibrational bands due to the N-H stretching are sharp and weak than those of O-H stretching vibrations by virtue of which they can be easily identified [47] and are sensitive to structural change. The two NH_2 at 3332 and 3382 cm^{-1} in the theoretically calculated frequency is assigned for N-H stretching mode of PAH molecule and the experimental wavenumber is calculated at 3312 cm^{-1}in the IR coincides with the theoretical value. The N-H stretching wavenumber is calculated at 3419 cm^{-1}.

Two intense bands observed at 1619 in IR and 1603 in Raman are assigned for N-H in-plane bending and 1243 and 1249 cm^{-1} in IR and Raman respectively for NH_2 out-of-plane bending.

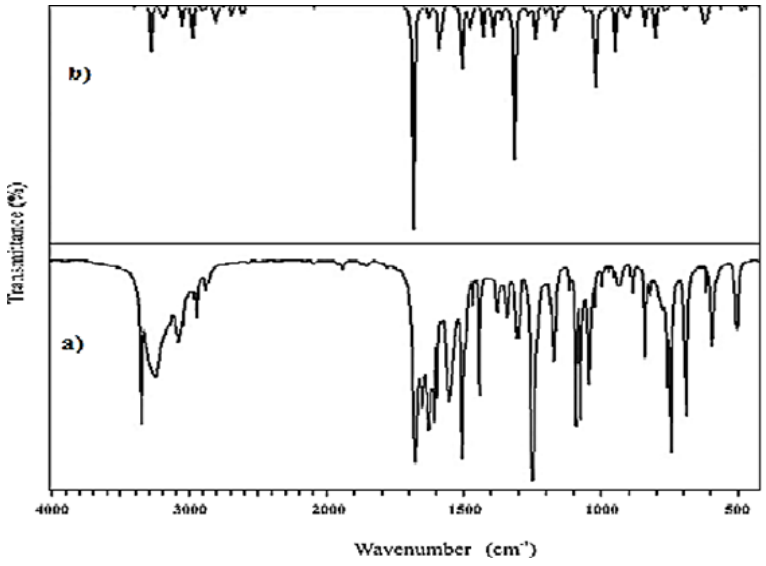

Figure 2: Comparison of Observed and Calculated Ftir Spectra Of Phenoxyacetohydrazide (A) Observed And (B) Calculated With B3lyp/6-311++G**

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C-H Vibrations

The C–H stretching vibrations of the phenyl ring are normally observed in the region 3100–3000 cm^{-1}[48, 49] which shows their uniqueness of the skeletal vibrations. In the title molecule the stretching vibrations appear at 3067, 3055, 3044, 3033, 3015 cm^{-1}. All the five bands are well within the expected range which shows the aromatic nature of the phenyl ring is not disturbed by any of the substitution group. All these vibrations are found active only in IR not in Raman.

Similarly, the C–H in-plane ring bending vibrations for aromatic CH occurs as strong to weak intensity bands in the region 1300–1200 cm_1 [50]. The bands observed at 1336, 1315, 1301, 1292 and 1270 cm^{-1} are assigned for in-plane bending and the values coincide with the theoretical data. The C–H out-of-plane bending vibrations are expected in the region 1000–800 cm_1 [51]. These vibrations are obtained in the region 929, 840,836, 766 and 760 cm^{-1} experimentally and the theoretical values also fall in the same range.

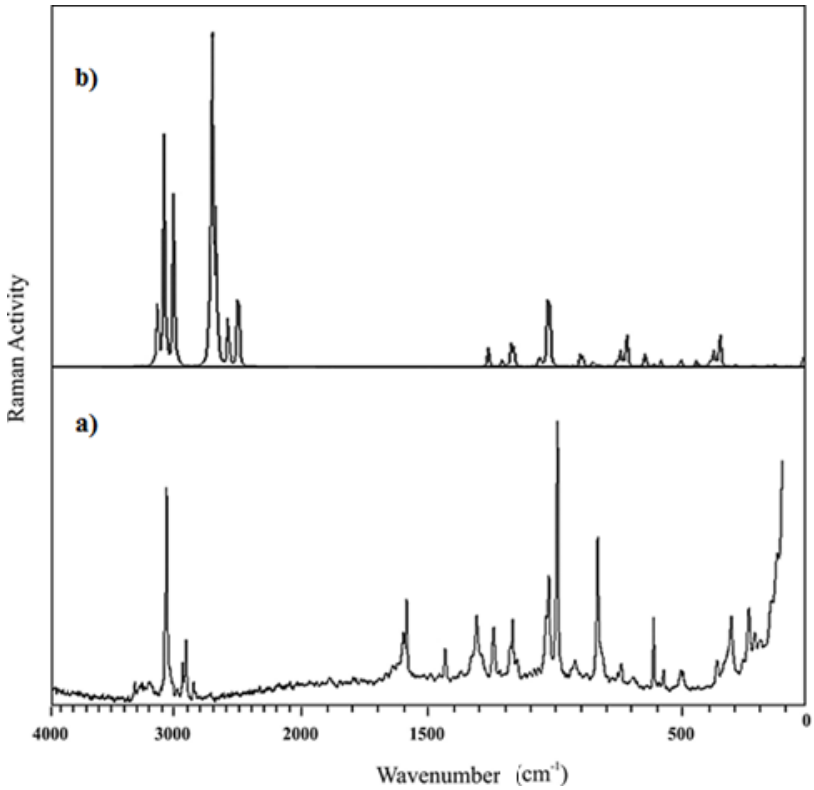

Figure 3: Comparison of Observed and Calculated Ft-Raman Spectra of Phenoxyacetohydrazide (A) Observed and (B) Calculated With B3lyp/6-311++G**

C-C Vibrations

The ring carbon–carbon stretching vibrations usually occur in the region 1625–1430 cm^{-1}. For aromatic six-membered rings, e.g., benzene and pyridines, there are two or three bands in this region due to skeletal vibrations, the strongest usually being at about 1500 cm^{-1}. In the case

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where the ring is conjugated further a band at about 1580 cm^{-1} is also observed. In general, the bands are of variable intensity and are observed at 1625–1590, 1590–1575, 1525–1470 and 1465–1430 cm^{-1} [52]. The three stretching vibrations observed at 1532, 1460, 1435 cm^{-1} in IR and 1591, 1439, 1401 cm^{-1} in Raman coincides well with the calculated data.

C-N Vibrations

Aromatic amines displays strong C-N stretching absorptions in the 1342–1266 cm_1 region, particularly, aromatic primary amine exhibit strong C-N stretching absorption at about 1300 cm^{-1}.The frequency in IR at 1370cm^{-1} is assigned for C-N stretching vibrations and the calculated value lies at the wavenumber 1414cm^{-1}.

4.6.UV ANALYSIS

The UV-Visible region allows strong $\pi - \pi^*$ or $\sigma - \sigma^*$ transition for all the structures. This is indicated in the natural bond analysis that molecular orbitals are mainly composed of σ and π atomic orbital. The low-lying excited states of PAH is determined TD-DFT/B3LYP/6-311++G**. The calculated results involving the vertical excitation energies, oscillator strength(S) and wavelength are carried out and tabulated in Table 3. The calculated λ_{max} values for the titled compound are found strong absorptions at 209.26, 201.08 and 197.29nm. These values shows that the transitions are between $\pi - \pi^*$. The highest contribution is observed at the wavelength 197.29nm and the transition mode is H-0->L+1(+56%) H-0->L+0(+28%).

Table 3: Theoretical electronic absorption spectra values of phenoxyacetohydraide(pah) using td-dft/b3lyp/6-31+g**

Excited state	Wavelength λ (nm)	Excitation energy(eV)	Oscillator strength(f)	Major contributions
S1	209.26	5.9248	0.0419	H-0->L+9(+41%) H-0->L+10(20%)
S2	201.08	6.1659	0.0116	H-0->L+11(27%) H-1->L+9(+24%)
S3	197.29	6.2842		H-0->L+1(+56%) H-0->L+0(+28%)

5. CONCLUSION

A complete vibrational assignment of Phenoxycetohydrazide have been performed based on the SQM force field obtained by DFT calculations at B3LYP/6-311++G** level. The molecular geometry, vibrational wave numbers, NBO analysis, NMR and UV–Vis spectral analysis and HOMO–LUMO of PAH in the ground state have been calculated by using density functional theory. Computational NMR method provides predictions of absolute chemical shift shielding tensors. The low value of the HOMO-LUMO energy gap reveals the molecule to be bioactive. Thus, the present investigation provides complete vibrational assignments, structural information and electronic properties of the compounds chosen.

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