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Ab initio and density functional computations of the vibrational spectrum, molecular geometry and some molecular properties of the antidepressant drug sertraline (Zoloft) hydrochloride

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Abstract

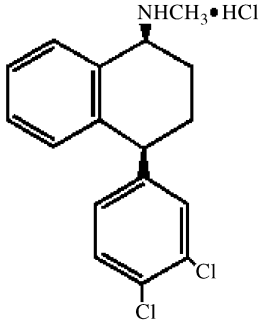
Sertraline hydrochloride is a highly potent and selective inhibitor of serotonin (5HT). It is a basic compound of pharmaceutical application for antidepressant treatment (brand name: Zoloft). Ab initio and density functional computations of the vibrational (IR) spectrum, the molecular geometry, the atomic charges and polarizabilities were carried out. The infrared spectrum of sertraline is recorded in the solid state. The observed IR wave numbers were analysed in light of the computed vibrational spectrum. On the basis of the comparison between calculated and experimental results and the comparison with related molecules, assignments of fundamental vibrational modes are examined. The X-ray geometry and experimental frequencies are compared with the results of our theoretical calculations.

Keywords: DFT and HF calculations; Sertraline hydrochloride; IR spectra

1. Introduction

Sertraline hydrochloride (**1**) (4-(3,4-dichlorophenyl)-1,2,3,4,-tetrahydro-*N*-methyl-1-naphthalenamine hydrochloride) selectively blocks serotonin reuptake and is used for the treatment of depression, as well as dependency- and other anxiety-related disorders. Sertraline belongs to those medicinal agents having one or more asymmetric centers in which the isomers show significant differences in their biological activity, and therefore, it is necessary to produce the biologically active 1*S*,4*S*-enantiomer, sertraline, with high optical purity [1].

Sertraline.HCl is the active ingredient in the antidepressant drug Zoloft. Due to the enormous commercial value of the drug, the patent literature on crystal forms of sertraline is substantial. Almarsson et al. reported 28 phases for sertraline (polymorphs, solvates, hydrates and an amorphous phase) which have extracted from five patents from 1992 to 2001 [2].



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In this study, density functional theory (DFT) by using BLYP and B3LYP hybrid functionals and ab initio Hartree–Fock (HF) computations of the vibrational spectrum, the molecular geometry, the atomic charges and molecular polarizability were carried out for sertraline·HCl molecule. The experimental geometric data of the molecule were taken from the crystallographic results of sertraline·HBr [Cambridge Crystallographic Database: CSD code: CAVVUQ [3]].

The main objective of this paper is to find effective theoretical methods that would offer a higher certainty of finding molecular

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parameters and vibrational wavenumbers. The calculated harmonic frequencies are usually higher than the corresponding experimental quantities, due to a combination of electron correlation effects and basis set deficiencies. It is well known that HF method tends to overestimate vibrational frequencies. In density functional theory (DFT) some correlation effects are taken into account through the effective exchange-correlation potential. Becke's three parameter exchange functional in combination with the LYP correlation functional (B3-LYP) and Becke's exchange functional in combination with the Lee, Yang and Par (LYP) correlation functional (BLYP) were the most widely used for molecular calculations by a fairly large margin [4,5].

2. Experimental

Sertraline·HCl, pharmaceutical grade, was kindly provided as a gift by Pfizer Pharmaceuticals Production Corporation Ringaskiddy, Co. Cork, Ireland.

The FTIR spectra were recorded using Shimadzu 8201PC and Mattson 1000 spectrometer with the KBr technique, in the region 4000–400 cm^{-1} that was calibrated by polystyrene.

3. Computational methods

Experimental molecular geometry [3] was used as the initial guess for optimization. In this structure, we have changed to the Br atom with the Cl atom. All the theoretical calculations (vibrational wavenumbers, geometric parameters, atomic charges and the other molecular properties) were performed using the Gaussian 03 program package [6].

Ab initio calculations were carried out using small basis set (HF/3-21G) and larger basis set with polarization functions on heavy atoms (HF/6-31G(d)). DFT calculations were carried out by using B3LYP/STO-3G, B3LYP/3-21G, B3LYP/6-31 G(d), BLYP/STO-3G, BLYP/3-21G. Semi-empirical AM1 method was also used for comparison. The harmonic unscaled vibrational frequencies were calculated by analytical differentiation algorithms, for every each completely optimized geometry.

4. Results and discussion

4.1. Geometric parameters

Crystallographic studies on sertraline·HCl have shown the existence of several forms depending on the crystal. No obvious differences were observed between the sertraline HCl and HBr salts that could explain the increased polymorphism of the HCl salt [7]. Therefore, the experimental X-ray data of sertraline·HBr were used to calculate geometrical parameters of sertraline·HCl. In structure, sertraline has two planar phenyl rings that are approximately perpendicular to each other and an unsaturated ring in a half-chair conformation. The distance from the 'center-of-mass' to an extreme halogen is approximately 6 Å [8].

The labelling of the atoms in the X-ray structure [3] is shown in Fig. 1(a). Fig. 1(b) presents the geometry of molecule optimized using DFT method at the B3LYP/6-31G(d) level. The optimized geometrical parameters determined using the ab initio, density functional and AM1 methods for molecule are collected in Table 1. In the second column of Table 1, the experimental data obtained by the X-ray study [3] on molecule are also included.

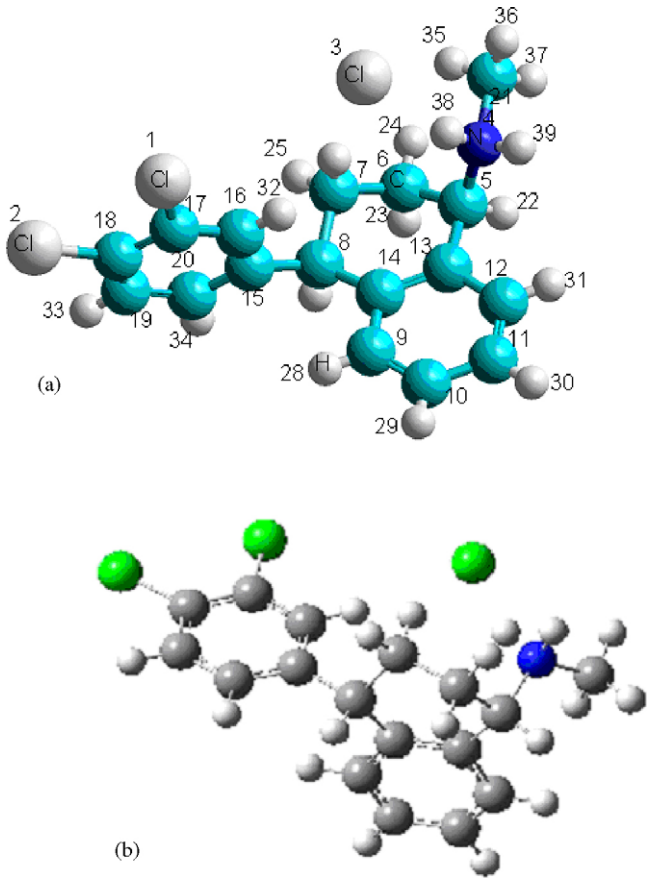


Fig. 1. (a) X-ray structure of sertraline hydrochloride (CSD code: CAVVUQ). (b) Geometry of the sertraline optimized at the B3LYP/6-31G(d) level.

As discussed by Jonson et al. [9] the BLYP functional leads to bond lengths which are systematically too long. The B3LYP method leads to geometry parameters which are much closer to experimental data [9–11]. A statistical treatment of these data (see at the bottom of Table 1) shows that for the bond lengths B3LYP/6-31G(d) (Fig. 2) is slightly better than the HF/6-31G(d) geometry. The lowest correlation coefficient for bond lengths was 0.9951 for BLYP/STO-3G method Electron correlation is important for on the overall geometry of the complete molecular model geometrical parameters.

The agreement between the calculated and the experimental bond angles is worse than for the bond lengths. The largest change between calculated and experimental bond angles are found in the C(21)–N(4)–H(39) angle which varying from 109° (optimized) to 103° (in the crystal). The reason for this is that the optimization is performed in an isolated condition, whereas the experimental X-ray structure was affected by the crystal environment. Torsion angles, as expected, are somewhat different because of the numerous degrees of conformational freedom present in the molecule.

The largest discrepancies are for the dihedral angles which involve amino nitrogen atom.

Table 1
Selected bond lengths (Å) and angles (°) values for sertraline hydrochloride

Parameter	X-ray[a]	B3LYP			BLYP		RHF		AM1	B3LYP[b]
		3-21G	6-31G(d)	STO-3G	3-21G	STO-3G	3-21G	6-31(d)		
Bond distance (Å)										
Cl(1)–C(17)	1.736	1.811	1.743	1.798	1.833	1.818	1.799	1.730	1.691	1.827
Cl(2)–C(18)	1.721	1.818	1.749	1.802	1.841	1.881	1.804	1.736	1.696	1.824
C(16)–C(17)	1.382	1.390	1.396	1.413	1.400	1.425	1.377	1.386	1.401	1.388
C(17)–C(18)	1.368	1.388	1.403	1.421	1.399	1.435	1.372	1.389	1.403	1.384
C(18)–C(19)	1.378	1.387	1.393	1.410	1.398	1.423	1.373	1.381	1.399	1.390
C(15)–C(8)	1.516	1.526	1.524	1.553	1.538	1.567	1.522	1.523	1.498	1.521
C(8)–C(14)	1.511	1.537	1.533	1.560	1.550	1.574	1.533	1.532	1.498	1.532
C(5)–N(4)	1.521	1.557	1.535	1.571	1.580	1.601	1.540	1.515	1.506	1.557
N(4)–H(38)	0.954	1.073	1.063	1.135	1.089	1.164	1.040	1.031	1.069	1.033
N(4)–H(39)	0.974	1.033	1.025	1.059	1.042	1.071	1.041	1.008	1.025	1.057
N(4)–C(21)	1.491	1.517	1.491	1.531	1.533	1.550	1.511	1.483	1.470	1.517
N(4)–Cl(3)	3.300	3.201	3.199	3.253	3.213	3.273	3.179	3.176	3.168	–
Cl(3)–H(39)	3.572	3.535	3.535	3.535	3.535	3.535	3.535	3.532	3.535	–
Cl(3)–H(38)	2.369	2.180	2.180	2.180	2.180	2.180	2.180	2.145	2.1800	–
CC		0.9967	0.9976	0.9964	0.9962	0.9951	0.9969	0.9974	0.9973	0.9890
Bond angle (°)										
C(21)–N(4)–H(39)	103.78	109.02	108.37	108.01	108.96	107.56	108.58	107.89	108.54	108.86
C(21)–N(4)–H(38)	103.66	106.05	106.96	105.69	105.86	105.70	105.97	106.26	109.14	108.38
C(21)–N(4)–C(5)	114.69	115.45	116.96	116.54	115.77	116.43	115.76	117.06	113.87	112.95
C(21)–N(4)–Cl(3)	93.26	96.07	96.08	96.08	96.07	96.079	96.08	96.08	96.79	–
CC		0.9790	0.9936	0.9928	0.9813	0.9954	0.9857	0.9961	0.9546	
Dihedral angle (°)										
C(13)–C(5)–N(4)–C(21)	−176.62	−71.58	−71.58	−71.83	−71.64	−70.33	−74.46	−72.90	−69.18	
C(6)–C(5)–N(4)–C(21)	52.22	164.11	164.11	165.02	165.97	166.72	162.10	162.76	167.07	
C(12)–C(13)–C(5)–N(4)	−74.04	82.01	82.01	82.19	83.63	83.50	82.27	81.67	79.64	
C(14)–C(13)–C(5)–N(4)	105.82	−98.32	−99.32	−98.07	−96.59	−96.70	−98.57	−100.14	−101.44	
C(20)–C(15)–C(8)–C(14)	−127.46	117.02	117.02	114.01	116.04	112.15	119.21	118.73	114.26	
C(15)–C(8)–C(14)–C(9)	36.47	−38.08	−38.08	−38.27	−37.35	−39.24	−36.84	−38.25	−40.51	
Energy (a.u.)		−2083.51 (6)	−2094.00 (6)	−2070.21 (6)	−2083.08 (6)	−2069.66 (6)	−2076.67 (6)	−2087.14 (6)	0.056 (6)	−1625.37 (6)
RMS gradient		0.002 (5)	0.002 (5)	0.007 (5)	0.002 (5)	0.007 (5)	0.002 (5)	0.002 (5)	0.004 (5)	0.005

[a] Data from Ref. [3].
[b] Sertralin (without Cl), CC: correlation coefficient.

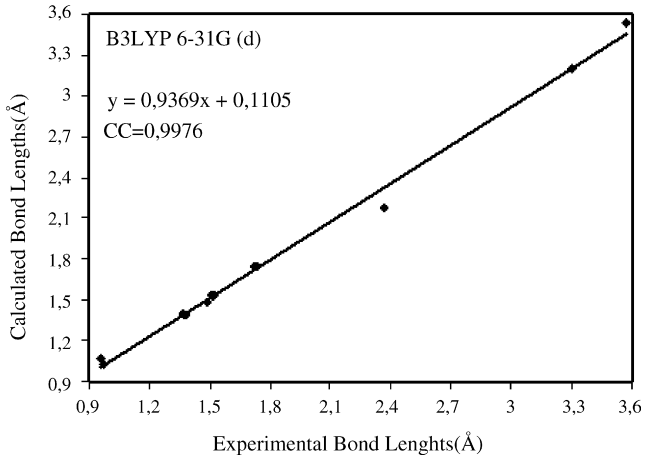
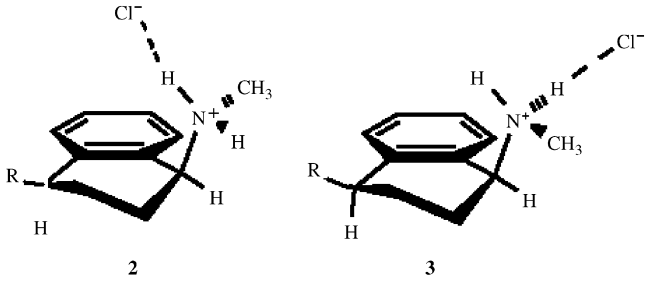


Fig. 2. Calculated (B3LYP/6-31G(d)) bond lengths in comparison with experimental data.



R : dichlorophenyl ring

Various polymorphic forms of **1** have been described in the literature and found as 64° for dihedral angle C(5)–C(6)–C(7)–C(8) of Forms I (**2**) and III (**3**) using solid-state CP/MAS ^{13}C NMR spectra [12–14]. According to X-ray study [8], sertraline hydrochloride has an unsaturated ring in a half-chair conformation. The C(5)–C(6)–C(7)–C(8) dihedral value measured as 62.3° by X-ray crystallography. We calculated this angle as 63.88°.

The patent reports that as 68.8° for C(6)–C(5)–N–*C*H$_3$ for Form III (**3**) whereas only Form I (**2**) has an antiperplanar type value (162.6°). In solid-state CP/MAS ^{13}C NMR spectra [14] of conformational polymorphs Forms I (**2**) and III of sertraline·HCl had also correlated with a γ-gauche effect resulting from the respective 162.6° antiperiplanar and 68.8° (+)-synclinal C(6)–C(5)–N–*C*H3 torsion angles as measured by X-ray crystallography. As can be seen from Table 1, we calculated ca 164° for this angle. According to calculation results, two phenyl groups are nearly perpendicular to each other.

In order to find molecular geometry of Form III (**3**), the molecule was constructed by keeping C(6)–C(5)–N–*C*H$_3$ angle fixed at 70°. We have not found a minimum for this structure. The results obtained were unrealistic, with the IR spectra having negative frequencies. If there are negative frequencies in an IR spectrum, it is a sign that you have not obtained the minimum energy for the analysed structure. A valid minimum energy structure has only positive frequencies. Moreover, the measured and calculated bond lengths and bond angles for two models are nearly the same as those appearing in X-ray study [3].

Sertraline is in the form of a pharmaceutically acceptable salt (e.g., chloride, lactate, acetate, aspartate). Comparison purpose, the molecular structure of sertraline without Cl$^-$ ion was also calculated by using B3LYP/6-31G(d) basis set (Table 1).

4.2. Other molecular properties

The calculation of effective atomic charges plays an important role in the application of quantum mechanical calculations to molecular systems. Our interest here is in the comparison of different methods to describe the electron distribution in sertraline as broadly as possible, and assess the sensitivity of the calculated charges to changes in (1) the choice of the basis set; (2) the choice of the quantum mechanical method.

Mulliken charges are calculated by determining the electron population of each atom as defined by the basis functions. The calculated Mulliken charge values using different levels and basis sets are listed in Table 2. The results can, however, better be represented in graphical form as has been done in Figs. 3 and 4. Fig. 3 shows that the Mulliken charge of atoms for B3LYP levels using STO-3G, 3-21G and 6-31G(d) basic sets and Fig. 4 shows that the Mulliken charge of the same atoms for B3LYP, BLYP and HF levels.

From those results, it will be possible to say to the change of charge distribution by a change basic set. The charges depending

Table 2
Selected atomic charges of sertraline hydrochloride for different levels and basis sets

Atom	B3LYP/3-21G	B3LYP/6-31G(d)	RB3LYP/STO-3G	RBLYP/3-21G	RBLYP/STO-3G	RHF/3-21G	RHF/6-31G(d)	AM1	UBLYP/6-31G
C(19)	−0.142754	−0.127742	−0.072780	−0.127539	−0.072318	−0.177364	−0.175062	−0.126944	−0.149134
C(16)	−0.163004	−0.179073	−0.073652	−0.158881	−0.072585	−0.179957	−0.191607	−0.097985	−0.144857
N(4)	−0.623164	−0.600919	−0.246940	−0.559245	−0.224727	−0.805426	−0.765850	−0.058491	−0.585622
H(39)	0.359991	0.376477	0.255503	0.344116	0.242913	0.399963	0.423217	0.217213	0.287778
H(38)	0.389893	0.380334	0.247767	0.358549	0.213338	0.479992	0.473132	0.310760	0.363914
Cl(3)	−0.767375	−0.746970	−0.751342	−0.732422	−0.682117	−0.857591	−0.837619	−0.879983	
C(21)	−0.443595	−0.337946	−0.134093	−0.426096	−0.133449	0.421207	−0.338245	−0.185599	−0.448424
C(5)	−0.150620	−0.086012	0.029077	−0.149034	0.023222	−0.095634	−0.054169	−0.016399	−0.209314
C(17)	−0.277355	0.095855	0.030222	−0.247565	0.026637	−0.316995	−0.145137	−0.055550	−0.252789
Cl(2)	0.135265	0.004868	−0.100369	0.113507	−0.094861	0.151629	0.029560	0.004683	0.118292
Cl(1)	0.175380	0.039314	−0.078772	0.152550	−0.074451	0.193671	0.063434	0.040442	0.110581
C(18)	−0.257603	−0.075415	0.026514	−0.227916	0.023138	−0.299433	−0.129651	−0.062863	

R: restricted; U: unrestricted.

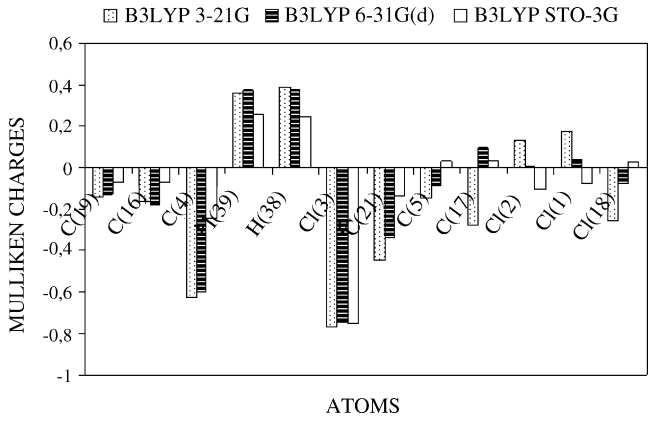


Fig. 3. Variance of the atomic charges for different basis sets of B3LYP level.

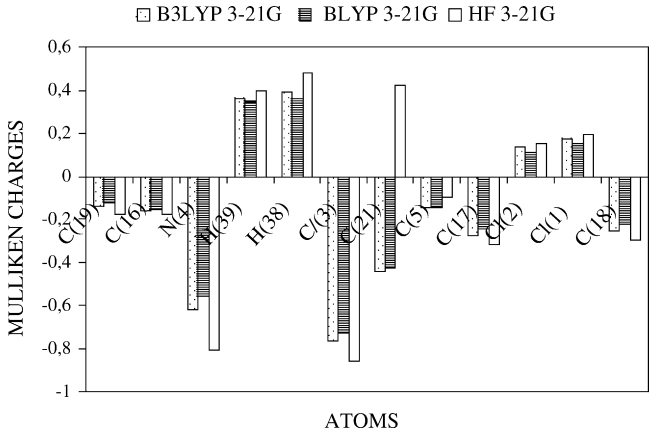


Fig. 4. Comparison of different methods for calculated atomic charges.

on basis set are changed due to polarization. For example, the charge of C19 atom is $-0.072780e^-$ for B3LYP/STO-3G, $-0.127742e^-$ for B3LYP/6-31G(d), $-0.142754e^-$ for B3LYP/3-21G and the charge of C16 atom is $-0.073652e^-$ for B3LYP/STO-3G, $-0.163004e^-$ for B3LYP/6-31G(d), $-0.179073e^-$ for B3LYP/3-21G.

One of the objectives of this investigation is to study the effect of the basis set on molecular polarizability of sertraline HCl using GAUSSIAN 03W. In this study the computation of molecular polarizability of sertraline with different basis sets starting with minimal basis set (STO-3G) and then with split valence basis sets (3-21G and 6-31G(d)) is reported. Here, α is a second rank tensor property called the dipole polarizability and

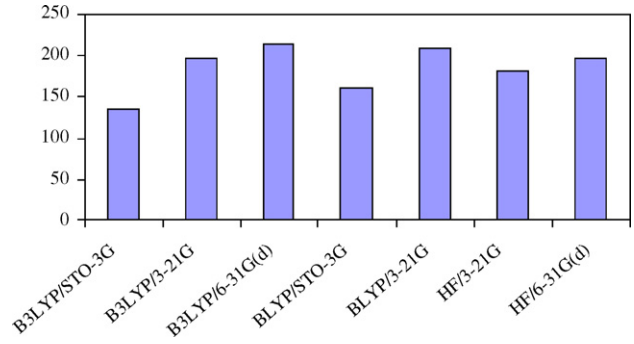


Fig. 5. Comparison of different methods for calculated polarizabilities.

mean polarizability $\langle\alpha\rangle$ are evaluated using Eq. (1)

$$\langle\alpha\rangle = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \quad (1)$$

The calculated polarizabilities using different basis sets for sertraline molecule are summarized in Table 3. As seen from the Fig. 5, the largest polarizability was observed for B3LYP/6-31G(d).

4.3. Infrared spectra

To our best knowledge, no vibrational analyses have been reported for sertraline HCl. The computed vibrational wavenumbers (raw values) in the 1850–400 cm^{-1} spectral region, their relative IR intensities, and the characterization established at the various levels are collected in Table 4. Table 4 also presents the observed FT-IR wavenumbers. The relative intensities were obtained by dividing the computed value by the intensity of the strongest line. The observed FT-IR spectrum is given in Fig. 6. The computed intensities show marked deviations from the observed values. One may note that the computed wavenumbers correspond to the isolated molecular state whereas the observed wavenumbers correspond to the solid-state spectra.

Sertraline·HCl molecule has three groups (a) methyl ammonium chloride, (b) a hydrophobic phenyl ring and (c) an aromatic ring with electronegative two Cl atoms [8]. We have assigned the fundamental modes of these groups on the basis of group vibrational concept and calculated vibrational frequencies.

The fundamental vibrational modes were calculated on the basis of DFT and ab initio calculations. GaussView 03 which is a graphical interface [6] was used to assign the calculated harmonic frequencies. On the whole, the predicted vibrational

Table 3
Calculated polarizabilities for sertraline hydrochloride

Basis set	α_{xx}	α_{xy}	α_{yy}	α_{xz}	α_{yz}	α_{zz}	$\langle\alpha\rangle$
B3LYP/STO-3G	183.313	−1.818	120.695	6.031	7.589	101.911	135.305
B3LYP/3-21G	263.439	2.636	172.321	3.558	−5.993	156.904	197.554
B3LYP/6-31G(d)	279.923	−0.137	189.479	5.497	−5.437	173.407	214.269
BLYP/ STO-3G	211.282	2.749	165.398	6.306	−7.399	106.281	160.987
BLYP/3-21G	281.092	−3.683	183.966	4.107	−1.505	162.181	209.079
HF/3-21G	239.878	−3.102	155.514	2.461	−5.221	148.518	181.303
HF/6-31G(d)	253.502	−2.415	172.071	4.757	7.591	163.801	196.458

Table 4
Observed and calculated IR wavenumbers (relative intensities) for sertraline hydrochloride using B3LYP/3-21G, B3LYP/ 6-31G(d), HF/3-21G(d), HF/6-31G(d), BLYP/3-21G methods

Tentative assignment	Observed	B3LYP		HF		BLYP	B3LYP
		3-21G	6-31G(d)	3-21G	6-31G(d)	3-21G	6-31G(d)[a]
$\delta_s(N^+H_2)$	1582 (mw)	1680 (68)	1658 (53)	1831 (100)	1820 (66)	1623 (74)	1623 (12)
ν_{ring}	1564 (vw)	1630 (6)	1641 (4)	1773 (7)	1810 (17)	1565 (8)	1573 (100)
ν_{ring}	1485 (w)	1594 (11)	1610 (11)	1736 (10)	1666 (39)	1542 (3)	1553 (28)
$\delta_a(CH_3) + \delta_s(CH_2)$	1468 (vs)	1573 (17)	1539 (41)	1682 (82)	1663 (100)	1535 (33)	1549 (5)
$\delta_s(CH_2) + \delta_s(NH_2)$	1428 (mw)	1563 (20)	1537 (26)	1669 (37)	1649 (41)	1528 (20)	1540 (3)
$\delta\nu_{ring} + \delta(CH)$	1401 (s)	1524 (65)	1517 (82)	1658 (68)	1652 (74)	1469 (79)	1506 (74)
$\delta(CH_2) + \delta(CH_3) + \delta(NH_2)$		1505 (11)	1510 (10)	1652 (11)	1634 (22)	1431 (24)	1415 (22)
$\delta(CH_3)_+ \ \nu$(N-C) + $\delta(CH_3)$	1365 vw	1478 (17)	1469 (28)	1624 (34)	1624 (24)		1394 (4)
C–NH_2 + $\delta(CH_3)$ + δ(CH)	1338 (mw)	1472 (100)	1460 (69)	1611 (92)	1612 (62)	1418 (100)	1357 (11)
$\omega(CH_2)$		1454 (21)	1446 (26)	1577 (25)	1572 (30)	1408 (24)	
$\omega(NH_2) + \delta$(CH)	1310 (vw)	1430 (32)	1432 (46)	1551 (20)	1503 (16)	1384 (37)	1344 (20)
$\delta(CH_3) + \delta$(CH) + ν_{ring} + ν(C–N)	1270 (w)	1373 (18)	1374 (26)	1493 (11)	1494 (22)	1363 (18)	1325 (33)
$\omega(CH_2) + \nu_{ring} + r(NH_2)$	1250 w	1259 (8)	1307 (4)	1358 (7)	1352 (16)	1288 (7)	1228 (2)
$r(CH_3) + \delta$(CH) + ν(CNC)	1212 (mw)	1245 (35)	1264 (8)	1259 (33)	1268 (9)	1230 (14)	1214 (25)
δ(CH) + $t(CH_2) + \omega$(N–H)	1171 vw						1173 (27)
$\delta_{ring} + \nu$(Ph–Cl)	1138 (s)	1162 (38)	1160 (100)	1160 (13)	1204 (12)	1152 (86)	1134 (20)
δ(CH)	1076 vw						
$\delta(CH_3) + \delta_{ring} + \nu$(C–N)	1058 vw	1140 (8)	1132 (6)	1150 (39)	1132 (55)	1100 (12)	
δ(CH) + ν(Ph–Cl)	1025 (m)	1097 (6)	1096 (5)			1020 (43)	
CN + $\omega(CH_2)$		1082 (13)		1108 (13)	1114 (41)		
γ(CH) + $r(CH_2) + \delta_{CCC}$	1005 (86) sh	1064 (10)	1080 (9)	1061 (59)	1105 (12)		1049 (8)
γ(CH) + δ_{ring}	975 vw					993 (10)	
$\delta_{CCC} + \gamma$(CH)	955 m	1061 (25)	1041 (42)	1006 (17)	1047 (23)	981 (8)	1047 (7)
$\omega(NH_2) + r(CH_2) + \gamma$(CH)	922 (mw)	1029 (8)	1033 (26)	990 (46)	998 (10)	943 (21)	964 (3)
γ(CH)	901 vw	996 (12)	1020 (6)	957 (17)	972 (3)	930 (12)	986 (12)
$r(CH_2) + \gamma$(CH)	891 (w)	969 (13)	970 (18)	944 (18)	932 (46)		941 (7)
$r(CH_2) + \gamma$(CH)	824 (m)	928 (21)	925 (13)	894 (13)	914 (7)	893 (21)	928 (19)
$\gamma(NH_2) + \gamma$(CH)	803 (w)	852 (37)	838 (14)	885 (39)	873 (35)	779 (30)	852 (34)
$r(NH_2) + r(CH_3) + r(CH_2)$	787 (s)	814 (27)	808 (24)	860 (37)	844 (25)		814 (25)
γ(CH) + $\gamma(NH_2)$							
γ_{ring}	762 (mw)	795 (9)	786 (10)	812	812 (3)	809 (39)	795 (8)
γ(CH) + $\gamma(NH_2)$	743 (vw)						
γPh	713 sh						
γ(CH) + γPh	704 (mw)	782 (55)	772 (38)	775 (19)	800 (3)	748 (70)	782 (51)
$\gamma_{ring} + \gamma$(NH)	672 (mw)	772 (3)	750 (1)	751 (10)	764 (17)	689 (18)	772 (3)
$\gamma_{ring} + \gamma$(CH)	621 (w)	716 (16)		725 (11)	739 (19)	670 (13)	716 (15)
γ_{ring}	590 (mw)	694 (11)	685 (18)		691 (9)	633 (10)	694 (10)
γ_{ring}	565 (w)	613 (6)	600 (5)	537 (13)	540 (26)	585 (8)	613 (6)
γ_{ring}	512 (vw)	513 (6)	511 (9)	534 (13)		494 (7)	513 (6)
γ_{ring}	495 (mw)	484 (14)	499 (24)	516 (18)		462 (16)	484 (13)
τ(ring)	448 (w)	483 (12)	466 (3)	442 (4)	462 (4)	456 (21)	483 (11)
γ(CH) + γ(C–Cl)	424 (w)	477 (10)	428 (5)	414 (6)		404 (5)	477 (9)

[a] For sertraline without chloride.

frequencies are in agreement with the experimental results. The calculated vibrational wavenumbers using different methods were compared with experimentally observed values. Some bands found in the predicted IR spectra were not observed in the experimental spectrum of sertraline·HCl.

The correlation graphs between the unscaled calculated and observed results for the assigned fundamentals in the fingerprint region (400–1600 cm^{-1}) are shown in Fig. 7.

NH and C–H stretching frequencies were not used as input data to the corelasyon procedure. These neglected fundamentals are which often show significant uncertainties.

Theoretical harmonic frequencies typically overestimate observed fundamentals due to the neglect of mechanical anharmonicity, electron correlation and basis set effects Theoretical harmonic frequencies are often scaled to compare with experimental wavenumbers. Unscaled harmonic frequencies show a tendency to overestimate experimental fundamentals, with a large number of frequencies overestimating the experimental data by more than 70 cm^{-1}.

The root mean square deviation of vibrations in the 400–1600 cm^{-1} range is 75.17 cm^{-1} for the BLYP/321-G and 69.22 for B3LYP/6-31G(d). In a second step an overall scaling factor has been applied to the calculated frequencies for these levels. The scaling factor is 1 for the BLYP method and 0.962 [15] for the B3LYP functional. With use of the scaling factor, the root mean square deviation decreased to 26.22 cm^{-1} for B3LYP.

For CH_3NH_2 group [16] the vibrational modes are the C–H stretching modes, the NH_2 scissors, N–H stretching modes, NH_2

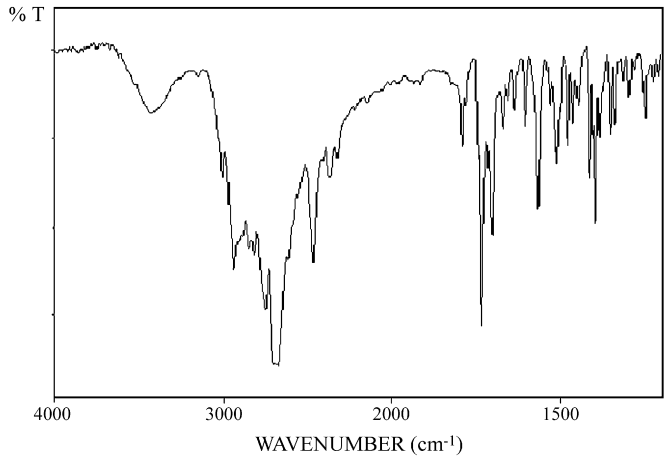


Fig. 6. Infrared spectrum of sertralin hydrochloride (KBr disc).

wag CH_3 rock C–N stretching and the torsion about the C–N bond. NH_2 symmetric stretching vibrations occur at 3361 cm^{-1}. The band at 780 cm^{-1} corresponds to the NH_2 wag and the band at 1616 cm^{-1} corresponds to the NH bending motions. The C–N stretching is located at 1044 cm^{-1}. The absorption of the N^+H_2 group are lower by about 200 cm^{-1}. In this region also occurs stretching modes of CH_3. The asymmetric stretching of N^+H_2 has been assigned to the ranges 2920–2915 cm^{-1}. We observed very weak band at 2918 cm^{-1}. The band observed at 2751 cm^{-1} is assigned to the symmetric stretching of N^+H_2. The calculated band at ca. 2620 cm^{-1} is assigned to the ν(NH···Cl).

The deformation vibration (scissors) of methyl bonded N^+H_2 group is found in the region 1620–1560 cm^{-1} [17]. The bands at 1582, 1428 and 803 cm^{-1} are assigned to the $\delta_S(N^+H_2)$, wagging and rocking modes of sertraline hydrochloride, respectively. The band at 891 cm^{-1} is assigned to ν(CN) stretching mode. This mode showed also coupling between the other modes. Table 4 indicates that most of the vibrational wave numbers arise on account of mixing of different normal modes.

The weak bands observed at 3076, 3037 and 3008 cm^{-1} are assigned to C–H stretching frequencies. The bands observed at 2817 and 2940 cm^{-1} are assigned to C–H stretching of N bonded CH_3 group and CH_2, respectively. The CH_2 group (for ring) gives rice to a band near 1465 cm^{-1} due to the scissoring

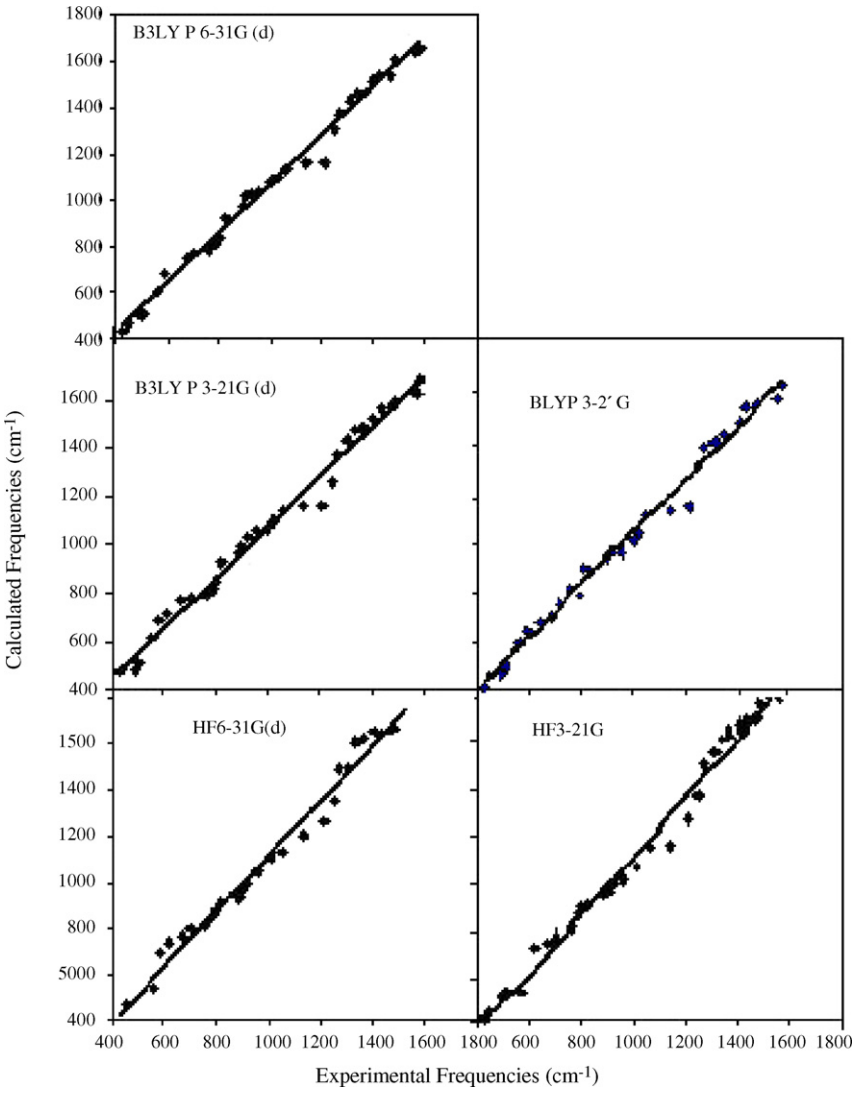


Fig. 7. Unscaled calculated vibrational frequencies in comparison to the experimentally obtained data. All units in cm^{-1}.

vibration. The asymmetrical CH_3 deformation is also found around 1460 cm^{-1}. A methyl group attached to a nitrogen atom gives rice to a band at 1408 cm^{-1} as a symmetric scissors. The observed IR band at 1468 cm^{-1} is assigned to the asymmetrical CH_3 and CH_2 scissoring vibration modes, corresponding to the computed spectra [18].

Vucis et al. [1] reported that the frequencies at 1130 and 1077 cm^{-1} were observed Ph–Cl bands in *N*-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]-methanamine *N*-oxide. In the IR spectrum of sertraline·HCl, the corresponding bands are observed at 1138 and 1025 cm^{-1}. The theoretical computations at the ab initio and density functional levels of the other vibrational modes of molecule studied are given in Table 4.

The calculated vibrational spectrum of sertraline without Cl^- atom using B3LYP/6-31G(d) is also evaluated. As can be seen from Table 4, computed wavenumbers of this molecule have lower wavenumbers and intensities than that of the sertraline·HCl.

5. Conclusions

The frequency assignments were performed for the first time from FT-IR spectrum recorded for sertraline·HCl. Theoretical DFT and ab initio calculations of the vibrational spectra of the molecule presented in this paper are compared with the infrared spectrum of the solid sertraline·HCl. Geometries were reproduced within the limits of accuracy of available experimental data The molecular geometry of sertralin.HCl is best reproduced at the B3LYP levels of DFT theory.

All frequencies of the bands can be approached practically by theoretical calculation performed for a single isolated molecule. Regarding the harmonic vibrational frequencies, we found that B3LYP is better for the frequencies compared to BLYP and HF. The Mulliken charges and molecular polarizability values of sertraline using different levels and basis sets were also calculated. The largest polarizability was observed for B3LYP/6-31G(d).

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