Vibrational analysis of boldine hydrochloride using QM/MM approach

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Abstract. A complete vibrational analysis was performed on the molecular structure of boldine hydrochloride using QM/MM method. The equilibrium geometry, harmonic vibrational frequencies and infrared intensities were calculated by QM/MM method with B3LYP/6-31G(d) 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 infrared spectra of boldine hydrochloride is reported. The scaled theoretical wave numbers are in perfect agreement with the experimental values. The FT-IR spectra of boldine hydrochloride in the region 4000–500 cm⁻¹ were recorded in CsI (solid phase) and in chloroform with concentration 5 and 10 mg/ml.

Keywords: QM/MM method, FT-IR spectra, boldine hydrochloride, vibrational spectra

1. Introduction

Boldine hydrochloride (5,6,6a,7-tetrahydro-1,10-dimethoxy-6-methyl 4H-dibenzo quinoline-2,9-diol) is an aporphine alkaloid noted for its antioxidant properties [1]. *Peumus boldus* Mol. (Monimiaceae) also known as Boldo is an endemic Chilean tree known for its medicinal properties [16]. In addition to boldine, isolated more than 100 years ago, several aporphines and one benzyloisoquinoline have been identified in the leaves [10,20,26]. Our title molecule is a aporphine alkaloid which has attracted our attention due to its potent antioxidant properties as it affords a highly stabilized free radical after reacting with species (HO₂), the degree of conjugation between the two aromatic rings, associated with the planarity of the biphenyl moiety, is a key factor in its antioxidant activity [1].

Here in the present communication, the experimental FT-IR frequencies of the title molecule are compared with the theoretical frequencies obtained by QM/MM method with B3LYP/6-31G(d) 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 boldine hydrochloride 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

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study is important because of further work on boldine hydrochloride, 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 infrared spectra of title compound with the use of standard B3LYP/6-31G(d) method and universal force field (UFF) combination. To the best of our knowledge neither the QM nor the MM calculations for boldine hydrochloride have been reported so far in the literature.

2. Experimental section

The FT-IR spectra of boldine hydrochloride has been recorded on a Perkin Elmer 1800 Spectrophotometer. Spectroscopic preparations of the sample were carried out under an atmosphere of prepurified nitrogen. The spectra were recorded for 1% and 5% solution of boldine. The FT-IR spectra of title molecule in solid phase (CsI) is shown in Fig. 1a and the FT-IR spectra of boldine hydrochloride in liquid phase (chloroform) using different concentration (5 and 10 mg/ml) were also recorded and are shown in Fig. 1b and c.

3. 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.

Fig. 1a. FT-IR spectra of boldine hydrochloride in CsI (solid phase).

Fig. 1b. FT-IR spectra of boldine hydrochloride in chloroform (5 mg/ml).

Fig. 1c. FT-IR spectra of boldine hydrochloride in chloroform (10 mg/ml).

Fig. 2. Model molecular structure of boldine hydrochloride.

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 [5,8,25].

Figure 2 shows the model molecular structure of boldine hydrochloride. In this molecule, atoms in ring R4 and its adjacent atoms are treated quantum mechanically and these atoms are shown by balls and sticks in Fig. 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) [19]. 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 [4].

The entire calculations were performed on a Pentium IV/1.66 GHz personal computer using Gaussian 03W [7] program package, invoking gradient geometry optimization [21]. 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) 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) [9] with the three-parameter hybrid functional (B3LYP) [2] for the exchange part and the Lee–Yang–Parr (LYP) correlation function [17], 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) [22,23]. Vibrational frequencies calculated at B3LYP/6-31G(d) 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 [24]. By combining the result of GAUSSVIEW program [6] 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.

4. Result and discussion

4.1. Geometry optimization

The optimized structural parameters of boldine hydrochloride calculated by QM/MM with B3LYP method and UFF combination with the 6-31G(d) basis set are listed in Table 1 in accordance with the atom numbering scheme given in Fig. 2. Experimental values of various bond lengths and bond angles of boldine hydrochloride were taken from the literature [1]. For example, the optimized bond lengths of C–C in ring R1 fall in the range from 1.390 to 1.426 Å, in good agreement with those of the experimental bond lengths [1.375–1.422 Å]. The optimized bond lengths of C–C in ring R2 fall in the range from 1.396 to 1.518 Å, also in good agreement with those of the experimental bond lengths [1.386–1.513 Å]. The optimized bond lengths of C–C in ring R3 fall in the range from 1.407 to 1.530 Å, also in good agreement with those of the experimental bond lengths [1.393–1.520 Å]. The optimized bond lengths of C–C in ring R4 fall in the range from 1.387 to 1.413 Å, also in good agreement with those of the experimental bond lengths [1.375–1.416 Å]. The optimized bond lengths of C–N fall in the range from 1.502 to 1.534 Å, also in good agreement with those of the experimental bond lengths [1.493–1.508 Å]. The optimized bond lengths of C–O fall in the range from 1.351 to 1.439 Å, also in good agreement with those of the experimental bond lengths [1.359–1.428 Å]. The values of other calculated bond lengths and bond 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.

4.2. Vibrational assignments

Boldine hydrochloride has 46 atoms and 132 normal modes of fundamental vibration. All of the 132 fundamental vibrations are IR 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-IR spectra with the wave numbers and intensities obtained from the QM/MM calculations given in Table 2.

The experimental FT-IR spectra are shown in Fig. 1a–c. The descriptions concerning the assignment have been listed in Table 2. Gauss View Program [6] was used for the assignment of the calculated frequencies. The observed frequencies for various modes of vibrations are also presented in Table 2.

4.3. 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 [14]. In the present study the C–H stretching vibrations are calculated at 3157, 3083, 3053 and 2928 cm^{-1} , which are supported by the literature [14]. Some bending vibrations of C–H are also calculated and supported by the literature [14].

4.4. 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} [15]. The

Table 1
Optimized geometrical parameters of boldine hydrochloride

S. No.	Bond lengths (Å)	X-ray	Calculated	Bond angles (degree)	X-ray	Calculated
1	N1–C11	1.493	1.515	C11–N1–C12	110.6	110.7
2	N1–C12	1.508	1.534	C11–N1–C22	109.7	110.9
3	N1–C22	1.496	1.502	C11–N1–H25		107.3
4	N1–H25		1.027	C12–N1–C22	111.6	113.3
5	O2–C16	1.370	1.351	C12–N1–H25		106.5
6	O2–H26		0.975	C22–N1–H25		107.9
7	O3–C17	1.379	1.365	C16–O2–H26		107.6
8	O3–C23	1.411	1.426	C17–O3–C23	117.8	118.7
9	O4–C6	1.385	1.367	C6–O4–C24	115.1	116.1
10	O4–C24	1.428	1.439	C7–O5–H27		109.8
11	O5–C7	1.359	1.357	O4–C6–C7	118.2	118.4
12	O5–H27		0.971	O4–C6–C20	121.1	121.0
13	C6–C7	1.401	1.413	C7–C6–C20	120.7	120.5
14	C6–C20	1.398	1.407	O5–C7–C6	116.3	116.6
15	C7–C8	1.375	1.390	O5–C7–C8	123.5	123.2
16	C8–C9	1.397	1.398	C6–C7–C8	120.1	120.3
17	C8–H28		1.088	C7–C8–C9	120.4	120.3
18	C9–C10	1.507	1.515	C7–C8–H28		119.8
19	C9–C21	1.386	1.396	C9–C8–H28		119.9
20	C10–C11	1.513	1.518	C8–C9–C10	118.8	118.7
21	C10–H29		1.096	C8–C9–C21	120.0	119.9
22	C10–H30		1.100	C10–C9–C21	121.2	121.5
23	C11–H31		1.094	C9–C10–C11	113.5	112.2
24	C11–H32		1.092	C9–C10–H29		110.5
25	C12–C13	1.518	1.530	C9–C10–H30		110.8
26	C12–C21	1.520	1.521	C11–C10–H29		107.8
27	C12–H33		1.099	C11–C10–H30		109.5
28	C13–C14	1.508	1.512	H29–C10–H30		105.7
29	C13–H34		1.093	N1–C11–C10	111.1	109.5
30	C13–H35		1.102	N1–C11–H31		106.0
31	C14–C15	1.392	1.396	N1–C11–H32		107.6
32	C14–C19	1.393	1.407	C10–C11–H31		112.3
33	C15–C16	1.375	1.390	C10–C11–H32		112.2
34	C15–H36		1.086	H31–C11–H32		108.9
35	C16–C17	1.396	1.413	N1–C12–C13	110.0	111.2
36	C17–C18	1.383	1.387	N1–C12–C21	110.6	110.9
37	C18–C19	1.416	1.413	N1–C12–H33		104.0
38	C18–H37		1.079	C13–C12–C21	109.6	109.9
39	C19–C20	1.486	1.484	C13–C12–H33		109.2
40	C20–C21	1.422	1.426	C21–C12–H33		111.5
41	C22–H38		1.091	C12–C13–C14	109.0	107.5
42	C22–H39		1.088	C12–C13–H34		112.1
43	C22–H40		1.091	C12–C13–H35		109.0
44	C23–H41		1.090	C14–C13–H34		109.1
45	C23–H42		1.096	C14–C13–H35		111.4

Table 1
(Continued)

S. No.	Bond lengths (Å)	X-ray	Calculated	Bond angles (degree)	X-ray	Calculated
46	C23–H43		1.096	H34–C13–H35		107.8
47	C24–H44		1.091	C13–C14–C15	119.7	120.0
48	C24–H45		1.096	C13–C14–C19	119.9	119.1
49	C24–H46		1.093	C15–C14–C19	120.3	120.9
50				C14–C15–C16	120.8	120.4
51				C14–C15–H36		121.2
52				C16–C15–H36		118.3
53				O2–C16–C15	117.8	120.2
54				O2–C16–C17	122.5	120.6
55				C15–C16–C17	119.8	119.2
56				O3–C17–C16	114.6	113.3
57				O3–C17–C18	125.3	126.2
58				C16–C17–C18	120.1	120.5
59				C17–C18–C19	120.5	120.6
60				C17–C18–H37		120.2
61				C19–C18–H37		119.3
62				C14–C19–C18	118.4	118.3
63				C14–C19–C20	118.0	118.5
64				C18–C19–C20	123.5	123.2
65				C6–C20–C19	123.3	123.1
66				C6–C20–C21	118.2	118.0
67				C19–C20–C21	118.4	118.9
68				C9–C21–C12	122.3	122.6
69				C9–C21–C20	120.4	121.0
70				C12–C21–C20	117.3	116.4
71				N1–C22–H38		108.5
72				N1–C22–H39		110.0
73				N1–C22–H40		108.4
74				H38–C22–H39		109.8
75				H38–C22–H40		110.0
76				H39–C22–H40		110.1
77				O3–C23–H41		105.9
78				O3–C23–H42		111.0
79				O3–C23–H43		111.0
80				H41–C23–H42		109.7
81				H41–C23–H43		109.6
82				H42–C23–H43		109.6
83				O4–C24–H44		105.7
84				O4–C24–H45		110.4
85				O4–C24–H46		111.1
86				H44–C24–H45		109.6
87				H44–C24–H46		109.5
88				H45–C24–H46		110.3

Table 2

Vibrational wave numbers obtained for boldine hydrochloride in cm^{-1} , experimental frequencies from FT-IR spectra in cm^{-1} , IR intensities ($K_m \text{ mol}^{-1}$) and assignment

S. No.	Wave number		Exp. IR freq. in solid phase	Exp. IR freq. (5 mg/ml) in CHCl_3	Exp. IR freq. (10 mg/ml) in CHCl_3	IR intensity	Assignment
	Unscal.	Scal.					
1	40	40				2	$\tau(\text{CC})\text{R1,R2,R3\&R4} + \tau(\text{CN}) + \tau(\text{CO})\text{R4}$
2	44	44				3	$\tau(\text{CC})\text{R1,R2,R3\&R4} + \tau(\text{CO})\text{R1\&R4}$
3	59	59				2	$\tau(\text{CO})\text{R1} + \tau(\text{CC})\text{R1,R2,R3\&R4}$
4	80	80				2	$\tau(\text{CO})\text{R1} + \gamma(\text{COC})\text{R1} + \tau(\text{CN}) + \tau(\text{CC})\text{R1\&R2}$
5	83	83				2	$\tau(\text{CO})\text{R1\&R4} + \gamma(\text{COC})\text{R4\&R1} + \tau(\text{CC})\text{R2,R3\&R4}$
6	98	98				3	$\tau(\text{CO})\text{R1\&R4} + \gamma(\text{COC})\text{R4\&R1} + \tau(\text{CC})\text{R3\&R4}$
7	117	117				2	$\tau(\text{CC})\text{R1,R2,R3\&R4}$
8	142	142				0	$\tau(\text{CO})\text{R1\&R4} + \tau(\text{CC})\text{R3\&R4}$
9	164	164				1	$\tau(\text{CN}) + \tau(\text{CO})\text{R4\&R1} + \tau(\text{CC})\text{R1,R2,R3\&R4} + \gamma(\text{CCC})\text{R3}$
10	177	177				0	$\tau(\text{CO})\text{R4\&R1} + \tau(\text{CN}) + \tau(\text{CC})\text{R3\&R4}$
11	182	182				1	$\tau(\text{CN}) + \gamma(\text{CCN}) + \tau(\text{CC})\text{R1\&R2} + \tau(\text{CO})\text{R4\&R1} + \gamma(\text{CNC})$
12	200	200				2	$\tau(\text{CO})\text{R4\&R1} + \tau(\text{CC})\text{R1,R2,R3\&R4} + \gamma(\text{COC})\text{R1\&R4} + \tau(\text{CN})$
13	220	220				2	$\tau(\text{CN}) + \tau(\text{CC})\text{R2,R3\&R4} + \tau(\text{CO})\text{R4\&R1}$
14	233	233				1	$\tau(\text{CO})\text{R4} + \tau(\text{CC})\text{R2,R3\&R4} + \gamma(\text{CCC})\text{R2\&R3}$
15	235	235				3	$\tau(\text{CO})\text{R4\&R1} + \tau(\text{CC})\text{R1,R2\&R3} + \gamma(\text{CCC})\text{R1} + \gamma(\text{COC})\text{R1}$
16	245	245				0	$\tau(\text{CC})\text{R1\&R2} + \gamma(\text{CCC})\text{R1\&R2}$
17	275	275				1	$\tau(\text{CN}) + \tau(\text{CO})\text{R4\&R1} + \tau(\text{CC})\text{R1,R2\&R3}$
18	293	293				1	$\tau(\text{CO})\text{R4} + \gamma(\text{CCC})\text{R1,R3\&R4} + \tau(\text{CC})\text{R1,R3\&R4}$
19	303	303				5	$\tau(\text{CO})\text{R4} + \gamma(\text{COC})\text{R3} + \tau(\text{CC})\text{R4}$
20	312	312				10	$\tau(\text{CC})\text{R1,R2,R3\&R4} + \tau(\text{CN})$
21	337	337				1	$\tau(\text{CO})\text{R1} + \gamma(\text{COC})\text{R1} + \beta(\text{CCO})\text{R1} + \tau(\text{CC})\text{R1,R2,R3\&R4}$
22	356	356				10	$\gamma(\text{COC})\text{R1\&R4} + \tau(\text{CO})\text{R4\&R1} + \tau(\text{CC})\text{R1,R2,R3\&R4} + \gamma(\text{CNC}) + \gamma(\text{CCN})$
23	377	377				53	$\gamma(\text{OH})\text{R1} + \tau(\text{CC})\text{R1,R2,R3\&R4} + \tau(\text{CO})\text{R1}$
24	383	383				8	$\gamma(\text{OH})\text{R1} + \tau(\text{CO})\text{R4} + \tau(\text{CN}) + \gamma(\text{COC})\text{R4} + \tau(\text{CC})\text{R2,R3\&R4}$

Table 2
(Continued)

S. No.	Wave number		Exp. IR freq. in solid phase	Exp. IR freq. (5 mg/ml) in CHCl ₃	Exp. IR freq. (10 mg/ml) in CHCl ₃	IR intensity	Assignment
	Unscal.	Scal.					
25	390	390				45	$\gamma(\text{OH})\text{R1} + \tau(\text{CN}) +$ $\tau(\text{CC})\text{R2,R3\&R4}$
26	400	400				4	$\tau(\text{CO})\text{R4\&R1} +$ $\tau(\text{CC})\text{R1,R2,R3\&R4} +$ $\gamma(\text{CCC})\text{R1,R2\&R3} +$ $\tau(\text{CN}) + \gamma(\text{CNC}) + \gamma(\text{CCN})$
27	437	437				4	$\tau(\text{CC})\text{R4,R3\&R1} +$ $\gamma(\text{CCO})\text{R4\&R1} + \gamma(\text{CCC})\text{R4,R3\&R1}$
28	447	447				5	$\beta(\text{CNC}) + \beta(\text{CCC})\text{R1\&R3} +$ $\beta(\text{COC})\text{R4}$
29	461	461				5	$\gamma(\text{CCC})\text{R4} + \gamma(\text{CCO})\text{R4}$
30	475	476				6	$\gamma(\text{CCC})\text{R1,R2,R3\&R4} +$ $\beta(\text{COC})\text{R1} + \gamma(\text{CNC}) +$ $\gamma(\text{CCO})\text{R1} + \gamma(\text{CCN})$
31	500	501				102	$\gamma(\text{OH})\text{R4}$
32	506	507	514	506	508	8	$\gamma(\text{OH})\text{R4} + \gamma(\text{CCC})\text{R1,R2,R3\&R4} +$ $\beta(\text{CNC}) + \beta(\text{CCN})$
33	521	522				0	$\beta(\text{CCC})\text{R4,R2\&R1} + \beta(\text{COC})\text{R4} +$ $\beta(\text{CCN}) + \beta(\text{CNC})$
34	533	534	530			9	$\gamma(\text{COC})\text{R4\&R1} +$ $\beta(\text{CCC})\text{R1,R2,R3\&R4} + \beta(\text{CCN})$
35	558	559	560			4	$\gamma(\text{CCC})\text{R1,R2,R3\&R4} + \gamma(\text{CCO})\text{R1}$
36	565	566				1	$\gamma(\text{CCC})\text{R1,R2,R3\&R4} + \gamma(\text{CNC}) +$ $\gamma(\text{CCN})$
37	615	616	620			18	$\beta(\text{CCC})\text{R3\&R4} + \gamma(\text{CCC})\text{R1\&R2} +$ $\gamma(\text{CCO})\text{R1} + \nu(\text{CN})$
38	632	633				1	$\beta(\text{CCC})\text{R2\&R4} + \beta(\text{CCO})\text{R4}$
39	661	662				6	$\gamma(\text{CCC})\text{R4,R3\&R1} + \gamma(\text{CCO})\text{R4\&R1}$
40	684	685	665	671	671	7	$\gamma(\text{CCC})\text{R1,R2,R3\&R4} +$ $\gamma(\text{CCO})\text{R4\&R1} + \gamma(\text{CCN})$
41	688	689				1	$\gamma(\text{CCC})\text{R1,R2,R3\&R4} +$ $\gamma(\text{CCO})\text{R4\&R1} + \beta(\text{COC})\text{R1} +$ $\rho(\text{CH}_2)\text{R2\&R3}$
42	713	714				2	$\gamma(\text{CCC})\text{R4,R3\&R1} +$ $\gamma(\text{CCO})\text{R4\&R1} + \beta(\text{COC})\text{R1}$
43	727	728				2	$\beta(\text{CCC})\text{R1\&R3} + \beta(\text{CCN}) +$ $\nu(\text{CN}) + \nu(\text{CO})\text{R1}$
44	760	761				3	$\gamma(\text{CCC})\text{R1} + \beta(\text{CCC})\text{R3\&R4} +$ $\gamma(\text{CCO})\text{R1} + \nu(\text{CN})$
45	762	763				4	$\gamma(\text{CCC})\text{R1,R3\&R4} + \gamma(\text{CCO})\text{R1}$
46	788	789	780	763	762	29	$\gamma(\text{CCC})\text{R1} + \beta(\text{CCC})\text{R4} +$ $\nu(\text{CC})\text{R2\&R4} + \beta(\text{COC})\text{R1\&R4}$
47	822	790				16	$\gamma(\text{CH})\text{R1} + \rho(\text{CH}_2)\text{R2} +$ $\gamma(\text{CCC})\text{R1\&R3} + \nu(\text{CN}) + \beta(\text{CNC})$

Table 2
(Continued)

S. No.	Wave number		Exp. IR freq. in solid phase	Exp. IR freq. (5 mg/ml) in CHCl ₃	Exp. IR freq. (10 mg/ml) in CHCl ₃	IR intensity	Assignment
	Unscal.	Scal.					
48	832	799				10	$\gamma(\text{CH})\text{R1} + \beta(\text{CCC})\text{R3} + \nu(\text{CN}) + \beta(\text{CNC}) + \gamma(\text{CCC})\text{R1} + \nu(\text{CO})\text{R4} + \nu(\text{CC})\text{R4}$
49	851	818				13	$\nu(\text{CN}) + \rho(\text{CH}_2)\text{R2} + \gamma(\text{CH})\text{R1} + \beta(\text{CCN})$
50	874	840	850		878	7	$\gamma(\text{CH})\text{R4} + \gamma(\text{CCC})\text{R4}$
51	894	859				10	$\beta(\text{CCC})\text{R1} + \nu(\text{CC})\text{R2,R3\&R4} + \beta(\text{CNC}) + \beta(\text{CCN}) + \nu(\text{CO})\text{R1\&R4}$
52	899	864				33	$\gamma(\text{CH})\text{R4}$
53	942	905				51	$\nu(\text{CN}) + \beta(\text{CCN}) + \beta(\text{CCC})\text{R2\&R3}$
54	949	912				7	$\nu(\text{CN}) + \beta(\text{CCN}) + \beta(\text{CCC})\text{R1\&R2} + \rho(\text{CH}_3)\text{R2} + \beta(\text{CNC})$
55	990	952	915	930	929	6	$\rho(\text{CH}_2)\text{R3} + \beta(\text{CCC})\text{R1,R2\&R3} + \nu(\text{CN}) + \nu(\text{CO})\text{R1} + \nu(\text{CC})\text{R1,R2,R3\&R4}$
56	1014	975				45	$\nu(\text{CO})\text{R1} + \nu(\text{CC})\text{R2} + \nu(\text{CN}) + \beta(\text{CCC})\text{R1\&R2} + \beta(\text{CCN})$
57	1023	983				2	$\nu(\text{CN}) + \nu(\text{CC})\text{R2\&R3} + \beta(\text{CCC})\text{R1,R3\&R4} + \rho(\text{CH}_2)\text{R2\&R3} + \nu(\text{CO})\text{R1}$
58	1045	1004				27	$\nu(\text{CO})\text{R4} + \nu(\text{CN}) + \nu(\text{CC})\text{R1,R3\&R4} + \rho(\text{CH}_2)\text{R2} + \beta(\text{CCC})\text{R4}$
59	1055	1014	1015	1003	1003	42	$\nu(\text{CO})\text{R4} + \nu(\text{CN}) + \nu(\text{CC})\text{R2,R3\&R4} + \beta(\text{CCC})\text{R4}$
60	1062	1021				14	$\nu(\text{CC})\text{R2\&R3} + \nu(\text{CN}) + \nu(\text{CO})\text{R1} + \beta(\text{CCC})\text{R1,R2\&R3}$
61	1085	1043	1035			44	$\nu(\text{CC})\text{R2\&R3} + \nu(\text{CN}) + \beta(\text{CCC})\text{R1\&R4} + \nu(\text{CO})\text{R1\&R4}$
62	1121	1078	1080	1087	1086	142	$\nu(\text{CO})\text{R1\&R4} + \beta(\text{CCC})\text{R4\&R1} + \nu(\text{CC})\text{R3} + \beta(\text{OH})\text{R1\&R4}$
63	1144	1100				4	$\rho(\text{CH}_3)\text{R2} + \text{t}(\text{CH}_2)\text{R2} + \nu(\text{CC})\text{R2\&R3} + \nu(\text{CO})\text{R1} + \beta(\text{CCC})\text{R1} + \beta(\text{CH})\text{R2\&R3} + \beta(\text{CNC})$
64	1151	1106				12	$\nu(\text{CN}) + \nu(\text{CC})\text{R2\&R3} + \nu(\text{CO})\text{R1\&R4} + \beta(\text{CCC})\text{R1\&R4}$
65	1177	1131				1	$\nu(\text{CN}) + \rho(\text{CH}_3)\text{R2\&R1} + \text{t}(\text{CH}_2)\text{R2} + \beta(\text{CH})\text{R2\&R3}$
66	1179	1133				5	$\rho(\text{CH}_3)\text{R1}$
67	1183	1137				1	$\rho(\text{CH}_3)\text{R4}$

Table 2
(Continued)

S. No.	Wave number		Exp. IR freq. in solid phase	Exp. IR freq. (5 mg/ml) in CHCl ₃	Exp. IR freq. (10 mg/ml) in CHCl ₃	IR intensity	Assignment
	Unscal.	Scal.					
68	1191	1145	1142			7	$\nu(\text{CC})\text{R1,R2,R3\&R4} +$ $\beta(\text{CH})\text{R1,R2,R3\&R4} +$ $\beta(\text{OH})\text{R1} + \rho(\text{CH}_3)\text{R4\&R1} +$ $\nu(\text{CO})\text{R4}$
69	1203	1157				16	$t(\text{CH}_2)\text{R3\&R2} + \beta(\text{CH})\text{R2\&R3} +$ $\beta(\text{NH}) + \rho(\text{CH}_3)\text{R1\&R2} +$ $\beta(\text{OH})\text{R1} + \nu(\text{CC})\text{R4}$
70	1211	1164				40	$\rho(\text{CH}_3)\text{R4} + \beta(\text{CH})\text{R4} + \beta(\text{OH})\text{R4} +$ $\nu(\text{CC})\text{R4} + \nu(\text{CO})\text{R4} + \beta(\text{CCC})\text{R4}$
71	1218	1170				43	$\rho(\text{CH}_3)\text{R1} + \beta(\text{OH})\text{R1} +$ $\nu(\text{CC})\text{R1\&R3} + \beta(\text{COC})\text{R1}$
72	1226	1179				12	$\beta(\text{CH})\text{R1\&R4} + \beta(\text{OH})\text{R1} +$ $\nu(\text{CC})\text{R1\&R3} + \rho(\text{CH}_3)\text{R1,R2\&R4} +$ $\nu(\text{CO})\text{R4}$
73	1236	1188	1185			84	$\nu(\text{CO})\text{R4} + \rho(\text{CH}_3)\text{R1\&R4} +$ $\nu(\text{CC})\text{R4\&R3} + \beta(\text{OH})\text{R1\&R4} +$ $t(\text{CH}_2)\text{R2} + \beta(\text{NH}) +$ $\beta(\text{CH})\text{R2\&R3} + \nu(\text{CN}) + \beta(\text{CCC})\text{R4}$
74	1247	1199				24	$\beta(\text{CH})\text{R1,R2,R3\&R4} +$ $t(\text{CH}_2)\text{R2\&R3} + \beta(\text{OH})\text{R4} +$ $\rho(\text{CH}_3)\text{R1\&R4} + \beta(\text{NH}) +$ $\nu(\text{CC})\text{R1,R2,R3\&R4}$
75	1250	1201				9	$\nu(\text{CC})\text{R1,R3\&R4} +$ $\beta(\text{CH})\text{R1,R2,R3\&R4} +$ $\beta(\text{OH})\text{R1\&R4} + \nu(\text{CO})\text{R1} +$ $\rho(\text{CH}_3)\text{R1\&R4}$
76	1278	1228	1213	1216	1216	73	$\beta(\text{CH})\text{R4} + t(\text{CH}_2)\text{R2\&R3} +$ $\nu(\text{CO})\text{R4} + \beta(\text{OH})\text{R4} + \beta(\text{CCC})\text{R4} +$ $\nu(\text{CC})\text{R3\&R4}$
77	1290	1240				167	$\nu(\text{CO})\text{R1} + \beta(\text{CH})\text{R1,R2,R3\&R4} +$ $\nu(\text{CC})\text{R1\&R3} + \beta(\text{CCC})\text{R1} +$ $\beta(\text{OH})\text{R1\&R4} + t(\text{CH}_2)\text{R2} +$ $\omega(\text{CH}_3)\text{R1}$
78	1291	1241	1245			179	$t(\text{CH}_2)\text{R2} + \nu(\text{CO})\text{R4\&R1} +$ $\nu(\text{CC})\text{R1,R2,R3\&R4} +$ $\beta(\text{CH})\text{R1,R2\&R3} + \beta(\text{OH})\text{R1\&R4}$
79	1306	1256				41	$\nu(\text{CC})\text{R1,R2,R3\&R4} +$ $\nu(\text{CO})\text{R4\&R1} + \beta(\text{CH})\text{R1\&R4} +$ $\beta(\text{OH})\text{R4} + t(\text{CH}_2)\text{R2}$
80	1330	1278				78	$\omega(\text{CH}_2)\text{R3\&R2} + \nu(\text{CO})\text{R4\&R1} +$ $\beta(\text{CH})\text{R2,R3\&R4} +$ $\nu(\text{CC})\text{R1,R2,R3\&R4} + t(\text{CH}_2)\text{R2} +$ $\beta(\text{OH})\text{R4}$

Table 2
(Continued)

S. No.	Wave number		Exp. IR freq. in solid phase	Exp. IR freq. (5 mg/ml) in CHCl ₃	Exp. IR freq. (10 mg/ml) in CHCl ₃	IR intensity	Assignment
	Unscal.	Scal.					
81	1339	1287				54	$\beta(\text{CH})\text{R2,R3\&R4} + \beta(\text{OH})\text{R1\&R4} + \nu(\text{CO})\text{R1\&R4} + \nu(\text{CC})\text{R1,R3\&R4} + \beta(\text{CCC})\text{R1\&R4} + \omega(\text{CH}_2)\text{R2}$
82	1352	1299	1295			68	$\nu(\text{CC})\text{R1,R2,R3\&R4} + \beta(\text{CH})\text{R2,R3\&R4} + \text{t}(\text{CH}_2)\text{R2} + \nu(\text{CO})\text{R1\&R4} + \beta(\text{OH})\text{R1\&R4}$
83	1365	1312				77	$\beta(\text{CH})\text{R2\&R3} + \nu(\text{CC})\text{R1,R3\&R4} + \nu(\text{CO})\text{R1\&R4} + \beta(\text{NH})$
84	1375	1322				24	$\beta(\text{CH})\text{R2\&R3} + \nu(\text{CC})\text{R1,R2,R3\&R4} + \nu(\text{CO})\text{R1\&R4}$
85	1389	1336	1340			51	$\omega(\text{CH}_2)\text{R2} + \nu(\text{CC})\text{R1,R2,R3\&R4} + \text{t}(\text{CH}_2)\text{R2} + \beta(\text{NH}) + \nu(\text{CO})\text{R1\&R4} + \beta(\text{OH})\text{R1} + \beta(\text{CH})\text{R2\&R3}$
86	1399	1345				55	$\omega(\text{CH}_2)\text{R2\&R3} + \beta(\text{NH}) + \nu(\text{CC})\text{R1,R2,R3\&R4} + \omega(\text{CH}_3)\text{R2} + \nu(\text{CO})\text{R4\&R1}$
87	1407	1353				98	$\nu(\text{CC})\text{R1,R2,R3\&R4} + \text{s}(\text{CH}_2)\text{R2\&R3} + \nu(\text{CO})\text{R4\&R1} + \beta(\text{NH}) + \beta(\text{OH})\text{R4\&R1} + \beta(\text{CH})\text{R2,R3\&R4} + \omega(\text{CH}_3)\text{R2}$
88	1424	1369				20	$\beta(\text{NH}) + \nu(\text{CC})\text{R4,R3\&R1} + \beta(\text{OH})\text{R4\&R1} + \beta(\text{CH})\text{R2\&R3} + \nu(\text{CO})\text{R4} + \nu(\text{CN}) + \omega(\text{CH}_3)\text{R2\&R4} + \omega(\text{CH}_2)\text{R2}$
89	1429	1374				81	$\beta(\text{NH}) + \beta(\text{CH})\text{R2\&R3} + \text{t}(\text{CH}_2)\text{R2} + \nu(\text{CC})\text{R4\&R3} + \beta(\text{OH})\text{R4} + \nu(\text{CN}) + \nu(\text{CO})\text{R4}$
90	1448	1392	1385	1372	1373	63	$\beta(\text{NH}) + \omega(\text{CH}_2)\text{R2} + \omega(\text{CH}_3)\text{R2} + \nu(\text{CN}) + \beta(\text{CH})\text{R2\&R3}$
91	1456	1400				69	$\nu(\text{CC})\text{R1,R2,R3\&R4} + \nu(\text{CO})\text{R1\&R4} + \omega(\text{CH}_2)\text{R2} + \omega(\text{CH}_3)\text{R2} + \beta(\text{OH})\text{R4} + \beta(\text{CH})\text{R2\&R3}$
92	1479	1422				8	$\omega(\text{CH}_3)\text{R2} + \omega(\text{CH}_2)\text{R2} + \beta(\text{CH})\text{R2\&R3}$
93	1482	1425				41	$\nu(\text{CC})\text{R1,R3\&R4} + \omega(\text{CH}_3)\text{R1\&R4} + \beta(\text{OH})\text{R1\&R4} + \nu(\text{CO})\text{R4} + \beta(\text{CH})\text{R4}$
94	1496	1438				12	$\omega(\text{CH}_3)\text{R1\&R4} + \nu(\text{CC})\text{R1,R3\&R4} + \text{s}(\text{CH}_2)\text{R3} + \beta(\text{OH})\text{R4\&R1} + \nu(\text{CO})\text{R4\&R1}$
95	1506	1447				12	$\omega(\text{CH}_3)\text{R4} + \text{s}(\text{CH}_2)\text{R3\&R2} + \text{s}(\text{CH}_3)\text{R2} + \nu(\text{CC})\text{R3\&R4} + \nu(\text{CO})\text{R4}$

Table 2
(Continued)

S. No.	Wave number		Exp. IR freq. in solid phase	Exp. IR freq. (5 mg/ml) in CHCl ₃	Exp. IR freq. (10 mg/ml) in CHCl ₃	IR intensity	Assignment
	Unscal.	Scal.					
96	1507	1449				2	s(CH ₂)R3&R2 + ω (CH ₃)R4&R1 + s(CH ₃)R2 + ν (CC)R3&R4
97	1512	1453				8	s(CH ₂)R2&R3 + s(CH ₃)R2
98	1516	1457				6	s(CH ₃)R1,R2&R4
99	1517	1459				2	s(CH ₃)R2&R1 + s(CH ₂)R2&R1
100	1519	1460				9	s(CH ₃)R4&R1
101	1529	1470				16	s(CH ₂)R2 + s(CH ₃)R2
102	1530	1471				90	s(CH ₃)R4
103	1533	1474	1472	1468	1468	26	s(CH ₃)R2 + s(CH ₂)R2&R3 + β (NH)
104	1534	1475				12	s(CH ₃)R1
105	1540	1481				89	ν (CO)R1&R4 + ν (CC)R1,R3&R4 + ω (CH ₃)R1 + s(CH ₃)R4 + β (CH)R1 + β (OH)R1&R4 + β (CCC)R3
106	1570	1510	1505	1514	1513	199	ν (CO)R4 + β (CH)R1&R4 + ν (CC)R1&R4 + ω (CH ₃)R4
107	1632	1568				101	ν (CC)R1&R4 + β (OH)R4&R1 + β (CH)R1&R3
108	1636	1573				95	ν (CC)R1&R4 + ν (CO)R1 + β (CH)R1 + β (OH)R1&R4
109	1647	1583				45	ν (CC)R1&R4 + β (OH)R4&R1 + β (CH)R1 + ν (CO)R1
110	1669	1605	1590	1591	1593	34	ν (CC)R4&R1 + ν (CO)R4 + β (CH)R4 + β (OH)R4&R1
111	3002	2886				26	ν_s (CH ₂)R3
112	3027	2909				19	ν_s (CH ₂)R2
113	3045	2927	2850	2847	2847	33	ν_s (CH ₃)R4
114	3046	2928				13	ν (CH)R2&R3 + ν_s (CH ₂)R3
115	3056	2938				44	ν_s (CH ₃)R1
116	3093	2973	2925	2935	2960	2	ν_{as} (CH ₂)R2 + ν_s (CH ₂)R2
117	3102	2982				8	ν_s (CH ₂)R2 + ν_s (CH ₃)R2 + ν_{as} (CH ₂)R2
118	3106	2986				2	ν_s (CH ₃)R2 + ν_s (CH ₂)R2 + ν_{as} (CH ₂)R3
119	3112	2992				28	ν_{as} (CH ₃)R4
120	3115	2994				25	ν_s (CH ₃)R2 + ν_{as} (CH ₂)R3
121	3140	3019	3000			25	ν_{as} (CH ₃)R1
122	3157	3034	3020	3022	3022	6	ν_{as} (CH ₂)R2
123	3175	3052				42	ν_{as} (CH ₃)R1
124	3176	3053				8	ν (CH)R1
125	3178	3055				15	ν_{as} (CH ₃)R4
126	3195	3071				2	ν_{as} (CH ₃)R2
127	3208	3083				5	ν (CH)R4

Table 2
(Continued)

S. No.	Wave number		Exp. IR freq. in solid phase	Exp. IR freq. (5 mg/ml) in CHCl ₃	Exp. IR freq. (10 mg/ml) in CHCl ₃	IR intensity	Assignment
	Unscal.	Scal.					
128	3220	3095				1	$\nu_{\text{as}}(\text{CH}_3)\text{R2}$
129	3284	3157				6	$\nu(\text{CH})\text{R4}$
130	3405	3273				22	$\nu(\text{NH})$
131	3688	3546	3420	3527	3430	151	$\nu(\text{OH})\text{R4}$
132	3747	3602	3680	3684	3682	90	$\nu(\text{OH})\text{R1}$

Notes: 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.

CH₂ asymmetric stretching vibrations are calculated at 3034 and 2973 cm⁻¹, whereas CH₂ symmetric stretching vibrations are calculated at 2982, 2909 and 2886 cm⁻¹. The bands corresponding to different bending vibrations of CH₂ group are summarized in Table 2 and are supported by the literature [15].

4.5. C–C vibrations

The C–C aromatic stretching band known as semi-circle stretching, calculated at 1583, 1299, 1145 and 1043 cm⁻¹, respectively, are supported by observed frequencies in FT-IR spectra (solid phase), i.e. 1590, 1295, 1142 and 1035 cm⁻¹. Some of the other C–C aromatic stretching band are also calculated at 1605, 1573, 1568, 1425, 1400, 1353, 1256, 1201 and 1021 cm⁻¹, which are also supported by the literature [12]. 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 [12].

4.6. Methyl group vibrations

The asymmetric CH₃ stretching vibrations are calculated at 3095, 3071, 3055, 3052, 3019 and 2992 cm⁻¹, while symmetric CH₃ stretching vibrations are calculated at 2994, 2986, 2938 and 2927 cm⁻¹. These assignments are supported by the experimental data and literature [3]. In the present study various bending vibrations of CH₃ group are also summarized in Table 2 and are supported by the literature [3].

4.7. C–O vibrations

In this study the C–O stretching vibrations are calculated at 1510, 1188, 1078 and 1014 cm⁻¹, are supported by the observed frequencies in FT-IR spectra (solid phase), i.e. 1505, 1185, 1080 and 1015 cm⁻¹. Some of the other C–O stretching vibrations are also calculated at 1481, 1240, 1004 and 975 cm⁻¹, are also supported by the literature [12]. The various bending and torsional vibrations assigned in this study are also supported by the literature [12].

4.8. 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 [13]. In this study boldine hydrochloride showed very strong absorption peaks at 3602 and 3546 cm⁻¹, which are due to the O–H stretching vibration and are

supported by observed frequencies in FT-IR spectra (solid phase), i.e. 3680 and 3420 cm^{-1} . The various bending vibrations of the hydroxyl groups are also found to be in good agreement with the observed spectra and literature [13].

4.9. N–H vibrations

In all the heterocyclic compounds, the N–H stretching vibrations [18] occurs in the region 3500–3000 cm^{-1} . In the present study the N–H vibration is calculated at 3273 cm^{-1} , which is supported by the literature [18]. Some bending vibrations of N–H are also calculated and are supported by the literature [18].

4.10. C–N vibrations

The identification of C–N vibrations is a difficult task, since the mixing of vibrations is possible in this region. In this study the C–N stretching vibrations are calculated at 1131, 1106, 983, 912, 905 and 818 cm^{-1} , respectively, and these are supported by the observed frequencies and literature [11]. The various bending and torsional vibrations assigned in this study are also supported by the literature [11].

5. Study of intermolecular interactions using IR spectra in different phase along with different concentrations

The FT-IR Spectra of the title molecule is recorded in the region 4000–500 cm^{-1} . To study intermolecular interaction forces we have compared the three spectra recorded in the solid and liquid phase at two different concentrations. In general, the more condense phase gives lower frequency ($\nu_{\text{gas}} > \nu_{\text{liquid}}, \nu_{\text{liquid}} > \nu_{\text{solid}}$). But as seen in the Table 2, some calculated frequencies were observed in the lower region as compared to the frequencies observed in solid/liquid phase, e.g., 3602, 1336, 1241, 1078 cm^{-1} , etc. It needs to be emphasized that the calculated frequencies represent vibrational signatures of the molecules in its gas phase. Moreover, there are some limitations of the model used to calculate the vibrational frequencies, e.g., combination of electron–electron correlation and basis set deficiencies and also we have ignored intermolecular bonding because we have studied single molecule in gas phase. So on comparison of these spectra it is observed that at places where calculated frequency comes out to be lower than the experimental frequency, weak intermolecular bonding can be held responsible for it. As it can be seen from the Table 2, some lower band frequency along with higher band frequency in the case of solid CsI solution falls in the higher region than the frequency in liquid phase. In lower region, e.g., 780 and 514 cm^{-1} vibrational levels are close to each other, so that mixing of band occurs and it is difficult to identify the corresponding band and also in higher frequency region, e.g., 2850, 1472 and 1385 cm^{-1} a strikingly surprising result is observed which possibly is due to lower degree of molecular interaction, impurities present in the sample, loose packing and antibonding repulsion, etc. On comparing the vibrational spectra in two different concentrations, i.e. 5 and 10 mg/ml it can be seen that nearly all frequencies lie at same level and this shows that intermolecular bonding nearly has no effect due to concentration of phase at some places in the vibrational spectra band in 10 mg/ml the frequencies lie at low region and this may be due to higher concentration and molecule have smaller space and hence cannot vibrate freely. But at some places this result reverses, e.g., 3527, 2935, 1593 and 1372 cm^{-1} . Shift of group of frequencies can arise due to particular interaction between different molecules. Thus, the group of frequencies depends upon degree of interaction of molecules, bonding

which lengthens and weakens the bond and hence lower frequencies. However, shift in the group of frequency position caused by resonance or intermolecular effect are in themselves highly characteristic and very useful for diagnostic purpose. We have seen that infrared spectra only appears if the vibration produces a permanent electric dipole of molecule. It is reasonable to assume that more polar the bond the more intense IR spectra arises due to the vibration of the molecule. So, it is difficult to match the intensity completely in different phases because generation of polarity depends on medium along with their concentration as well as impurity in the sample (due to difference in electronegativity). But nearly all IR intensities matches well in the same phase but different concentration.

6. Conclusion

The equilibrium geometries and harmonic frequencies of boldine hydrochloride were determined and analysed by QM/MM method with B3LYP/6-31G(d) and universal force field (UFF) 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 boldine hydrochloride 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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