Research Article

Vibrational Spectroscopic Studies of Tenofovir Using Density Functional Theory Method

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A systematic vibrational spectroscopic assignment and analysis of tenofovir has been carried out by using FTIR and FT-Raman spectral data. The vibrational analysis was aided by electronic structure calculations—hybrid density functional methods (B3LYP/6-311++G(d,p), B3LYP/6-31G(d,p), and B3PW91/6-31G(d,p)). Molecular equilibrium geometries, electronic energies, IR intensities, and harmonic vibrational frequencies have been computed. The assignments proposed based on the experimental IR and Raman spectra have been reviewed and complete assignment of the observed spectra have been proposed. UV-visible spectrum of the compound was also recorded and the electronic properties such as HOMO and LUMO energies and λ_{max} were determined by time-dependent DFT (TD-DFT) method. The geometrical, thermodynamical parameters, and absorption wavelengths were compared with the experimental data. The B3LYP/6-311++G(d,p)-, B3LYP/6-31G(d,p)-, and B3PW91/6-31G(d,p)-based NMR calculation procedure was also done. It was used to assign the ¹³C and ¹H NMR chemical shift of tenofovir.

1. Introduction

A recent addition to the antiretroviral armamentarium is the nucleotide analogue tenofovir disoproxil fumarate (Viread), approved for use in the USA and the European Union. Tenofovir is unique among the NRTIs in that it is an acyclic nucleoside phosphonate, analogous to the monophosphate form of the other NRTIs [1]. Tenofovir disoproxil fumarate is an oral prodrug of tenofovir that is rapidly converted into tenofovir upon absorption [2, 3]. Tenofovir has activity in vitro against both HIV-1 and HIV-2 [4, 5], and in resting and activated T cells, monocytes and macrophages [5, 6]. Cross-resistance within the NRTI class of drugs has important clinical consequences for patients who are highly treatment experienced, or for those patients in whom primary HIV infection is associated with the transmission of a resistant virus [7].

Literature survey reveals that to the best of our knowledge, neither the complete IR, Raman spectra, nor the quantum mechanical calculations for molecular structure of

tenofovir have been reported so far. In the present communication, we report detailed quantum chemical studies of the molecular structure and IR, Raman spectra of tenofovir using basis set. Information about the geometry and structure of the molecule, together with analysis of the IR, Raman spectra, based on frequency and intensity should help in understanding the structural and spectral characteristics. The band assignments have made by assuming C₁ point group symmetry. Density Functional Theory (DFT) calculations have been performed to support our wave number assignments.

2. Experimental Details

The compound tenofovir in powder form was procured from Reputed pharmaceutical company, Chennai, India with more than 98% purity and was used as such without further purification to record FTIR and FT-Raman spectra. The FTIR spectrum of the compound was recorded in the region

FIGURE 1: Atom numbering scheme of tenofovir.

4000–450 cm^{-1} in evacuation mode on Bruker IFS 66V spectrophotometer using KBr pellet technique (solid phase) 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.

3. Computational Details

To provide complete information regarding the structural characteristics and the fundamental vibrational modes of tenofovir of B3LYP/6-311++G(d,p), B3LYP/6-31G(d,p), and B3PW91/6-31G(d,p) correlation functional calculations have been carried out. The calculations of geometrical parameters in the ground state were performed using the Gaussian 03 [9] programs, invoking gradient geometry optimization [10] on Intel core i4/2.93 GHz processor. The geometry optimization was carried out using the initial geometry generated from standard geometrical parameters at B3LYP and B3PW91 methods adopting 6-31G(d,p) and 6-311++G(d,p) basis sets to characterize all stationary points as minima. The optimized structural parameters of the compound tenofovir were used for harmonic vibrational frequency calculations resulting in IR and Raman frequencies together with intensities. In DFT methods, Becke's three parameter exchange-functional (B3) [11, 12] combined with gradient-corrected correlation functional of Johnson and Frisch [13] and Burke et al. [14–19] by implementing the split-valence polarized 6-31G(d,p) basis set [20, 21] have been utilized for the computation of molecular structure optimization, vibrational frequencies, thermodynamic properties, and energies of the optimized structures. 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 visualized using the SWizard program [22]. The ^{13}C and ^1H NMR chemical shifts of the title compound were calculated using the keyword NMR in the DFT-B3LYP and B3PW91 levels.

4. Results and Discussion

4.1. Molecular Geometry. To compare the structural parameters of tenofovir and with the available experimental data, they are subjected to geometry optimization in their ground state. For each method, geometry optimizations were performed. The requested convergence on the maximum density matrix was 1026 a.u. the threshold value of the maximum displacement was 0.0018 Å and that of the maximum force was 0.00045 Hartree/Bohr using the Berny analytical gradient optimization routine [10, 23]. The nature of stationary points is checked by diagonalising the Hessian matrix to determine the number of imaginary wave numbers (zero for local minimum). The optimized bond lengths and bond angles of tenofovir calculated by B3LYP/6-311++G(d,p), B3LYP/6-31G(d,p), and B3PW91/6-31G(d,p) levels are listed in Table 1, in accordance with the atom numbering scheme shown in Figure 1. Table 1 shows the comparison of the calculated optimized structure parameters for tenofovir with those experimentally available data [8]. It is observed that most of the optimized structure parameters are slightly larger than the available data values. The bond lengths and bond angles computed by the DFT-B3LYP and B3PW91 levels show excellent agreement with the available computed values.

The bond distance of carbon-carbon in the benzene ring in the range of 1.524 Å confirms the double-bond character and in the range of 1.370 Å supports the single-bond character. The bond distances of C–N and C–O were in the expected range and agree with the experimental values. Although there is a slight difference between the calculated and experimental structure parameters, the calculated geometric parameters represent a good approximation, and they are the bases for calculating other parameters such as atomic charges, NMR chemical shift values, vibrational modes, and thermodynamic properties.

4.2. Bond-Order Analysis. The bond order of tenofovir is presented in Table 2. Bond order is related to bond strength. The bonds with the higher bond order values have short bond length and vice versa. The bond-order analysis may predict that the weakest bonds may be cleaved preferentially and they may possess a relatively low pi-bond character. From Table 2,

TABLE 1: Structural parameters of tenofovir calculated by DFT methods.

Structural parameters	Tenofovir			
	Experimental [8]	B3LYP/6-311++G(d,p)	B3LYP/6-31G(d,p)	B3PW91/6-31G(d,p)
		Internuclear distance (Å°)		
<i>R</i> (1-2)	1.402	1.412	1.427	1.421
<i>R</i> (1-16)	1.856	1.837	1.841	1.838
<i>R</i> (1-20)	1.113	1.096	1.096	1.096
<i>R</i> (1-21)	1.113	1.093	1.095	1.096
<i>R</i> (2-4)	1.402	1.443	1.444	1.437
<i>R</i> (3-4)	1.523	1.532	1.531	1.527
<i>R</i> (3-8)	1.470	1.456	1.454	1.448
<i>R</i> (3-22)	1.113	1.091	1.093	1.093
<i>R</i> (3-23)	1.113	1.092	1.095	1.095
<i>R</i> (4-5)	1.523	1.524	1.526	1.521
<i>R</i> (4-24)	1.113	1.095	1.098	1.099
<i>R</i> (5-25)	1.113	1.091	1.093	1.093
<i>R</i> (5-26)	1.113	1.094	1.095	1.095
<i>R</i> (5-27)	1.113	1.094	1.096	1.096
<i>R</i> (6-7)	1.369	1.310	1.312	1.310
<i>R</i> (6-14)	1.366	1.382	1.385	1.380
<i>R</i> (7-8)	1.315	1.381	1.383	1.378
<i>R</i> (7-28)	1.100	1.080	1.081	1.082
<i>R</i> (8-9)	1.369	1.379	1.381	1.377
<i>R</i> (9-10)	1.345	1.337	1.339	1.337
<i>R</i> (9-14)	1.384	1.396	1.398	1.396
<i>R</i> (10-11)	1.340	1.335	1.337	1.335
<i>R</i> (11-12)	1.352	1.341	1.343	1.340
<i>R</i> (11-29)	1.100	1.086	1.088	1.089
<i>R</i> (12-13)	1.349	1.343	1.346	1.343
<i>R</i> (13-14)	1.376	1.408	1.411	1.410
<i>R</i> (13-15)	1.266	1.354	1.356	1.350
<i>R</i> (15-30)	1.050	1.006	1.007	1.006
<i>R</i> (15-31)	1.050	1.007	1.008	1.006
<i>R</i> (16-17)	1.615	1.617	1.619	1.616
<i>R</i> (16-18)	1.615	1.626	1.619	1.614
<i>R</i> (16-19)	1.480	1.484	1.486	1.484
<i>R</i> (17-32)	0.942	0.965	0.969	0.967
<i>R</i> (18-33)	0.942	0.965	0.972	0.972
Bond angle (°)				
<i>A</i> (2-1-16)	109.5	111.9	109.1	109.2
<i>A</i> (2-1-20)	109.4	112.5	112.1	112.2
<i>A</i> (2-1-21)	109.5	108.3	108.1	108.0
<i>A</i> (1-2-4)	120.0	117.6	116.9	116.5
<i>A</i> (16-1-20)	109.4	108.0	110.1	110.2
<i>A</i> (16-1-21)	109.5	107.7	108.9	108.7
<i>A</i> (1-16-17)	109.5	102.7	103.7	103.8
<i>A</i> (1-16-18)	109.4	105.2	101.1	100.5
<i>A</i> (1-16-19)	109.5	117.7	116.3	116.6
<i>A</i> (20-1-21)	109.5	108.3	108.5	108.4
<i>A</i> (2-4-3)	109.5	106.5	105.9	105.9
<i>A</i> (2-4-5)	109.4	111.1	112.0	112.2
<i>A</i> (2-4-24)	109.5	109.0	108.5	108.5
<i>A</i> (4-3-8)	109.5	113.0	113.2	113.2
<i>A</i> (4-3-22)	109.4	109.6	109.5	109.4

TABLE 1: Continued.

Structural parameters	Tenofovir			
	Experimental [8]	B3LYP/6-311++G(d,p)	B3LYP/6-31G(d,p)	B3PW91/6-31G(d,p)
Bond angle (°)				
A(4-3-23)	109.5	109.4	109.4	109.5
A(3-4-5)	109.4	111.5	111.9	111.8
A(3-4-24)	109.5	108.6	108.3	108.2
A(8-3-22)	109.4	107.7	107.0	107.0
A(8-3-23)	109.5	108.4	109.1	109.2
A(3-8-7)	127.5	128.0	128.5	128.6
A(3-8-9)	127.5	126.1	125.6	125.5
A(22-3-23)	109.5	108.6	108.5	108.4
A(5-4-24)	109.5	110.0	110.1	110.1
A(4-5-25)	109.5	110.3	110.9	111.0
A(4-5-26)	109.4	110.3	110.3	110.3
A(4-5-27)	109.5	110.4	110.6	110.7
A(25-5-26)	109.4	108.5	108.5	108.4
A(25-5-27)	109.5	108.8	108.2	108.2
A(26-5-27)	109.5	108.4	108.2	108.2
A(7-6-14)	107.5	104.0	103.8	103.7
A(6-7-8)	111.8	113.9	114.0	114.0
A(6-7-28)	124.1	125.3	125.4	125.3
A(6-14-9)	104.8	111.0	111.3	111.3
A(6-14-13)	135.0	133.0	133.0	133.0
A(8-7-28)	124.1	120.8	120.7	120.7
A(7-8-9)	105.0	105.8	105.8	105.9
A(8-9-10)	125.7	128.1	127.9	127.8
A(8-9-14)	110.9	105.2	105.1	105.0
A(10-9-14)	104.8	126.6	127.0	127.2
A(9-10-11)	112.6	111.6	111.2	111.0
A(9-14-13)	120.3	116.0	115.8	115.6
A(10-11-12)	128.1	128.4	128.8	128.9
A(10-11-29)	115.9	116.1	115.9	115.9
A(12-11-29)	115.9	115.4	115.3	115.2
A(11-12-13)	118.1	118.7	118.4	118.4
A(12-13-14)	117.6	118.7	118.9	118.9
A(12-13-15)	121.2	118.9	118.8	118.8
A(14-13-15)	121.2	122.4	122.3	122.3
A(13-15-30)	120.0	119.9	119.0	119.5
A(13-15-31)	120.0	118.7	117.9	118.3
A(30-15-31)	120.0	119.9	119.4	120.0
A(17-16-18)	109.4	102.8	101.8	102.2
A(17-16-19)	109.5	116.9	114.2	113.9
A(16-17-32)	120.0	114.2	109.7	109.3
A(18-16-19)	109.5	113.1	117.5	117.6
A(16-18-33)	120.0	111.9	108.6	107.9

it is noted that bond between O2–C4 possess relatively low pi-bond character with low-bond-order value of 0.848 obtained DFT-B3LYP method, respectively. The P16–O19 bond order values are in the range 1.947, which depict the double bond

character, while the C4–C5 and N8–C9 bond-order value is approximately unity, which shows the single-bond character. The optimized geometrical values are in support of the bond-order analysis.

FIGURE 2: The HOMO and LUMO of tenofovir.

TABLE 2: Bond orders of tenofovir.

Bond order	B3LYP/6-31G(d,p)
C1-O2	0.913
C1-P16	0.845
C1-H20	0.921
C1-H21	0.909
O2-C4	0.848
C3-C4	0.923
C3-N8	0.862
C3-H22	0.94
C3-H23	0.934
C4-C5	1.001
C4-H24	0.815
C5-H25	0.96
C5-H26	0.954
C5-H27	0.956
N6-C7	1.517
N6-C14	1.138
C7-N8	1.185
C7-H28	0.949
N8-C9	1.04
C9-N10	1.123
C9-C14	1.311
N10-C11	1.464
C11-N12	1.396
C11-H29	0.948
N12-C13	1.3
C13-C14	1.187
C13-N15	1.109
N15-H30	0.876
N15-H31	0.878
P16-O17	1.021
P16-O18	1.038
P16-O19	1.947
O17-H32	0.856
O18-H33	0.853

4.3. Electronic Properties. The energies of four important molecular orbitals of tenofovir: the highest and second highest occupied MOs (HOMO and HOMO-1), the lowest and the second lowest unoccupied MOs (LUMO and LUMO+1)

were calculated and are presented in Table 3. The lowest singlet $\rightarrow$ singlet spin-allowed excited states of tenofovir were taken into account for the TD-DFT calculation in order to investigate the properties of electronic absorption. The experimental $\lambda_{\max}$ values are obtained from the UV/visible spectra recorded in methanol as reported earlier [24]. The calculations were also performed with methanol solvent effect. The calculated absorption wavelengths ($\lambda_{\max}$), 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 [25]. In the electronic absorption spectrum of tenofovir, there are three absorption bands with a maximum 268.67, 250, and 230.69 nm. The strong absorption band 268.67 nm is caused by the $n-\pi^*$ and the other two moderately intense bands are due to $\pi-\pi^*$ transitions. The $\pi-\pi^*$ 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 tenofovir are represented in Figure 2.

4.4. 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 (B3LYP and B3PW91) to describe the electron distribution in tenofovir as broadly as possible, and to assess the sensitivity of the calculated charges to changes in the choice of the quantum chemical method. The calculated natural atomic charge values from the natural population analysis (NPA) and Mulliken population analysis (MPA) procedures using the B3LYP/6-311++G(d,p), B3LYP/6-31G(d,p), and B3PW91/6-31G(d,p) 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 tenofovir from both MPA and NPA methods. The NPA of tenofovir shows that the presence of three oxygen atoms in the nitrate moiety [O17 = -0.979 (B3LYP/6-311++G(d,p)), -1.023 (B3LYP/6-31G(d,p)) and -1.023 (B3PW91/6-31G(d,p)); O18 = -0.983 (B3LYP/6-311++G(d,p)), -1.027 (B3LYP/6-31G(d,p)) and -1.027 (B3PW91/6-31G(d,p)); O19 = -1.070 (B3LYP/6-311++G(d,p)), -1.092 (B3LYP/6-31G(d,p)) and -1.087 (B3PW91/6-31G(d,p))] imposes large positive charges on the Phosphorus atom [P16 = 2.265 (B3LYP/6-311++G(d,p)), 2.388 (B3LYP/6-31G(d,p)) and 2.373 (B3PW91/6-31G(d,p))]. However, the

TABLE 3: Experimental and calculated absorption wavelength (λ), excitation energies (E), oscillator strength (f), and frontier orbital energies of tenofovir by TD-DFT method.

λ (Exp.; nm)	λ (Cal.; nm)	E (eV)	f	Assignment	E_{HOMO} (eV)	E_{LUMO} (eV)	$E_{\text{HOMO}-1}$ (eV)	$E_{\text{LUMO}+1}$ (eV)
268.67	286.26	4.3311	0.0004	$n \rightarrow \pi^*$				
250	252.03	4.9194	0.0019	$\pi \rightarrow \pi^*$	-5.95	-0.6631	-5.9882	0.0117
230.69	249.13	4.9768	0.2253	$\pi \rightarrow \pi^*$

FIGURE 3: Theoretical and experimental IR spectrum of tenofovir.

FIGURE 4: FT-Raman spectrum of tenofovir.

nitrogen atoms N6, N8, N10, and N12 possess large negative charges, resulting in the positive charges on the carbon atoms C7, C9, C11, C13, and C14. Moreover, there is no difference in charge distribution observed on all hydrogen atoms except the H30, H31, H32, and H33 hydrogen atoms. The positive charge on H30, H31, H32, and H33 hydrogen atoms is due to

the negative charge accumulated on the N15, O17, and O18 atoms.

4.5. Vibrational Spectra. The experimental FTIR, calculated (B3LYP, B3PW91) and FT-Raman and vibrational spectra were shown in Figures 3 and 4. 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. [26] by using the expression:

$$\nu_{\text{obs}} = (1.0087 - 0.0000163\nu_{\text{calc.}})\nu_{\text{calc.}} \quad (1)$$

Comparison of the frequencies calculated at B3LYP and B3PW91 with experimental values (Table 5) reveals the overestimation of the calculated vibrational modes due to the neglect anharmonicity in real system. According to the theoretical calculations, tenofovir has a nonplanar structure of C_1 point group symmetry. The molecule has 33 atoms and 93 normal modes of vibration active in both IR and Raman. Since the title molecule possess C_1 point group symmetry, all the modes of vibration belong to A species only. 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.

TABLE 4: Natural atomic charges of tenofovir.

Atom with numbering	MPA			NPA		
	B3LYP/ 6-311++G(d,p)	B3LYP/ 6-31G(d,p)	B3PW91/ 6-31G(d,p)	B3LYP/ 6-311++G(d,p)	B3LYP/ 6-31G(d,p)	B3PW91/ 6-31G(d,p)
C1	-0.153	-0.124	-0.190	-0.362	-0.493	-0.511
O2	-0.527	-0.508	-0.506	-0.617	-0.599	-0.596
C3	-0.059	-0.077	-0.122	-0.184	-0.287	-0.305
C4	0.163	0.133	0.090	0.050	0.044	0.035
C5	-0.347	-0.333	-0.404	-0.577	-0.703	-0.729
N6	-0.539	-0.587	-0.602	-0.516	-0.510	-0.510
C7	0.285	0.247	0.242	0.248	0.205	0.198
N8	-0.513	-0.479	-0.516	-0.412	-0.393	-0.391
C9	0.512	0.511	0.542	0.383	0.369	0.366
N10	-0.524	-0.564	-0.596	-0.583	-0.587	-0.586
C11	0.227	0.226	0.217	0.313	0.264	0.257
N12	-0.521	-0.548	-0.568	-0.558	-0.557	-0.556
C13	0.480	0.561	0.594	0.401	0.418	0.412
C14	0.195	0.248	0.223	-0.002	0.007	0.004
N15	-0.639	-0.662	-0.709	-0.727	-0.788	-0.796
P16	1.072	1.054	1.081	2.265	2.388	2.373
O17	-0.556	-0.548	-0.564	-0.979	-1.023	-1.023
O18	-0.555	-0.552	-0.567	-0.983	-1.027	-1.027
O19	-0.550	-0.549	-0.554	-1.070	-1.092	-1.087
H20	0.137	0.129	0.156	0.204	0.238	0.247
H21	0.156	0.089	0.112	0.170	0.199	0.207
H22	0.153	0.128	0.157	0.208	0.248	0.257
H23	0.123	0.128	0.155	0.208	0.244	0.253
H24	0.113	0.223	0.260	0.259	0.295	0.301
H25	0.165	0.124	0.151	0.219	0.254	0.263
H26	0.116	0.104	0.130	0.204	0.239	0.249
H27	0.106	0.095	0.120	0.194	0.225	0.234
H28	0.122	0.127	0.159	0.203	0.238	0.246
H29	0.100	0.109	0.141	0.179	0.225	0.232
H30	0.288	0.304	0.326	0.419	0.445	0.452
H31	0.280	0.289	0.311	0.411	0.438	0.445
H32	0.353	0.349	0.362	0.514	0.537	0.541
H33	0.340	0.353	0.366	0.520	0.541	0.545

The CH and OH stretching modes are expected to be observed at the high wave number region. The CH stretching bands are observed between 3106 cm^{-1} and 3051 cm^{-1} in FTIR spectrum. The CH stretching modes in the ring and methylene groups were identified and their effect in tenofovir was examined. Let us start considering the contribution of theoretical methods B3LYP/6-311++G(d,p), B3LYP/6-31G(d,p) and B3PW91/6-31G(d,p), the OH stretching mode is predicted at 3650 cm^{-1} , 3583 cm^{-1} in B3PW91 and 3620 cm^{-1} , 3563 cm^{-1} in B3LYP and 3629 cm^{-1} , 3619 cm^{-1} in B3LYP/6-311++G(d,p) after scaling. This OH stretching mode is affected in the presence of water molecules. The CH_2 scissoring and wagging mode was also identified. A major

coincidence of theoretical values with that of experimental evaluations is found in the asymmetric and symmetric vibrations of the methylene ($-\text{CH}_2-$) moiety. The $-\text{CH}_2-$ wagging mode at 1330 cm^{-1} in FT-Raman deviates positively by 20 cm^{-1} from the reported value of 1350 cm^{-1} [25] and theoretically coincide with 1321 cm^{-1} in B3LYP and 1334 cm^{-1} in B3PW91. The vibrational frequency 1455 cm^{-1} in B3LYP and 1449 cm^{-1} in B3PW91 is found neater to FTIR- CH_2 -scissoring mode of 1447 cm^{-1} .

The scaled NH_2 asymmetric and symmetric stretching vibrations of theoretical values are 3570 cm^{-1} and 3456 cm^{-1} . The computed NH_2 scissoring vibration at 1588 cm^{-1} in

FIGURE 5: (a) ^{13}C NMR spectrum of tenofovir. (b) ^1H NMR spectrum of tenofovir.

B3LYP and 1595 cm^{-1} in B3PW91 is in agreement with the expected characteristic value, 1600 cm^{-1} [27, 28]. In the presence of water molecules in the tenofovir, the NH stretching vibrations were red shifted by 10 cm^{-1} . But however, the NH_2 scissoring mode does not get affected. 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 tenofovir was presented in Table 5.

5. ^{13}C and ^1H -NMR Chemical Shift Assignment

The ^{13}C and ^1H NMR simulated theoretically with the aid of ChemDraw Ultra 10.0 is shown in Figures 5(a) and 5(b). Table 6 present the predicted chemical shift values of tenofovir obtained by the B3LYP/6-311++G(d,p), B3LYP/6-31G(d,p), B3PW91/6-31G(d,p) and ChemDraw Ultra 10.0 software package and its assignment along with the shielding values. In general, highly shielded electrons appear downfield and vice versa. The predicted chemical shift values by the theoretical methods both DFT values slightly deviates from the computed values of ChemDraw Ultra. The carbon atom C11 appearing at very higher chemical shift value (177.0 in B3LYP/6-311++G(d,p), 157.1 ppm in B3LYP/6-31G(d,p) and 152.6 ppm in B3PW91/6-31G(d,p)) due to negative charge of two nitrogen atoms (N10 and N12). Similarly C7, C9, and C13 appearing at higher chemical shift values (163.5, 174.7 and 166.4 ppm in B3LYP/6-311++G(d,p), 143.3, 155.1 and 144.9 ppm in B3LYP/6-31G(d,p), 141.1, 152.6 and 143.1 ppm in B3PW91/6-31G(d,p)) are due to nitrogen atoms N6, N8, and N15, respectively.

The carbon atoms C7, C9, C11, C13, and C14 are electropositive and possess more positive charges than the other carbon atoms, and hence the shielding is very small and appears upfield (see Table 6). In both molecules, the DFT-calculated atomic charges revealed that the more electron-rich atoms are C1, C3, C4, and C5; they are highly shielded atoms and hence appear at downfield (lower chemical shift). The carbon atoms in the benzene ring are deshielded than the carbon atoms in Aliphatic, so that the benzene carbon atoms in purine appear at higher chemical shift values than the aliphatic carbon atoms that were made by DFT methods. In this study, a good correlation between atomic charges and chemical shift was made. It is to be noted that ^{13}C NMR chemical shifts for tenofovir which agree with the ChemDraw Ultra.

Table 6 gives the ^1H NMR predicted chemical shift values obtained by the DFT methods and ChemDraw Ultra 10.0 software program [8] along with assignments. The predicted shielding values for each atom in the tenofovir molecule by B3LYP/6-311++G(d,p), B3LYP/6-31G(d,p), and B3PW91/6-31G(d,p) are given in Table 6. The predicted chemical shift values by the ChemDraw Ultra software program are in good agreement with the two DFT methods.

The spectrum of tenofovir showed a singlet at 7.0 ppm for the proton of the aromatic (H31) group, which is in good agreement with the chemDraw ultra value. Triplet is predicted at 2.9, 2.3, and 2.3 ppm for the methyl group of hydrogen atoms (H25, H26, and H27). This higher chemical shift for methyl group hydrogen is mainly due to the carbon atom (C5). The predicted value of singlet peak at higher chemical shift at 16.2 ppm for methine group of the indole proton (H24). Doublet is predicted at 7.0 ppm for the aromatic group of hydrogen atoms (H30 and H31). This

TABLE 5: Observed and theoretical vibrational assignments of tenofovir.

Experimental		Theoretical frequency						Vibrational assignment	
FTIR	FT-RAMAN	B3LYP/6-311++G(d,p)		B3LYP/6-31G(d,p)		B3PW91/6-31G(d,p)			
		Unscal	Scaled	Int.	Unscal	Scaled	Int.	Unscal	Scaled
		3835	3629	17	3825	3620	20	3859	3650
		3824	3619	19	3761	3563	15	3783	3583
		3735	3540	8	3750	3553	7	3769	3570
3227		3605	3425	15	3613	3432	14	3640	3456
3106		3241	3098	0	3268	3122	0	3277	3130
3051	3052	3166	3030	3	3178	3041	4	3186	3048
		3124	2992	0	3142	3008	0	3153	3018
		3117	2986	1	3137	3004	0	3149	3015
2986	2991	3092	2963	3	3116	2985	2	3136	3003
		3091	2962	0	3111	2980	0	3126	2994
2939	2942	3064	2938	4	3072	2945	5	3082	2954
		3034	2910	2	3051	2926	1	3061	2935
		3028	2905	0	3045	2920	1	3053	2928
	2836	3027	2904	3	3037	2913	1	3045	2920
1679	1656	1655	1625	100	1673	1642	100	1687	1655
	1574	1606	1578	3	1617	1588	1	1624	1595
1504	1505	1525	1500	5	1543	1518	6	1556	1530
		1494	1471	2	1510	1486	0	1504	1480
1472		1469	1447	1	1480	1457	0	1478	1455
	1447	1459	1437	2	1478	1455	1	1472	1449
1421	1424	1419	1399	3	1435	1414	1	1428	1407
	1330	1330	1313	4	1339	1321	2	1334	1317

TABLE 6: The calculated ^{13}C and ^1H NMR chemical shifts of tenofovir.

Atom position	B3LYP/6-311++		B3LYP/6-31		B3PW91/6-31		ChemDraw Ultra	Assignment
	Absolute shielding	Chemical shift	Absolute shielding	Chemical shift	Absolute shielding	Chemical shift		
1	114.7	85.3	126.6	73.3	129.7	70.3	73.4	C1 in Aliphatic
3	124.7	75.3	136.6	63.4	139.3	60.7	58.6	C3 in Aliphatic
4	122.5	77.4	134.7	65.3	137.5	62.4	76	C4 in Aliphatic
5	153.9	46.1	163.3	36.7	166.4	33.6	20	C5 in Aliphatic
7	36.4	163.5	56.7	143.3	58.8	141.1	143	C7 in Purine
9	25.3	174.7	44.9	155.1	47.3	152.6	149.8	C9 in Purine
11	23.0	177.0	42.9	157.1	45.1	154.9	152.4	C11 in Purine
13	33.6	166.4	55.0	144.9	56.9	143.1	156.1	C13 in Purine
14	62.8	137.2	81.3	118.6	83.6	116.4	119.4	C14 in Purine
20	27.8	4.8	28.0	4.6	27.9	4.7	3.4	H20 in Methylene
21	27.9	4.7	28.0	4.6	28.0	4.6	3.4	H21 in Methylene
22	27.5	5.1	27.5	5.1	27.4	5.2	3.9	H22 in Methylene
23	26.8	5.8	26.7	5.9	26.6	6.0	3.7	H23 in Methylene
24	16.4	16.2	16.3	16.3	16.2	16.4	12.0	H24 in Methine
25	29.7	2.9	29.7	2.9	29.6	3.0	1.2	H25 in Methyl
26	30.3	2.3	30.2	2.4	30.2	2.4	1.2	H26 in Methyl
27	30.3	2.3	30.3	2.3	30.2	2.4	1.2	H27 in Methyl
28	23.8	8.8	23.8	8.8	23.6	9.0	8.1	H28 in Purine
29	23.3	9.3	23.1	9.5	22.9	9.7	8.2	H29 in Purine
30	25.0	7.6	25.2	7.4	25.0	7.6	7.0	H30 in Aromatic
31	25.6	7.0	25.9	6.7	25.7	6.9	7.0	H31 in Aromatic
32	29.2	3.4	29.0	3.6	28.9	3.7	12.0	H32 in Alcohol
33	28.3	4.3	28.2	4.4	28.1	4.5	12.0	H33 in Alcohol

TABLE 7: The calculated thermodynamic parameters of tenofovir.

Parameter	B3LYP/6-311++G(d,p)	B3LYP/6-31G(d,p)	B3PW91/6-31G(d,p)
Total energy (a.u)	-1267.50	-1267.25	-1266.851702
Zero-point energy (Kcal/Mol)	158.540	160.017	160.67362
Rotational constants (GHz)	0.6560	0.7940	0.8079
	0.1625	0.1463	0.1466
	0.1537	0.1368	0.1373
Entropy			
Total	150.214	146.784	146.812
Translational	42.862	42.862	42.862
Rotational	34.239	34.269	34.246
Vibrational	73.113	69.653	69.702
Dipole moment (Debye)	2.3152	1.5973	1.6778
HOMO (eV)	-6.27	-5.94	-6.04
LUMO (eV)	-0.95	-0.51	-0.57
Energy gap (eV)	5.31	5.43	5.46

higher chemical shift for methyl group hydrogen is mainly due to the nitrogen atom (N15). The hydrogen atoms of methylene group attached with C1 and C3 atoms show a multiplet at 3.4–3.9 ppm, which is due to the presence of

oxygen and nitrogen atoms, respectively. In all the DFT methods predict the chemical shifts value of the hydrogen in hydroxyl group(H32, H33) is contradicting to chemDraw ultra value, but other hydrogen atoms fairly agrees.

6. Thermodynamic Properties

Several calculated thermodynamic parameters at room temperature are presented in Table 7. According to Koopmann's theorem, ionization potential (I) is the negative of the highest occupied molecular orbital (HOMO) energy, that is, $I = -\text{EHOMO}$, and affinity potential (A) is the negative of the lowest unoccupied molecular orbital (LUMO) energy, that is, $A = -\text{ELUMO}$, which are summarized in Table 7.

Knowledge of permanent dipole moment of a molecule provides a wealth of information to determine the exact molecular conformation. The total dipole moment value of tenofovir in both DFTs and B3PW91 methods was observed. The variations in the entropy and zero-point vibrational energies seem to be insignificant.

7. Conclusion

The geometry of tenofovir was optimized with both DFT and B3PW91 methods using 6-31G(d,p) and 6-311++G(d,p) basis sets. The complete molecular structural parameters and thermodynamic properties of the optimized geometry of the compound have been obtained from DFT calculations. The vibrational frequencies of the fundamental modes of the compound have been precisely assigned and analyzed and the theoretical results were compared with the experimental vibrations. The bond order and atomic charges of the title molecule have been studied by DFT and B3PW91 methods. The energies of important MOs, absorption wavelength (λ_{max}), oscillator strength, and excitation energies of the compound were also determined from TD-DFT method and compared with the experimental values. This study predicted that the molecular geometry, vibrational wave numbers and ^{13}C and ^1H NMR chemical shifts for tenofovir could be successfully elucidated by the B3LYP/6-311++G(d,p), B3LYP/6-31G(d,p) and B3PW91/6-31G(d,p) methods using Gaussian program. Thus, the present investigation provides complete vibrational assignments, structural informations and electronic properties of the compound which may be useful to upgrade the knowledge on tenofovir.

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