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Quantum chemical and experimental studies on anti-viral drug Lamivudine (3TC)

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ABSTRACT

The Fourier transform Raman (FT-Raman) and Fourier transform infrared (FTIR) spectra for Lamivudine in the solid phase have been recorded in the region 4000–100 and 4000–400 cm^{-1}, respectively, compared with the harmonic vibrational frequencies calculated using density functional theory (DFT) (B3LYP) and Restricted Hartee Fock (RHF) method by employing 6-31G (d,p) basis set with appropriate scale factors. Optimised geometries of the molecule have been interpreted and compared with the reported experimental values. The experimental geometrical parameters show satisfactory agreement with the theoretical prediction from DFT. The scaled vibrational frequencies seem to coincide with the experimentally observed values with acceptable deviations. The theoretical spectrograms (IR and Raman) have been constructed and compared with the experimental FTIR and FT-Raman spectra. The UV spectrum was measured in methanol. In order to gain some insight into the recorded spectrum, the quantum mechanical calculations were performed for Lamivudine using TD DFT with B3LYP/6-31G(d,p) basis set. The optimized molecular geometry, bond orders, harmonic vibrational wavenumbers of Lamivudine were calculated by Restricted Hartree Fock and Density functional B3LYP method with the 6-31G(d,p) basis set using Gaussian 03W program.

Introduction

Acquired Immunodeficiency Syndrome (AIDS), which is now a plague in several countries, was first identified in California in 1981. It is a disease in which the body's immune system breaks down and is unable to fight off infections caused by human immunodeficiency virus (HIV). HIVinfects human cells and uses the energy and nutrients provided by those cells to grow and reproduce and it is often necessary to take several medicines for prolonged periods. Lamivudine, (2',3'-dideoxy-3'-thiacytidine, commonly called 3TC) has proven anti-viral activity. It is in clinical use for HIV positive and Hepatitis B positive patients [UK Patent Application 1991, 9111902.4]. Lamivudine is a synthetic nucleoside analog that is being increasingly used as the core of an antiretroviral regimen for the treatment of HIV infection [1,2]. Lamivudine is rapidly absorbed after oral administration with an absolute bioavailability of 86% ± 16%, peak serum concentration of Lamivudine (C_{max}) of 1.5 ± 0.5 mcg/mL and mean elimination half-life of 5 to 7 hours, thus necessitating frequent administration to maintain constant therapeutic drug levels[3]. Vibrational spectroscopy has significant contributions towards the studies of structure and physico-chemical properties of molecular systems. Density functional theory (DFT) and ab initio quantum chemistry are cost-effective general procedures for studying the physical properties of the molecules. Chu et al[4] utilized a synthesis based on D-mannose, whilst Jeong et al developed[5] an alternative synthesis using D-galactose, which was employed to evaluate biological aspects of Lamivudine[6]. Literature survey reveals that there is no detailed study on vibrational spectroscopic features of Lamivudine using experimentally obtained FTIR and FT-Raman spectrum and theoretically by ab initio and DFT methods have not been reported so far. Hence, in this work, by using the RHF and B3LYP methods, we calculated the vibrational wavenumber of Lamivudine and molecular geometric parameters. These calculations are valuable for providing insight into the vibrational spectrum and molecular parameters.

Experimental

The spectroscopic pure sample of Lamivudine was obtained from Sigma-Aldrich chemical company, USA with stated purity of greater than 99% and it was used as such without further purification. The solid phase FTIR spectrum was recorded in the region 4000-400 cm^{-1} in evacuation mode on Nexus 670 DTGS using KBr pellet technique with 4.0 cm^{-1} resolution. The FT-Raman spectrum was recorded using 1064 nm line of Nd: YAG laser as excitation wavelength in the region 5000-10 cm^{-1} on Bruker IFS 66V spectrometer equipped with FRA 106 Raman module was used as an accessory. The UV–vis spectral measurements were carried out using a varian cary 5E-UV-NIR spectrophotometer. The spectral measurements were carried out at sophisticated instrumentation Analysis Facility, IIT, Chennai, India.

Computational details

All the theoretical computations were performed at Restricted Hartree Fock (RHF) and B3LYP levels on a Pentium IV/1.6 GHz personal computer using the Gaussian 03W program package[7]. The geometry optimization was carried out using the initial geometry generated from standard geometrical parameters

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at Restricted Hartree Fock level and DFT methods adopting 6-31G(d,p) basis set to characterize all stationary points as minima. In DFT methods, Becke's three parameters exchange-functional (B3)[8,9] combined with gradient-corrected correlation functional of Lee, Yang and Parr(LYP)[10] by implementing the split-valance polarized 6-31G(d,p) basis set[11,12] have been utilized for the computation of molecular structure optimization and vibrational frequencies. The optimized geometry was used in the vibrational frequency calculations at the RHF and DFT levels to characterize all stationary points as minima. Finally, calculated normal mode vibrational wave numbers provide thermodynamic properties by way of statistical mechanics. The vibrational frequency assignments were made with a high degree of accuracy with the help of Chemcraft software program[13]. The time-dependent density functional theory (TD-DFT) methods were used for the calculation of the UV–vis spectra. The IR and UV–vis spectra were calculated and visualised using the SWizard program[14].

Results and discussion

Molecular geometry

The molecular structure of Lamivudine belongs to C1 point group symmetry. All vibrations are active in both IR and Raman. The optimized structure parameters of Lamivudine calculated by HF and DFT-B3LYP levels are listed in the Table 1 in accordance with the given Figure 1 atom numbering scheme of Lamivudine.

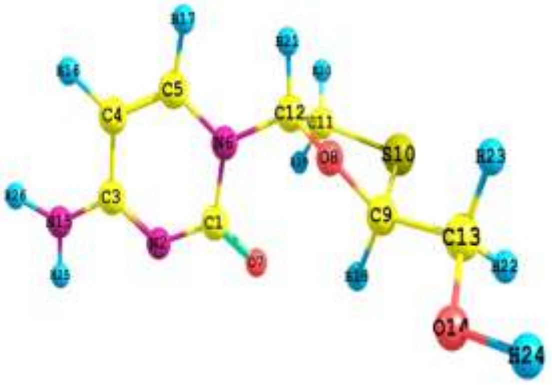

Figure 1. Atom numbering scheme of Lamivudine

Table 1 compares the calculated bond lengths and angles for Lamivudine with those experimentally available data [15]. From the calculated values, we can find that most of the optimized bond length and bond angles are slightly larger than the experimental values, due to this the theoretical calculation belongs to the isolated molecules in the gaseous phase whereas the experimental results belong to the molecules in the solid phase. It is to be noticed that there is an appreciable bond angle difference and insignificant bond length difference is observed in both RHF and B3LYP methods. In spite of the differences, calculated geometric parameters represent a good approximation and they are the basis for calculating other parameters, such as vibrational frequencies and thermodynamic properties. The conformational stability of Lamivudine was investigated by scanning the dihedral angle N2-C3-N15-H26. The potential energy determined from both RHF and DFT-B3LYP methods is presented in Figure 2. Maximum potential energy are clearly identified in this figure around 80◦ in both HF and DFT-B3LYP methods.

Bond order analysis

Table 2 presents the bond order of Lamivudine. Bond order is related to bond strength. The weakest bonds, which are assumed to be cleaved preferentially and relatively low pi bond character. From Table 2, it is noted that bond between N6-C12 possess relatively low pi bond character with low bond order value of 0.84 and 0.9 obtained from RHF and B3LYP method respectively. Hence, N6-C12 has the smallest bond order and refers to the possible cleavage site in Lamivudine. The bond distance of N6-C12 is somehow longer than the other N-C bond distance in the title molecule, it once again confirms the weakest bond and it is the preferential site for cleavage to occur. The very strongest bond is C1-O7 with the bond order value of 1.65 predicted from both RHF and B3LYP methods confirms the double bond character. The optimised geometrical values are in support of the bond order analysis.

Electronic properties

The energies of four important molecular orbitals of Lamivudine: the highest and second highest occupied MO's (HOMO and HOMO−1), the lowest and the second lowest unoccupied MO's (LUMO and LUMO+1) were calculated and are presented in Table 3. The lowest singlet→singlet spin-allowed excited states of lamivudine were taken into account for the TD-DFT calculation in order to investigate the properties of electronic absorption. The experimental and theoretical studies on the electronic absorption spectrum of lamivudine were made to explain each observed band, which was not done earlier. The experimental λ_{max} values are obtained from the UV/visible spectra recorded in methanol. The calculations were also performed with methanol solvent effect. The present experiment revealed three bands at 242, 294 and 310 nm in the UV region. The calculated absorption wavelengths (λ_{max}), oscillator strength, excitation energies and the experimental wavelengths are also given in Table 3. The energy gap between HOMO and LUMO is a critical parameter in determining molecular electrical transport properties[16]. In the electronic absorption spectrum of Lamivudine, there are three absorption bands with a maximum 310 nm. The strong absorption band 310 nm is caused by the $n\rightarrow\pi^*$ and the other two calculated value moderately intense bands are due to $\pi\rightarrow\pi^*$ transitions. The $\pi\rightarrow\pi^*$ transitions are expected to occur relatively at lower wavelength, due to the consequence of the extended aromaticity of the benzene ring. The HOMO and LUMO of Lamivudine are represented in Figure 2.

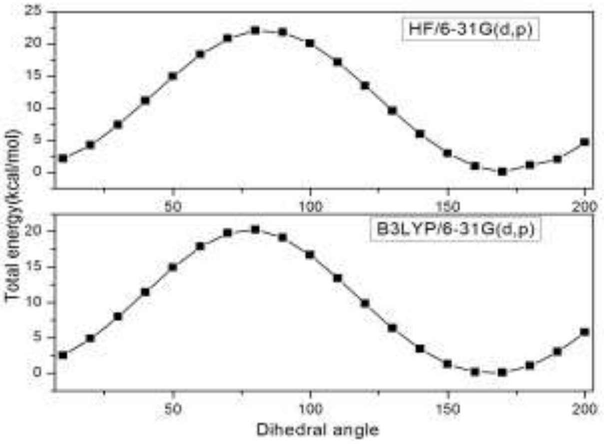

Figure 2. Potential energy curve of Lamivudine for rotation about N2-C3-N15-H26

Natural population analysis

The calculation of effective atomic charges plays an important role in the application of quantum mechanical calculations to molecular systems. Our interest here is in the comparison of different methods (RHF and DFT) to describe the electron distribution in Lamivudine as broadly as possible, and to assess the sensitivity of the calculated charges to change the choice of quantum chemical method. The calculated natural atomic charge values from the natural population analysis (NPA) and Mulliken population analysis (MPA) procedures using the RHF and DFT methods are listed in Table 4. The NPA from the natural bonding orbital (NBO) method is better than the MPA scheme. Table 4 compares the atomic charge site of Lamivudine from both MPA and NPA methods. It may be noted that the nitrogen atoms N2, N6 and N15 have large net negative charge was observed in the two methods. Also the electronegative oxygen atoms O7 and O8 possess large net negative charge. The carbon atoms C1, C3, C5 and C12 are adjoining the nitrogen an atom (N2, N6 and N15) has a large positive charge. Being attached to more electronegative carbon atoms, all the hydrogen atoms have a net positive charge.

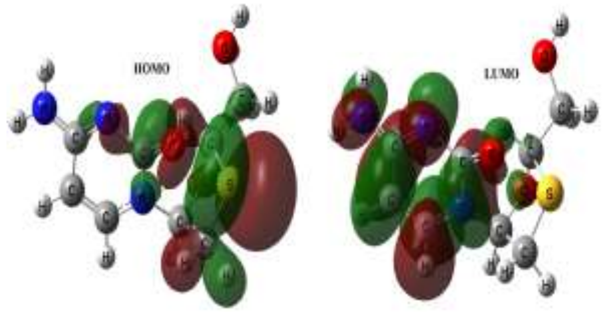

Figure 3. The HOMO and LUMO of Lamivudine

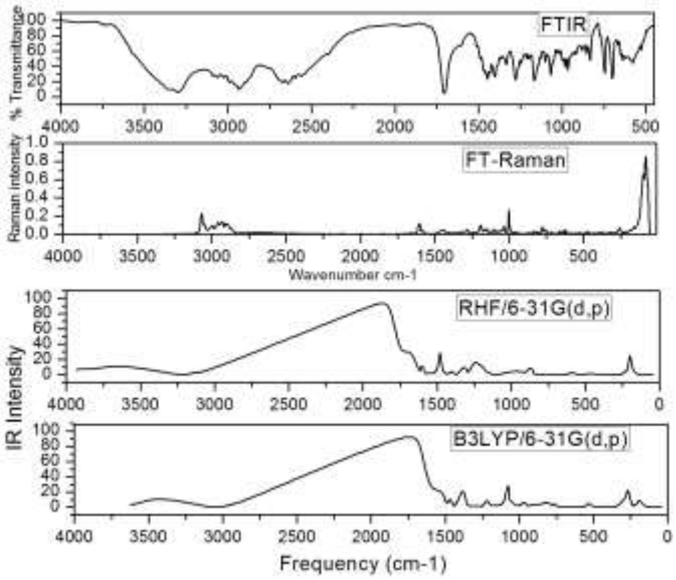

Figure 4. Experimental and Theoretical IR spectrum of Lamivudine

Vibrational spectra

The experimental FTIR, FT-Raman and calculated (RHF & B3LYP) vibrational spectra were shown in Figure 3 (a),(b) (c) & (d). Since the calculated vibrational wave numbers were known to be higher than the experimental ones, they were scaled down by the wavenumber linear scaling procedure of Yoshida et al[17] by using the expression **:** $\nu_{obs} = (1.0087 - 0.0000163\nu_{calc.})\ \nu_{calc.}$ Comparison of the frequencies calculated at RHF and B3LYP with experimental values (Table 5) reveals the over estimation of the calculated vibrational modes due to the neglect anharmonicity in real system. Inclusion of electron correlation in DFT to a certain extent makes the frequency values smaller in comparison with the RHF frequency data. According to the theoretical calculations, Lamivudine has a non-planar structure of C_1 point group symmetry. The molecule has 26 atoms and 72 normal modes of vibration active in both IR and Raman. The Chemcraft program was used to display the vibrational modes. Vibrational wave number assignments were made on the basis of combining the results of Chemcraft program with the symmetry, and taking the atomic displacements into consideration based on the frequency calculation and also made in analogy with the structurally related molecules.

The CH, NH and OH stretching modes are expected to be observed at the high wave number region. The CH stretching bands are observed between 3062 and 2936 cm^{-1} in FTIR and 3068 and 2930 cm^{-1} in FT-Raman spectrum respectively. A very weak band at 3400 to 3296 cm^{-1} in FTIR was attributed to NH stretching vibration. The carbonyl stretching mode corresponds to the band at 1706 cm^{-1} in FTIR. The CH2 scissoring and wagging mode was also identified. Let us start considering the contribution of theoretical methods RHF and B3LYP, the OH stretching mode is predicted at 3623 cm^{-1} in B3LYP and 3716 cm^{-1} in RHF after scaling. The scaled NH2 symmetric and asymmetric stretching vibrations in the range 3444-3554 cm^{-1} are in good agreement with experimental values of 3429 and 3483 cm^{-1}. In NH2 scissoring vibration at 1603 cm^{-1} in FT-Raman and the computed NH2 scissoring vibration at 1671 cm^{-1} is in excellent agreement with the expected characteristic value 1624 cm^{-1} [18]. The OH stretching vibrational wave number is decreasing in DFT and increasing in RHF is observed may be due to electron correlation and polarisation effect inclusion in DFT method.

The scaled NH2 symmetric and asymmetric stretching vibrations in the range 3444-3554 cm^{-1} are in good agreement with the experimental spectrum. The computed NH2 scissoring vibration at 1611 cm^{-1} in DFT and 1679 cm^{-1} in RHF is in excellent agreement with the expected characteristic value 1624 cm^{-1} [18]. In the presence of water molecules in the Lamivudine, the NH stretching vibrations were red shifted by 10 cm^{-1}. But however, the NH2 scissoring mode does not get affected.

The calculated bands in the region 1402–1550 cm^{-1} are assigned for CC stretching mode and are in good agreement with the literature values[19]. Also, the C=C stretching modes have been assigned at 1671 – 1752 cm^{-1} in DFT and RHF methods. Notice that the most evident discrepancies between the experimental and calculated spectra are associated with the stretching modes showing the effect of water molecules. List of selected observed and calculated bands of Lamivudine was presented in Table 5.

Thermodynamic Parameters

The thermodynamic parameters of Lamivudine have also been computed by RHF and B3LYP methods and are presented in Table 6. The total energies, vibrational motion contribution to entropy, rotational constants, Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital energy (LUMO), energy gap between HOMO and LUMO and dipole moment values obtained from RHF method are slightly over estimated than that of DFT/B3LYP methods. The energies of Lamivudine by RHF method are -1094.60 a.u, whereas by B3LYP methods are -1099.40 a.u. respectively. The variation in the ZPVEs seems to be insignificant. The total energies found to decrease with increase of the basis sets dimension. The changes in the total entropy of Lamivudine at room temperature at different basis sets are only marginal.

Conclusion

The geometry of Lamivudine was optimized with RHF and DFT-B3LYP methods using 6-31G(d,p) basis set. The complete molecular structural parameters and thermodynamic properties of the optimized geometry of the Lamivudine have been obtained from ab initio and DFT calculations. The vibrational frequencies of the fundamental modes of Lamivudine have been precisely assigned and analyzed and the theoretical results were compared with the experimental vibrations. The energies of important MO's, absorption wavelength (λmax), oscillator strength and excitation energies of the compound were also determined from TD-DFT methods are compared with the experimental values. The predicted geometry, bond order, Natural population analysis, FTIR, FT-Raman and UV-vis spectra of characteristic of Lamivudine was investigated.

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Table 1 Selected geometrical parameters of Lamivudine

Parameter				
	RHF	B3LYP	Exp*	
bond length (Å)				
C1-N2	1.36	1.37	1.46	
C1-N6	1.41	1.44	1.44	
C1-O7	1.20	1.22	1.21	
N2-C3	1.30	1.32	1.29	
C3-C4	1.44	1.44	1.47	
C3-N15	1.34	1.36	1.27	
C4-C5	1.34	1.36	1.33	
C5-N6	1.36	1.36	1.36	
N6-C12	1.46	1.48	1.45	
O8-C9	1.40	1.42	1.40	
O8-C12	1.39	1.41	1.40	
C9-S10	1.83	1.85	1.82	
C9-C13	1.51	1.52	1.52	
S10-C11	1.81	1.83	1.78	
C11-C12	1.54	1.55	1.52	
C13-O14	1.40	1.42	1.40	
bond angle (deg)				
N6-C1-N2	117.7	117.3	116.4	
O7-C1-N2	123.6	124.1	121.8	
O7-C1-N6	118.7	118.6	121.7	
N15-C3-C4	119.1	119.6	116.1	
C5-C4-C3	115.6	116.1	114.7	
N6-C5-C4	122.2	121.8	122.2	
C5-N6-C1	120.2	120.4	120.4	
C12-N6-C1	120.0	120.0	119.8	
C12-N6-C5	119.3	119.3	119.8	
C12-O8-C9	115.6	114.2	103.9	
S10-C9-O8	105.6	105.7	104.0	
C13-C9-S10	111.2	110.8	110.8	
C11-S10-C9	89.5	88.6	90.2	
C12-C11-S10	105.1	105.7	104.9	
O8-C12-N6	111.3	111.6	110.8	
C11-C12-N6	113.4	112.6	110.8	
C11-C12-O8	110.9	111.2	104.0	
O14-C13-C9	108.0	107.9	109.4	
*Ref[15]				

Table 2 Bond orders of Lamivudine

Bond	RHF	B3LYP
C1-N2	1.1	1.1
C1-N6	0.9	0.9
C1-O7	1.6	1.6
N2-C3	1.5	1.5
C3-C4	1.1	1.1
C3-N15	1.1	1.1
C4-C5	1.8	1.7
C5-N6	1.0	1.1
C9-S10	1.0	0.9
C9-C13	1.0	1.0
S10-C11	1.0	0.9
C11-C12	1.0	1.0
C13-O14	0.8	0.9

Table 3. Experimental and calculated absorption wavelenght(λ), excitation energies(E), oscillator strength(f) and frontier orbital energies of Lamivudine by TD-DFT method

λ(Expt.;nm)	λ(Cal.;nm)	E(eV)	f	Assignment	E_{HOMO} (eV)	E_{LUMO} (eV)	E_{HOMO-1} (eV)	E_{LUMO+1} (eV)
245	315.84	3.3084	0.0007	$n\rightarrow\pi^{*}$				
294	437.03	5.3304	0.0060	$\pi\rightarrow\pi^{-*}$	-3.9640	-0.6558	-5.9862	-0.0634
310	470.75	5.9228	0.0021	$\pi\rightarrow\pi^{*}$				

Table 4 Natural population analysis of Lamivudine

	MPA		NPA	
Atom	RHF	B3LYP	RHF	B3LYP
C1	0.9994	0.7222	0.9917	0.7979
N2	-0.7245	-0.5665	-0.7003	-0.5764
C3	0.6533	0.5088	0.5782	0.4340
C4	-0.3198	-0.1701	-0.4360	-0.3784
C5	0.2670	0.1715	0.1436	0.0464
N6	-0.7836	-0.4909	-0.6153	-0.5005
O7	-0.6372	-0.5277	-0.7554	-0.6377
O8	-0.6330	-0.4717	-0.6416	-0.5607
C9	0.0508	0.0243	-0.0649	-0.1096
S10	0.1138	0.0778	0.2945	0.2877
C11	-0.4336	-0.3805	-0.6482	-0.6664
C12	0.4687	0.3289	0.3387	0.2586
C13	0.1147	0.0534	-0.0443	-0.1105
O14	-0.6366	-0.5336	-0.8299	-0.7782
N15	-0.7543	-0.6268	-0.8689	-0.7912

Table 5 Observed and theoretical vibrational assignments of Lamivudine

Theoretical				Experimental		
RHF		B3LYP				
unscaled	scaled	unscaled	scaled	FTIR	FT-RAMAN	Assignment
3934	3716	3829	3623			OH stretching
3771	3572	3746	3550			NH asymmetric stretching
3645	3460	3609	3428	3296		NH symmetric stretching
3246	3102	3233	3091			C4-H16 symmetric stretching
3225	3084	3201	3062	3062	3068	C5-H17 symmetric stretching
3202	3063	3183	3046	3024		CH asymmetric stretching in methyleneC11
3167	3031	3123	2991			C9-H18 stretching
3118	2987	3104	2974	2992	2994	CH symmetric stretching in methyleneC11
3101	2971	3058	2932	2936	2956	C12-H21 stretching
3079	2951	3040	2916		2930	CH asymmetric stretching in methyleneC13
1903	1861	1781	1745	1706		C=O stretching
1752	1717	1641	1611		1603	NH2 scissoring
1682	1651	1570	1543	1508	1583	C=C stretching
1614	1586	1518	1494	1489		CH2 scissoring
1595	1567	1486	1463	1469		CH2 scissoring
1587	1560	1474	1451	1402		CH2 wagging

Table 6 The calculated thermodynamic parameters of Lamivudine

Parameter			
	RHF	B3LYP	
Total Energy(a.u)	-1094.6	-1099.4	
Zero point energy(Kcal/Mol)	136.83	126.46	
Rotational Constants(GHz)	1.153	1.1308	
	0.3047	0.2997	
	0.2846	0.2806	
Vibrational entropy	42.28	45.44	
Dipole moment(Debye)	6.66	5.92	
HOMO(eV)	-9.1779	-6.0409	
LUMO(eV)	3.178	-0.9456	
Energy gap(eV)	12.3559	5.0953	