

HF, DFT Computations and Spectroscopic Study of the Vibrational and Thermodynamic Properties of Metformin

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Abstract: The molecular vibrations of metformin, one of the important anti-diabetic drugs to treat Non Insulin Dependent Diabetes Mellitus (NIDDM) have been investigated at room temperature by Fourier transform infrared (FTIR) and Fourier transform Raman (FTR) spectroscopy. The solid phase FTIR and FT-Raman spectra of the title compound have been recorded in the regions 4000-400 and 3500-250 cm^{-1} . A satisfactory band assignment has been made on the fundamental modes of vibration. Employing the *ab - initio* Hartree-Fock (HF) and Density Function Theory (DFT) methods, the theoretical vibrational frequencies and geometry parameters like bond lengths, bond angles etc have been calculated and compared with the experimental values. HF and DFT calculations were performed using the standard B3LYP/6-31G** method and basis set combination. Optimized geometries were obtained using the global optimization procedure. Theoretical investigations of harmonic vibrational frequencies and thermodynamic properties viz. the zero point vibrational energy (ZPVE), entropy, heat capacity have been carried out. It has been found that both methods gave consistent data for geometric parameters, but DFT yielded vibrational frequencies much closer to the experimental values.

Keywords: Metformin, FTIR, FT Raman, *ab - initio*, DFT, thermodynamic functions.

INTRODUCTION

Type 2 or NIDDM is a metabolic disorder that affects more than 200 million people world- wide¹. The different classes of oral hypoglycemic agents used to treat NIDDM have complementary mechanisms of action, and their use in combination often results in blood glucose reduction that are significantly greater than those that can be obtained with maximal dose of any single drug^{2,3}. Metformin belongs to the class of biguanides and it is chemically known as 1, 1' - dimethyl biguanide hydrochloride. It is a white hygroscopic crystalline powder with a bitter taste with a molecular formula $\text{C}_4\text{H}_{11}\text{N}_5 \text{HCl}$. Metformin is an

exciting drug having major impact on the treatment of type 2 diabetes is that it increases insulin sensitivity by both decreasing hepatic glucose output and enhancing peripheral glucose uptake. Metformin also decreases plasma Very Low Density Lipoprotein (VLDL) and triglycerides resulting in modest decreases in plasma total cholesterol, which in turn reduces cardiovascular risk factors⁴.

In the present study, a detailed vibrational analysis has been made using FTIR and FTR spectra of metformin. The *ab-initio* and density function theory (DFT) methods have become powerful tools for the investigation of molecular structure and vibrational

spectra⁵. Literature survey shows that molecular mechanics computational studies have been done so far on the titled compound⁶. The evolution of DFT that includes electron correlation in an alternative way is affording opportunities of performing vibrational analysis of moderately large molecules. The present work has been performed with a view point of getting vibrational frequencies on an optimized geometry of metformin using DFT based Becke3-Lee-Yang-Parr (B3LYP) functional with standard 6-31G** basis set which has not been carried out so far. These frequencies are analyzed and compared with the experimental data. In the study of chemical kinetics and chemical equilibria, the knowledge of various thermodynamic functions is of immense importance⁷. Understanding the molecular properties as well as the nature of reaction mechanism has been the subject of many experimental and theoretical studies. The molecular parameters like IR intensity of harmonic frequency of vibration, reduced mass, force constants and various thermodynamic parameters like entropy, heat capacity and energy have been evaluated.

EXPERIMENTAL DETAILS

The spectroscopically pure grade sample of metformin was procured from a reputed

pharmaceutical company, Sun Pharmaceutical Industries Ltd, Mumbai, India and was used as such for the spectral measurements. The room temperature FTIR spectrum of the title compound has been recorded in the range 4000 - 400 cm^{-1} in the solid state at SAIF, IIT Madras, Chennai, India. The BRUKER IFS 66V model FTIR spectrometer had globar as the source and the interferometer chamber had KBr beam splitter. The sampling technique used was KBr pellet method. The FTIR spectrometer had a resolution of $\pm 1\text{cm}^{-1}$. They had the facilities of signal averaging, signal enhancement; baseline correction and other spectral manipulation made possible with multitasking OPUS software on the dedicated PC/INTEL-4.

The FT-Raman spectrum of metformin was recorded on a computer interfaced BRUKER IFS 66V model interferometer equipped with FRA-106 FT-Raman accessories at IITM, Chennai. The spectrum was recorded in the Stokes region 3500-250 cm^{-1} using Nd: YAG laser operating at 200 mw power continuously with 1064 nm excitation. The reported wave numbers are expected to be accurate within $\pm 1\text{cm}^{-1}$. The FTIR and FTR spectra of metformin are presented in the **Figure 1 and 2** respectively.

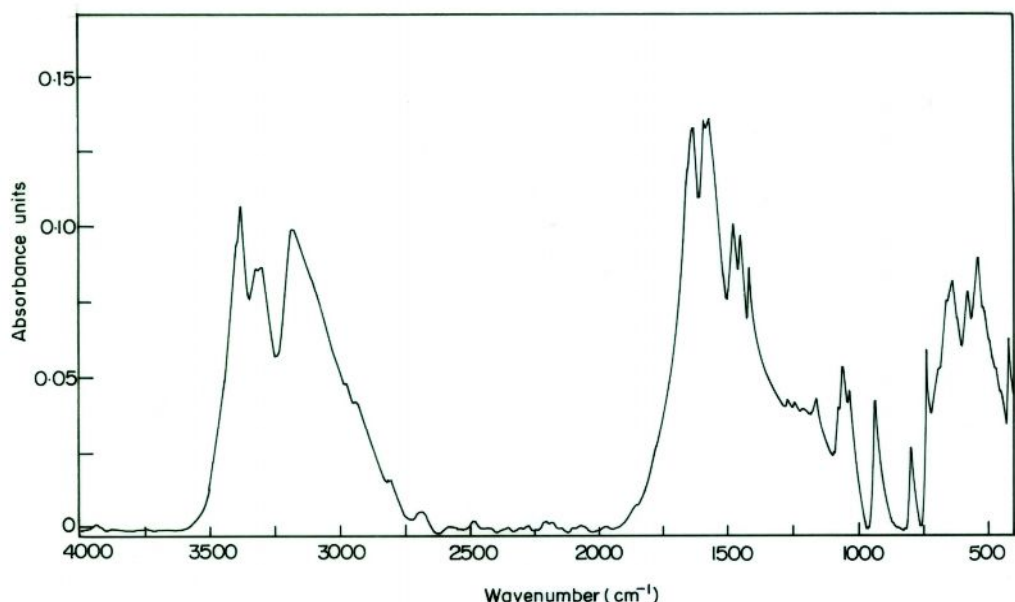


Fig1 - FTIR spectrum of metformin

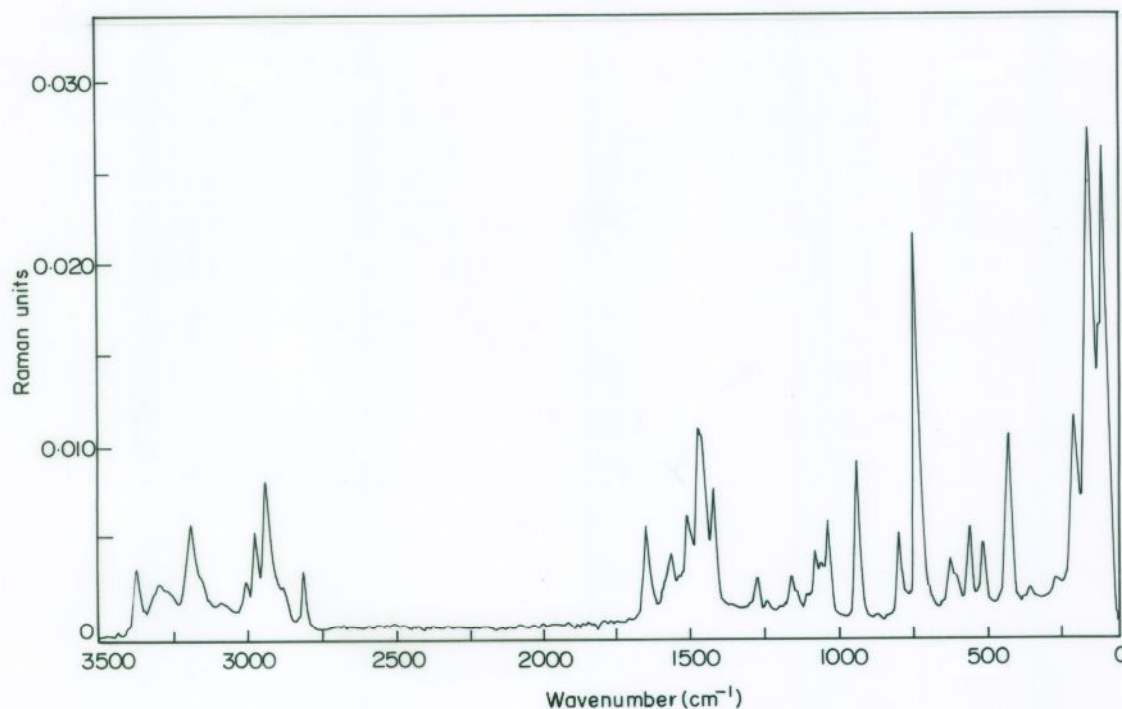


Fig 2 - FT Raman spectrum of metformin

RESULTS AND DISCUSSION

Vibrational band assignment

The aim of the vibrational analysis is to decide which of the vibrational modes in the molecule give rise to each of the observed bands at specific wave numbers in the FTIR and FTR spectra. The functional groups present in the molecule were identified and a satisfactory vibrational band assignment has been made for the fundamental modes of vibration by observing the position, shape and intensity of the bands. Vibrational frequencies of similar compounds like guanidines and their hydro halide derivatives have been taken into consideration for the assignment of fundamental vibrations of Metformin^{8,9}.

N-H Vibrations

The N-H stretching of C=N-H group occurs in the region 3400 - 3100 cm⁻¹. Usually the frequency of this vibration is decreased in the presence of hydrogen bond¹⁰. The medium intensity bands at 3392, 3372 cm⁻¹ and 3297, 3176 cm⁻¹ have been assigned to N-H asymmetric and symmetric stretching vibrations respectively. N, N' di substituted guanidine hydrochlorides have medium intensity bands at 1590 - 1530 cm⁻¹ due to in plane NH₂ deformation⁹. Bands at 1566, 1533 and 1508 cm⁻¹ have been assigned for NH₂ in plane deformation vibrations. N-H wagging vibrations occur in the region 910 - 660 cm⁻¹. The

bands of very weak intensity at 936, 800 and 736 cm⁻¹ are due to N-H wagging.

C=N, C-N Vibrations

Guanidines absorb strongly at 1685 - 1580 cm⁻¹ due to C=N stretching vibrations⁹. Metformin being a biguanide, has strong absorption bands at 1626 and 1583 cm⁻¹ which are due to C=N stretching vibrations. It has been reported that C-N stretching of aliphatic amine compounds is generally weak and occurs in the region 1220 - 1020 cm⁻¹¹¹. The weak intensity bands in the FTIR spectra at 1205, 1160, 1151, 1142, 1080, 1061 and 1035 cm⁻¹ have been assigned to C-N stretching vibrations. Medium to weak intensity bands in the frequency range 600 - 400 cm⁻¹ are due to CNC deformation vibrations⁹. The peaks at 571, 541, 517, 482, 464, 446 and 420 cm⁻¹ are assigned for CNC deformation.

C-H Vibrations

For aliphatic compounds, CH asymmetric stretching vibration of the methyl group occurs at 2975 - 2950 cm⁻¹ and the symmetric CH₃ stretching vibration absorbs at 2885 - 2865 cm⁻¹. The presence of an adjacent group alters the position of CH₃ symmetric stretching vibration whereas the asymmetric band is insensitive to it¹². In Metformin, the presence of nitrogen near methyl group reduces the symmetric CH₃

stretching range as 2835 – 2815 cm^{-1} ^{13, 14}. Bands at 2964 and 2821 cm^{-1} are assigned to CH asymmetric and symmetric stretching vibrations of the methyl group respectively. The methyl groups give rise to two deformation bands, the asymmetric one in the region 1475 - 1445 cm^{-1} and the symmetric at 1390 – 1370 cm^{-1} ⁹. Bands of medium intensity at 1475, 1455 and 1417 cm^{-1} are due to CH₃ asymmetric deformation. Weakly intense bands at 1383 and 1357 cm^{-1} belong to CH₃ symmetric deformation.

The infrared and Raman spectral assignments and the experimental vibrational frequencies of metformin have been presented in **Table 1**. The theoretically calculated vibrational frequencies, IR intensity, reduced mass, force constants for the molecule metformin using HF and DFT methods are presented in **Table 2**. The vibrational frequencies are in accordance with the experimental data

Table 1 – Vibrational band assignment of metformin

Observed frequency (cm^{-1})		Band assignment
FTIR	FTR	
3392 (m)	-	N-H asym. stretching
3372 (s)	3375 (vw)	N-H asym. stretching
3297 (m)	-	N-H sym. stretching
3176 (w)	3197 (w)	N-H sym. stretching
2964 (w)	2980 (vw)	CH ₃ asym. stretching
2821 (w)	2821 (vw)	CH ₃ sym. stretching
1626 (vs)	1653 (vw)	C=N stretching
1583 (vs)	1571 (vw)	C=N stretching
1566 (vs)	-	N-H in plane deformation
1553 (s)	1535 (vw)	N-H in plane deformation
1508 (m)	1515 (w)	N-H in plane deformation
1475 (s)	1472 (w)	CH ₃ asym. deformation
1455 (m)	1446 (w)	CH ₃ asym. deformation
1417 (m)	1427 (w)	CH ₃ asym. deformation
1383 (w)	-	CH ₃ sym. deformation
1357 (w)	-	CH ₃ sym. deformation
1205 (w)	-	C-N stretching
1160 (w)	1169 (vw)	C-N stretching
1151 (w)	1151 (vw)	C-N stretching
1142 (w)	-	C-N stretching
1080 (w)	1087 (vw)	C-N stretching
1061 (w)	1071 (vw)	C-N stretching
1035 (w)	1043 (vw)	C-N stretching
936 (w)	943 (w)	N-H wagging
800 (w)	806 (vw)	N-H wagging
736 (w)	744 (s)	N-H wagging
571 (m)	569 (vw)	C-N-C deformation
541 (m)	-	C-N-C deformation
482 (w)	-	C-N-C deformation
464 (w)	-	C-N-C deformation
446 (w)	432 (w)	C-N-C deformation

vs-very strong, s-strong, m-medium, w-weak, vw-very weak

Table 2 Vibrational wave numbers obtained for metformin by B3LYP/6-31Glevel:
(wave number (cm⁻¹);IRintensity (km mol⁻¹) reduced mass (amu) force constants (m dyne A⁻¹)**

Frequency		IR intensities		Force constants		Reduced Mass	
HF	DFT	HF	DFT	HF	DFT	HF	DFT
66	65	4.9086	4.2157	0.0083	0.0082	3.1471	3.2619
83	84	0.9272	0.6272	0.0177	0.0167	4.3636	4.0299
125	117	1.7947	1.1060	0.0429	0.0392	4.6854	4.8321
151	155	4.2698	3.8682	0.0288	0.0214	1.5491	1.5023
177	187	2.0923	1.3077	0.0408	0.0311	1.6760	1.4995
203	221	0.4608	1.1098	0.0464	0.0389	1.1728	1.3403
259	290	9.5345	11.8770	0.1702	0.1323	2.7988	2.6579
321	315	6.5042	3.4514	0.2754	0.2526	4.1246	4.3269
336	341	42.6809	26.9807	0.0785	0.0719	1.0555	1.0462
355	370	2.9198	3.2144	0.2687	0.2329	2.9074	2.8838
396	422	3.7309	3.1709	0.4756	0.4092	3.8844	3.8855
455	458	7.0172	5.0176	0.4511	0.4051	3.1381	3.2756
493	537	135.757	116.2947	0.2340	0.2073	1.1904	1.2165
577	578	146.497	54.3772	0.4016	0.5652	1.7418	2.8669
625	607	81.6905	139.7491	0.4534	0.3107	1.8636	1.4297
642	660	14.8926	14.5358	1.1762	0.9429	3.8046	3.6634
724	703	9.9862	15.5738	1.1589	0.9238	3.2068	3.1707
783	739	30.8034	32.6996	2.3880	1.8928	5.9297	5.8821
826	788	171.8206	140.0319	0.6332	0.4814	1.3660	1.3150
887	876	22.5340	15.1283	1.8816	1.6393	3.5878	3.6215
943	947	70.3457	67.5331	0.8504	0.6015	1.3290	1.1384
1042	969	46.1143	4.7992	1.9361	2.4464	2.9796	4.4209
1050	1039	52.7659	58.5136	2.0311	1.7904	2.7480	2.8160
1120	1078	15.5794	10.8300	1.2026	1.0163	1.5097	1.4838
1162	1098	25.4387	25.7578	1.7136	1.3915	2.0465	1.9592
1192	1125	6.0813	4.3056	1.0786	0.9203	1.2323	1.2337
1230	1136	40.8327	15.2517	1.0879	0.9383	1.2187	1.2326
1255	1153	240.4975	265.0393	1.7557	1.3808	1.8899	1.7618
1291	1183	6.8529	2.3837	1.4339	1.1942	1.4590	1.4477
1356	1245	10.0531	5.4315	3.6506	3.4689	3.3667	3.7996
1415	1311	75.8166	71.7784	1.9280	1.7019	1.6332	1.6792
1477	1349	156.0301	102.7704	2.2001	1.7968	1.7098	1.6764
1552	1426	83.4409	89.2716	3.3999	2.7332	2.3954	2.2818
1580	1452	6.7477	1.3290	1.7440	1.4291	1.1857	1.1499
1611	1482	8.7062	11.2956	1.6510	1.5171	1.0787	1.1726
1616	1490	0.7724	9.7402	1.8044	1.4211	1.1721	1.0858
1630	1506	7.7368	13.2776	1.6728	1.4510	1.0686	1.0853
1632	1513	12.8847	16.5630	1.6500	1.4245	1.0509	1.0557
1652	1532	4.2918	96.6636	1.7361	1.7572	1.0790	1.2703
1703	1546	681.9783	474.0950	3.8095	2.5417	2.2272	1.8047
1795	1644	80.0203	77.6071	2.2827	1.9034	1.2016	1.1948
1882	1717	33.4647	4.0453	10.1714	8.9367	4.8725	5.1422
1948	1766	514.0875	368.3873	18.6428	12.9101	8.3368	7.0260
3151	2983	58.3712	67.8205	6.1612	5.5374	1.0526	1.0561
3180	3012	61.2556	64.2322	6.2125	5.6061	1.0425	1.0486
3241	3083	9.6236	23.4351	6.7917	6.0706	1.0973	1.0834
3247	3088	88.2163	54.1333	6.7664	6.1293	1.0892	1.0911
3293	3148	43.7006	27.8978	7.0377	6.4115	1.1012	1.0983
3313	3167	21.6083	9.9595	7.1132	6.4938	1.0997	1.0982
3784	3464	3.0082	87.9917	9.0779	7.5888	1.0760	1.0734
3793	3509	89.6840	4.4044	9.1167	7.8060	1.0750	1.0759
3806	3552	26.2269	11.6369	8.9624	7.8017	1.0497	1.0491

3880	3619	47.8723	22.4142	9.5593	8.3037	1.0776	1.0759
3920	3666	26.9073	12.6475	9.9557	8.6897	1.0995	1.0970

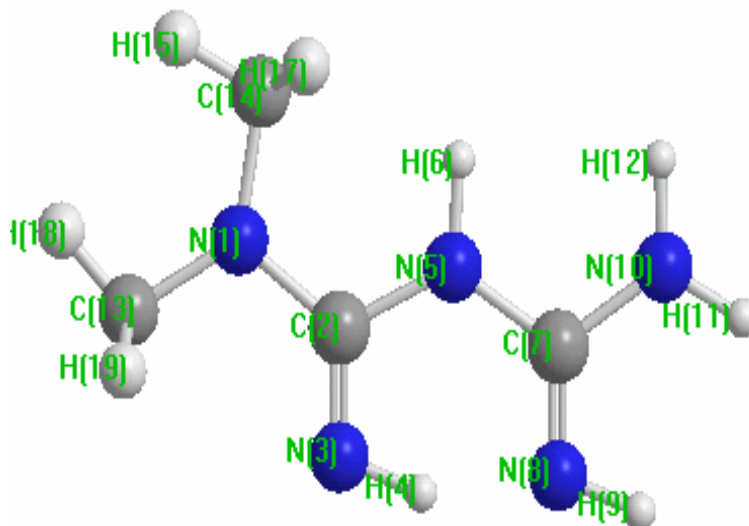


Fig. 3 — Optimized Geometry of metformin obtained by DFT Method

Molecular Geometry

The optimized molecular structure of metformin is shown in **figure 3**. The global minimum energy for metformin using the DFT structure optimization calculated as 432.6759 Hartrees and in HF method as 429.9791 Hartrees. Further the optimized geometrical parameters such as bond lengths and bond angles are obtained by the large basis set calculations (the global minimum energy) for the molecule and are presented in **Table 3**. These structural parameters are in good agreement with the literature values^{15, 16}.

Thermodynamic function analysis

The total energy of a molecule is the sum of translational, rotational, vibrational and electronic energies.

$$\text{ie, } E = E_t + E_r + E_v + E_e$$

Thus the molecular partition function is the product of the translational, rotational, vibrational and electronic partition functions of the molecule¹⁷. The relations between partition functions and various thermodynamic functions were used to evaluate the

latter due to translation, vibration and rotation degrees of freedom of molecular motions⁹.

The statistical thermo chemical analysis of metformin is carried out considering the molecule to be at room temperature of 298.15 K and one atmospheric pressure. In the methodology of B3LYP computations, the contributions due to internal rotations are not considered. The free energy of the molecule is calculated including zero point vibrational energy. The values of zero point vibrational energy (ZPVE) of the molecule were 107.9710 kcal/mol by DFT method and 116.2475 kcal/mol by HF method respectively.

Microscopically, the thermal energy is the kinetic energy of a system's constituent particles, which may be atoms, molecules, electrons, or particles in plasmas. The titled molecule is considered as an asymmetric top having rotational symmetry number one and the total thermal energy has been arrived at as the sum of electronic, translational, rotational and vibrational energies. **Table 4** summarizes the calculated thermodynamic parameters namely heat capacity, entropy, rotational constants and dipole moments of metformin.

Table 3 Geometry parameters of metformin

Bond Length(AU)				Bond Angle (deg)			
Nature	Literature Value	Calculated Value		Nature	Literature Value	Calculated Value	
		HF	DFT			HF	DFT
N (1) - C(2)	1.462	1.3804	1.3911	C(2)-N(1)-C(13)	116.000	119.466	119.0069
N (1) - C (13)	1.470	1.4525	1.4596	C(2)-N(1)-C(14)	116.000	117.928	117.7075
N (1) - C (14)	1.470	1.4567	1.464	C(13)-N(1)-C(14)	127.998	124.419	126.7495
C (2) - N (3)	1.260	1.2478	1.2718	N(1)-C(2)-N(3)	126.000	124.655	126.9736
C(2) - N (5)	1.462	1.406	1.4204	N(1)-C(2)-N(5)	119.999	119.034	119.141
N (3) -H (4)	1.022	0.9951	1.0112	N(3)-C(2)-N(5)	113.999	116.300	114.2042
N (5) - C (7)	1.462	1.3873	1.4025	C(2)-N(3)-H(4)	110.000	113.681	113.6872
N (5) - H (6)	1.050	1.0288	1.0193	C(2)-N(5)-C(7)	124.000	130.609	127.4142
C (7) - N (8)	1.260	1.2501	1.2819	C(2)-N(5)-H(6)	117.999	116.633	117.7075
C (7) - N (10)	1.462	1.4043	1.4098	H(6)-N(5)-C(7)	117.999	114.214	116.3635
N (8) – H (9)	1.022	0.9964	1.0133	N(5)-C(7)-N(8)	122.000	126.893	122.4059
N (10) -H (11)	1.050	0.9943	1.0107	N(5)-C(7)-N(10)	115.999	116.718	114.8419
N (10) -H (12)	1.050	1.0254	1.0228	N(8)-C(7)-N(10)	121.999	122.388	122.4059
C (13) -H (18)	1.113	1.0845	1.0947	C(7)-N(8)-H(9)	110.000	112.190	112.2263
C (13) -H (19)	1.113	1.0809	1.0998	C(7)-N(10)-H(11)	119.733	114.512	119.2042
C (13) -H (20)	1.113	1.0835	1.0946	C(7)-N(10)-H(12)	119.732	114.031	119.0997
C (14) -H (15)	1.113	1.0905	1.1025	H(11)-N(10)-(12)	120.532	111.148	119.5742
C (14) -H (16)	1.113	1.0908	1.1104	N(1)-C(13)-H(18)	107.5	111.401	109.6812
C (14) -H (17)	1.113	1.0947	1.1127	N(1)-C(13)-H(19)	107.5	111.024	109.5415
				N(1)-C(13)-H(20)	107.5	110.967	110.8389
				H(18)-C(13)-H(19)	109	109.293	109.3914
				H(18)-C(13)-H(20)	109	106.032	107.7985
				H(19)-C(13)-H(20)	116.018	107.942	108.2859
				N(1)-C(14)-H(15)	107.5	111.692	111.1936
				N(1)-C(14)-H(16)	107.5	111.078	111..0302
				N(1)-C(14)-H(17)	107.5	110.850	110.5288
				H(15)-C(14)-H(16)	109	106.037	107.6812
				H(15)-C(14)-H(17)	109	109.015	108.9986
				H(16)-C(14)-H(17)	116.018	107.982	108.4366

Table 4 Thermodynamic Parameters of metformin

Position	Energy (kCal/Mol)		Heat Capacity (Cal/Mol-Kelvin)		Entropy (Cal/Mol-Kelvin)	
	HF	DFT	HF	DFT	HF	DFT
Electronic	0.000	0.000	0.000	0.000	0.000	0.000
Translational	0.889	0.889	2.981	2.981	40.479	40.479
Rotational	0.889	0.889	2.981	2.981	29.173	29.230
Vibrational	120.487	112.640	28.454	31.506	25.305	28.395
Total	122.264	114.418	34.416	37.468	94.958	98.105
Rotational Constants (GHz)	3.39617	0.97580	0.80460	3.31480	0.97170	0.7863
Dipole moment (Debye)	X = 2.2270 Y = -4.9594 Z = 0.0875 Tot = 5.4372			X = -2.1199 Y = 4.7732 Z = 0.1879 Tot = 5.2261		

CONCLUSION

The DFT based quantum mechanical approach provides the most reliable theoretical information on the vibrational and thermodynamic properties of metformin. In the present investigation, a complete vibrational band assignment has been made available for metformin using FTIR and FTR spectra. The optimized geometrical parameters and vibrational frequencies of the fundamental modes of metformin were performed and analyzed both at HF and DFT level of theories utilizing B3LYP functional and standard basis set 6-31G (d, p). Geometry parameters

obtained during the course of present investigation show that a better agreement between the experimental data in the literature and the computed data is obtained by using DFT method. The statistical thermo chemical analysis of metformin carried out considering the molecule to be at room temperature of 298.15 K and one atmospheric pressure provided various thermodynamic functions of metformin. The results confirm the ability of the methodology applied for the interpretation of the vibrational spectra of the title compound in the solid phase.

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