

**DENSITY FUNCTIONAL THEORY, RESTRICTED HARTREE- FOCK SIMULATIONS AND FTIR, FT-RAMAN STUDIES ON GABAPENTIN****T.RAMYA^{1,4*}, S.GUNASEKARAN² AND G.R.RAMKUMAAR³.**¹*Department of Physics, C.T.T.E College for Women, Perambur, Chennai - 600011, TN, India*²*Research and Development, St. Peter's Institute of Higher Education and Research, St. Peter's University, Avadi, Chennai – 600054, TN, India*³*Department of Physics, C. Kandaswami Naidu College for Men, Anna Nagar East, Chennai - 600102, TN, India*⁴*PG and Research Department of Physics, Pachaiyappa's College, Chennai-600030, TN, India.***ABSTRACT**

Gabapentin purposefully synthesized to mimic the chemical structures of the neurotransmitter γ -aminobutyric acid and for use as an adjunctive medication to control partial seizures. In this work, the vibrational spectral analysis was carried out on Gabapentin by using FT-Raman and FTIR spectroscopy in the range 5000 - 50 cm^{-1} and 4000 - 450 cm^{-1} respectively. Quantum chemical calculations of geometrical structure, vibrational wavenumber and infra red intensities were carried out by the ab initio Restricted Hartree Fock (RHF) and Density Functional Theory DFT (B3LYP) with complete relaxation in the potential energy surface using 6-311++G(d,p) basis set. The complete vibrational assignments of wave numbers were made on the basis of potential energy distribution (PED). The results of the calculations were applied to simulated spectra which shows good agreement with the observed spectra. Natural Population analysis (NPA), HOMO and LUMO energy, electric dipole moment (μ), hyperpolarizability (β), chemical reactivity, ^1H NMR and ^{13}C NMR and thermodynamic properties are also calculated using RHF and DFT methods.

KEY WORDS: FTIR, FT Raman, RHF, DFT, Potential energy distribution and hyperpolarizability**T.RAMYA**Department of Physics, C.T.T.E College for Women,
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INTRODUCTION

Gabapentin chemically known as 2-[1-(AminoMethyl) Cyclohexyl]Acetic acid works by stabilizing electrical activity in the brain. Gabapentin interacts with cortical neurons at auxiliary subunits of voltage-sensitive calcium channels¹ and increases the synaptic concentration of GABA (Gamma- Aminobutyric acid), enhances GABA responses at non-synaptic sites in neuronal tissues, and reduces the release of mono-amine neurotransmitters. In the present work a detailed quantum chemical investigation has aided the understanding and computations of the vibrational modes of gabapentin, to be compared with the experimental data available for this molecule. The vibrational wavenumbers of gabapentin and molecular parameters have been calculated by using the RHF and DFT methods. These calculations are valuable for providing a deeper insight into the vibrational spectrum and molecular parameters.

EXPERIMENTAL

The spectroscopically pure grade sample of gabapentin was purchased from a reputed Pharmaceutical company, Chennai, India and was used as such for the spectral measurements. FTIR spectrum of the title compound has been recorded in the range 4000 - 450 cm^{-1} in the solid state at SAIF, IIT Madras, Chennai, India. The FT-Raman spectrum of gabapentin was recorded in the range 4000 - 50 cm^{-1} on a computer interfaced

BRUKER IFS 66V model Interferometer at IITM, Chennai. Quantum chemical methods have proved to be an essential tool for interpreting the vibrational spectra. Hence in this study Restricted Hartree Fock and Density functional theory based on Becke 3-Lee-Yang-parr have been performed to support the vibrational spectra of gabapentin.

QUANTUM CHEMICAL CALCULATIONS

All the theoretical computations have been performed at Ab-initio restricted Hartree Fock (RHF) and Density Functional Theory calculations (B3LYP) with 6-31++G(d,p) basis set on a Pentium IV/1.6GHz personal computer using the Gaussian 03W program². All the computations have been done by adding polarization function 'p' and diffuse function 'd' on hydrogen atoms for better description. The optimized geometry has been used in the vibrational frequency calculations to characterize all the stationary points as minima. The vibrational frequency assignments have been made with a high degree of accuracy with the help of Chemcraft software. Finally calculated normal mode vibrational frequencies have been used to provide the hyperpolarizability and thermodynamic properties defined by statistical mechanics.

(i) Molecular geometry

The optimized geometry of gabapentin obtained by RHF and B3LYP level of calculations, is provided in (Tables 1 and 2) in accordance with the atom numbering scheme given in (Fig 1).

Table 1
Bond lengths (Å) of Gabapentin

Parameters	RHF/6-311++G(d,p)	B3LYP/6-311++G(d,p)	Exp.value ^a
C ₁ -C ₂	1.493	1.494	1.498
C ₁ -O ₃	1.212	1.234	1.260
C ₁ -O ₄	1.354	1.389	1.360
C ₂ -C ₅	1.558	1.567	1.505
C ₂ -H ₁₃	1.079	1.09	0.970
C ₂ -H ₁₄	1.077	1.091	0.970
O ₄ -H ₁₅	0.950	0.978	0.977
C ₅ -C ₆	1.551	1.557	1.498
C ₅ -C ₁₀	1.549	1.554	1.498
C ₅ -C ₁₁	1.551	1.564	1.498
C ₆ -C ₇	1.534	1.543	1.498
C ₆ -H ₁₆	1.088	1.098	0.970
C ₆ -H ₁₇	1.082	1.092	0.970
C ₇ -C ₈	1.529	1.537	1.498
C ₇ -H ₁₈	1.084	1.094	0.970
C ₇ -H ₁₉	1.080	1.091	0.970
C ₈ -C ₉	1.529	1.537	1.498
C ₈ -H ₂₀	1.087	1.097	0.970
C ₈ -H ₂₁	1.084	1.094	0.970
C ₉ -C ₁₀	1.534	1.539	1.498
C ₉ -H ₂₂	1.084	1.094	0.970
C ₉ -H ₂₃	1.082	1.092	0.970
C ₁₀ -H ₂₄	1.086	1.097	0.970
C ₁₀ -H ₂₅	1.084	1.094	1.09
C ₁₁ -N ₁₂	1.457	1.465	1.47
C ₁₁ -H ₂₆	1.082	1.093	0.970
C ₁₁ -H ₂₇	1.086	1.098	0.978
N ₁₂ -H ₂₈	0.994	1.009	1.04
N ₁₂ -H ₂₉	0.993	1.008	1.04

Table 2
Bond Angles of Gabapentin

Parameter	RHF/6-311++G(d,p)	B3LYP/6-311++G(d,p)	Exp. value ^a
C ₂ -C ₁ -O ₃	126.53	126.66	126
C ₂ -C ₁ -O ₄	112.99	112.742	112
O ₃ -C ₁ -O ₄	120.41	120.569	122
C ₁ -C ₂ -C ₅	118.88	119.186	112
C ₁ -C ₂ -H ₁₃	106.9	108.18	108.8
C ₁ -C ₂ -H ₁₄	107.29	107.866	108.8
C ₅ -C ₂ -H ₁₃	107.83	107.866	108.8
C ₅ -C ₂ -H ₁₄	107.51	105.542	108.8
H ₁₃ -C ₂ -H ₁₄	107.99	108.641	109.5
C ₁ -O ₄ -H ₁₅	113.26	110.236	112
C ₂ -C ₅ -C ₆	113.16	113.428	112
C ₂ -C ₅ -C ₁₀	112.6	112.595	112
C ₂ -C ₅ -C ₁₁	105.13	104.837	107
C ₆ -C ₅ -C ₁₀	110.6	110.502	112
C ₆ -C ₅ -C ₁₁	108.11	108.256	107
C ₁₀ -C ₅ -C ₁₁	106.76	106.75	107
C ₅ -C ₆ -C ₇	116.14	115.806	112
C ₅ -C ₆ -H ₁₆	107.2	107.096	108.8

C ₅ -C ₆ -H ₁₇	109.34	109.418	108.8
C ₇ -C ₆ -H ₁₆	107.43	107.614	108.8
C ₇ -C ₆ -H ₁₇	109.64	109.666	108.8
H ₁₆ -C ₆ -H ₁₇	106.62	106.829	-
C ₆ -C ₇ -C ₈	111.55	112.025	112
C ₆ -C ₇ -H ₁₈	108.47	108.563	108.8
C ₆ -C ₇ -H ₁₉	110.44	110.289	108.8
C ₈ -C ₇ -H ₁₈	110.02	110.121	108.8
C ₈ -C ₇ -H ₁₉	109.79	109.68	108.8
H ₁₈ -C ₇ -H ₁₉	106.41	105.976	106.2
C ₇ -C ₈ -C ₉	110.63	110.8	109.5
C ₇ -C ₈ -H ₂₀	109.7	109.587	109.5
C ₇ -C ₈ -H ₂₁	110.17	110.13	109.5
C ₉ -C ₈ -H ₂₀	109.43	109.313	109.5
C ₉ -C ₈ -H ₂₁	110.15	110.326	109.5
H ₂₀ -C ₈ -H ₂₁	106.64	106.586	106.2
C ₈ -C ₉ -C ₁₀	111.59	111.151	109.5
C ₈ -C ₉ -H ₂₂	110.25	110.211	109.5
C ₈ -C ₉ -H ₂₃	109.38	109.913	109.5
C ₁₀ -C ₉ -H ₂₂	108.64	108.96	109.5
C ₁₀ -C ₉ -H ₂₃	110.77	110.099	109.5
H ₂₂ -C ₉ -H ₂₃	106.03	106.388	106.2
C ₅ -C ₁₀ -C ₉	115.62	115.325	109.5
C ₅ -C ₁₀ -H ₂₄	107.71	107.647	108.8
C ₅ -C ₁₀ -H ₂₅	109.3	109.111	108.8
C ₉ -C ₁₀ -H ₂₄	107.44	107.808	108.8
C ₉ -C ₁₀ -H ₂₅	109.91	110.157	-
H ₂₄ -C ₁₀ -H ₂₅	106.4	106.381	-
C ₅ -C ₁₁ -N ₁₂	113.64	113.596	109
C ₅ -C ₁₁ -H ₂₆	108.65	108.493	108.8
C ₅ -C ₁₁ -H ₂₇	107.69	107.099	108.8
N ₁₂ -C ₁₁ -H ₂₆	107.9	107.88	107.4
N ₁₂ -C ₁₁ -H ₂₇	111.85	112.526	107.4
H ₂₆ -C ₁₁ -H ₂₇	106.82	106.989	106.2
C ₁₁ -N ₁₂ -H ₂₈	115.86	115.958	112.2
C ₁₁ -N ₁₂ -H ₂₉	115.63	115.979	112.2
H ₂₈ -N ₁₂ -H ₂₉	112.02	112.219	106.8

a- Ref. 3

All the calculated C-C bonds well coincides with the experimental value . But the value of N₁₂-H₂₈ and N₁₂-H₂₉ calculated by RHF differs slightly from the experimental value. The O-H bond distance is very small compared to all other bond length distances. The density functional calculation gives the very high bond angle of C₂-C₁-O₃ as 126⁰.The C-C-H angle is constant which is 107⁰. The bond angle of C-N-H remains constant as 115⁰ which coincides exactly with the experimental value. The variation in bond angle depends on the electro

negativity of the central atom, the presence of lone pair of electrons and the conjugation of the double bond. If the electro negativity of the central atom decreases, the bond angle decreases. Further the results of our calculations, the experimental and calculated geometric parameters agree well with remaining geometrical parameters. The small deviations observed are probably due to the inter molecular interactions in the crystalline state of the molecule.

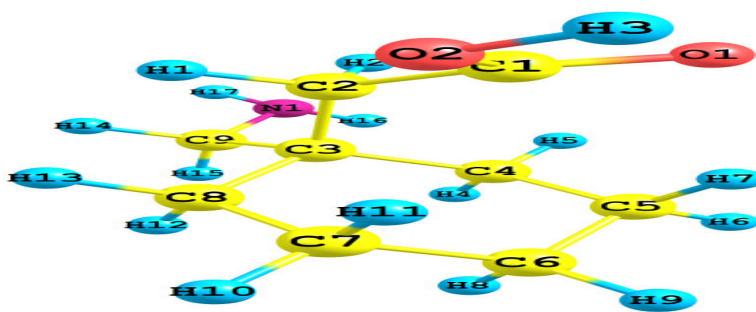


Figure 1
Atom numbering scheme of Gabapentin

(ii) Vibrational assignment

Infrared and Raman spectra contain a number of bands at specific wave numbers. The assignments for the fundamental modes of vibrations have been made on the basis of the position shape and intensity and compared with Restricted HF and DFT functional basis methods. The FTIR and FT Raman spectra of

gabapentin were shown in (Fig 2 and 3) respectively. The observed FTIR and FT-Raman frequencies for various modes of vibrations and the theoretically calculated vibrational frequencies, IR intensity for gabapentin using RHF and DFT methods are presented in (Table 3)

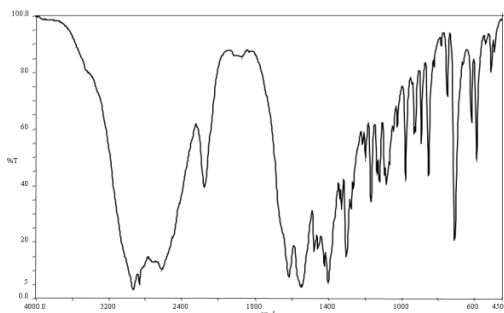


Figure 2
FTIR Spectrum of Gabapentin

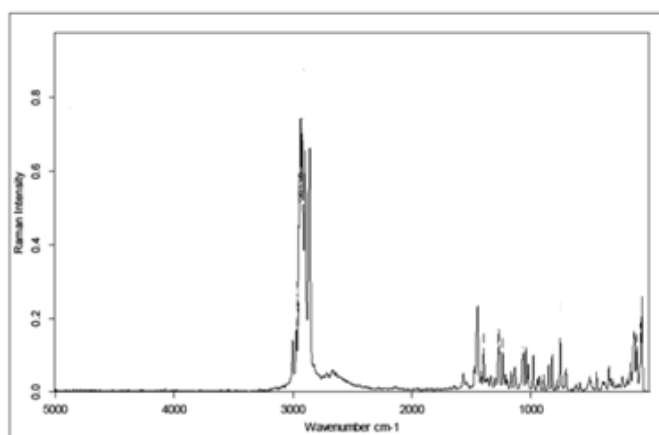


Figure 3
FT Raman Spectrum of Gabapentin

N-H vibrations

The molecule gabapentin possess one NH₂ group and hence can expect one asymmetric and one symmetric N-H stretching vibrations. In all hetero cyclic compounds the N-H stretching vibrations occur in the region 3600-3300cm⁻¹ ⁴. The position of absorption in this region depends on the degree of hydrogen bonding and physical state of the sample. In the present

study the N-H stretching vibrations in FTIR spectrum is observed at 3656cm⁻¹ with the 100% of PED contribution. The theoretically computed N-H vibration is calculated at the wavenumber 3628cm⁻¹ and 3499cm⁻¹ for asymmetric and at 3394 cm⁻¹ and 3393cm⁻¹ for symmetric vibrations by RHF and B3LYP levels.

Table 3
Calculated and Experimental wave numbers (cm⁻¹) of Gabapentin

Mode	Ferquency(cm ⁻¹)		RHF/6-311++G(d,p)		B3LYP/6-311++G(d,p)		Vibrational assignment
	FTIR	FT Raman	Freq.(cm ⁻¹)	IR Intensity KM/Mole	Freq.(cm ⁻¹)	IR Intensity KM/Mole	
1	3656vw		3628	84.8	3499	4	v asyNH2(100)
2			3494	5.34	3474	33	v sym O-H(100)
3			3394	1.04	3393	0.59	v symNH2(100)
4	2970w	2972w	2958	7.41	2965	17	v asyCH2(99)
5	2920w		2913	42.3	2942	58	v asyCH2(71)
6			2902	25.3	2931	18	v asyCH2(81)
7			2889	66.6	2920	16	v asyCH2(76)
8			2878	16.8	2915	65	v asyCH2(80)
9			2875	66.8	2908	8	v asyCH2(99)+v C-H(69)
10			2864	48	2905	71	v asyCH2(96)+v C-H(90)
11	2858m		2860	88.6	2899	36	v symCH2(96)
12			2844	36	2886	46	v symCH2(69)
13			2843	90.8	2882	36	v symCH2(86)
14			2825	82.9	2873	10	v symCH2(79)
15			2812	33.3	2851	15	v symCH2(89)+v C-H(74)
16			2811	16.3	2843	18	v symCH2(80)
17			2803	21.9	2824	40	v symCH2(89)
18	1657w		1681	3.27	1637	48	v symCH2(88)
19	1611m		1666	52.8	1663	24	β HNH(85)+ v OC(76)
20	1541s		1502	5.14	1524	6	β HCH(87)
21			1497	12.2	1513	8	β HCH(80)
22			1492	5.27	1510	10	β HCN(91)
23			1489	4.03	1501	3	β HCH(76)
24			1480	10.3	1500	13	β HCH(73)
25			1476	2.69	1495	4	β HCH(73)
26	1474m	1445m	1471	5.98	1489	3	β HCH(80)
27	1419m		1399	18.2	1400	9	β HCH(70)
28			1386	7.99	1387	2	β HCN(26)+τ HCCC(26)
29		1396w	1381	1.46	1384	1	τ HCCC(16)
30			1370	32.2	1374	0.28	β HCC(16)
31			1365	0.65	1370	1	β HCC(38) +β HCN(38)
32			1362	0.36	1364	14	τ HCCC(60)
33			1357	3.23	1359	12	β HCC(56) +τ HCCC(56)
34	1347vw		1337	16.5	1342	5	β HCC(30)
35	1326w		1316	3.46	1321	14	β HCC(32) +τ HCCC(32)
36			1294	6.58	1305	2	β HCN(31) +τ HCCC(30)
37			1289	5.24	1297	5	β HCH(54) +τ HCCO(54)
38	1297s		1269	10.4	1278	1	β HCC(27) +τ HCCC(28)

39	1259w	1273w	1267	1.32	1271	13	⊥ HCCC(27)
40		1235w	1208	18.5	1214	14	β HCC(44)
41	1196vw		1187	10.2	1194	3	β HOC(20)
42			1155	53.5	1165	18	β HOC(31) +β HCC(34)
43	1164m		1145	16.9	1150	0.94	β HCC(10)
44			1117	15.2	1108	67	β HCC(28) +⊥ HCCC(28)
45			1093	30.1	1097	32	β HNC(37) +β HCN(38)+⊥ HCCC(28)
46	1118m		1078	34.8	1079	66	β HOC(12)
47	1080w		1048	19.9	1057	11	v CN(53)+v CC(56)
48	1071w	1064w	1039	29.3	1049	13	v CN(36)+v CC(37)
49			1018	5.04	1034	5	v CN(42)+v CC(42)
50	1020vw		997	3.15	1000	8	v CN(42)+v CC(42)+v OC(22)
51			946	0.27	958	1	v CN(12)
52	975m		941	0.16	948	2	v CC(25)
53	940vw		920	0.05	934	0.06	β HCC(13)
54	921m		900	15.3	900	30	v CC(11)
55	890m		871	3.43	883	1	v CC(42)+v OC(22)+⊥ HCCC(28)
56			846	6.9	856	9	v CC(35)
57			828	3.02	832	5	⊥ HCCC(20)
58	849m	820w	812	4.82	827	2	v CC(35)
59	791vw		775	0.8	788	0.65	γ OCOC(21)
60	748vw	751w	745	18.9	751	9	v CC(35)+⊥ HCCC(37)
61			658	64.1	666	11	γ OCOC(21)
62			644	24.8	639	78	v CC(69)+⊥ HOCC(69)+γ OCOC(21)
63	616m		602	54.3	601	44	β OCO(41) +β NCC(38)+⊥ HOCC(41)
64	587s		567	93.7	566	13	β OCO(54) +⊥ HNCC(54)+⊥ HOCC(41)
65			534	32.2	540	17	⊥ HNCC(40)
66	489w		479	7.84	494	9	β OCO(39) +β CCC(26)
67			437	0.07	451	0.05	β CCC(32) +⊥ CCCC(32)
68			423	3.35	434	5	β OCC(67) +⊥ HCCO(67)
69			395	1.16	409	0.5	β CCC(11)
70			381	0.7	388	0.35	β CCC(53)+γ CCCC(53)
71			334	1.42	337	1	β OCC(16)
72			306	0.59	317	0.9	β CCC(16) +β HOCC(16)+⊥ CCCC(53)
73			285	2.18	290	3	β CCC(37)+γ CCCC(53)
74			215	1.14	223	29	⊥ HNCC(71)
75			194	33.7	219	2	β NCC(36) +β CCC(37)
76			179	6.67	186	4	β CCC(38) +⊥ HCCC(38)
77			148	2.29	155	0.65	β CCC(73) +⊥ OCOC(79)
78		129m	120	0.64	130	0.89	⊥ NCCC(54)+γ CCCC(54)
79			110	0.78	115	1.2	⊥ NCCC(66)+⊥ CCCC(41)
80		64m	71	2.31	72	0.91	⊥ CCCC(29)+⊥ OCC(79)
81			28	0.77	24	1.18	⊥ HCCC(87)+⊥ OCC(87)

vw- very weak, w- weak, m-medium, s-strong, v asy- asymmetric stretching; v sym- symmetric stretching; β-In plane bending; γ- out of plane bending; ⊥ -torsion.

Methylene vibrations

The asymmetrical and symmetrical stretching CH₂ vibrations will appear around 3000 cm⁻¹ and in the region 3000-2800cm⁻¹ respectively⁵. The vibrations at 2970, 2920cm⁻¹ in FT-IR and 2972 cm⁻¹ in FT-Raman spectrum corresponds to asymmetric stretching. The symmetric stretching in FTIR is 2858cm⁻¹. These modes are calculated in the range 2958, 2913 cm⁻¹ (Asym) and 2860cm⁻¹(Sym.) with RHF/6-

311++G(d,p) and 2965, 2942cm⁻¹(Asym) and 2899 cm⁻¹(Sym.) with B3LYP/6-311++G(d,p) method. As expected these modes are pure stretching modes for asymmetric and symmetric with contribution 81% and 79% by PED method respectively. Methylene group normally has deformation vibrations in the region 1465-1440 cm⁻¹ and around 1600 cm⁻¹. The band at 1541, 1474 and 1419 cm⁻¹ in FT-

IR and 1445 cm^{-1} in FT-Raman are assigned to CH_2 in plane bending vibrations.

C-N and C-C stretching

The intense bands observed in the FTIR and FT-Raman spectra at 1080, 1071, 1020 cm^{-1} and 1064 cm^{-1} are attributed to CC and CN stretching vibrations. A very strong band observed at 1235 cm^{-1} in the Raman spectra, and also an intense band at 1164 cm^{-1} in the FTIR spectrum, corresponds to HCC bending vibrations. The corresponding PED contribution is 44%. The in plane bending of CCC occurs theoretically at 423, 395 cm^{-1} in RHF and 434, 409 cm^{-1} in B3LYP with the PED percentage of 32%.

Bending vibrations

The deformation vibrations contribute to the vibrational modes in the lower frequency region. The theoretically calculated values at 1386, 1316, 1294 cm^{-1} (RHF), and 1387, 1321, 1305 cm^{-1} (B3LYP) attributes to the torsion of

HCCC and the corresponding Raman vibration is at 1326 cm^{-1} . The out of bending vibration of CCCC and NCCC occurs theoretically at 120, 110 cm^{-1} (RHF) and 130, 115 cm^{-1} (B3LYP) with a PED contribution of 54% and 66%. The Raman vibration occurs at 129 cm^{-1} . The bending vibration of OCCC occurs at 71, 28 cm^{-1} (RHF), and 72, 24 cm^{-1} (B3LYP).

(iii) Natural population analysis

Natural population analysis calculation has an important role in the application of quantum chemical calculation to molecular system because of atomic charges effect, dipole moment, molecular polarizability, electronic structure and a lot of properties of molecular system^{6,7}. The charge distribution over the atoms suggest the formation of donor and acceptor pairs involving the charge transfer in the molecule. The NPA analysis of gabapentin molecule is calculated by using RHF and B3LYP level with 6-311++G(d,p) basis set and presented in (Table 4).

Table 4
Natural population analysis of Gabapentin

Parameter	Natural population Analysis	
	RHF/ 6-311++G(d,p)	B3LYP/6-311++G(d,P)
C ₁	0.9816	0.8159
C ₂	-0.475	-0.5066
O ₃	-0.7092	-0.6107
O ₄	-0.776	-0.7104
C ₅	-0.0434	-0.0521
C ₆	-0.3425	-0.3932
C ₇	-0.3364	-0.3862
C ₈	-0.3262	-0.3784
C ₉	-0.3362	-0.3866
C ₁₀	-0.3326	-0.3828
C ₁₁	-0.0975	-0.1692
N ₁₂	-0.8902	-0.875
H ₁₃	0.1977	0.2212
H ₁₄	0.2438	0.2619
H ₁₅	0.4912	0.4841
H ₁₆	0.1626	0.1893
H ₁₇	0.1908	0.2153
H ₁₈	0.1716	0.1978
H ₁₉	0.1821	0.2048
H ₂₀	0.1562	0.1822
H ₂₁	0.1729	0.1991
H ₂₂	0.1711	0.1969
H ₂₃	0.1748	0.1994
H ₂₄	0.167	0.1928
H ₂₅	0.1758	0.2016
H ₂₆	0.1601	0.1878
H ₂₇	0.1441	0.1697
H ₂₈	0.3565	0.3631
H ₂₉	0.3612	0.368

The NPA plot of gabapentin is shown in (Fig 4). The NPA analysis shows the presence of one negatively charged Nitrogen atom $N_{12} = -0.8902(\text{RHF})$ and $-0.8750(\text{B3LYP})$, and two Oxygen atoms $O_3 = -0.7092(\text{RHF})$ and $0.6107(\text{B3LYP})$ and $O_4 = -0.7760(\text{RHF})$ and -

$0.7104(\text{B3LYP})$ imposing the positive charge on carbon atom $C_1 = 0.9816(\text{RHF})$ and $0.8159(\text{B3LYP})$. The Hydrogen atoms from H_{13} to H_{29} possess positive charge distributions due to large negative charges on carbon atoms $C_1, C_2, C_6, C_7, C_8, C_9, C_{10}$ and C_{11} .

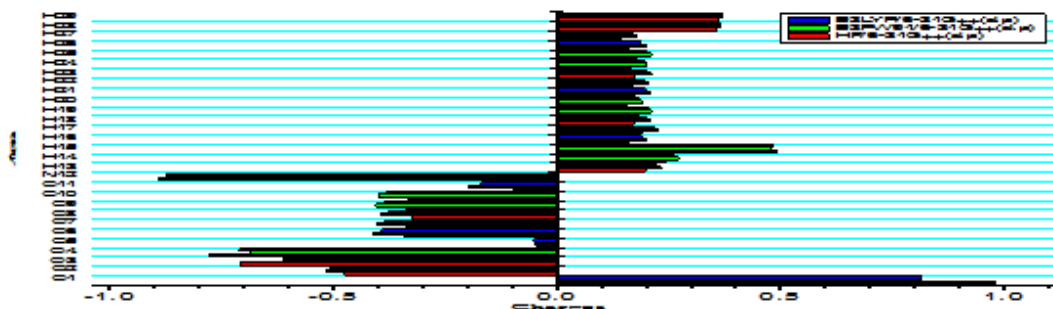


Figure 4
NPA plot of Gabapentin

(iv) Hyperpolarizability

Recent research works have shown that the organic non linear materials are having high optical non linearity than inorganic materials⁸. Non linear optical effects arise from the interactions of electromagnetic fields in various media to produce new fields altered in phase,

frequency, amplitude or other propagation characteristics from the incident fields⁹. The non-linear optical relation of an isolated molecule in an electric field(ω) can be represented as a Taylor series expansion of the total dipole moment, μ_{tot} . Induced by the fields

$$\mu_{\text{tot}} = \mu_0 + \alpha_{ij} E_j + \beta_{ijk} E_j E_k + \dots$$

Where α is the linear polarizability, μ_0 is the dipole moment and β_{ijk} is the first hyperpolarizability tensor components. The average linear polarizability is defined as

$$\alpha_{\text{total}} = 1/3(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$$

First hyperpolarizability is a third rank tensor that can be described by 3x3x3 matrix. By Kleinman symmetry 27 components can be reduced to 10 components which is produced as output from Gaussian as $\beta_{xxx}, \beta_{xyy}, \beta_{xzz}, \beta_{yyy}, \beta_{yzz}, \beta_{yxx}, \beta_{zzz}, \beta_{zxx}$ and β_{zyy} .

The complete equation for calculating the magnitude of β from a Gaussian output is given as

$$\beta_{\text{total}} = [(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yzz} + \beta_{yxx})^2 + (\beta_{zzz} + \beta_{zxx} + \beta_{zyy})^2]^{1/2}$$

The total dipole moment (μ), linear polarizability(α) and first order hyperpolarizability(β) from the Gaussian are shown in (Table 5).

Table 5
Values of μ , α and β of Gabapentin

Parameters	RHF/6-31G++(d,p)	B3LYP/6-31G++(d,p)
μ_x	-0.701	-0.6036
μ_y	0.6118	0.4956
μ_z	-0.629	-0.5932
μ	1.1231	0.9808
α_{xx}	113.138	130.3227
α_{xy}	1.3113	0.805
α_{yy}	103.176	116.0033
α_{xz}	0.5828	-0.0132
α_{yz}	-1.8951	-1.7698
α_{zz}	104.9346	115.1955
α_{total}	107.0829	120.5071
$\Delta\alpha$	10.0879	15.1196
β_{xxx}	16.9484	103.676
β_{xxv}	-3.4197	-44.0483
β_{xv}	-0.3214	34.8227
β_{yy}	55.12	67.754
β_{xxz}	4.9481	-10.247
β_{xvz}	-10.9688	-18.3223
β_{vz}	-17.3881	-29.9997
β_{zz}	-32.2893	-32.6939
β_{vzz}	21.8115	23.2663
β_{zzz}	-49.5516	-71.9375
β_{total}	97.4281	176.7489
$\beta_{total(esu)}$	14.4378×10^{-24}	26.1924×10^{-24}

NLO properties of Urea are used as threshold value for comparative purposes as urea is a prototypical molecule in the study of the NLO properties of the molecular systems. The calculated values of μ , α and β of gabapentin by RHF method is 1.1231, 107.0829 and 14.4378×10^{-24} esu and by B3LYP method is 0.9808, 12.5071 and 26.1924×10^{-24} esu respectively. Theoretically, the first order hyperpolarizability of gabapentin is of 64 times the magnitude of urea. These results indicate that the title compound is highly suitable NLO material.

(v) Chemical reactivity

Electron density is a property that contains all of the information about the molecular system and plays an important role in calculating almost all the chemical quantities. The electron

density-based local reactivity descriptors such as Fukui functions have been proposed to explain the chemical selectivity or reactivity at a particular site of a chemical system. Parr and Yang¹⁰ proposed a finite difference approach to calculate Fukui function indices, that is, nucleophilic, electrophilic and radical attacks. The individual atomic charges calculated by Mulliken population analysis have been used to calculate the Fukui function. The DFT calculated Mulliken atomic charge have been used to explain the preferred position of nucleophilic (f_k^+) or electrophilic (f_k^-) attack of gabapentin. In addition to Fukui function the local softness (S_k^+, S_k^-, S_k^0) is also used to describe the reactivity of the molecular system. Fukui function and local softness for selected atomic sites in gabapentin have been listed in the (Table 6).

Table 6
Chemical reactivity of Gabapentin

Atom	f_k^+	f_k^-	f_k^0	Sf_k^+	Sf_k^-	Sf_k^0
C ₁	0.00283	0.00008	0.00275	0.00092	0.00002	0.0009
C ₂	-0.00373	-0.02167	-0.02542	-0.00122	-0.00706	-0.00835
O ₃	-0.01529	-0.13417	-0.14946	-0.00502	-0.04408	-0.0491
O ₄	-0.02137	-0.04578	-0.06715	-0.00702	-0.01504	-0.02206
C ₅	-0.01213	0.05935	-0.04916	-0.00398	0.0195	-0.01615
C ₆	-0.0051	0.00342	-0.00168	-0.00167	0.00111	-0.00054
C ₇	0.00145	-0.00365	-0.0022	0.00047	-0.00172	-0.00072
C ₈	0.00042	0.00526	0.00568	0.00013	0.00178	0.00186
C ₉	-0.00633	-0.00531	-0.01164	-0.00207	-0.00174	-0.00382
C ₁₀	-0.00343	0.008	0.00457	-0.00112	0.00262	0.0015
C ₁₁	-0.01736	0.04131	0.02395	-0.0057	0.01357	0.00786
N ₁₂	-0.02214	-0.41233	-0.43447	-0.00727	-0.13547	-0.14275
H ₁₃	-0.01772	-0.03253	-0.05025	-0.00582	-0.01068	-0.01651
H ₁₄	-0.00727	0.02177	0.0145	-0.00023	0.00715	0.00476
H ₁₅	-0.15895	-0.02153	-0.18048	-0.05222	-0.00707	-0.0593
H ₁₆	-0.03446	-0.01669	-0.05115	-0.01132	-0.00548	-0.0168
H ₁₇	-0.00715	0.00089	-0.00626	-0.00234	0.00029	-0.00205
H ₁₈	-0.01731	-0.03044	-0.04775	-0.00568	-0.01	-0.01664
H ₁₉	-0.00823	-0.00387	-0.0121	-0.0027	-0.00127	-0.00397
H ₂₀	-0.02442	-0.01406	-0.03848	-0.00802	-0.00461	-0.01264
H ₂₁	-0.03392	-0.02924	-0.06316	-0.01114	-0.00916	-0.02075
H ₂₂	-0.03604	-0.02789	-0.06393	-0.01184	-0.00927	-0.021
H ₂₃	-0.03513	-0.0056	-0.04018	-0.01154	-0.00183	-0.0132
H ₂₄	-0.02353	-0.01593	-0.03946	-0.00773	-0.00523	-0.01296
H ₂₅	-0.01839	-0.01673	-0.03512	-0.00604	-0.00549	-0.01152
H ₂₆	-0.08802	-0.03905	-0.12707	-0.02892	-0.01283	-0.04175
H ₂₇	-0.10199	-0.09975	-0.20174	-0.03351	-0.03277	-0.06628
H ₂₈	-0.10546	-0.0324	-0.13786	-0.03465	-0.01064	-0.04529
H ₂₉	-0.17984	-0.03544	-0.21528	-0.05909	-0.01164	-0.07073

From the values reported the highest nucleophilic attack is exclusively on C₇ and C₈ with C₇ > C₈. The electrophilic attack is observed on C₁₀ and H₁₄. The radial attack were on C₈ and H₁₄. S_k^+ , S_k^- and S_k^0 predicts the most nucleophilic and electrophilic and radial attack in a molecule is the one which has the $S_k^{+,-/0}$ value, in turn is the softest region in a molecule.

(vi) ¹³C NMR and ¹H-NMR chemical shift assignments

The ¹³C NMR and ¹H-NMR values were simulated theoretically with the aid of ChemDraw Ultra 10. The experimental and predicted chemical shift values of gabapentin obtained by RHF, DFT - B3LYP and ChemDraw Ultra 10.0 software package and its assignment along with shielding values¹¹ is listed in (Table 7).

Table 7
Chemical shift of Gabapentin

¹³ C Chemical shift					¹ H Chemical shift				
Atom number	RHF/6-311++G(d,p)	B3LYP/6-311++G(d,p)	Chem. Ultra	Exp. Value	Atom number	RHF/6-311++G(d,p)	B3LYP/6-311++G(d,p)	Chem. Ultra	Exp. Value
1	201.003	207.774	177.3	174.334	13	1.864	2.361	2.57	2.5
2	44.083	59.563	47.4	-	14	3.936	4.384	5.11	-
5	43.012	65.705	41.3	-	15	6.788	6.775	5.11	5.74
6	35.375	51.507	32.3	-	16	1.116	1.584	1.49	1.236
7	27.628	42.732	26.6	40.365	17	2.218	2.747	2.57	2.629
8	30.758	45.947	32.3	40.411	18	1.534	1.993	1.46	1.403
9	27.936	43.31	26.3	-	19	1.761	2.2	2.15	2.493
10	41.034	57.98	41.3	-	20	1.309	1.673	1.48	1.396
11	59.707	79.057	47.4	-	21	1.736	2.188	2.15	2.497
					22	1.624	2.116	2.15	2.493
					23	2.003	2.562	2.15	2.503
					24	1.221	1.722	1.48	1.403
					25	1.598	2.139	1.53	2.235
					26	2.18	2.668	2.15	2.507
					27	2.592	3.284	2.57	3.444
					28	1.003	1.235	1.48	1.222
					29	1.218	1.508	1.49	1.403

The (Fig 5 and 6) gives the experimental ¹³C NMR and ¹H-NMR spectrum. In general, highly shielded electrons appear downfield and vice versa. The present study reveals that the

predicted chemical shift values by the theoretical methods RHF, B3LYP are slightly deviates from the computed values of ChemDraw Ultra and the experimental values.

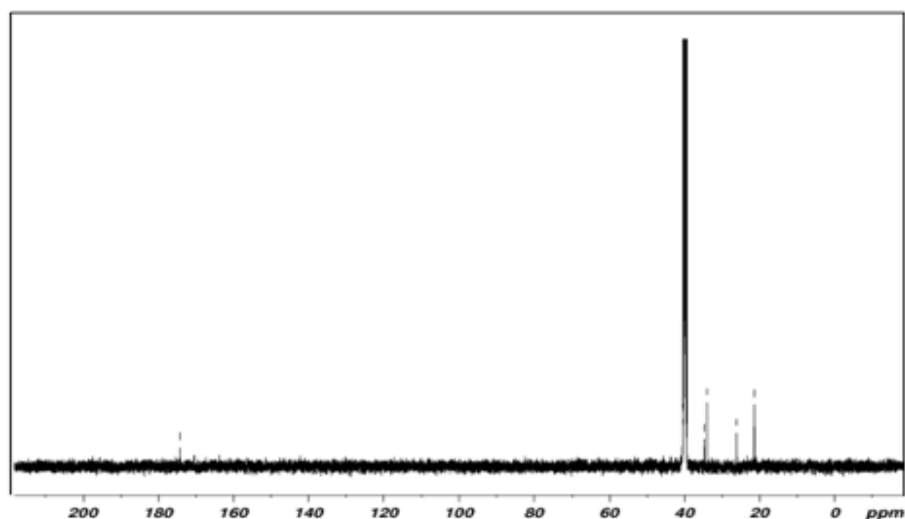


Figure 5
Experimental ¹³C NMR shift of Gabapentin

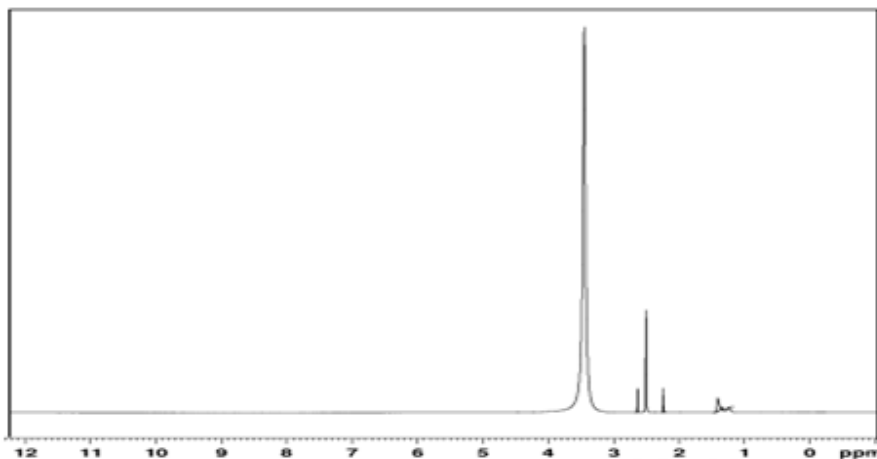


Figure 6
Experimental ¹H NMR shift of Gabapentin

(vii) Thermodynamic properties

The Koopmanns' theorem states that the ionization potential (I) is the negative of the highest occupied molecular orbital (HOMO) energy, $I = -E_{\text{HOMO}}$, and affinity potential (A) is the negative of the lowest unoccupied molecular orbital (LUMO) energy, $A = -E_{\text{LUMO}}$ which are summarized along with the thermodynamic parameters at room temperature in (Table 8). In general, the

HOMO becomes less bound while the LUMO becomes more bound. It is also concluded that the lowest energy gap was found at the B3LYP/6311++G(d,p) basis set and the variation in the entropy and zero point energy seem to be insignificant. The thermal energy of gabapentin is found to be smaller in the B3LYP method.

Table 8
Thermodynamic Parameters of Gabapentin

Parameters	RHF/	B3LYP/
	6-311++G(d,p)	6-311++G(d,p)
Rotational constants(GHz)		
A	1.0095	0.9857
B	0.8552	0.8531
C	0.6425	0.6408
ZPVE(Kcal/mol)	173.89	162.4482
Energy(Kcal/mol)		
Translational	0.889	0.889
Rotational	0.889	0.889
Vibrational	179.498	168.471
Total	181.275	170.248
Heat capacity (Kcal/mol-Kelvin)	44.818	48.204
Entropy (Cal/mol-Kelvin)	110.642	109.665
Dipole moment (Debye)		
μ_x	-2.0291	-1.7072
μ_y	0.8344	1.3672
μ_z	-1.973	-1.4312

CONCLUSION

The optimized molecular structure, Vibrational frequencies, hyperpolarizability and thermodynamic properties of gabapentin are calculated by RHF and DFT based B3LYP levels. The optimized geometric parameters theoretically determined were compared with the available experimental data. The Vibrational FTIR and FT-Raman spectra are recorded and

on the basis of agreement between the calculated and experimental results, the assignments of all the fundamental Vibrational modes were made based on the results of PED output obtained by normal coordinate analysis. Hyperpolarizability, chemical reactivity, ^1H NMR, ^{13}C NMR and thermodynamic properties at room temperature of gabapentin are calculated.

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