Journal of Applied Science and Engineering Methodologies
Volume.2, No.3, (2016): Page.322-325
www.scientistlink.com/jasem

Vibrational Spectra and Natural Bond Orbital Analysis of Temozolomide Acid

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ABSTRACT

The structural and spectroscopic analysis of Temozolomide acid (TMZA) have been performed using computation technique. The DFT computation of TMZA was done using Gaussian '09 program package using B3LYP method with the 6-311G(D,P) basis set, which has been successfully applied in order to derive the optimized geometry and vibrational wavenumber of the normal modes. Vibrational spectroscopy is an efficient tool for the charecterization of bioactive materials. This work focuses on the spectral investigation using FT-Raman and IR spectra along with the density functional theory (DFT) calculations. The hydrogen bonding interaction is well demonstrated by the natural bond orbital (NBO) analysis. The Mulliken population analysis on atomic charges and the HOMO-LUMO energy were also calculated.

KEYWORDS – *DFT, NBO, HOMO-LUMO*

1. INTRODUCTION

Malignant gliomas(glioblastoma multiforme and anaplastic astrocytoma) occur more frequently than other types of primary central nervous system tumors, having a combined incidence of 5-8/100,000 population. *In vitro,* temozolomide acid has demonstrated schedule-dependent antitumor activity against highly resistant malignancies, including high grade glioma. Temozolomide acid (TMZA) is a carboxylic acid metabolite of Temozolomide (TMZ) with similar activity to TMZ against TLX5 lymphoma cells [1]. Vibrational spectroscopy is used to identify funtional groups and determine the molecular structure of the compound. It also characterizes the bioactivity of the material. Density functional theory (DFT) method is used for the computation of molecular structure, vibrational wavenumbers and energies of chemical reactions.

2. COMPUTATIONAL DETAILS

The DFT computations of Temozolomide acid was performed using Gaussian '09 program package [2] at DFT level. The computed wavenumbers are scaled by an empirical scaling factor of 0.9682 to fit with the experimental wavenumbers. The Raman activities (S_i) calculated by Gaussian '09 are converted to relative Raman intensities (I_i) using the following relationship derived from the basic theory of Raman scattering [3]:

$$I_i = \frac{f(v_0 - v_i)^4 S_i}{v_i \left[1 - exp\left(\frac{-hcv_i}{kT}\right)\right]}$$

in order to investigate the optimized geometry corresponding to hydrogen bonding. The hyperconjugative interaction energy was deduced from where ν_0 is the exciting wavenumber, ν_i is the vibrational wavenumber of the i^{th} normal mode, *h*,*c* and *k* are the universal constants and *f* is the suitably chosen common scaling factor for all peak intensities. The natural bonding orbital (NBO) analysis was performed the second-order perturbation approach [4]:

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

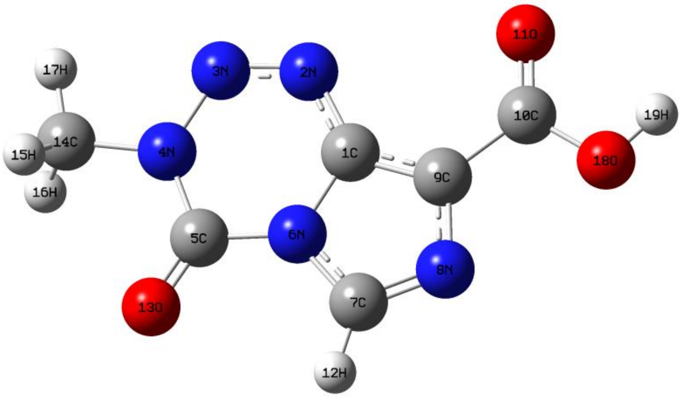
where $\langle \sigma | F | \sigma \rangle^2$ or F_{ij}^2 is the Fock matrix element between the *ith* and *jth* NBOs, ε_σ and ε_{σ^*} are the energies of σ and σ^* and n_σ is the population of the donor σ orbital. The HOMO-LUMO energy gap have been computed and analyzed.

3. RESULTS AND DISCUSSION

3.1. OPTIMIZED GEOMETRY

The optimized geometry of Temozolomide acid was obtained at B3LYP level. The theoretical and experimental values were compared and small deviations in some values were observed. The optimized structure of Temozolomide acid is shown in figure 1.

Figure 1: Optimized structure of TMZA



The presence of carbonyl group results a deviation in C_5-N_6 bond length (1.402 Å) from the experimental value. The decrease in N2-N3 bond length (1.259 Å) shows the double bond character. The presence of OH results a change in C_{10}-O_{11} bond length (1.206Å). The bond angles come within the ring N2-C1-N6 and C1-N2-N3 has the values 121.1^o and 119.6^o respectively. This deviation in bond angle is due to the non-aromatic nature of the ring. Using the dihedral angle values one can determine the planarity of a molecule. Most of the dihedral angles of TMZA are having 0^o and 180^o show the planar nature of the molecule.

Table 1: Optimized parameters of the TMZA

Optimized bond length(Å)			**Bond angle(^{o})**		
Bond length	**Calculated value**	**Experimental value**	**Bond angle**	**Calculated value**	**Experimental value**
N_2-N_3	1.264	1.261	C_1-N_2-N_3	119.3	119.6
C_5-N_6	1.396	1.402	N_2-C_1-N_6	120.6	121.1
C_7-H_{12}	0.895	1.078	N_8-C_7-H_{12}	127.5	126.9
C_{10}-O_{11}	1.197	1.206	C_1-C_9-C_{10}	127.9	126.6

3.2. NBO ANALYSIS

The Natural Bond Orbital (NBO) analysis is proved to be an effective tool for chemical interpretation of hyperconjugative interaction and electron density transfer from the filled lone pair electron. In TMZA the stabilization energy contribution from $\sigma(N_2$-$N_3) \rightarrow \sigma^*(C_1$-$C_9)$ are 61.755 KJ mol $^{-1}$. This increase in stabilization energy is due to addition of carbonyl group. The stabilization energy of $\sigma(C_1$-$C_9) \rightarrow \sigma^*(C_5$-$N_6)$ is 19.079 KJ mol $^{-1}$ is more positive than other values, this is because the hyper conjugative interaction are formed by the orbital overlap between $\sigma(C_1$-$C_9)$ bond orbital to $\sigma^*(C_5$-$N_6)$ anti bonding orbitals which results in charge transfer causing stabilization of the system. This interaction can be identified by finding the increase in electron density (ED) in anti bonding orbital.

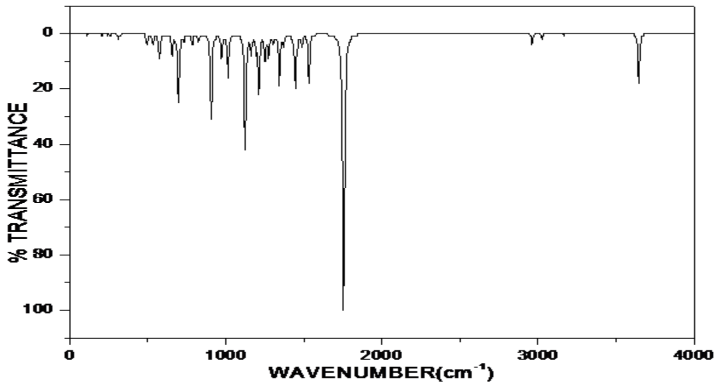
3.3. CHARGE ANALYSIS

The charge distribution on a molecule has a significant influence on the vibrational spectra. The charge distribution analysis of TMZA molecule was made on the basis of the natural charge analysis [5] and Mulliken population analysis using the NBO program implemented in the Gaussian 09 package. The atom C_5 shows more positive charge (0.820e) due to the adjacent nitrogen atoms. The C_{14} atom has electron donating nature by having negative Mulliken and Natural charge (-0.131e and -0.350e). Among all the nitrogen atoms, N_3 posses positive charge due to the neighboring electron donating nitrogen atoms. The carbonyl group adjacent to the C_9 atom leads to a negative charge at C_9 (-0.039e). All these charge variation shows the charge transfer within the molecule.

3.4. VIBRATIONAL SPECTRAL ANALYSIS

The vibrational spectral analysis of temozolomide acid was performed on the basis of the characteristic vibrations of the tetrazine ring, imidazole ring, methyl group, carbonyl group and nitro group. The computed vibrational wavenumbers, their IR intensities and Raman activities as well as the atomic displacements corresponding to the different normal modes were employed to identify the vibrational modes unambiguously. Figure 2 shows the FT-IR spectrum of Temozolomide acid.

Figure 2: FT-IR spectrum of TMZA



The C=O stretching vibrations give raise to the characteristic bands in IR and Raman and the intensity of those bands can increase owing to hyperconjugation. The C=O stretching band is often intense and appears in the range 1680-1630 cm^{-1}. The position of C=O stretching depends upon conjugation, hydrogen bonding and the size of the ring to which it is attached .In TMZA the O–H stretching vibration is observed as a weak band at 3607 cm^{-1} in IR.

Table 2: Vibrationanl distribution of TMZA

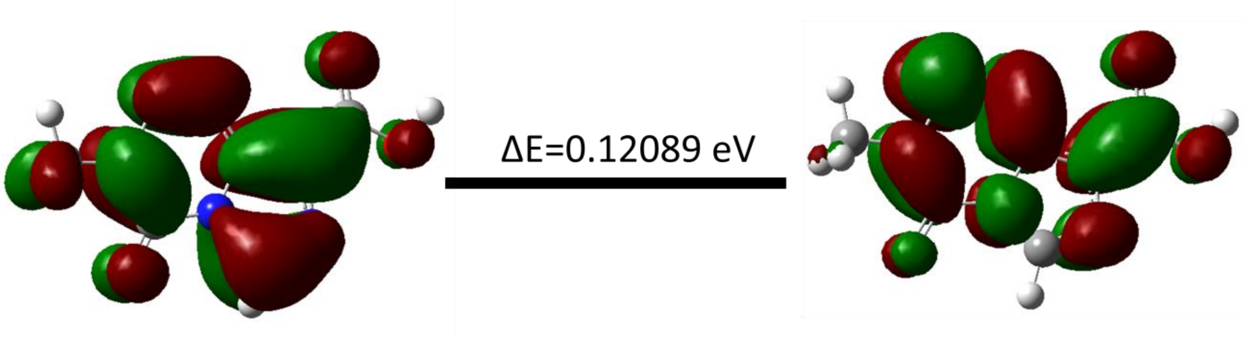
Experimental wave number		**Calculated wave number**	**Assignments with PED (%)**
FTIR cm^{-1}	**Raman cm^{-1}**		
3188vs		3165	υ_{O18H19}(100)
3114vs	3115s	3075	υ_{C14H15}(99)
1758w	1782w	1759	$\upsilon_{C5=O13}$(87)
1678vs	1672w	1632	$\beta_{(H19-O18-H20)}$67
1354vs	1356s	1370	υ_{N6C7}(43)
802s		825	$\tau_{C1C9N8C7}$(68)
512vs	508m	532	$\tau_{H19O18C10C9}$(75)

The corresponding calculated value lies at 3625 cm^{-1} with a PED of 100 %. Methyl group is generally referred to electron-donating substituent in the aromatic rings system. There are seven fundamentals that can be associated to each methyl group, namely the symmetric and asymmetric stretching, the symmetric and asymmetric deformation, rocking, wagging and twisting. The asymmetric stretching vibrations of the methyl group are generally observed around 2980cm^{-1}, while the symmetric stretch is expected around a lower wavenumber of 2870cm^{-1}[6]. The observed FT-IR of TMZA shows an intense band at 3114cm^{-1} results the asymmetric stretching of methyl group. This shift in the wavenumber is due to the N-H…N hydrogen bonding.

3.5. HOMO-LUMO

The conjugated molecules are characterized by a small highest occupied molecular orbital – lowest unoccupied molecular orbital (HOMO-LUMO) separation, which is the result of a significant degree of intra molecular charge transfer from the end capping electron donor groups to the efficient electron acceptor groups through π- conjugated path. The atomic orbital is shown in fig.3

Figure 3 HOMO-LUMO of TMZA



The HOMO is located over methyl group, carbonyl group and CH in imidazole ring. LUMO is located over the tetrazine ring. The energy gap between HOMO and LUMO is 0.12089eV. This very low energy gap explains the charge transfer within the molecule and its anti-cancer activity.

4. CONCLUSION

Vibrational spectral analysis is carried out using FT-IR and Raman spectroscopy in the anticancer drug temozolomide acid. The detailed interpretation of the normal modes has been made on the basis of PED calculations. The computed optimized parameters are in good agreement with those obtained by experimental data. NBO analysis also reveals the N-H...N hydrogen bonding which leads to the stability of the molecule. The lowering of the HOMO-LUMO energy gap value has substantial influence on the intramolecular charge transfer and bioactivity of the molecule.

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