

Ab Initio and Density Functional Theory (DFT) Study on Clonazepam

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ABSTRACT

Quantum chemical calculations have been carried out to investigate the vibrational frequencies of clonazepam. The FTIR spectrum of clonazepam was recorded in the region 4000 to 400 cm^{-1} in the solid phase. The optimized geometry, wave number and intensity of the vibrational bands of clonazepam were obtained by *ab initio* Restricted Hartree Fock (RHF) and Density Functional Theory (DFT) methods with complete relaxation in the potential energy surface using the 6-31G (d,p) basis set. A complete vibrational assignment aided by the theoretical harmonic frequency analysis is proposed. The observed and the calculated wavenumbers are found to be in good agreement. The experimental spectra also coincide satisfactorily with those of theoretical spectra. Theoretical spectrograms for the IR spectrum were also constructed in RHF and B3LYP levels. In addition to this the RHF and DFT based NMR calculation procedure was used to assign the ¹H NMR chemical shift of clonazepam. Theoretical values are compared with the experimental data.

Keywords: FTIR; *Ab Initio*; DFT; Clonazepam; Vibrational Analysis; Chemical Shift

1. Introduction

Vibrational spectroscopy is an important tool for the structural investigation of the organic molecules. Benzodiazepines and their polycyclic derivatives are a very important class of bioactive compounds. Clonazepam is a benzodiazepine derivative drug having anticonvulsant, muscle relaxant and anxiolytic properties. Clonazepam is a benzodiazepine derivative drug with highly potent anticonvulsant, muscle relaxant, and anxiolytic properties. Chemical formula of clonazepam is $\text{C}_{15}\text{H}_{10}\text{ClN}_3\text{O}_3$. Clonazepam exerts its action by binding to the benzodiazepine site of the GABA receptors, which causes an enhancement of the electric effect of GABA binding on neurons resulting in an increased influx of chloride ions into the neurons. This results in an inhibition of synaptic transmission across the central nervous system [1,2]. In spite of its importance for pharmaceutical purposes, however, the reported spectroscopical studies on clonazepam are scarce. The evolution of density function theory that includes electron correlation in an alternative way has affording opportunities of performing vibrational analysis of moderately large organic molecules. The results from DFT theory with results obtained from experiments has shown that the methods using B3LYP are the most promising in providing correct vibrational wave numbers. A scan of literature survey reveals that to the

best of our knowledge, no DFT and RHF calculations of clonazepam have been reported so far.

Hence in this work, a systematic study on the structure and vibrational spectra of clonazepam with the aid of RHF and B3LYP methods, have been carried out.

2. Experimental Details

The Spectroscopic pure samples of clonazepam were procured from reputed pharmaceutical firm in Chennai. Fourier Transform Infrared (FTIR) spectrum was recorded on Bruker IFS 66V spectrophotometer by adopting the KBr pellet technique, in the region 4000 to 400 cm^{-1} . Nuclear magnetic resonance spectrum was recorded using Bruker AVANCE III 500 MHz FT-NMR Spectrometer.

3. Computational Details

All the theoretical computations were performed at RHF and B3LYP levels on a Pentium dual core/1.6 GHz personal computer using the Gaussian 03W program package [3] The geometries were first optimized at the RHF level of theory employing the 6-31G (d,p) basis set. The optimized geometry was used in the vibrational frequency calculations at the RHF and DFT levels to characterize all stationary points as minima. The vibrational frequency assignments were made with a high degree of

accuracy with the help Chemcraft software program. The ^1H chemical shifts of the title compound were calculated using the keyword NMR in both RHF and DFT calculations with 6-31G (d,p) basis set.

4. Results and Discussion

4.1. Molecular Geometry

The optimized molecular structure for clonazepam in the ground state (*in vacuo*) was computed by RHF and B3LYP calculations with the 6-31G (d,p) basis set. The

calculated geometrical parameters (bond lengths and bond angles) were compared with experimental geometrical parameters of structurally related molecules [4]. The optimized structural parameters obtained from the RHF and B3LYP/6-31G (d,p) calculations and the literature values are listed in **Table 1**, in accordance with the atom numbering scheme given in **Figure 1**. The slight deviation in literature data from the computed geometry is probably due to the fact that the intermolecular interactions in the crystalline state are dominant. A statistical treatment of these data shows that, for the bond lengths,

Table 1. Selected bond length (Å) and bond angles (deg) values for clonazepam.

Bond length	RHF	B3LYP	Exp [*]	Bond angle	RHF	B3LYP	Exp [*]
N ₁ -C ₂	1.377	1.394	1.371	C ₂ -N ₁ -C ₇	127.7	128.2	126.1
N ₁ -C ₇	1.39	1.395	1.406	N ₁ -C ₂ -C ₃	115.6	114.8	115.7
C ₂ -C ₃	1.514	1.524	1.513	N ₁ -C ₂ -O ₁₈	120.6	120.7	120.9
C ₂ -O ₁₈	1.191	1.214	1.225	N ₁ -C ₇ -C ₆	122.3	122.3	122.7
C ₃ -N ₄	1.446	1.456	1.46	N ₁ -C ₇ -C ₈	117.8	117.9	116.2
N ₄ -C ₅	1.255	1.283	1.289	C ₃ -C ₂ -O ₁₈	123.7	124.6	123.4
C ₅ -C ₆	1.494	1.49	1.48	C ₂ -C ₃ -N ₄	111.9	112	112.7
C ₅ -C ₁₂	1.502	1.5	1.494	C ₃ -N ₄ -C ₅	120.4	119.3	118.1
C ₆ -C ₇	1.4	1.418	1.413	N ₄ -C ₅ -C ₆	125.5	125.8	125.3
C ₆ -C ₁₁	1.391	1.401	1.403	N ₄ -C ₅ -C ₁₂	116.6	116	116.2
C ₇ -C ₈	1.398	1.409	1.397	C ₆ -C ₅ -C ₁₂	117.8	118.1	118.5
C ₈ -C ₉	1.373	1.383	1.383	C ₅ -C ₆ -C ₇	122.1	122.4	122.8
C ₉ -C ₁₀	1.386	1.396	1.387	C ₅ -C ₆ -C ₁₁	119.2	119.1	119.8
C ₁₀ -C ₁₁	1.376	1.387	1.377	C ₅ -C ₁₂ -C ₁₃	118.4	118.2	121.6
C ₁₀ -N ₂₀	1.453	1.467	1.474	C ₅ -C ₁₂ -C ₁₇	123.7	124.2	124
C ₁₂ -C ₁₃	1.391	1.404	1.393	C ₇ -C ₆ -C ₁₁	118.7	118.4	117.3
C ₁₂ -C ₁₇	1.39	1.404	1.393	C ₆ -C ₇ -C ₈	119.8	119.7	120.9
C ₁₃ -C ₁₄	1.382	1.392	1.384	C ₆ -C ₁₁ -C ₁₀	120.3	120.5	120.1
C ₁₄ -C ₁₅	1.384	1.395	1.373	C ₇ -C ₈ -C ₉	121	121.2	120.8
C ₁₅ -C ₁₆	1.383	1.394	1.377	C ₈ -C ₉ -C ₁₀	118.7	118.6	118
C ₁₆ -C ₁₇	1.384	1.394	1.369	C ₉ -C ₁₀ -C ₁₁	121.5	121.6	122.7
C ₁₇ -Cl ₁₉	1.746	1.762	1.742	C ₉ -C ₁₀ -N ₂₀	119.3	119.2	119
N ₂₀ -O ₂₁	1.194	1.231	1.217	C ₁₁ -C ₁₀ -N ₂₀	119.2	119.2	119.1
N ₂₀ -O ₂₂	1.194	1.232	1.217	C ₁₀ -N ₂₀ -O ₂₁	117.8	117.8	118.4
CC	0.994	0.995		C ₁₀ -N ₂₀ -O ₂₂	117.5	117.5	118
				C ₁₃ -C ₁₂ -C ₁₇	117.9	117.6	118.1
				C ₁₂ -C ₁₃ -C ₁₄	121.3	121.5	120.3
				C ₁₂ -C ₁₇ -C ₁₆	121.3	121.5	121
				C ₁₂ -C ₁₇ -Cl ₁₉	120.9	121	120.8
				C ₁₃ -C ₁₄ -C ₁₅	119.7	119.7	120.6
				C ₁₄ -C ₁₅ -C ₁₆	120	120	119.4
				C ₁₅ -C ₁₆ -C ₁₇	119.7	119.7	120.6
				C ₁₆ -C ₁₇ -Cl ₁₉	117.7	117.5	117
				O ₂₁ -N ₂₀ -O ₂₂	124.7	124.7	123.7
				CC	0.94	0.946	

CC—Correlation coefficient; *Ref [4].

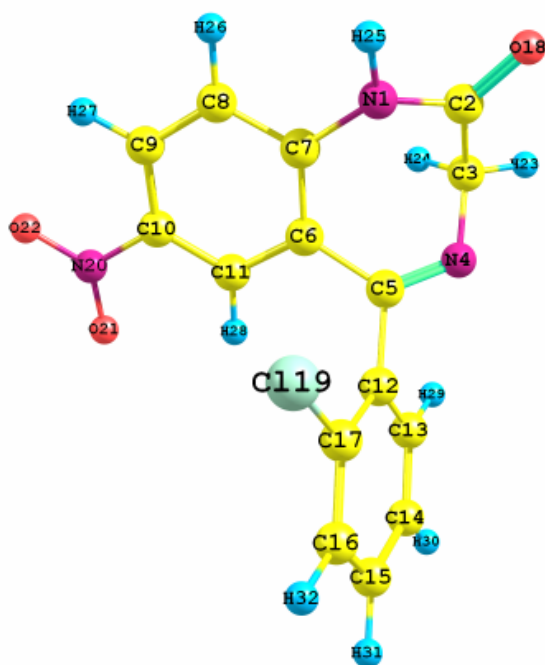


Figure 1. Molecular structure of clonazepam with atom numbering.

B3LYP/6-31G (d,p) is better than the RHF/6-31G (d,p) geometry. It can be noted from the correlation coefficient values that the theoretical predictions are in fairly agreement with the experimental value for bond length and bond angles.

4.2. Atomic Charge and ^1H NMR Spectral Analysis

The calculation of effective atomic charges plays an important role in the application of quantum mechanical calculations to molecular systems. The charge distribution on different atoms (C, N, O and Cl) for clonazepam from Mulliken population analysis (MPA) procedures using RHF and B3LYP methods is listed in **Table 2**. From **Table 2**, it is observed that the calculated Mulliken charge trends are consistent when comparing the RHF and DFT calculations. It is noticed that the carbon atom attached to oxygen and nitrogen atoms (C_2 , C_5 , C_7 and C_{10}) in both RHF and B3LYP is an electron-deficient atom (*i.e.* it possesses positive electronic charge due to electronegativity character). The most negative values are those that are present at nitrogen and oxygen, in the order: N_1 , O_{18} , N_4 , O_{22} , O_{21} , O_{12} . The remaining carbon atoms possess negative electronic charge. As the carbon atom C_2 is attached with both nitrogen and oxygen in either side, it pulls more charge from C_2 atom resulting in more positive charge on the site C_2 as compared with that of other carbon atoms. The atomic charges on C_9 atom become less negative as compared with that other carbon.

Table 2. Mulliken atomic charges.

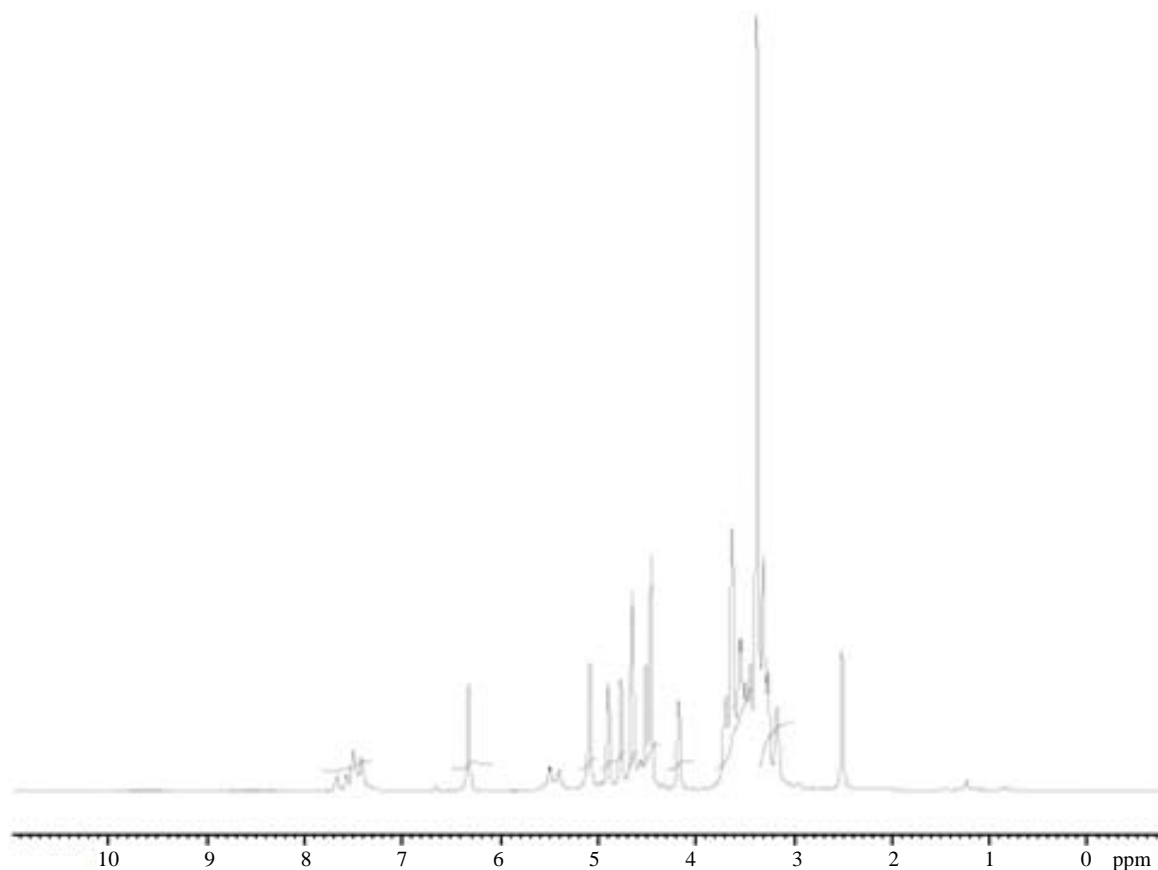
Atom numbering	Mulliken charge	
	RHF/6-31G (d,p)	B3LYP/6-31G (d,p)
N_1	-0.831	-0.632
C_2	0.749	0.559
C_3	-0.127	-0.123
N_4	-0.512	-0.417
C_5	0.28	0.125
C_6	-0.124	0.053
C_7	0.38	0.317
C_8	-0.196	-0.133
C_9	-0.091	-0.098
C_{10}	0.152	0.285
C_{11}	-0.103	-0.166
O_{12}	-0.19	-0.022
C_{13}	-0.059	-0.075
C_{14}	-0.221	-0.119
C_{15}	-0.085	-0.052
C_{16}	-0.284	-0.215
C_{17}	0.228	0.192
O_{18}	-0.577	-0.468
Cl_{19}	0.076	0.091
N_{20}	0.402	0.305
O_{21}	-0.393	-0.355
O_{22}	-0.483	-0.4
H_{23}	0.195	0.152
H_{24}	0.143	0.122
H_{25}	0.349	0.287
H_{26}	0.185	0.112
H_{27}	0.239	0.15
H_{28}	0.251	0.16
H_{29}	0.179	0.102
H_{30}	0.146	0.083
H_{31}	0.16	0.09
H_{32}	0.159	0.09
Dipole moment (Debye)	1.617	1.856

From **Table 2**, it is noticed that calculated atomic charges of clonazepam are not exactly the same, and hence variations in the dipole moment values were observed. The dipole moment value obtained from RHF is small (1.617 Debye), whereas by B3LYP method gives higher dipole moment values (1.856 Debye). This dipole moment value discrepancy is mainly attributed to the variation of atomic charges.

Table 3 gives the predicted chemical shift values obtained by the RHF, DFT and experimental NMR spectrum

Table 3. Experimental and calculated ^1H NMR chemical shift for clonazepam.

Atom	RHF/6-31G (d,p)		B3LYP/6-31G (d,p)		Expt.
	Absolute shielding	Chemical shift	Absolute shielding	Chemical shift	
H ₂₃	26.1	6.5	25.8	6.8	3.4
H ₂₄	27.9	4.7	27	5.6	3.4
H ₂₅	24.1	8.5	24	8.6	8.1
H ₂₆	24.4	8.2	24.5	8.1	7.6
H ₂₇	22.1	10.5	22.8	9.8	
H ₂₈	22.8	9.8	23.3	9.3	
H ₂₉	23.8	8.8	24.1	8.5	
H ₃₀	25.5	7.1	25.2	7.4	7.4
H ₃₁	24.3	8.3	24.4	8.2	7.3
H ₃₂	25	7.6	25	7.6	7.3

**Figure 2. ^1H NMR spectrum of clonazepam.**

and its assignment along with the shielding values. In general, highly shielded electrons appear downfield and vice versa. The present study reveals that the theoretically predicted chemical shifts slightly deviate from the experimental values. It is observed that the predicted chemical shift values by the B3LYP method are in close agreement with the reported literature values. The spectrum of clonazepam showed a singlet at 3.4 ppm for the

proton of the methylene hydrogen (H₂₃ and H₂₄) in the seven membered rings which contradicts the theoretical calculations. Multiplet peaks at 7 - 8 ppm mark the aromatic hydrogen atoms, *i.e.* in the benzene ring.

4.3. Vibrational Band Assignment

According to theoretical calculations, clonazepam mini-

imum energy structure belongs to the C_1 point group symmetry. The molecule has 32 atoms and 90 normal modes of fundamental vibrations. The fundamental modes of these groups are assigned on the basis of group vibrational concept and calculated vibrational frequencies. The harmonic vibrational modes calculated for clonazepam at the RHF and B3LYP levels using the 6-31G (d,p) basis set along with diffuse and polarization function have been summarized in **Table 4**. The experimentally observed FTIR bands for various modes of vibrations are assigned and presented in **Table 4**. The fundamental modes of clonazepam were assigned with the aid of animated Chemcraft program. The FTIR spectrum

of the title molecule along with theoretically simulated IR spectrum is given in **Figure 3**. It is noticed that the best representation of low frequency region IR spectrum is obtained in both the methods. From **Table 4**, both B3LYP and RHF produce the same result which agrees with the experimental values. The scaling factors 0.960 and 0.899 for DFT and RHF values, respectively, have to be necessarily used to find a good agreement with the experimental values. The DFT values were found to be in good agreement with the experimental values after scaling the vibrational frequencies in comparison to RHF values.

CC stretching: The ring CC stretching vibrations occur

Table 4. Calculated IR wavenumber (cm^{-1}) and intensities ($\text{km}\cdot\text{mol}^{-1}$) of clonazepam.

S. No	RHF			B3LYP			Vibrational assignment
	Unscaled wavenumber	Scaled wavenumber	Intensity	Unscaled wavenumber	Scaled wavenumber	Intensity	
1	3854	3465	69	3595	3451	44	ν NH
2	3423	3077	2.6	3250	3120	3.1	ν CH
3	3422	3076	2.7	3245	3115	2.5	ν CH
4	3390	3048	7.5	3224	3095	5.8	ν CH
5	3383	3041	10.1	3219	3090	6.4	ν CH
6	3370	3030	12.6	3208	3080	9.6	ν CH
7	3366	3026	6.3	3196	3068	6.3	ν CH
8	3355	3016	1.3	3195	3067	1.4	ν CH
9	3319	2984	18.3	3148	3022	14.6	ν_{as} CH ₂
10	3175	2854	22.8	2997	2877	20.7	ν_{s} CH ₂
11	2008	1805	709	1824	1751	560.6	ν C=O
12	1916	1722	167	1690	1622	71.7	ν C=N
13	1865	1677	471.2	1670	1603	167.4	ν C=C
14	1800	1618	64.8	1647	1581	25.6	ν C=C
15	1798	1616	42	1640	1574	88.5	ν C=C
16	1768	1589	9	1619	1554	2.5	ν C=C
17	1766	1588	3.2	1611	1547	30.9	ν_{as} NO ₂
18	1668	1500	6	1523	1462	41.4	ν C=C
19	1646	1480	3.3	1510	1450	12	ν C=C
20	1643	1477	23.8	1505	1445	37.2	δ CH ₂
21	1631	1466	174.4	1500	1440	38.4	β NH
24	1542	1386	4.2	1395	1339	357.6	ν_{s} NO ₂
25	1494	1343	134.4	1384	1329	72.2	ν C-N
26	1455	1308	190.1	1342	1288	9.8	ω CH ₂
27	1435	1290	60.3	1335	1282	19.3	β CH
29	1391	1251	31	1312	1260	120.5	ν C-N
30	1385	1245	13.9	1286	1235	10.3	β CCH
31	1334	1199	21.7	1277	1226	11.7	β CH
32	1322	1188	2.9	1260	1210	27.8	t CH ₂
33	1297	1166	10	1218	1169	27.6	β CN, δ NO ₂
34	1275	1146	14	1191	1143	1.3	β CH
35	1246	1120	10.8	1187	1140	27.7	β CH
36	1243	1117	7.1	1165	1118	6.6	β CCH, β CCC
37	1227	1103	74.2	1154	1108	2.4	β CH

Continued

38	1202	1081	2.8	1121	1076	84	β CH
39	1167	1049	26.3	1077	1034	11.8	β CH
40	1150	1034	11.9	1060	1018	30.3	CCC trigonal bending
41	1136	1021	17.9	1042	1000	8.9	γ CCC
42	1126	1012	0.5	1023	982	25.5	γ CH
43	1122	1009	20.6	996	956	0.2	γ CH
44	1115	1002	1.5	983	944	0.6	Ring deformation
45	1086	976	3.2	973	934	5	β CCN
46	1082	973	4.8	961	923	2.6	γ CH
47	1052	946	19.2	953	915	18.7	β CNH, β NCO
48	1001	900	4.9	920	883	10.2	ν NCC
49	996	895	11.3	902	866	11	δ NO ₂
50	985	886	18.8	882	847	0.7	γ CH
51	959	862	30.9	863	828	25.2	Ring breathing
52	932	838	31	842	808	20.7	γ CH
53	868	780	27.1	786	755	23.2	γ CH
54	859	772	59.2	780	749	26.5	ω NO ₂
55	858	771	49.2	765	734	17.9	γ CH
56	845	760	10.5	754	724	26.1	γ CNO
57	818	735	4.8	739	709	15.7	ρ CH ₂
58	802	721	25.5	734	705	5.3	Ring pluckering
59	769	691	22	709	681	18.4	β CCC
60	748	672	9.3	681	654	4.2	γ C=O
61	722	649	11.3	665	638	14.8	γ NH
62	702	631	14.6	654	628	23.8	δ NO ₂
63	643	578	27.2	606	582	63.8	γ CCl
64	625	562	79.8	586	563	12.2	β CCC, γ NCO, β CCN
65	604	543	9.5	557	535	4.9	γ CCC
66	596	536	4.2	551	529	1.9	β CCN
67	574	516	4.8	528	507	2	CCH
68	546	491	6.7	503	483	5.9	β CCN
69	524	471	9.4	479	460	7.5	CCl bending
70	512	460	4.6	472	453	3.7	γ CCH
71	499	449	3.2	460	442	1.9	γ HCH
72	458	412	1.4	423	406	1	Ring wagging
73	440	396	1.1	409	393	0.7	γ CCH
74	419	377	4.2	388	372	3.6	ρ NO ₂
75	409	368	3.7	375	360	2.7	γ CCH
76	341	307	5.7	313	300	4.8	ω CH ₂
77	331	298	2.1	306	294	2.5	Ring torsion
78	310	279	1.1	283	272	0.9	Structure deformation
79	273	245	2.6	249	239	2.2	γ NCH
80	247	222	0.2	231	222	0.1	ω CH ₂
81	213	191	3.4	196	188	2.4	Phenyl ring floating
82	189	170	1.8	180	173	1.2	CCl bending
83	163	147	0.9	151	145	0.5	ω CH ₂ , γ NH
84	140	126	1.4	128	123	1.2	Phenyl ring floating
85	118	106	4.3	112	108	3.1	C=O bending
86	74	67	3.5	73	70	2.5	τ NO ₂ , Ring torsion
87	66	59	1.5	62	60	1.6	Phenyl ring floating
88	50	45	0.1	50	48	0.1	Phenyl ring butterfly
89	47	42	2.1	44	42	1.9	Phenyl ring butterfly
90	28	25	0.4	26	25	0.4	Phenyl ring butterfly

ν_s —sym stretching; ν_{as} —asym stretching; β —in plane bending; γ —out of plane bending; ω —wagging; ρ —rocking; τ —torsion; t —twisting; δ —scissoring.

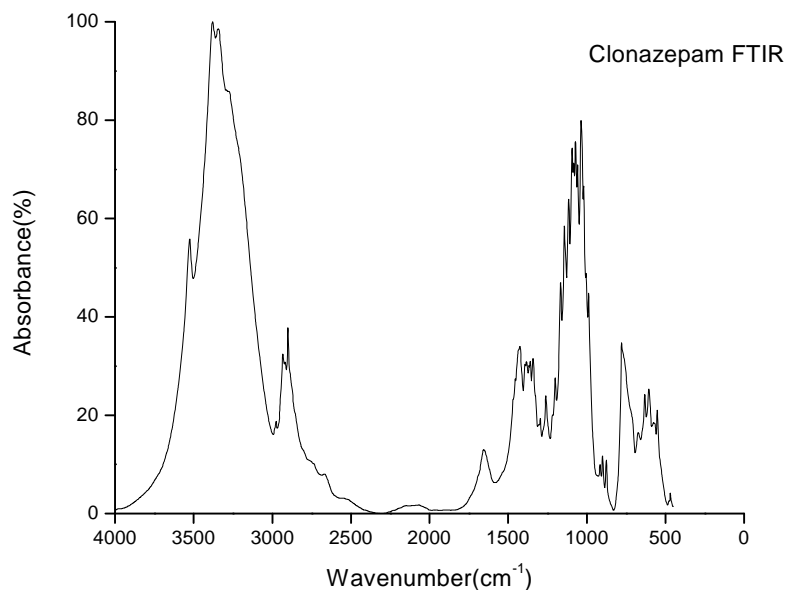


Figure 3. RHF, DFT simulated and experimental FTIR spectrum of clonazepam.

Table 5. FTIR band assignment of clonazepam.

S.No	FTIR wavenumbers (cm ⁻¹)	Band intensity	Vibrational band assignment
1	3202	Very strong	NH stretching
2	3070	Medium	CH stretching
3	2976	Medium	CH stretching
4	2932	Strong	CH ₂ asymmetric stretching
5	2918	Strong	CH stretching
6	2853	Strong	CH ₂ symmetric stretching
7	1654	Weak	C=O stretching
8	1605	Weak	C=N stretching
9	1530	Medium	NO ₂ asymmetric stretching
10	1490	Strong	CC stretching
11	1455	Strong	CC stretching
12	1388	Strong	HCH bending
13	1366	Strong	CN stretching
14	1359	Strong	NO ₂ symmetric stretching
15	1296	Medium	CH in plane bending
16	1260	Medium	CN stretching
17	1201	Strong	CC stretching
18	1167	Very strong	CCN stretching
19	1115	Very strong	CH in plane bending
20	1093	Very strong	CCC bending
21	1083	Very strong	CH in plane bending
22	1072	Very strong	CH in plane bending
23	1058	Very strong	CH in plane bending
24	1036	Very strong	CH in plane bending
25	1020	Very strong	CH in plane bending
26	988	Strong	CH out of plane bending
27	915	Weak	CH out of plane bending
28	876	Weak	CCN bending
29	778	Strong	CH out of plane bending
30	673	Medium	CC=O bending
31	632	Medium	NH bending
32	605	Medium	ONO bending
33	575	Medium	CCl stretching
34	552	Medium	CCC in plane bending
35	468	Very weak	CCCl bending

in the region 1625 to 1430 cm^{-1} . Mohan and Settu [5] have identified the IR bands at 1470 , 1484 , 1561 and 1575 cm^{-1} in closely related compound of benzodiazepines due to aromatic CC stretching vibrations. Neville and Beckstead [6] have identified the IR bands at 1488 and 1452 cm^{-1} in clonazepam. Based on these factors, the FTIR bands at 1490 , 1455 cm^{-1} are assigned to CC stretching vibrations. The calculated bands at B3LYP and RHF levels in the same region are in excellent agreement with experimental observation in FTIR spectrum of clonazepam. As is seen from **Table 5**, the predicted vibrational bands by both RHF and B3LYP agree well with the observed ones.

CH stretching: The aromatic structure shows the presence of CH stretching vibrations in the region 3100 to 3000 cm^{-1} . Krishnakumar [7] identified the strong CH stretching absorption of methylene group centered on 2925 cm^{-1} . According to Neville and Beckstead [6] the CH stretching is observed at 3104 and 3060 cm^{-1} in clonazepam. Hence, in the present study, the FTIR band at 3070 and 2976 cm^{-1} is assigned to CH stretching vibration. The CH stretching mode of vibrations due to methylene is identified and presented in the **Table 4**. The calculated wavenumbers through RHF and DFT techniques are in good agreement with the experimental data.

C=O stretching: The carbonyl stretching frequency is very sensitive to the factors that disturb the nature of carbonyl group and its precise frequency is characteristic of the type of the carbonyl compound being studied. This region is considered as a very important region by organic chemists. The band due to C=O stretching vibration is observed in the region $1850 - 1550\text{ cm}^{-1}$ due to tautomerism, pyrimidines substituted with hydroxyl groups are generally in the keto form and therefore have a strong band due to carbonyl group [8]. According to Neville and Beckstead [6] the C=O stretching is observed at 1693 cm^{-1} . Therefore in this present study the C=O stretching vibration was observed at 1654 cm^{-1} in FTIR is in excellent agreement with theoretically predicted frequency obtained in B3LYP/6-31G (d,p).

5. Conclusion

Attempts have been made in the present work for the proper vibrational band assignments for the compound

clonazepam from FTIR spectrum. The difference between observed and calculated wavenumbers values of most of the fundamental modes is very small. Any discrepancy noted between the observed and the calculated vibrational band contrary to the experimental values recorded in the presence of intermolecular interactions. Therefore the assignments made at higher levels of theory with only reasonable deviations from the experimental values seem to be correct.

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