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VIBRATIONAL (FT-IR AND FT-RAMAN) SPECTROSCOPIC STUDIES USING AB INITIO (HF) AND DFT (B3LYP) CALCULATIONS OF PARACETAMOL

JAMELAH S. AL-OTAIBI*

Department of Chemistry, College of Science, Princess Nourahbint Abdulrahman University, Riyadh 11951, Saudi Arabia

***To corresponding author: e-mail: dr.jamelah@gmail.com**

ABSTRACT

The FT-IR and FT-Raman spectra for paracetamol have been recorded and compared with the harmonic vibrational frequencies calculated using Ab initio (HF) and DFT(B3LYP) methods with 6-311++G (d,p) basis set. IR intensities and Raman activities are also calculated by HF and B3LYP methods. Optimized geometries of the molecule have been interpreted and compared with the reported experimental values. The calculated frequencies are scaled and compared with experimental values. The scaled B3LYP/6 311++G (d,p) results show the best agreement with the experimental values.

Keywords: FT-IR, FT-Raman, Ab initio, DFT, paracetamol

INTRODUCTION

Paracetamol [N-(4-Hydroxyphenyl) ethanamide] or acetaminophen (in United States) is an analgesic and antipyretic drug, widely used for pain (back and neck) and fever for approximately 50 years and has relatively few side effects [1,2]. However, it is ineffective in the pain originating from smooth muscle spasm in internal organs. Several guidelines published in Australia, New Zealand, and Europe consistently recommend the prescription of paracetamol for chronic low back pain [1,3]. Hence, it became one of the most popular and extensively used drug in the world for the treatment of pain and fever; especially for children. Initial literature report suggests that paracetamol acts through cyclooxygenases enzyme inhibition. In addition, a recent study showed a new mechanism of action i.e. indirect activation of cannabinoid CB1 receptors in brain and spinal cord [2,4].It is a major ingredient in numerous cold and flu remedies and is commonly used for the relief of headaches

and other minor aches and pains. In combination with opioid analgesics, paracetamol can also be used in the control of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients [5].

The structural formulas and some physicochemical properties of this compound have been known for decades. Detailed investigations of their crystal forms, however, were started in recent years [6-13].For paracetamol, three polymorphic modifications were described [6, 14, 15]. Low temperature [8-11] and high-pressure [12, 13] diffraction experiments indicate that an important role in crystal structure formation for paracetamol modifications is played by the OH…O and NH…O intermolecular hydrogen bonds [6-13]. few works reporting the IR spectra of paracetamol are available[16]. Literature survey revealed that IR [17-21] and Raman [22, 23] studies of Paracetamol have been reported. In spite of these numerous applications and consequent interest in their qualitative and quantitative characterization, However, to the best of our knowledge, according to literature survey there is no results based on quantum chemical calculations of paracetamol compound. Investigations on structure of paracetamol have been subjects of great interest because of pharmacological uses. Hence in the present work, we reported interpretations of the infrared and Raman spectra based on the experimental and theoretical results. Reconsidering the vibrational analysis of paracetamol with more accurate FT-IR and FT-Raman measurements and highly accurate simulation programs lead to new improved vibrational assignments.

Experimental details

The paracetamol sample was purchased from Sigma–Aldrich with a stated purity of 99% and were used without further purification. FT-IR spectrum of paracetamolhas been recorded in the region 4000-400 cm^{-1} using a Thermo Nicolet Nexus 870 FT-IR instrument. The instrument is equipped with a KBr beam splitter and an In GaAs detector. The spectral resolution is ±2 cm^{-1}. The Raman spectrum was measured using a dispersive Nexus 870 FT-Raman instrument. The instrument is equipped with Nd:YAG laser source operating at 1.064 μm line widths with 200 mW powers. The spectra were recorded with scanning speed of 30 cm^{-1} min^{-1} of spectral width 2 cm^{-1}.

Computational details

The molecular structure optimization of Paracetamolcompound and corresponding vibrational frequencies were calculated using Hartree-Fock (HF) and the Density Functional Theory (DFT) with Beckee-3-

Lee-Yag-Parr (B3LYP) combined with 6-311++G(d,p) basis set using GAUSSIAN 03W program package without any constraint on the geometry[24]. Geometries have been first optimized with full relaxation on the potential energy surfaces at HF/6-311++g(d,p) level. The geometry was then re-optimized at B3LYP/6-311++g(d,p) level. The optimized geometrical parameters, fundamental vibrational frequencies, IR intensity and Ramanactivity were calculated using the GAUSSIAN 03W program package. By combining the results of the GAUSS-VIEW program [25] with symmetry considerations, along with the available related molecules, vibrational frequency assignments were made with a high degree of accuracy. However, the defined coordinate form complete set and matches quite well with the motions observed using the GAUSS-VIEW program.

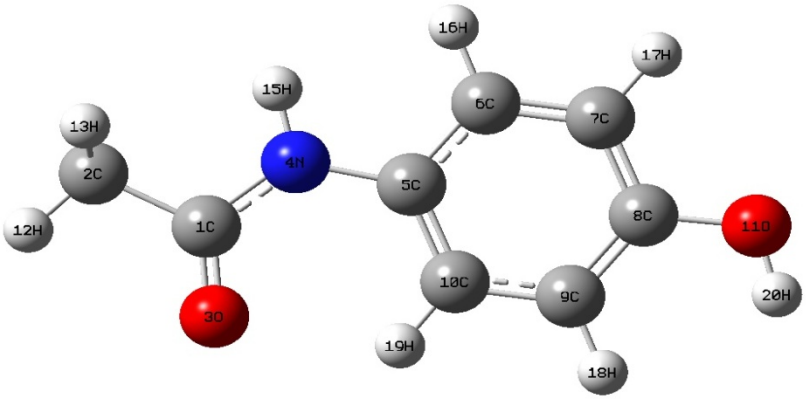

Fig. 1: Optimized geometry of paracetamol structure and atoms numbering.

RESULTS AND DISCUSSION

Molecular geometry

The molecular structure along with numbering of atoms of paracetamol is obtained from GAUSS-VIEW program is as shown in Fig. 1. Optimized geometrical parameters (bond length and bond angle) calculated by HF/6-311G++(d,p) and B3LYP/6-311G++(d,p) are represented in Table 1. The global minimum energy obtained by Ab initio/ HF and DFT/ B3LYP structure optimization using 6-311++G(d,p) basis set for paracetamolas -512.5112526 and -515.6370377 a.u., respectively.

From Table 1, the C-H bond lengths are shorter than experimental values (1.081Å) for HF method, While for B3LYP the C-H bond lengths are in good agreement with experimental values. C-C bond lengths are

calculated by HF method are little shorter than B3LYP method compared with experimental value. Bond length of C5-C6 for HF is 1.392 Å which is closer to the experimental data (1.395 Å), the other C-C bonds are less than 1.392 Å, While for B3LYP all C-C bonds are in good agreement with experimental value. The average bond distances of C-C and C-H in the aromatic ring calculated by B3LYP method are 1.394 and 1.083 Å, respectively. The bond lengths of C-C bond are differing in value, which is due to the substitutions on the benzene ring in the place of hydrogen atom.

The optimized N-H bond length are calculated 0.992 Å and 1.009 Åby HF and B3LYP with 6-311++G(d,p) basis set, respectively. By comparing those values with experimental value of 1.001 Å, it is observed that B3LYP estimate the N-H bond length better than HF, which underestimates this bond than experimental values. The optimized O–H bond lengths by two methods are 0.940 Å for HF/6-311++G(d,p) and 0.962 Åfor B3LYP/6-311++G(d,p), which are in good agreement with those of reported values of 0.990Å[26]. C-N bond length by two methods are 1.380, 1.385 Å for B3LYP/6-311++ G(d,p) and 1.361, 1.733 Å for HF/6-311++G(d,p) methods. The C-N bond lengths are shorter than experimental values (1.388 Å) and B3LYP values are closer than HF values.

The ring appears little distorted and angles slightly out of perfect hexagonal structure. The asymmetry of the aromatic ring is evident from the positive deviation of C6-C5-C10, C6-C7-C8, C7-C8-C9 and C5-C10-C9 angles which are calculated 119°. The C5-C6-C7, C8-C9-C10 angles are same with 120°[27].

Table 1: Optimized geometrical parameters for paracetamol molecule (bond lengths in A° , angles in °).

Bond length (A°)	HF/6-311++g(d,p)	B3LYP/6-311++g(d,p)	Angles (°)	HF/6-311++g(d,p)	B3LYP/6-311++g(d,p)
C1-C2	1.514	1.521	C2-C1-O3	122.115	122.458
C1-O3	1.194	1.218	C2-C1-N4	113.753	113.692
N4-C1	1.361	1.380	O3-C1-N4	124.131	123.848
C2-H12	1.079	1.087	C1-C2-H12	108.662	108.422
C2-H13	1.075	1.083	C1-C2-H13	110.565	111.099
C2-H14	1.075	1.083	C1-C2-H14	110.568	111.104
N4-C5	1.733	1.385	H12-C2-H13	109.366	109.044
N4-H15	0.992	1.009	H12-C2-H14	109.367	109.046
C5-C6	1.392	1.399	H13-C2-C14	108.291	108.083
C5-C10	1.385	1.398	C1-N4-C5	129.099	129.275
C6-C7	1.379	1.387	C1-N4-H15	116.016	115.940
C6-H16	1.077	1.086	C-N4-H15	114.884	114.783
C7-C8	1.385	1.395	N4-C-C6	117.260	117.549
C7-H17	1.074	1.083	N4-C5-C10	124.148	123.624
C8-C9	1.380	1.393	C6-C5-C10	118.591	119.026
C8-O11	1.354	1.371	C5-C6-C7	121.382	120.201

C9-C10	**1.389**	**1.394**	**C5-C6-H16**	**119.795**	**119.774**
C9-H18	**1.077**	**1.086**	**C7-C6-H16**	**118.822**	**119.024**
C10-H19	**1.068**	**1.080**	**C6-C7-C8**	**119.829**	**119.784**
O11-H20	**0.940**	**0.962**	**C6-C7-H17**	**120.748**	**120.876**
			C8-C7-H17	**119.422**	**119.339**
			C7-C8-C9	**119.186**	**119.390**
			C7-C8-O11	**117.762**	**117.503**
			C9-C8-O11	**123.050**	**123.106**
			C8-C9-C10	**121.101**	**120.441**
			C8-C9-H18	**120.056**	**119.996**
			C10-C9-H18	**118.842**	**119.012**
			C5-C10-C9	**119.908**	**119.805**
			C5-C10-H19	**119.284**	**119.687**
			C9-C10-H19	**120.806**	**120.506**
			C8-O11-H20	**109.977**	**109.708**

Vibrational assignments

The paracetamol molecule consists of 20 atoms, which have 54 normal modes of Fundamental Vibrations. All the 54 fundamental vibrations are active in both Raman scattering and Infrared absorption. These molecules belong to the C1 symmetry group. The detailed analysis of fundamental modes of vibration with FT-IR and FT-Raman experimental frequencies are tabulated in Table 2 for paracetamol. Vibrational frequencies, IR intensity and Raman activity of paracetamolusing HF and B3LYP methods with 6-311++G(d,p) basis set is reported in Tables 3. In this study, we followed two different scaling factors [28] viz. 0.89 for HF and 0.96 for B3LYP to correct the theoretical error in this work. The comparative graphs of the observed and simulated FT-IR and FT-Raman spectra for paracetamolare presented in Figs. 2 and 3, respectively. Aromatic C–H stretching vibrations normally occur at 3100–3000 cm^{-1}[29]. The FT-IR band at 3035 cm^{-1} and FT-Raman band at 3033 cm^{-1} assigned to C-H aromatic stretching modes. The calculated frequencies of the C-H symmetric stretching vibrations by B3LYP/6-311++G(d,p) method at 3042 cm^{-1} showed very good agreement with the experimental data. The calculated frequencies 1092 cm^{-1} for the C–H out-of-plane deformation (832 cm^{-1} for the C–H in-plane deformation) falls in the FT-IR values of 1099 cm^{-1} and 838 cm^{-1}, respectively and at 1098 cm^{-1} and 835 cm^{-1} in the FT-Raman spectrum. The stretching vibrational for the aliphatic methyl group appeared at 3110 cm^{-1} (asymmetric stretching) and 2989 cm^{-1} (symmetric stretching) in FT-IR spectrum. In FT-Raman spectrum, two asymmetric and symmetric stretching bands appeared at 3108 cm^{-1} and 2988 cm^{-1}, respectively. The calculated vibration of CH_3 group asymmetric stretching for molecule by B3LYP/6-311++G (d,p) was 3111 cm^{-1}.(2986cm^{-1}symmetric stretching). The CH_3 bending vibration appeared at 1497 cm^{-1} in FT-IR spectrum. The theoretically

calculated values at 1491 cm^{-1} coincide very well with the experimental value. The rocking mode for CH_3 group is calculated at 1027$cm^{-1}$and assigned to the observed peak at 1026 cm^{-1}in FT-IR spectrum and at 1025 cm^{-1}in FT-Raman spectrum.It is well known that, The N–H stretching vibrations occur at the region of 3500–3200 cm^{-1}[30]. The band observed at 3340 cm^{-1} in the FT-IR spectrum (in FT-Raman spectrum 3341 cm^{-1}) was assigned to N–H stretching vibration, this band show best agreement with the predicted value by B3LYP/6-311++G(d,p) level at 3346 cm^{-1}. The N–H deformation vibrations (i.e. in-plane and out-of-plane) calculated at 1248 and 713 cm^{-1} by B3LYP/6-311++G (d,p) level show the best agreement with recorded FT-IR bands at 1240 cm^{-1} (in FT-Raman 1242 cm^{-1}) and 711 cm^{-1} (in FT-Raman 712 cm^{-1}), respectively. The calculated N–H wagging mode at 533 cm^{-1} is assigned to the observed at 521 cm^{-1} in the FT-IR spectrum (in FT-Raman 520 cm^{-1}).The carbonyl stretching vibration is expected in the region 1800–1700 $cm^{-1}$and in the present study, it appeared at 1625 cm^{-1}in the FT-IR spectrum and at 1623 cm^{-1} in the FT-Raman spectrum. The DFT/B3LYP calculations give this band at 1626 cm^{-1}shows correlation with our experimental observation. The C-O asymmetric and symmetric stretching vibration occurred at 1171 $cm^{-1}$and 965 cm^{-1}in FT-IR, respectively. The same band in the FT-Raman spectrum appeared at 1168 cm^{-1} and 965 cm^{-1}, respectively. The computed values at 1179 cm^{-1} for C-O asymmetric stretching vibration and 965 cm^{-1} for C-O symmetric stretching vibration by B3LYP/6-311++G(d,p) exactly correlate with the measured values. Because of the mixing of several bands, the identification of C-N vibrations is a very difficult task. Silverstein assigned C-N stretching absorption in the region 1382–1266 cm^{-1}[31]. In the present work, the bands are observed at 1368 and in FT-IR spectrum has been assigned to C-N stretching vibration. The modes are calculated at 1365 cm^{-1} in B3LYP/6-311++G(d,p) which in good agreement with experimental value.The band in FT-IR spectrum at 3164 cm^{-1} (3161 cm^{-1}in FT-Raman spectrum)is assigned to OH stretching vibration. The calculated value by in B3LYP/6-311++G(d,p) of this vibration at 3165 cm^{-1} shows excellent agreement with experimental results.The ring carbon–carbon stretching vibration occurs in the region 1625–1430 cm^{-1}[32, 33]. In the present work, the frequencies observed in the FT-IR spectrum at 1610 cm^{-1} (1613 cm^{-1} in FT-Raman) and predicted frequency by BLYP/6-311++G(d,p) at 1612 cm^{-1} were assigned to C–C stretching vibrations. The

bands at 693 cm^{-1} and 514 cm^{-1} in FT-IR (691 cm^{-1} and 515 cm^{-1} in FT-Raman) and the calculated value of 682 cm^{-1} and 513 cm^{-1} are assigned to C–C–C deformation of phenyl ring.

Table 2: Experimental FT-IR, FT-Raman frequencies and assignment for paracetamol.

FT-IR frequency (cm^{-1})	FT-Raman frequency (cm^{-1})	Assignment
3340	**3341**	**N-H stretch**
3164	**3161**	**OH stretch**
3110	3108	**CH_3 asym stretch**
3035	**30**33	**C-H stretch**
2989	2988	**CH_3 sym stretch**
1625	**1623**	**C=O stretch**
1610	**1613**	**C=C stretch**
1497	**-**	**CH_3 bend**
1368	**-**	**C-N stretch**
1240	**1242**	**N-H (ip) deformation**
1171	**1168**	**C-O asym stretch**
1099	1098	**C-H (ip) deformation**
1026	**1025**	**CH_3 rocking**
965	**965**	**C-O sym stretch**
838	835	**C-H (op) deformation**
711	**712**	**N-H (op) deformation**
693	**691**	**C-C-C deformation**
521	**520**	**N-H Wagging**
514	**515**	**C-C-C deformation**

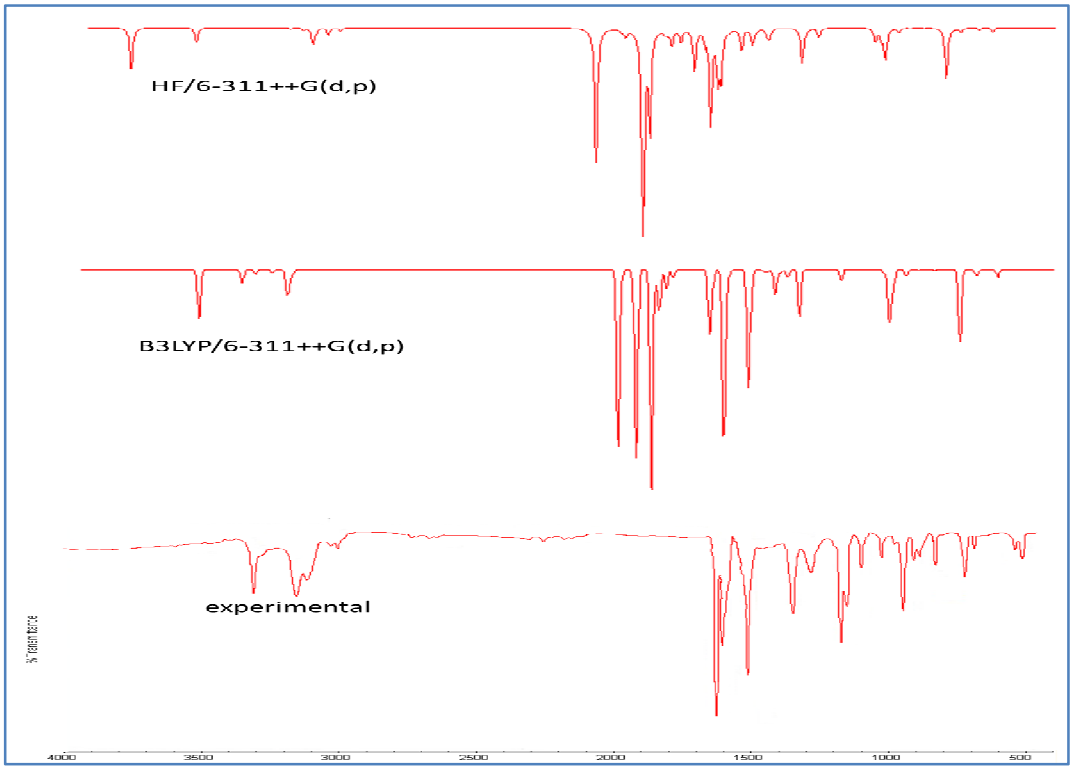

Fig. 2. Comparison of experimental and calculated IR spectra ofparacetamol

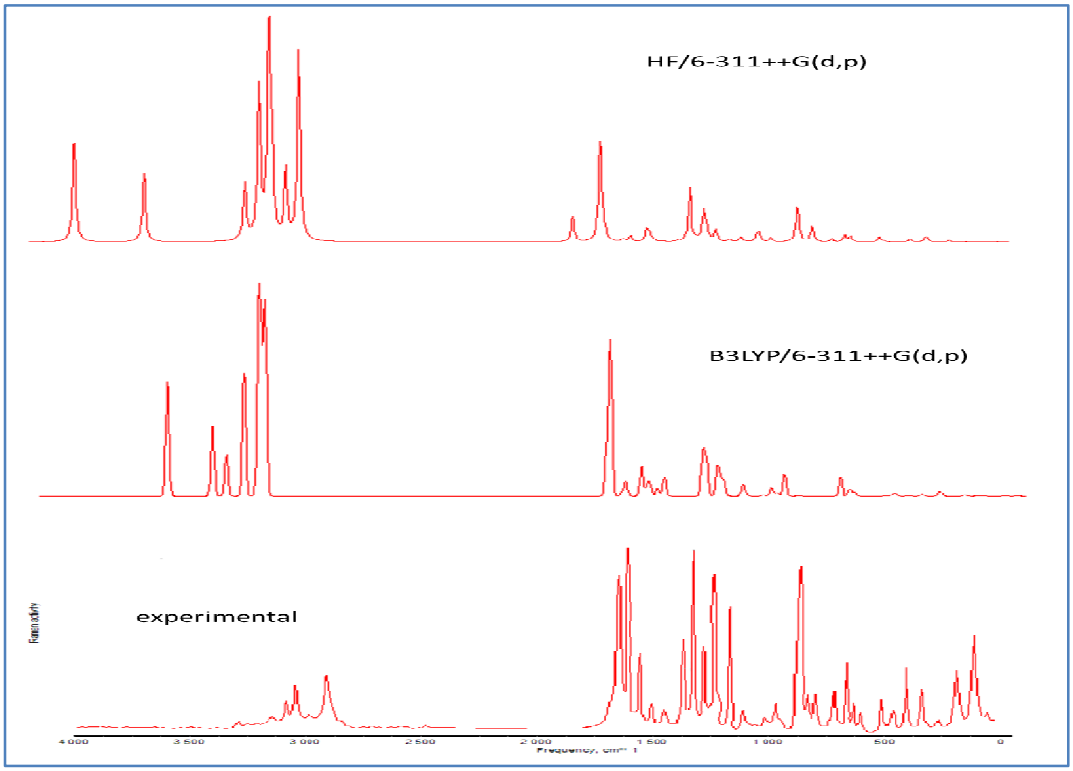

Fig. 3. Comparison of experimental and calculated Raman spectra of paracetamol

Table 3: calculated fundamental frequencies at HF/6-311++g(d,p) and B3LYP/6-311++g(d,p)levels calculated vibrational frequencies for paracetamol.

Mode of vibration	Calculated frequency (cm^{-1})							
	HF/6-311++g(d,p)				B3LYP/6-311++g(d,p)			
	Wave number		IR intensity	Raman activity	Wave number		IR intensity	Raman activity
	Unscaled	Scaled			Unscaled	Scaled		
1	4196	3734	104.25	85.39	3485	3346	106.79	81.23
2	3888	3460	34.58	53.75	3297	3165	34.12	53.62
3	3442	3063	4.40	46.81	3241	3111	33.90	45.65
4	3378	3006	6.73	124.42	3169	3042	17.29	45.65
5	3335	2968	7.30	146.13	3110	2986	66.66	122.99
6	3332	2965	31.26	20.33	3108	2984	3.73	7.52
7	3320	2955	8.98	77.32	3101	2977	10.81	74.04
8	3255	2897	16.13	57.80	3097	2973	1.26	53.94
9	3194	2843	9.15	142.06	3084	2961	8.81	151.40
10	1942	1728	320.74	20.09	1694	1626	328.89	19.59
11	1820	1620	5.22	79.86	1679	1612	522.82	79.13
12	1798	1600	18.81	5.70	1632	1567	18.54	5.57
13	1715	1526	530.32	2.19	1617	1552	5.13	2.20
14	1684	1499	248.70	4.58	1553	1491	246.62	4.31
1	1607	1430	9.01	11.16	1531	1470	8.98	9.18
16	1594	1419	7.91	7.00	1523	1462	10.23	6.15
17	1576	1403	42.18	1.21	1519	1458	39.25	0.95
18	1535	1366	32.50	0.58	1489	1429	32.84	0.31
19	1466	1305	100.80	1.11	1422	1365	102.20	0.96
20	1416	1260	28.59	42.40	1300	1248	242.16	42.35
21	1385	1233	247.04	2.22	1286	1235	32.66	2.13
22	1347	1199	68.55	28.69	1241	1191	11.84	23.67
23	1326	1180	128.87	5.25	1228	1179	116.08	8.89
24	1293	1151	3.51	8.79	1215	1166	4.00	8.89
25	1233	1097	74.09	2.28	1137	1092	54.25	2.01
26	1190	1059	41.01	3.51	1124	1079	5.51	3.84
27	1157	1030	5.44	0.33	1070	1027	41.27	0.25
28	1110	988	13.44	3.25	1055	1013	15.40	3.64
29	1097	976	20.07	7.87	1023	982	1.65	7.38
30	1094	974	1.38	0.07	1005	965	23.58	0.05

31	1060	943	0.30	0.06	1000	960	0.71	0.03
32	1042	927	0.26	2.85	991	951	0.30	2.89
33	942	838	98.13	0.12	970	931	8.99	0.09
34	924	822	3.96	28.52	867	832	4.24	27.87
35	918	817	3.31	0.95	912	876	2.46	0.56
36	857	763	23.34	12.13	743	713	23.13	12.02
37	777	692	0.01	3.12	710	682	29.65	2.34
38	709	631	0.28	5.59	700	672	0.28	5.40
39	682	607	0.34	3.81	682	655	0.29	3.93
40	665	592	0.01	0.64	555	533	73.46	0.74
41	576	513	33.42	0.08	534	513	31.25	0.07
42	547	487	29.37	3.64	527	506	0.05	3.77
43	544	484	77.53	1.07	517	496	3.26	0.92
44	463	412	11.59	0.15	462	444	11.18	0.13
45	461	410	0.00	0.05	458	440	0.00	0.07
46	410	365	1.49	2.96	409	393	1.55	2.38
47	342	304	0.86	2.02	341	327	0.81	1.86
48	336	299	0.19	3.23	334	321	0.22	3.24
49	259	231	131.59	1.74	235	226	12.28	1.34
50	190	169	0.31	0.03	189	181	1.31	0.02
51	166	148	10.31	0.26	164	157	9.96	0.27
52	77	69	5.76	0.21	76	73	5.73	0.20
53	46	41	9.89	0.54	69	66	0.16	0.13
54	16	14	0.07	0.11	18	17	9.98	0.53

Atomic charges

Mulliken atomic charges of paracetamol molecule have been calculated using HF and B3LYP method with 6-311++G(d,p) basis set are combined in Table 4. The calculated charges by B3LYP are relatively lesser than HF method. The atomic charge of C1 in paracetamol is 0.541 and 0.321 using B3LYP/6-311++G(d,p) and HF/6-311++G(d,p), respectively. The maximum atomic charge is obtained for C1 when compare with other atoms in paracetamolmolecule. Illustration of atomic charges plotted for HF and B3LYP method with 6-311++G(d,p) basis set has been shown in Fig. 4.

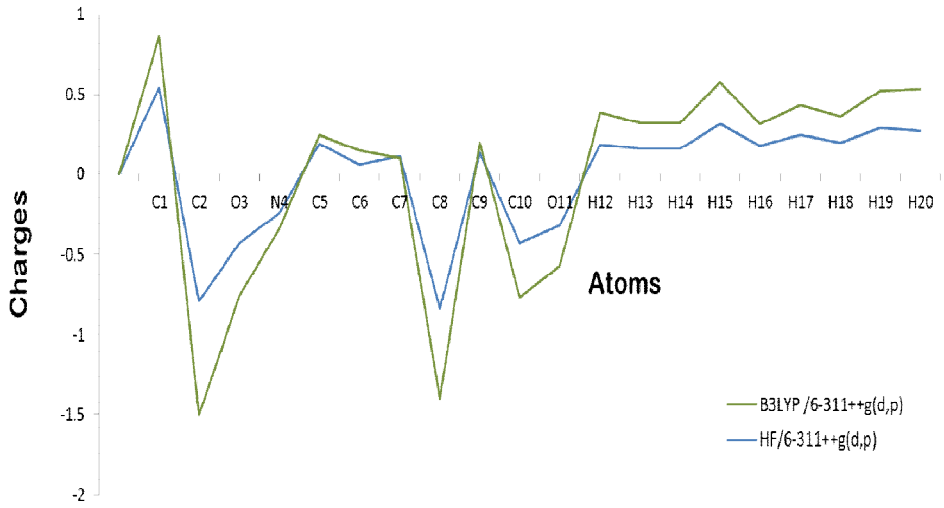

Fig. 4. The atomic charges for paracetamol

Table 4: Mulliken's atomic charges of paracetamolmolecule at HF and B3LYP methods with 6-311++G(d, p) basis set.

Atoms	HF/6-311++g(d,p)	B3LYP /6-311++g(d,p)
C1	0.541	0.321
C2	-0.792	-0.713
O3	-0.427	-0.331
N4	-0.242	-0.092
C5	0.191	0.057
C6	0.059	0.091
C7	0.114	-0.011
C8	-0.842	-0.558
C9	0.135	0.063
C10	-0.427	-0.340
O11	-0.320	-0.249
H12	0.189	0.196
H13	0.163	0.157
H14	0.163	0.157
H15	0.311	0.268
H16	0.181	0.132
H17	0.244	0.191
H18	0.199	0.162
H19	0.287	0.236
H20	0.272	0.263

Other molecular properties

Several calculated thermodynamic parameters for paracetamol are presented in Table 5. The Zero-Point Vibration Energies (ZPVEs), Rotational constants and the entropy of the molecule were calculated with HF/6-311++G(d,p) and B3LYP/6-311++G(d,p) levels.The variations in the ZPVEs seem to be insignificant. The total energies are found to decrease with the increase of the level. The changes in the total entropy of paracetamol at room temperature at HF/6-311++G and B3LYP/6-311++G (d, p) levels are only marginal.

Table 5: Theoretically computed total energies (a.u.), zero-point vibrational energies (kcal mol^{-1}), rotational constants (GHz) and entropies (cal mol^{-1} K^{-1}) for paracetamol.

Parameters	HF/ 6-31++(d,p)	B3LYP/ 6-31++(d,p)
Total energy	-512.5112526	-515.6370377
Zero-point energy	100.16344	99.18875
Rotational constants	3.69618	3.61265
	0.54916	0.54337
	0.47954	0.47372
Entropy		
Total	98.500	97.666
Translational	40.948	40.948
Rotational	30.181	30.226
Vibrational	27.371	26.492

CONCLUSION

The FT-IR and FT-Raman spectra of paracetamol were studied. The molecular geometry and vibrational wavenumbers have been calculated using Ab initio/HF and DFT/B3LYP levels with 6-

311++G(d,p) basis set. The assignments proposed at B3LYP level of theory with 6-311++G(d,p) basis set with only reasonable deviations from the experimental values seem to be correct. All the data have been compared with exact experimental values and shown to have a good agreement with each other. The Mulliken's atomic charges of paracetamol were also discussed elaborately.

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