Interaction of Isoniazid with Al(OH)₃: A DFT Study

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The harmonic and anharmonic vibrational wavenumbers of isoniazid (INH) interacting with Al(OH)₃ through the ring nitrogen have been calculated by using the density functional theory (DFT) method with Becke3Lyp functional and 6-31++G(d,p) basis set, in order to investigate coordination through the ring nitrogen effects on INH vibrational wavenumbers. The total energy distributions (TED) of the vibrational modes were calculated by using scaled quantum mechanical (SQM) analysis. Fundamentals were characterized by their total energy distributions. Coordination sensitive modes of isoniazid were determined.

Key Words: Density functional theory, Isoniazid, Isoniazid complex, Aluminium hydroxide.

INTRODUCTION

Isoniazid (isonicotinic acid hydrazide, abbreviated as INH) is widely used as antituberculosis drug[1]. It also seems to be effective in the treatment of extrapulmonary illnesses such as meningitis and genito-urinary infections[1,2]. The crystal structure of INH was investigated by Jensen[3]. The SER spectra of INH were studied by Wang *et al.*[4] and Silva *et al.*[2] studied the experimental and theoretical structure characterization of two isoniazid derivatives. The IR spectra of matrix isolated species of isoniazid were investigated by Borba *et al.*[5]. In our previous work[6] the vibrational spectra of free hydrogen bonded complexes of INH were reported. As a continuation of our studies on INH, in this study harmonic and anharmonic vibrational spectra of INH interacting with Al(OH)₃ through the ring nitrogen, at the DFT/B3LYP level with the 6-31++G(d,p) basis set, have been calculated and compared with the calculated wavenumbers of free INH. To the best of our knowledge, harmonic and anharmonic vibrational wavenumbers of INH-Al(OH)₃ complex have not been reported earlier.

COMPUTATIONAL DETAILS

The geometry optimizations and vibrational wavenumber (both harmonic and anharmonic) calculations of INH interacting with Al(OH)₃ through the ring nitrogen (Fig. 1) were carried out with the Gaussian 03 package[7]. The DFT method with the

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Becke3Lyp functional[8] and 6-31G++(d,p) Pople *et al.*[9] basis set have been used. The total energy distribution (TED) of the vibrational modes of the molecules was calculated with the scaled quantum mechanics (SQM) method by using the parallel quantum mechanics solutions (PQS) program[10] and the fundamental vibrational modes were characterized by their total energy distribution. Anharmonic corrections to wavenumbers of INH were obtained by means of vibrational second-order pertur-bation theory. Third and fourth energy derivatives with respect to normal coordinates were evaluated through a numerical differentiation procedure as described in detail by Barone *et al.*[11,12] and implemented in Gaussian 03 package[7].

RESULTS AND DISCUSSION

The molecular models of free INH and INH-Al(OH)$_3$ complex together with the atom numbering used in this study are given in Fig. 1. The optimized geometrical parameters of the INH-Al(OH)$_3$ complex are presented in Table-1. As seen from Table-1, C1-N6 and C5-N6 bonds of the pyridine ring were slightly increased by interaction of pyridine ring nitrogen (N6) with Al(OH)$_3$ and as a compensation, C1-C2 and C4-C5 bonds of the pyridine ring were decreased. All geometric alterations INH-Al(OH)$_3$ complex in comparison to those of free isoniazid are found as a result of interaction with Al(OH)$_3$ and marked as bold in Table-1.
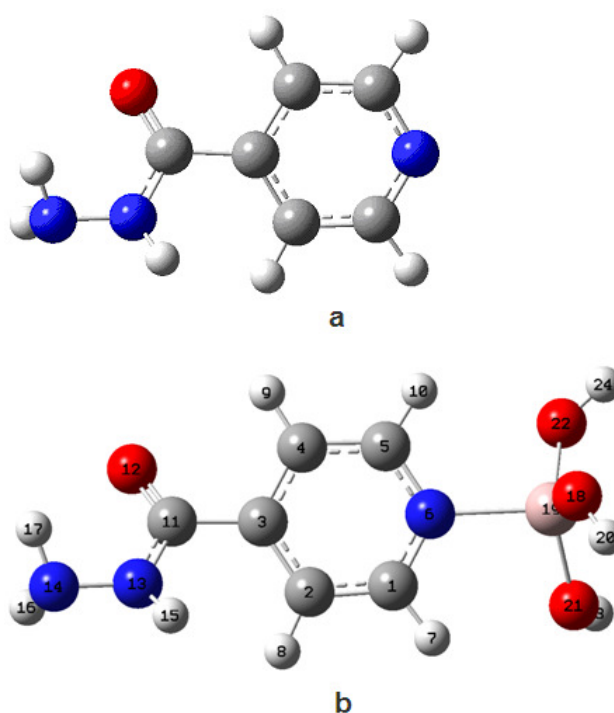

Fig. 1.   Molecular model of isoniazid. Free (a) and coordinated to Al(OH)$_3$ group through the ring nitrogen. The atom numbering used in this study are given in (b)

TABLE-1
OPTIMIZED GEOMETRICAL PARAMETERS OF ISONIAZID (A) AND ISONIZID
INTERACTING WITH Al(OH)$_3$ (B) OBTAINED BY B3LYP/6-31++G(D,P) CALCULATIONS

Bond length	Value (Å)		Bond angle	Value (°)		Dihedral angle	Value (°)	
	A	B		A	B		A	B
C1-C2	**1.397**	**1.391**	**C2-C1-N6**	**123.7**	**122.0**	N6-C1-C2-C3	0.2	0.4
C1-N6	**1.339**	**1.346**	**C2-C1-H7**	**120.1**	**122.4**	N6-C1-C2-H8	178.1	178.3
C1-H7	**1.088**	**1.085**	**N6-C1-H7**	**116.2**	**115.5**	H7-C1-C2-C3	-179.5	-178.2
C2-C3	1.400	1.401	C1-C2-C3	118.7	119.0	**H7-C1-C2-H8**	-1.5	-0.4
C2-H8	1.086	1.085	C1-C2-H8	119.6	119.1	**C2-C1-N6-C5**	-0.6	-1.6
C3-C4	1.399	1.399	C3-C2-H8	121.7	121.8	**H7-C1-N6-C5**	179.0	177.2
C3-C11	1.505	1.508	C2-C3-C4	118.0	118.5	C1-C2-C3-C4	0.7	1.2
C4-C5	**1.395**	**1.390**	C2-C3-C11	123.7	123.5	C1-C2-C3-C11	179.4	179.2
C4-H9	1.085	1.084	C4-C3-C11	118.3	118.0	H8-C2-C3-C4	-177.2	-176.7
C5-N6	**1.341**	**1.347**	C3-C4-C5	118.7	119.1	H8-C2-C3-C11	1.5	1.4
C5-H10	**1.088**	**1.085**	C3-C4-H9	119.9	120.0	C2-C3-C4-C5	-1.0	-1.6
C11-O12	1.229	1.227	C5-C4-H9	121.4	120.9	C2-C3-C4-H9	178.7	177.9
C11-N13	1.371	1.368	**C4-C5-N6**	**123.7**	**122.0**	C11-C3-C4-C5	-179.8	-179.7
N13-N14	1.409	1.408	**C4-C5-H10**	**120.3**	**122.7**	C11-C3-C4-H9	-0.1	-0.3
N13-H15	1.010	1.010	N6-C5-H10	116.0	115.4	C3-C4-C5-N6	0.6	0.5
N14-H16	1.019	1.019	**C1-N6-C5**	**117.2**	**119.4**	C3-C4-C5-H10	-179.5	179.4
N14-H17	1.021	1.020	C3-C11-O12	122.2	121.6	H9-C4-C5-N6	-179.1	-179.0
N6-Al19		2.028	C3-C11-N13	115.9	115.9	H9-C4-C5-H10	0.8	-0.1
Al19-O18		1.741	O12-C11-N13	121.9	122.5	**C4-C5-N6-C1**	0.2	1.1
O18-H20		0.961	C11-N13-N14	121.2	121.4	**H10-C5-N6-C1**	-179.7	-177.9
Al19-O21		1.747	C11-N13-H15	120.1	120.4	C3-C11-N13-N14	174.6	174.9
O21-H23		0.961	N14-N13-H15	114.1	114.2	C3-C11-N13-H15	19.8	18.8
Al19-O22		1.745	N13-N14-H16	108.1	108.2	O12-C11-N13-N14	-5.6	-5.3
O22-H24		0.961	N13-N14-H17	107.8	108.0	O12-C11-N13-H15	-160.3	-161.4
			H16-N14-H17	106.3	106.6	C11-N13-N14-H16	79.9	78.7
			C1-N6-Al19		119.7	**C11-N13-N14-H17**	-34.6	-36.3
			C5-N6-Al19		120.9	H15-N13-N14-H16	-123.9	-123.8
			Al19-O18-H20		120.1	H15-N13-N14-H17	121.5	121.2
			N6-Al19-O18		103.8	**C2-C3-C11-O12**	-154.4	-152.3
			N6-Al19-O21		99.8	**C2-C3-C11-N13**	25.5	27.6
			N6-Al19-O22		97.2	C4-C3-C11-O12	24.3	25.8
			O18-Al19-O21		113.9	C4-C3-C11-N13	-155.8	-154.4
			O18-Al19-O22		115.8	C4-C5-N6-Al19		-176.8
			O21-Al19-O22		121.1	H10-C5-N6-Al19		4.2
			Al19-O21-H23		121.9	C1-N6-Al19-O18		-88.8
			Al19-O22-H24		120.6	C1-N6-Al19-O21		29.0
						C1-N6-Al19-O22		152.3
						C5-N6-Al19-O18		89.1
						C5-N6-Al19-O21		-153.1
						C5-N6-Al19-O22		-29.8
						H20-O18-Al19-N6		115.2
						H20-O18-Al19-O21		7.7
						H20-O18-Al19-O22		-139.6
						N6-Al19-O21-H23		109.3
						O18-Al19-O21-H23		-140.7
						O22-Al19-O21-H23		4.7
						N6-Al19-O22-H24		143.8
						O18-Al19-O22-H24		34.6
						O21-Al19-O22-H24		-110.2

A = Free isoniazid; B = Isoniazid-Al(OH)₃ complex; Atom numbering is given in Fig. 1(b) for isoniazid-Al(OH)₃ complex and is taken as the same for free isoniazid.

In order to clarify the influence of the formation of metal ligand bond through the ring nitrogen on the vibrational wavenumbers of isoniazid, we tried to find evidence for coordination through ring nitrogen sensitive vibrational bands of INH. Table-2 represents experimental IR and Raman spectra of solid INH, the IR spectra of INH in a Xe matrix[13] together with the calculated wavenumbers of both free INH and INH-Al(OH)$_3$ complex in harmonic and anharmonic approximations. Coordination through the ring nitrogen sensitive vibrations of INH are marked in bold. As seen in the Table-1, the ν_{13}, ν_{15}, ν_{17}, ν_{21}, ν_{24}, ν_{27}, ν_{29}, ν_{33}, ν_{36}, ν_{37}, ν_{44}, ν_{46} modes have been predicted by DFT calculations to be the most sensitive modes on coordination of INH through the ring nitrogen. The ν_{27} mode is known as ring breathing mode of the pyridine ring of isoniazid. In the case of pyridine complexes, a shift to higher wavenumber in the ring breathing mode is used as a guide to metal coordination[14,15]. In addition to the ring breathing mode, the ring and CH stretching vibrations around 1600-1400 cm^{-1} increase in wavenumber upon coordination through the ring nitrogen[16]. As seen from Table-1, the ring breathing mode (ν_{27}) is increased upon coordination of isoniazid to a aluminium as a result of alterations of ring and also mechanical coupling with metal-ligand bond (Al-N bond stretching mode contribution is 6 %). It is also observed some increase in pyridine modes around 1600-1400 cm^{-1} upon formation of isoniazid - Al(OH)$_3$ complex (ν_{13}, ν_{15}, ν_{17}).

TABLE-2
CALCULATED WAVENUMBERS (cm^{-1}) OF FREE ISONIZID AND ISONIAZID-Al(OH)$_3$ BY B3LYP/6-31++G(d,p) TOGETHER WITH THE CALCULATED TED (%) OF ISONIAZID-Al(OH)$_3$ COMPARED TO THE OBSERVED WAVENUMBERS FOR ISONIAZID

| | Isoniazid | | | | | Isoniazid-Al(OH)$_3$ | | |
| | Observed | | | Calculated | | Calculated | | TED^b (%) |
	IR	Ra	Xe	Harm	Anh	Harm	Anh	
ν_1						3933	3781	νOH (99)
ν_2						3928	3747	νOH (99)
ν_3						3926	3746	νOH (100)
ν_4	3304	3301	3462-3449	3634	3461	3630	3456	νNH (100)
ν_5	3111	3110	3332	3542	3357	3547	3360	νNH$_2$ (100)
ν_6			3264	3465	3336	3468	3334	νNH$_2$ (100)
ν_7		3092	3178	3224	3090	3238	3108	νCH (99)
ν_8	3064	3065	3063	3203	3068	3226	3109	νCH (100)
ν_9	3012	3027	3036	3180	3029	3224	3096	νCH (100)
ν_{10}	3049	3054	2985	3174	3045	3212	3065	νCH (100)
ν_{11}	1665	1669	1695	1740	1706	1746	1713	νCO (82)
ν_{12}	1636	1642	1628	1708	1641	1707	1638	NH$_2$ scissoring (88)
ν_{13}	**1602**	**1602**	**1598**	**1641**	**1595**	**1670**	**1628**	**νring (65) + δCH (17)**
ν_{14}	1559	1552	1557	1605	1563	1601	1562	νring (77)
ν_{15}	**1491**	**1494**	**1501/1497**	**1531**	**1495**	**1538**	**1539**	**δCH (55) + νring (24)**
ν_{16}	1459		1470	1502	1455	1504	1476	δ(NNH)$_x$ (28) + δ(CNH)$_x$ (27) + ν(CN)$_x$ (18)
ν_{17}	**1412**	**1411**	**1405**	**1443**	**1417**	**1458**	**1451**	**δCH (54) + νring (30)**
ν_{18}	1334	1332	1322	1354	1327	1352	1330	δCH (83)
ν_{19}	1322	1322	1322	1347	1316	1346	1310	NH$_2$ rock (95)
ν_{20}	1389		1292	1313	1333	1314	1350	νring (24) + δ(NNH)$_x$ (19) + ν(CN)$_x$ (16) + ν(CC)$_x$ (12) + ν(NN)$_x$ (8)
ν_{21}	**1256**		**1273**	**1296**	**1255**	**1303**	**1263**	**νring (74) + ν(NN)$_x$ (6) + ν(CN)$_x$ (5)**
ν_{22}	1220	1218	1225/1219	1247	1220	1246	1149	δCH (64) + νring (32)

	Harm	Anh		Harm	Anh	Harm	Anh	TED (%)
ν_{23}	1190	1187	1183	1216	1197	1215	1183	$\nu(NN)_x$ (34) + $\nu(CC)_x$ (17) + δCH (9) + νring (6)
ν_{24}	**1141**	**1131**	1096	**1120**	**1101**	**1129**	**1117**	**δCH (40) + νring (26)**
ν_{25}	1098	1095	1087	1107	1082	1114	1080	$\nu(CN)_x$ (21) + δCH (17) + νring (17)
ν_{26}	1061	1056	1066/1063	1090	1074	1091	1072	νring (50) + δCH (22) + δring (7)
ν_{27}	**995**	**1002**	992	**1011**	**995**	**1055**	**1039**	**δring (41) + νring (31) + νAlN(6)**
ν_{28}			982	1006	986	1020	998	γCH (87)
ν_{29}	**964**	**965**	960	**985**	**967**	**1003**	**979**	**γCH (75)**
ν_{30}	942		933	956	923	951	909	$\nu(NN)_x$ (34) + NH$_2$ twist (23) + $\delta(NNH)_x$ (17)
ν_{31}	887	888	872	897	878	899	881	γCH (90)
ν_{32}	876		871	890	872	893	871	$\delta(NCO)_x$ (16) + $\delta(CNN)_x$ (8) + νring (8) + $\nu(CN)_x$ (7) + $\nu(CC)_x$ (6) + $\nu(CO)_x$ (6)
ν_{33}	**845**	**848**	841/837	**854**	**846**	**869**	**858**	**γCH (66) + $\tau(CC)_x$ (8)**
ν_{34}			-			841	765	νAlO (89) + δAlOH (6)
ν_{35}			-			829	819	νAlO (89)
ν_{36}	**746**	**757**	757-750	**769**	**758**	**779**	**769**	**γCH (27) + γring (23) + $\tau(CC)_x$ (22) + $\tau(CN)_x$ (13)**
ν_{37}	**672**	**682**	678/677	**688**	**678**	**722**	**713**	**δring (18) + δNCO (7) + νAlN (6) + $\nu(CC)_x$ (5)**
ν_{38}	716		708/704	720	714	712	703	γring (26) + $\tau(CN)_x$ (13) + γCH (10) + $\tau(CC)_x$ (9)
ν_{39}						686	689	δAlOH (68) + νAlO (22)
ν_{40}	659	665		681	675	677	671	δring (56) + δCH (24)
ν_{41}						660	632	δAlOH(83) + νAlO (13)
ν_{42}						651	651	δAlOH (70) + νAlO (25)
ν_{43}						624	618	νAlO (56) + δAlOH (41)
ν_{44}	**502**	**504**		**522**	**490**	**534**	**526**	**$\delta(NCO)_x$ (20) + γCH (19) + γring (10) + $\tau(CC)_x$ (7) + $\nu(CN)_x$ (5)**
ν_{45}	436	437		528	463	525	443	$\tau(CN)_x$ (44) + $\tau(NN)_x$ (37)
ν_{46}	**419**	**398**		**423**	**415**	**436**	**427**	**$\delta(NCO)_x$ (26) + γring (10) + $\nu(CC)_x$ (6) + νAlN (5)**
ν_{47}						406	397	νAlN (31) + $\nu(CC)_x$ (17) + $\delta(CC)_x$ (6)
ν_{48}		364		387	379	404	393	γring (54) + γCH (24) + γNAl (9) + $\gamma(CC)_x$ (8)
ν_{49}						324	303	τAlO (94) + δNAlO (6)
ν_{50}						323	304	τAlO (67) + $\nu(CC)_x$ (10) + δNAlO (5)
ν_{51}				303	300	312	311	$\delta(CN)_x$ (18) + $\delta(CC)_x$ (17) + $\delta(CO)_x$ (17) + δAlN (11)
ν_{52}						293	292	τAlO (22) + $\tau(CN)_x$ (9) + $\gamma(CC)_x$ (9) + $\delta(CC)_x$ (8) + δAlN (7)
ν_{53}						269	277	τAlO (77) + δAlN (8) + δAlO (6)
ν_{54}						263	273	τAlO (67) + δOAlO (11) + τAlN (6)
ν_{55}						243	422	τAlO (64) + δOAlO (17) + τAlN (5)
ν_{56}						223	233	τAlO (23) + δOAlO (16) + $\tau(CN)_x$ (16) + τAlN (11)
ν_{57}						177	185	τAlO (31) + δOAlO (15) + $\delta(CCO)_x$ (11) + νAlN (8) + τAlN (6)
ν_{58}						167	184	τAlO (36) + νAlN (35) + δCNAl (5)
ν_{59}						156	154	$\tau(CN)_x$ (26) + τAlO (18) + $\tau(NN)_x$ (13) + δOAlO (12) + δCNAl (7)
ν_{60}		221		133	209	130	74	$\tau(NN)_x$ (64) + $\tau(CN)_x$ (11) + τAlO (6)
ν_{61}						120	182	τAlO (57) + δOAlN (25) + δOAlO (11) + $\delta(CCC)_x$ (11) + $\delta(CCN)_x$ (6)
ν_{62}						105	106	δOAlN (25) + τAlO (23) + $\gamma(CC)_x$ (13) + $\tau(CN)_x$ (10) + $\tau(CC)_x$ (8)
ν_{63}						80	77	δCNAl (48) + $\delta(CCC)_x$ (15) + τAlO (14) + δOAlN (13)
ν_{64}		82		55	53	57	41	$\tau(CC)_x$ (80)
ν_{65}						40	45	γNAl (37) + $\gamma(CC)_x$ (22) + τNAl (16)

Harm = Harmonic and Anh = Anharmonic approximations. TED = Total energy distribution of vibrational modes of Isoniazid-Al(OH)$_3$. Xe = IR spectral wavenumbers of isoniazid in a Xe matrix taken from ref [13].

Conclusion

Vibrational analysis of isoniazid molecule together with its $Al(OH)_3$ complex have been performed based on DFT method with Becke3Lyp functional and 6-31G++(d,p) Pople and co-workers basis set both at harmonic and anharmonic levels. Calculations indicate that in addition to the pyridine ring and CH modes around 1600-1400 cm^{-1} (ν_{13}, ν_{15}, ν_{17}), ring breathing mode (ν_{27}), some other pyridine ring, in-plane stretching and bending modes and CH out-of-plane bending modes (ν_{21}, ν_{24}, ν_{29}, ν_{33}, ν_{36}, ν_{37}, ν_{44}, ν_{46}) are also sensitive to coordination of isoniazid to a metal through the ring nitrogen.

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