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Vibrational spectroscopic investigation of ipolamiide using QM/MM method

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ABSTRACT

The combination of Quantum Mechanics (QM) and Molecular Mechanics (MM) methods has become an alternative tool for many applications for which pure QM and MM are not suitable. The QM/MM method has been used for different types of problems, for example: structural biology, surface phenomena, and liquid phase. In this paper we have used this method on the molecular structure of ipolamiide. The equilibrium geometry, harmonic vibrational frequencies and Raman activities were calculated by QM/MM method with B3LYP/6-31G(d,p) and universal force field (UFF) combination using ONIOM code. We found the geometry obtained by the QM/MM method to be very accurate, and we can use this rapid method in place of time consuming ab initio methods for large molecules. A detailed interpretation of the Raman spectra of ipolamiide is reported. The scaled theoretical wave numbers are in perfect agreement with the experimental values. The FT-Raman spectra of ipolamiide has been taken from the literatures.

KEYWORDS

QM/MM method;
FT-Raman spectra;
Ipolamiide;
Vibrational spectra;
DFT;
UFF.

INTRODUCTION

The iridoid glycosides represent a large group of cyclopentano[c]pyran monoterpenoids and are found as natural constituents in a large number of plant families. They have been shown to possess various biological activities such as antimicrobial, antitumoral, hemodynamic, choleretic, and hepatoprotective, as well as being anti-inflammatory agents[1]. Ipolamiide is isolated from Stachytarpheta indica VAHL, which is used locally as an anti-inflammatory agent[2]. Ipolamiide has been also reported to be antinociceptive, anti ulcerogenic, antidiarrheoal as well as sedative and hypotensive[3-8].

Here in the present communication, the experimental FT-Raman frequencies of the title molecule are compared with the theoretical frequencies obtained by QM/MM method with B3LYP/6-31G(d,p) and universal force field (UFF) combination using ONIOM code. To gain a better understanding of the performance and limitation of QM/MM method, as a general approach to the vibrational problems of organic molecules, we calculated harmonic frequencies of ipolamiide by this method and compared these results with the observed fundamental vibrational frequencies. Thus the evaluation of the advantages of this method is useful for obtaining a reliable assignment of the vibrational spectra.

The purpose of this study is important because of further work on ipolamiide, in which presumably some modification by chemical reaction such as oxidation/ reduction on polyfunctional bioactive natural product should possibly generate a new reactive site in the molecule. The aim of this study is to check the performance of QM/MM method for simulation of Raman spectra of title compound with the use of standard B3LYP/6-31G(d,p) method and universal force field (UFF) combination. To the best of our knowledge neither the QM nor the MM calculations for ipolamiide have been reported so far in the literature.

EXPERIMENTAL

The FT-Raman Spectra of ipolamiide has been taken from the literature[9]. The FT-Raman Spectra of title molecule in the region 3500-250 cm^{-1} is shown in Figure 1.

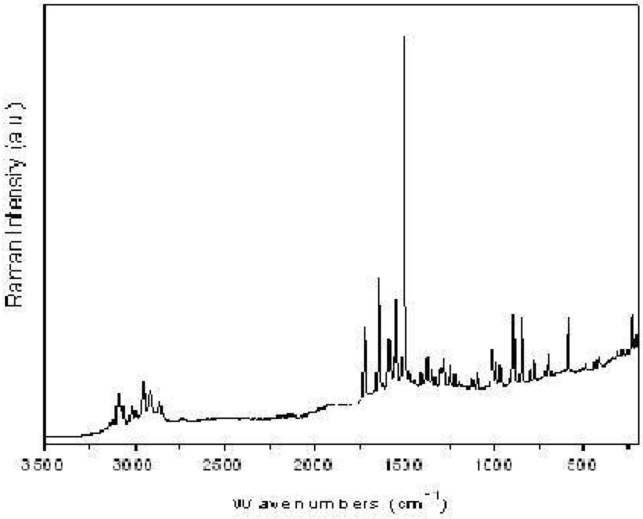

Figure 1 : FT-Raman spectra of ipolamiide

THEORETICAL APPROACH AND COMPUTATIONAL DETAILS

ONIOM is the hybrid method of Morokuma and co-workers that enables different levels of theory to be applied to different parts of a molecule/system and combined to produce a consistent energy expression. The objective is to perform a high-level calculation on just a small part of the system and to include the effects of the remainder at lower levels of theory, with the end result being of similar accuracy to a high-level calculation on the full system[10-12].

Figure 2 shows the model molecular structure of ipolamiide. In this molecule, atoms in ring R3 and its adjacent atoms are treated quantum mechanically and these atoms are shown by balls and sticks in figure 2, while the remaining part of the molecule is treated by molecular mechanics method. In molecular mechanics method we have used universal force field (UFF)[13]. UFF correctly predicts the structures of unstrained and uncongested hydrocarbons, silanes, alkenes, saturated amines, saturated ethers and phosphines, aromatic systems, and simple unconjugated multiple bond containing compounds such as nitriles, ketones, and imines well[14].

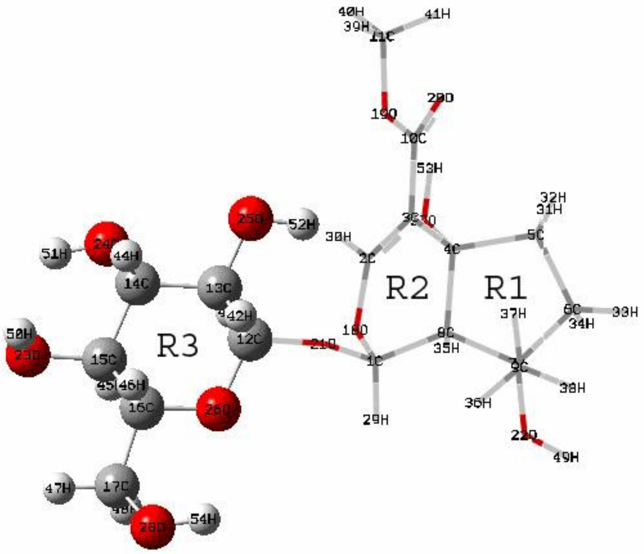

Figure 2 : Model molecular structure of ipolamiide

The entire calculations were performed on a Pentium IV/1.66 GHZ personal computer using Gaussian 03W[15] program package, invoking gradient geometry optimization[16]. Initial geometry was generated from standard geometrical parameters and was minimized without any constraint in the potential energy surface at B3LYP level and UFF combination, adopting the standard 6-31G(d,p) basis set. The optimized structural parameters were used in the vibrational frequency calculations to characterize all the stationary points as minima. We have utilized the gradient corrected density functional theory (DFT)[17] with the three-parameter hybrid functional (B3LYP)[18] for the exchange part and the Lee-Yang-Parr (LYP) correlation function[19], for the computation of molecular structure, vibrational frequencies, and energies of the optimized structures. Density functional theory offers electron correlation which is frequently comparable to second-order Moller-Plesset theory (MP2)[20,21]. Vibrational frequencies calculated at B3LYP/6-31G(d,p) level and UFF combination below 800 cm^{-1} were scaled by a factor of 1.0013 and above 800 cm^{-1} were scaled by a factor of 0.9613[22]. By combining the result of GAUSSVIEW program[23] with symmetry considerations, vibrational frequency assignments were made with a high degree of accuracy. There is always some ambiguity in defining internal coordination. However, the defined coordinate form complete set and matches quite well with the motions observed using the GAUSSVIEW program.

RESULTS AND DISCUSSION

Geometry optimization

The optimized structural parameters of ipolamiide calculated by QM/MM with B3LYP method and UFF combination with the 6-31G(d,p) basis set are listed in TABLE 1 in accordance with the atom numbering scheme given in Figure 2. Experimental values of various bond lengths and bond angles of ipolamiide were taken from the literature[2]. For example, the optimized bond lengths of C-C in ring R1 fall in the range from 1.539Å to 1.571Å, in good agreement with those of the experimental bond lengths [1.529Å -1.550Å]. The optimized bond lengths of C-C in ring R2 fall in the range from 1.345Å to 1.549Å, also in good agreement with those of the experimental bond lengths [1.332Å-1.546Å]. The optimized bond lengths of C-C in ring R3 fall in the range from 1.524Å to 1.538Å, also in good agreement with those of the experimental bond lengths [1.507Å-1.532Å]. The optimized bond lengths of C-O in ring R2&R3 fall in the range from 1.352Å to 1.438Å, also in good agreement with those of the experimental bond lengths [1.362Å-1.437Å]. The optimized bond lengths of C-O adjacent to the ring R1,R2&R3 fall in the range from 1.349Å to 1.439Å, also in good agreement with those of the experimental bond lengths [1.340Å-1.447Å]. The optimized C = O bond length is 1.225Å, also in excellent agreement with the experimental value 1.208Å. The values of other calculated bond lengths, bond angles and dihedral angles are given in TABLE 1 and they are in excellent agreement with experimental values. Thus, although there are some difference between the theoretical values and experimental values, the optimized structural parameters can well reproduce the experimental ones and they are the basis for the thereafter discussion.

Vibrational assignments

Ipolamiide has 54 atoms and 156 normal modes of fundamental vibration. All of the 156 fundamental vibrations are Raman active. Detailed description of vibrational modes can be given by means of normal coordinate analysis. The detailed vibrational assignments can be analysed by comparing the band positions and intensities observed in FT-Raman spectra with the wave numbers and intensities obtained from the QM/MM calculations given in TABLE 2.

The experimental FT-Raman spectra is shown in Figure 1. The descriptions concerning the assignment have been listed in TABLE 2. Gauss View Program[23] was used for the assignment of the calculated frequencies. The observed frequencies for various modes of vibrations are also presented in TABLE 2.

Carbonyl absorption

Carbonyl absorptions are sensitive and both the carbon and oxygen atoms of the carbonyl group move during the vibration and they have nearly equal amplitudes. In the present study the C=O stretching vibrations is observed at 1715 cm^{-1}, which are in agreement with the calculated frequency obtained at 1689 cm^{-1}.

C-H vibrations

The hetero aromatic structure shows the presence of C-H stretching vibrations in the region 3000-3100 cm^{-1}, which is the characteristic region for the ready identification of the C-H stretching vibration[24]. In the present study the C-H stretching vibration of the title compound are observed at 3085 and 2855 cm^{-1}, in good agreement with the calculated frequencies obtained at 3103 and 2840 cm^{-1}. Some other C-H stretching vibrations are also calculated at 2982, 2976, 2960, 2909, 2894 and 2807 cm^{-1}, which are supported by the literature[24]. Some bending vibrations of C-H are also calculated and supported by the literature[24].

TABLE 1 : Optimized geometrical parameters of ipolamiide

S. No	Parameters	X-ray	Calculated	S. No	Parameters	Calculated
	Bond lengths (Å)				**Dihedral angles (degree)**	
1	C1-C8	1.506	1.520	1	O18-C1-C8-C4	-48.5
2	C1-O18	1.434	1.438	2	O18-C1-C8-C7	78.0
3	C1-O21	1.414	1.413	3	O18-C1-C8-H35	-164.8
4	C1-H29		1.093	4	O21-C1-C8-C4	73.0
5	C2-C3	1.332	1.345	5	O21-C1-C8-C7	-160.5
6	C2-O18	1.362	1.352	6	O21-C1-C8-H35	-43.4
7	C2-H30		1.084	7	H29-C1-C8-C4	-166.3
8	C3-C4	1.513	1.518	8	H29-C1-C8-C7	-39.8
9	C3-C10	1.470	1.471	9	H29-C1-C8-H35	77.3
10	C4-C5	1.550	1.571	10	C8-C1-O18-C2	40.7
11	C4-C8	1.546	1.549	11	O21-C1-O18-C2	-76.6
12	C4-O27	1.441	1.437	12	H29-C1-O18-C2	163.6
13	C5-C6	1.534	1.539	13	C8-C1-O21-C12	-158.9
14	C5-H31		1.094	14	O18-C1-O21-C12	-36.2
15	C5-H32		1.092	15	H29-C1-O21-C12	79.2
16	C6-C7	1.529	1.545	16	O18-C2-C3-C4	-1.2
17	C6-H33		1.095	17	O18-C2-C3-C10	173.0
18	C6-H34		1.095	18	H30-C2-C3-C4	178.4
19	C7-C8	1.548	1.546	19	H30-C2-C3-C10	-7.4
20	C7-C9	1.519	1.535	20	C3-C2-O18-C1	-16.1
21	C7-O22	1.442	1.430	21	H30-C2-O18-C1	164.2
22	C5-H35		1.094	22	C2-C3-C4-C5	-123.1
23	C9-H36		1.093	23	C2-C3-C4-C8	-7.2
24	C9-H37		1.093	24	C2-C3-C4-O27	112.6
25	C9-H38		1.097	25	C10-C3-C4-C5	62.4
26	C10-O19	1.340	1.349	26	C10-C3-C4-C8	178.3
27	C10 = O20	1.208	1.225	27	C10-C3-C4-O27	-61.8
28	C11-O19	1.447	1.439	28	C2-C3-C10-O19	14.0
29	C11-H39		1.089	29	C2-C3-C10-O20	-165.3
30	C11-H40		1.092	30	C4-C3-C10-O19	-171.5
31	C11-H41		1.092	31	C4-C3-C10-O20	9.3
32	C12-C13	1.507	1.538	32	C3-C4-C5-C6	126.0
33	C12-O21	1.403	1.394	33	C3-C4-C5-H31	5.7
34	C12-O26	1.424	1.422	34	C3-C4-C5-H32	-112.1
35	C12-H42		1.100	35	C8-C4-C5-C6	5.8
36	C13-C14	1.520	1.524	36	C8-C4-C5-H31	-114.5
37	C13-O25	1.424	1.410	37	C8-C4-C5-H32	127.7
38	C13-H43		1.101	38	O27-C4-C5-C6	-111.0
39	C14-C15	1.512	1.538	39	O27-C4-C5-H31	128.7
40	C14-O24	1.429	1.413	40	O27-C4-C5-H32	10.9
41	C14-H44		1.108	41	C3-C4-C8-C1	31.1
42	C15-C16	1.532	1.534	42	C3-C4-C8-C7	-100.7
43	C15-O23	1.435	1.430	43	C3-C4-C8-H35	146.9

S. No	Parameters	X-ray	Calculated	S. No	Parameters	Calculated
44	C15-H45		1.096	44	C5-C4-C8-C1	152.0
45	C16-C17	1.510	1.524	45	C5-C4-C8-C7	20.2
46	C16-O26	1.437	1.434	46	C5-C4-C8-H35	-92.1
47	C16-H46		1.106	47	O27-C4-C8-C1	-89.2
48	C17-O28	1.427	1.415	48	O27-C4-C8-C7	139.0
49	C17-H47		1.093	49	O27-C4-C8-H35	26.6
50	C17-H48		1.102	50	C3-C4-O27-H53	59.4
51	O22-H49		0.967	51	C5-C4-O27-H53	-65.3
52	O23-H50		0.969	52	C8-C4-O27-H53	-179.2
53	O24-H51		0.969	53	C4-C5-C6-C7	-29.6
54	O25-H52		0.975	54	C4-C5-C6-H33	-152.9
55	O27-H53		0.974	55	C4-C5-C6-H34	86.0
56	O28-H54		0.968	56	H31-C5-C6-C7	90.5
	Bond Angles (degree)			57	H31-C5-C6-H33	-32.8
1	C8-C1-O18	114.4	113.4	58	H31-C5-C6-H34	-153.9
2	C8-C1-O21	106.3	104.3	59	H32-C5-C6-C7	-149.6
3	C8-C1-H29		112.9	60	H32-C5-C6-H33	87.2
4	O18-C1-O21	109.6	111.5	61	H32-C5-C6-H34	-33.9
5	O18-C1-H29		103.9	62	C5-C6-C7-C8	41.0
6	O21-C1-H29		111.1	63	C5-C6-C7-C9	-82.3
7	C3-C2-O18	127.1	125.3	64	C5-C6-C7-O22	153.4
8	C3-C2-H30		122.8	65	H33-C6-C7-C8	164.3
9	O18-C2-H30		111.9	66	H33-C6-C7-C9	41.1
10	C2-C3-C4	121.6	122.1	67	H33-C6-C7-O22	-83.2
11	C2-C3-C10	118.9	121.0	68	H34-C6-C7-C8	-76.9
12	C4-C3-C10	119.3	116.6	69	H34-C6-C7-C9	159.8
13	C3-C4-C5	112.9	112.3	70	H34-C6-C7-O22	35.5
14	C3-C4-C8	111.0	111.1	71	C6-C7-C8-C1	-167.5
15	C3-C4-O27	111.0	109.3	72	C6-C7-C8-C4	-37.9
16	C5-C4-C8	104.1	103.9	73	C6-C7-C8-H35	75.2
17	C5-C4-O27	110.4	111.5	74	C9-C7-C8-C1	-46.9
18	C8-C4-O27	107.0	108.6	75	C9-C7-C8-C4	82.7
19	C4-C5-C6	106.2	106.1	76	C9-C7-C8-H35	-164.1
20	C4-C5-H31		110.5	77	O22-C7-C8-C1	74.4
21	C4-C5-H32		109.6	78	O22-C7-C8-C4	-155.9
22	C6-C5-H31		110.9	79	O22-C7-C8-H35	-42.8
23	C6-C5-H32		112.6	80	C6-C7-C9-H36	176.4
24	H31-C5-H32		107.1	81	C6-C7-C9-H37	54.8
25	C5-C6-C7	102.8	104.8	82	C6-C7-C9-H38	-64.2
26	C5-C6-H33		113.0	83	C8-C7-C9-H36	62.1
27	C5-C6-H34		110.8	84	C8-C7-C9-H37	-59.5
28	C7-C6-H33		112.8	85	C8-C7-C9-H38	-178.5
29	C7-C6-H34		107.5	86	O22-C7-C9-H36	-57.2
30	C33-C6-C34		107.8	87	O22-C7-C9-H37	-178.8
31	C6-C7-C8	100.7	100.6	88	O22-C7-C9-H38	62.2

S. No	Parameters	X-ray	Calculated	S. No	Parameters	Calculated
32	C6-C7-C9	111.9	111.9	89	C6-C7-O22-H49	74.5
33	C6-C7-O22	113.4	113.2	90	C8-C7-O22-H49	-176.3
34	C8-C7-C9	114.4	115.6	91	C9-C7-O22-H49	-51.1
35	C8-C7-O22	111.1	105.8	92	C3-C10-O19-C11	-176.1
36	C9-C7-O22	105.6	109.5	93	O20-C10-O19-C11	3.1
37	C1-C8-C4	115.4	113.7	94	H39-C11-O19-C10	179.3
38	C1-C8-C7	116.8	117.6	95	H40-C11-O19-C10	59.7
39	C1-C8-H35		105.6	96	H41-C11-O19-C10	-61.1
40	C4-C8-C7	105.8	107.2	97	O21-C12-C13-C14	176.1
41	C4-C8-H35		106.5	98	O21-C12-C13-O25	-63.3
42	C7-C8-H35		105.4	99	O21-C12-C13-H43	58.6
43	C7-C9-H36		111.3	100	O26-C12-C13-C14	57.4
44	C7-C9-H37		112.3	101	O26-C12-C13-O25	177.9
45	C7-C9-H38		109.4	102	O26-C12-C13-H43	-60.1
46	H36-C9-H37		108.3	103	H42-C12-C13-C14	-64.4
47	H36-C9-H38		108.1	104	H42-C12-C13-O25	56.2
48	H37-C9-H38		107.3	105	H42-C12-C13-H43	178.1
49	C3-C10-O19	113.3	114.3	106	C13-C12-O21-C1	154.9
50	C3-C10 = O20	124.1	122.9	107	O26-C12-O21-C1	-84.7
51	O19-C10 = O20	122.7	122.8	108	H42-C12-O21-C1	36.3
52	O19-C11-H39		105.5	109	C13-C12-O26-C16	-63.4
53	O19-C11-H40		110.6	110	O21-C12-O26-C16	-179.3
54	O19-C11-H41		110.6	111	H42-C12-O26-C16	58.6
55	H39-C11-H40		110.6	112	C12-C13-C14-C15	-50.9
56	H39-C11-H41		110.6	113	C12-C13-C14-O24	-172.8
57	H40-C11-H41		109.0	114	C12-C13-C14-H44	66.7
58	C13-C12-O21	107.7	104.8	115	O25-C13-C14-C15	-171.2
59	C13-C12-O26	109.7	112.0	116	O25-C13-C14-O24	66.9
60	C13-C12-H42		109.8	117	O25-C13-C14-H44	-53.6
61	O21-C12-O26	108.0	109.6	118	H43-C13-C14-C15	65.8
62	O21-C12-H42		111.2	119	H43-C13-C14-O24	-56.0
63	O26-C12-H42		109.4	120	H43-C13-C14-H44	-176.5
64	C12-C13-C14	109.6	108.9	121	C12-C13-O25-H52	61.6
65	C12-C13-O25	111.8	109.6	122	C14-C13-O25-H52	-178.6
66	C12-C13-H43		107.5	123	H43-C13-O25-H52	-57.6
67	C14-C13-O25	107.4	110.2	124	C13-C14-C15-C16	51.6
68	C14-C13-H43		108.6	125	C13-C14-C15-O23	177.6
69	O25-C13-H43		112.0	126	C13-C14-C15-H45	-68.3
70	C13-C14-C15	111.5	110.3	127	O24-C14-C15-C16	173.4
71	C13-C14-O24	110.9	110.1	128	O24-C14-C15-O23	-60.6
72	C13-C14-H44		107.4	129	O24-C14-C15-H45	53.6
73	C15-C14-O24	109.0	110.2	130	H44-C14-C15-C16	-65.6
74	C15-C14-H44		108.1	131	H44-C14-C15-O23	60.4
75	O24-C14-H44		110.6	132	H44-C14-C15-H45	174.5
76	C14-C15-C16	110.5	112.1	133	C13-C14-O24-H51	165.8

S. No	Parameters	X-ray	Calculated	S. No	Parameters	Calculated
77	C14-C15-O23	108.3	110.0	134	C15-C14-O24-H51	43.8
78	C14-C15-H45		108.1	135	H44-C14-O24-H51	-75.6
79	C16-C15-O23	109.2	112.6	136	C14-C15-C16-C17	-173.5
80	C16-C15-H45		108.8	137	C14-C15-C16-O26	-55.0
81	O23-C15-H45		105.1	138	C14-C15-C16-H46	64.8
82	C15-C16-C17	112.8	113.9	139	O23-C15-C16-C17	61.9
83	C15-C16-O26	109.7	109.4	140	O23-C15-C16-O26	-179.5
84	C15-C16-H46		109.6	141	O23-C15-C16-H46	-59.8
85	C17-C16-O26	105.9	106.1	142	H45-C15-C16-C17	-54.1
86	C17-C16-H46		108.5	143	H45-C15-C16-O26	64.4
87	O26-C16-H46		109.2	144	H45-C15-C16-H46	-175.8
88	C16-C17-O28	112.4	111.3	145	C14-C15-O23-H50	-65.3
89	C16-C17-H47		109.5	146	C16-C15-O23-H50	60.4
90	C16-C17-H48		108.6	147	H45-C15-O23-H50	178.6
91	O28-C17-H47		107.6	148	C15-C16-C17-O28	-179.2
92	O28-C17-H48		111.8	149	C15-C16-C17-H47	-60.3
93	H47-C17-H48		107.9	150	C15-C16-C17-H48	57.3
94	C1-O18-C2	115.4	117.1	151	O26-C16-C17-O28	60.4
95	C10-O19-C11	116.8	115.5	152	O26-C16-C17-H47	179.3
96	C1-O21-C12	116.2	121.9	153	O26-C16-C17-H48	-63.1
97	C7-O22-H49		107.9	154	H46-C16-C17-O28	-56.9
98	C15-O23-H50		107.7	155	H46-C16-C17-H47	62.0
99	C14-O24-H51		105.7	156	H46-C16-C17-H48	179.6
100	C13-O25-H52		107.0	157	C15-C16-O26-C12	60.7
101	C12-O26-C16	111.2	112.0	158	C17-C16-O26-C12	-176.1
102	C4-O27-H53		104.6	159	H46-C16-O26-C12	-59.3
103	C17-O28-H54		105.7	160	C16-C17-O28-H54	-52.9
				161	H47-C17-O28-H54	-172.9
				162	H48-C17-O28-H54	68.7

TABLE 2 : Vibrational wave numbers obtained for ipolamiide in cm^{-1}, experimental frequencies from FT-Raman spectra in cm^{-1}, Raman scattering activities (Å^{4} amu^{-1}) and assignment.

Sr. No	Wave Number		Exp. Freq. FT-Raman	Raman Intensity	Assignment
	Unscal.	Scal.			
1	16	16		0	τ(CO)adj R2&R3+τ(CC)R1,R2&R3
2	19	19		0	τ(CO)adj R2&R3+τ(CC)R1,R2&R3
3	35	35		1	τ(CC)R1,R2&R3+τ(CO)adj R2&R3
4	50	50		0	τ(CC)R1,R3&adj R2+τ(CO)adj R2&R3
5	74	74		1	τ(CC)R1,R2&R3
6	78	78		1	τ(CC)R1,R2&adj R2+τ(CO)adj R2
7	83	83		0	τ(CC)R1,R2,R3&adj R3+τ(CO)adj R2&R3
8	101	101		0	τ(CO)adj R2&R3
9	110	110		0	τ(CO)R3,adj R2&R3+τ(CC)R3&adj R3
10	116	116		0	τ(CO)adj R2&R3+τ(CC)R3

Sr. No	Wave Number		Exp. Freq. FT-Raman	Raman Intensity	Assignment
	Unscal.	Scal.			
11	127	127		0	τ(CO)adj R2+τ(CC)R1,R2&adj R2
12	130	130		0	τ(CO)adj R2&R3+τ(CC)R1,R2&R3
13	137	137		0	τ(CC)R1&adj R1+τ(CO)adj R2
14	151	151		1	τ(CO)R3,adj R3&R2+τ(CC)R1&R2
15	170	170		0	τ(CC)R1,R2&R3+τ(CO)R3&adj R2
16	186	186		1	τ(CO)R3,adj R3&R2+γ(COC)adj R2+τ(CC)R1&adj R2
17	191	191		0	τ(CC)R3,R2,R1&adj R3
18	216	216	220	2	τ(CO)R3,adj R3&R2+τ(CC)R3,R2,R1&adj R3
19	249	249	240	1	τ(CC)R2&adj R1+τ(CO)adj R1
20	255	255		0	τ(CO)R3&adj R3+τ(CC)R3
21	274	274		2	τ(CC)R2,adj R1&R2+τ(CO)adj R2&R3+γ(OH)R1
22	280	280		2	τ(CO)adj R3+τ(CC)adj R1
23	285	285		1	τ(CC)adj R1+γ(OH)R1
24	293	293		0	τ(CC)R3,R1,R2 &adj R1+τ(CO)adj R3&R2
25	303	303	301	2	γ(OH)R1+τ(CC)adj R1
26	305	305		1	τ(CO)adj R3&R2+τ(CC)R2,R3&adj R2&R3+ γ(OH)R1
27	315	315		0	τ(CO)R3&adj R3+τ(CC)R3,R2&R1+ γ(CCO)R3&adj R3+
28	324	324		1	γ(CCO)R2&adj R2+γ(OH)R1+τ(CO)adj R3+ τ(CC)R1,R2&R3
29	333	333	330	2	τ(CC)R1,R2&adj R1&R2+τ(CO)adj R2+γ(OH)R3+ γ(CCO)R2
30	347	347		3	γ(OH)R3+τ(CC)R1&R3+τ(CO)R3,adj R3&R2+ γ(COC)R2+γ(CCC)R2
31	364	364		2	τ(CO)adj R2+γ(OH)R3+γ(CCO)R2&adj R2&R1+ γ(COC)R2+β(COC)adj R2
32	367	367	370	2	γ(OH)R3+τ(CC)R1,R2&R3+τ(CO)adj R3&R2
33	376	376		2	τ(CC)R1&R3+γ(CCO)R2+γ(OH)R3
34	401	401		2	γ(CCC)R3+τ(CC)R3+γ(OH)R3+τ(CO)R3&adj R3
35	422	422		3	γ(CCC)R3+γ(OH)R3+τ(CC)R3+γ(CCO)adj R3+ γ(COC)R3
36	435	435	430	2	γ(OH)R3&R1+γ(CCC)R1,R2&R3+γ(CCO)R2&adj R1+ γ(COC)R2
37	443	443	450	4	γ(OH)R3+γ(CCC)R1,R2&R3+τ(CC)R3+ γ(CCO)R3,R2&adj R3
38	471	471		3	γ(OH)R3+τ(CC)R3+γ(CCC)R1,R2&R3+γ(COC)R2+ γ(CCO)R2,R3&adj R2&R3+
39	477	477		3	γ(OH)R3+γ(CCO)R3,adj R2&R1+γ(CCC)R1,R2&R3+ β(CC=O)+γ(COC)R3
40	479	480		2	γ(OH)R3+γ(CCC)R3&R1+γ(CCO)adj R3+γ(COC)R2
41	488	489		2	γ(OH)R3+γ(CCC)R3,R2&R1+γ(CCO)R3+γ(COC)R3
42	501	502	500	8	γ(COC)R2,R3&adj R2+γ(OH)R3+γ(CCC)R2,R3&R1+ γ(CCO)R2,R3&R1+β(CC=O)
43	538	539		1	γ(CCC)R2,R3&R1+γ(OC=O)+γ(COC)adj R2+ γ(CCO)R3&R1
44	551	552		2	γ(CCC)R2,R3&R1+γ(CCO)R3,R2&adj R1+ γ(COC)R3&R2
45	562	563		2	γ(CCC)R3,R2&R1+γ(COC)R2&R3+γ(CCO)R3&R1+ γ(OH)R2
46	590	591	594	1	γ(CCC)R1,R2&R3+γ(OH)R2+γ(COC)R2&adj R2+ γ(CCO)R3
47	603	604		1	γ(OH)R2+γ(CCC)R3+γ(CCO)R3+γ(COC)R3+
48	617	618		3	γ(OH)R2+γ(CCC)R2&R3+γ(CCO)R2&R3+ ρ(CH$_2$)R1&R3
49	624	625		0	γ(OH)R2&R3+β(OCO)R3+β(COC)R3
50	635	636		1	γ(OH)R3&R2+β(OCO)R3
51	647	648		1	γ(OH)R3&R2+β(CCO)R3&adj R3+β(COC)R3+ β(CCC)R3&R1

Sr. No	Wave Number		Exp. Freq. FT-Raman	Raman Intensity	Assignment
	Unscal.	Scal.			
52	653	654		2	γ(OH)R2&R3+β(CCC)R3&R1+β(CCO)R3+ β(COC)R3+γ(CCC)R3+γ(OC=O)
53	675	676		4	β(OCO)R2+β(COC)R2,adj R2&R3+γ(CCC)R2&R3+ γ(CCO)R2+β(CCC)R1
54	704	705	710	1	β(CCC)R2&R1+β(OC=O)+β(COC)adj R2+ ρ(CH_2)R1+γ(OH)R2
55	750	751	730	8	β(COC)R2+ν(CC)R1+γ(OC=O)+γ(CCO)adj R2+ γ(COC)adj R2
56	776	777		5	γ(OC=O)+γ(CCO)adj R2+γ(CC=O)+γ(CCC)R2&adj R2 +ρ(CH_2)R1+γ(OH)R2
57	787	788		3	γ(OC=O)+γ(CCO)adj R2+γ(CC=O)+γ(CCC)R2&adjR2 +ρ(CH_2)R1
58	820	789	791	3	β(OC=O)+β(COC)R2&adj R2+β(CCO)R2&adj R2+ ρ(CH_3)adj R2
59	852	819	810	3	ρ(CH_2)R1+β(CCC)R1+ν(CC)R2+β(CCO)adj R2
60	879	845		1	ν(CO)R2+β(COC)adj R2+β(OC=O)+β(CCO)adj R2+ β(CCC)R1+ρ(CH_3)adj R2
61	896	861	870	5	ρ(CH_2)R3+ν(CO)R3+β(COC)R3
62	945	909	910	4	γ(CH)R2+γ(CCO)R2+γ(CCC)R2+ρ(CH_2)R1
63	949	912		2	ρ(CH_3)R1+ν(CC)R1+β(CCC)R1
64	955	918		7	γ(CH)R2+ρ(CH_2)R1+ν(CO)adj R2+γ(CCC)R1&R2+ ν(CC)R1
65	978	940	930	6	ρ(CH_3)R1+ν(CO)adj R1+β(CCC)R1,R2&R3+ β(COC)R3
66	984	946		5	ν(CO)adj R2&R1+β(COC)R2&R3+β(CCO)R2+ β(CCC)R2,R1&R3+ρ(CH_2)R1+ν(CC)R1&R3
67	994	955		1	ν(CC)R3&adj R3+ν(CO)adj R3+β(OH)R3+β(CCC)R3+ β(CCO)R3
68	1000	962		5	ν(CC)R1+β(CCC)R1+ν(CO)adj R1
69	1010	971	978	7	ν(CO)adj R2+ν(CC)R1,R2&R3+β(COC)R2&R3+ β(CCO)R2+β(CCC)R1&R2
70	1025	986		2	ν(CC)R1&R2+ν(CO)R2&adj R2+t(CH_2)R1+β(OH)R1+ β(CCO)R2&adj R2+β(COC)R2&adj R2
71	1036	996		3	ν(CO)R3&adj R3+ν(CC)R3&adj R3+β(CCC)R3+ β(CCO)R3+β(COC)R3
72	1063	1022	1023	6	ν(CC)R1+β(CCC)R2&R1+β(COC)R2+β(CCO)R2+ β(OH)R2+t(CH_2)R2
73	1065	1024		4	ν(CC)R3+ν(CO)R3&adj R3+β(OH)R3+β(CCC)R3+ β(CCO)R3+β(COC)R3
74	1072	1031		4	ν(CO)R3&adj R3+β(OH)R3+ν(CC)R3
75	1075	1033		1	ν(CO)R3&adj R3+β(CCO)R3+β(COC)R3+β(CCC)R3+ β(OH)R3
76	1086	1044		4	β(CCC)R1+ν(CO)adj R1&R2+β(CH)R3
77	1099	1057		2	ν(CO)R3&adj R3+ ν(CC)R3&adj R3+β(CCC)R3+ β(CCO)R3+β(COC)R3
78	1102	1059		2	ν(CO)R3,R2&adj R3+ν(CC)R3+β(OH)R3
79	1115	1072		3	ν(CO)R3,R2&adj R2+β(CCC)R1&R2+ ν(CC)R1,R2&R3+β(OH)R1
80	1116	1073		3	ν(CC)R1&R3+β(CCC)R1&R2+ν(CO)R2&adj R1+ t(CH_2)R1
81	1123	1079		9	ν(CC)R3+ν(CO)R3&adj R3&R2+β(CCC)R3&R2+ β(CCO)R3+β(COC)R3+β(OH)R3
82	1131	1087		3	ν(CO)adj R3&R2+β(CCC)R3&R2+β(CCO)R3&R2+ β(COC)R3&R2
83	1135	1091		2	β(OH)R1+ν(CO)adj R1&R2+ν(CC)R1&R3+ β(CCC)R1,R2&R3
84	1139	1095		5	ν(CC)R3+ν(CO)adj R3+β(CCO)R3+β(OH)R1&R3
85	1154	1109	1102	9	ν(CO)adj R3+β(CCC)R3+ ν(CC)R1&R2
86	1160	1115		3	ν(CO)R3,R2&adj R3+ν(CC)R1,R2&R3+ t(CH_2)R1&adj R3+β(OH)R1,R2&R3
87	1177	1132	1130	5	ρ(CH_3)adj R2
88	1192	1146		2	ν(CO)adj R3+ν(CC)R1&R2+R3 breathing+ β(OH)R1&R3+t(CH_2)adj R3+β(CH)R3

Sr. No	Wave Number		Exp. Freq. FT-Raman	Raman Intensity	Assignment
	Unscal.	Scal.			
89	1201	1155		4	β(CH)R3+β(OH)R3+ν(CO)adj R3
90	1212	1166		6	ν(CC)R1+ρ(CH_3)adj R1&R2+β(CH)R1+ν(CO)adj R1
91	1214	1167		8	β(OH)R1+t(CH_2)R1+ν(CC)R1+ω(CH_2)R1
92	1216	1169		6	ω(CH_3)adj R2+ν(CO)R2&adj R2+ν(CC)R1
93	1230	1182		5	t(CH_2)R3&R1+β(CH)R3+β(OH)R3+ν(CO)R2&adj R3
94	1237	1190		2	ν(CO)R2&adj R2&R1+β(CH)R3+t(CH_2)R1&R3+ β(OH)R3
95	1247	1199		4	t(CH_2)R3+β(OH)R3+β(CH)R3
96	1258	1210	1205	4	t(CH_2)R1+ν(CO)R2+ν(CC)R1&R2+ν(CO)adj R1&R2
97	1281	1232	1231	1	β(CH)R3,R2&R1+β(OH)R3
98	1291	1241		3	β(CH)R1,R2&R3+ν(CC)R1+ω(CH_2)R1+β(OH)R3
99	1311	1260	1252	6	β(OH)R3+β(CH)R3+ν(CC)R3
100	1320	1269		5	β(CH)R3&R2+β(OH)R3+ν(CC)R3+ω(CH_2)R1
101	1334	1282		7	β(CH)R2+ν(CO)adj R2+ν(CC)adj R2+ω(CH_2)R1
102	1336	1284		9	ω(CH_2)R1+ν(CO)adj R2+β(CH)R2+ ν(CC)R2&R1
103	1341	1289		3	β(CH)R1&R2+ν(CC)R1+ β(OH)R2
104	1347	1295	1295	12	β(CH)R2&R3+ν(CC)R2&R1+ν(CO)adj R2+ω(CH_3)R3
105	1348	1296	1303	12	β(CH)R3&R2+ω(CH_3)R3+ν(CO)R3+β(OH)R3&R2
106	1377	1324		8	β(CH)R3+ν(CC)R3+β(OH)R3+ν(CO)R3
107	1380	1327		7	β(OH)R1+ν(CC)R1&R2+β(CH)R1&R2+ω(CH_3)adj R1
108	1384	1331		5	β(CH)R2&R3+β(OH)R2&R3+ν(CC)R3+ν(CO)adj R2
109	1390	1337		5	ν(CC)R1,R2&R3+β(CH)R1,R2&R3+β(OH)R1,R2&R3
110	1394	1340		4	β(CH)R3&R2+ν(CC)R2&R3+β(OH)R1&R3
111	1398	1344	1343	14	β(OH)R3+ν(CC)R3+β(CH)R3+t(CH_2)R3
112	1408	1353		9	β(OH)R3+β(CH)R3&R2+ν(CC)R3&R2
113	1417	1362		1	β(OH)R3+β(CH)R3&R2+ν(CC)R3&R2+ν(CO)R3
114	1422	1367		4	β(CH)R2&R3+β(OH)R2&R3+ν(CC)R2&R3
115	1427	1372	1373	6	β(CH)R3+β(OH)R2+β(OH)R3+β(CH)R2+ν(CC)R2
116	1430	1374		3	β(CH)R3+β(OH)R3+ν(CC)adj R1&R2+β(CH)R2
117	1431	1375		2	ω(CH_3)adj R1+ν(CC)adj R1+β(CH)R1&R3
118	1440	1384		4	ω(CH_2)adj R3+β(CH)R3+β(OH)R3+β(CH)R2
119	1444	1388		1	ω(CH_2)adj R3+β(CH)R3+β(OH)R3+β(CH)R2
120	1484	1427	1410	3	β(OH)R3+β(CH)R3+ν(CC)adj R2+ω(CH_3)adj R2
121	1485	1428		3	ω(CH_3)adj R2+ν(CC)adj R2+β(OH)R3+β(CH)R3
122	1487	1429		14	s(CH_2)R1
123	1496	1438	1440	21	s(CH_3)adj R2
124	1505	1447		15	s(CH_3)R1+s(CH_2)R1
125	1510	1452		13	s(CH_3)adj R2
126	1512	1454		4	s(CH_3)R1
127	1516	1457		12	s(CH_2)adj R3
128	1519	1460	1460	10	s(CH_2)R1+s(CH_3)R1
129	1696	1630	1640	32	ν(CC)R2+β(CH)R2
130	1757	1689	1715	62	ν(C=O)+ν(CC)R2+β(OH)adj R2+s(CH_3)adj R2
131	2920	2807		40	ν(CH)R3

Sr. No	Wave Number Unscal.	Wave Number Scal.	Exp. Freq. FT-Raman	Raman Intensity	Assignment
132	2954	2840	2855	75	ν(CH)R3
133	2997	2881		59	ν_s(CH$_2$)adj R3
134	3011	2894		77	ν(CH)R3
135	3026	2909		9	ν(CH)R3
136	3041	2924	2920	94	ν_s(CH$_3$)adj R1
137	3056	2937		126	ν_s(CH$_2$)R1
138	3068	2949	2950	128	ν_s(CH$_3$)adj R2
139	3075	2956		69	ν_s(CH$_2$)R1
140	3080	2960		57	ν(CH)R3
141	3096	2976		40	ν(CH)R2+ν_{as}(CH$_2$)R1
142	3102	2982		100	ν(CH)R2+ν_{as}(CH$_2$)R1
143	3103	2983		68	ν_{as}(CH$_2$)R1
144	3114	2993		55	ν_{as}(CH$_3$)adj R1
145	3120	2999	3000	94	ν_{as}(CH$_2$)adj R3
146	3132	3011		54	ν_{as}(CH$_2$)R1
147	3144	3023	3020	38	ν_{as}(CH$_3$)adj R1
148	3148	3026		51	ν_{as}(CH$_3$)adj R2
149	3178	3055	3070	74	ν_{as}(CH$_3$)adj R2
150	3228	3103	3085	66	ν(CH)R2
151	3676	3534		165	ν(OH)adj R3&R2
152	3707	3563		51	ν(OH)adj R2&R3
153	3771	3625		120	ν(OH)adj R3
154	3776	3630		39	ν(OH)adj R3
155	3794	3647		48	N(OH)adj R3&C
156	3808	3661		146	ν(OH)adj R1

ν: stretching; ν_s: symmetric stretching; ν_{as}: asymmetric stretching; β: in-plane-bending; γ: out-of-plane bending; ω: wagging; ρ: rocking; t: twisting; τ: torsion, s: scissoring

Methylene group vibrations

The asymmetric CH$_2$ stretching vibrations are generally observed in the region 3100-3000 cm^{-1}, while the symmetric stretching vibrations are generally observed between 3000-2900 cm^{-1}[25]. The CH$_2$ asymmetric stretching vibrations are calculated at 3011, 2999 and 2983 cm^{-1}, Whereas CH$_2$ symmetric stretching vibrations are also calculated at 2956, 2937 and 2881 cm^{-1}. The bands corresponding to different bending vibrations of CH$_2$ group are summarized in TABLE 2 and are supported by the literature[25].

C-C vibrations

The C-C aromatic stretching band known as semicircle stretching, calculated at 1630, 1337, 1166, 1095, 1079, 1073, 1024, 1022, 986, 962 and 955 cm^{-1} respectively, and are supported by the literature[26]. The theoretically calculated C-C-C bending modes and C-C torsional modes have been found to be consistent with the recorded spectral values and the literature[26].

Methyl group vibrations

The asymmetric CH$_3$ stretching vibrations are calculated at 3055, 3026, 3023, and 2993 cm^{-1}, while symmetric CH$_3$ stretching vibrations are calculated at 2949 and 2924 cm^{-1}. These assignments are also supported by the literature[27]. In the present study various bending vibrations of CH$_3$ group are also summarized in TABLE 2 and are supported by the literature[27].

C-O vibrations

In this study the C-O stretching vibrations are calculated at 1190, 1146, 1115, 1109, 1087, 1072, 1059, 1057, 1033, 1031, 996, 971, 946 and 845 cm^{-1}, are supported by the literature[26]. The various bending and torsional vibrations assigned in this study are also supported by the literature[26].

O-H vibrations

In a vibrational spectra, the strength of hydrogen bond determines the position of O-H band. Usually the O-H stretching appears at 3600-3400 cm^{-1}[28]. In this study ipolamiide showed very strong absorption peaks at 3661, 3647, 3630, 3625, 3563 and 3534 cm^{-1}, which is due to the O-H stretching vibration. The various bending vibrations of the hydroxyl groups are also found to be in good agreement with the observed spectra and literature[28].

CONCLUSION

The equilibrium geometries and harmonic frequencies of ipolamiide were determined and analyzed by QM/MM method with B3LYP/6-31G(d,p) and universal force field (u.f.f.) combination using ONIOM code. The vibrational frequency calculation proved that the structure is stable (no imaginary frequencies). We found the geometry obtained by the QM/MM method to be very accurate, and we can use this rapid method in place of time consuming ab initio methods for large molecules. The difference between the observed and scaled wave number values of most of the fundamentals is very small. Any discrepancy noted between the observed and calculated frequencies may be due to the fact that the calculations have been actually done on a single molecule in the gaseous state contrary to the experimental values recorded in the presence of intermolecular interactions. The normal mode analysis of ipolamiide opens up an avenue for further conformational research. With the continuing need for novel structures and the difficulty of gaining access to large tracts of bio diversity in habitats, combinatorial chemistry blended with modern quantum chemical methods can be proved to be blessing for the researchers.

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