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Theoretical and experimental study of Aripriprazole molecule

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We report here a joint theoretical and experimental study on the geometry and molecular properties such as: vibrational and NMR spectra and molecular electrostatic potential of Aripriprazole molecule. The molecular vibrations of Aripriprazole were investigated by FTIR and FT-Raman spectroscopies. In parallel, quantum chemical calculations based on Density Functional Theory (DFT) at B3LYP/6-31G(d) level of theory are used to determine the geometrical, energetic and vibrational characteristics of the molecule. The molecular electrostatic potential of the molecule has been calculated and used for predicting site candidates of electrophilic attack. ^{1}H and ^{13}C NMR spectra of Aripriprazole were obtained in DMSO solution and they were also calculated using the GIAO (Gauge-Including Atomic Orbitals) method implemented in the Gaussian package. Again, a very good correlation was found between experimental and theoretical NMR data especially for proton chemical shifts and this allows us to validate the calculated structure and geometrical parameters of the molecule. The calculations reveal also that magnetic properties are particularly sensitive to the basis sets used for calculations.

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Keywords: Aripriprazole, FTIR/ATR, Raman, NMR, DFT

1. Introduction

DFT methods are increasingly applied to representative pharmacological compounds aiming to elucidate their molecular structures and electronic properties and further to elucidate the influence of electronic and structural factors on the reactions in which these compounds are involved. These studies contribute to the recognition of structure-activity relationships and to the understanding of the properties and system behavior. Theoretical studies of bioactive compounds are of interest in order to gain a deeper insight into their action and thus helping in the design of new drugs with certain therapeutic effects. The knowledge of physicochemical properties and sites of reaction of Aripriprazole will provide a deeper insight of its probable action. Particularly, the molecular electrostatic potential (MEP) is well suited for analyzing processes based on the "recognition" of one molecule by another, as in drug–receptor, and enzyme–substrate interaction, because it is through their potentials that the two species first "see" each other.

For a proper understanding of IR and Raman spectra, a reliable assignment of all vibrational bands is essential. For this purpose, the quantum chemical methods, ranging from semiempirical to DFT approaches, are invaluable tools [1-3], each method having its own advantages. DFT methods, particularly those using hybrid exchange-correlation functionals [4], have evolved to a powerful quantum chemical tool for the determination of the electronic structure of molecules. In the framework of DFT approach, different exchange and correlation functionals are routinely used. Among these, the B3LYP combination [5,6] is the most used since it proved its ability in reproducing various molecular properties, including vibrational spectra. The combined use of B3LYP functional and standard split valence basis set 6-31G(d) has been previously shown [7-9] to provide an excellent compromise between accuracy and computational efficiency of vibrational spectra for large and medium-size molecules.

This study is focused on the molecular structure and vibrational and NMR spectra of Aripriprazole molecule (also in pharmacy known as Abilify), which is a psychotropic drug used in the treatment of schizophrenia. Recently, this compound entered Phase III trials for patients with schizophrenia in several countries.

2. Experimental

FTIR/ATR spectra for Aripriprazole powder sample were recorded at room temperature on a conventional Equinox 55 FTIR spectrometer, coupled with a Bruker Miracle ATR sampling device. FT-Raman spectra were recorded in a backscattering geometry with a Bruker FRA 106/S Raman accessory equipped with a nitrogen cooled Ge detector. The 1064 nm Nd:YAg laser was used as excitation source, and the laser power was set to 400 mW. All spectra were recorded with a resolution of 4 cm^{-1} by co-adding 32 scans.

The ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AVANCE NMR spectrometer, using the TMS as internal standard.

The samples were prepared by the dissolution of Aripriprazole in DMSO (signal for ^{1}H at 2.51 ppm and at 39.5 ppm for ^{13}C). The spectra were recorded using a single excitation pulse of 12 μs for ^{1}H and 9 μs for ^{13}C. The FID signal was acquired 100 times for ^{1}H and 400 times for ^{13}C.

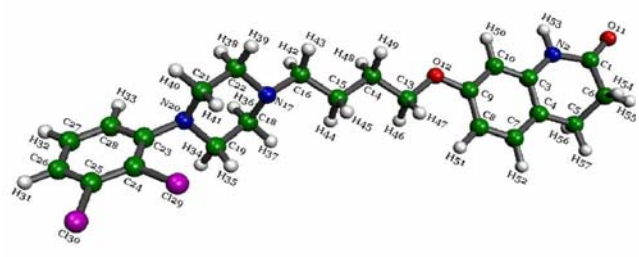

Fig. 1. Molecular structure and atom numbering scheme for Aripriprazole molecule.

3. Computational details

The molecular geometry optimizations, vibrational normal modes and NMR spectra calculations were performed with the Gaussian 98W software package [10] by using DFT methods with B3LYP and BLYP functionals [4-6]. Hybrid B3LYP functional has been previously shown to perform very well for a large variety of molecular properties, while BLYP functional was proved to be particularly useful for calculating normal vibrational modes [11]. The Becke's exchange functional has the advantage of frequency scaling factor very close to unity [13] so that the DFT calculated wave-numbers based on BLYP method are not affected by scaling procedures. The basis set used in these calculations is 6-31G(d). Raman activities were computed by numerical differentiation of analytic second derivatives implemented in Gaussian 98 program. Being particularly time consuming, this calculation was carried out only with B3LYP functional.

The calculation of NMR spectrum of Aripriprazole were performed using the GIAO (Gauge-Including Atomic Orbitals) method [15, 16], implemented in the Gaussian package [12], with the B3LYP exchange-correlation functional, in conjunction with 6-31G(d) and cc-pVDZ basis sets. In order to express the chemical shifts in ppm, the geometry of the tetramethysilane (TMS) molecule has been optimized and then its NMR spectrum was calculated by using the same method and basis set as for the calculation on Aripriprazole molecule.

4. Results and discussion

First we optimized the geometry for Aripriprazole molecule at B3LYP/6-31G(d) level of theory without any constraint. After stationary point was located, vibrational frequencies were calculated in order to ascertain that the structure found corresponds to a minimum on the potential energy surfaces. No imaginary frequencies were obtained for optimized geometry and thus it represents a true minimum on the potential energy surface.

In Fig. 2 are given the experimental FTIR and FT-Raman spectra and in Table 1 are summarized the experimental and calculated normal modes along with their IR intensities and Raman activities. The experimental and calculated intensities are expressed as percentage of the most intense experimental or calculated intensity, respectively.

The last column in Table 1 contains the motions that contribute the most to different normal modes according to B3LYP/6-31G(d) method.

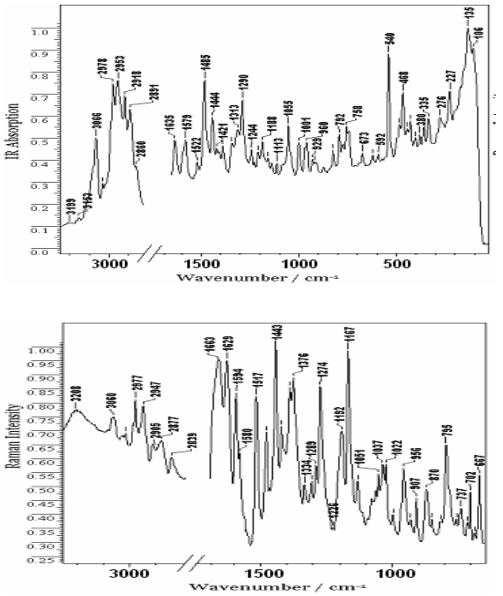

Fig. 2. Experimental FTIR (left) and FT-Raman (right) spectra of Aripriprazole molecule.

The computed wave-numbers have been scaled by 0.9614 as proposed by Scott and Radom [13]. Vibrational mode assignments were made by visual inspection of modes animated by using the Molekel program [12]. To aid in mode assignment, we based on the direct comparison between the experimental and calculated spectra by considering both the frequency sequence and intensity pattern and by comparisons with vibrational spectra of similar compounds [20-22]. Although the relative intensities are not well predicted for all IR or Raman bands, they still provide useful help for the assignment of the normal modes in the experimental spectra [23].

Table 1. Selected experimental and calculated wavenumbers and vibrational band intensities of Aripriprazole molecule.

Mode	Experimental wavenumbers (cm^{-1})		I%	A%	Calculated wavenumbers (cm^{-1})*		I%	A%	Band Assignment**
	IR	Raman			BLYP	B3LYP			
1	3200		77		3470	3453	4	49	ν(NH)
2	3060		75		3116	3079	1	38	ν(CH)
3	3014	3016	69	29	3013	3013	3	78	ν(CH_2)
4		2978		75	3003	2978	2	59	ν(CH_2)
5	2977		81		3012	2977	12	2	ν(CH_2)
6		2960		73	2993	2960	9	43	ν(CH_2)
7	2955	2953	74	76	2988	2955	0	22	ν(CH_2), ν(CH)
8	2947		79		2975	2941	5	18	ν(CH)
9	2895	2891	64	63	2922	2894	9	27	ν(CH_2)
10	2839	2812	61	20	2843	2822	25	69	ν(CH)
11	1719		30		1726	1740	100	16	ν(CO), ν(CN), ν(CC), δ(NH), ν(CH)
12	1663	1668	95	33	1612	1616	50	20	ν(CO), ν(CC), ν(NC), δ(CH), ν(NH)
13	1580	1579	62	49	1572	1575	9	15	ν(CC), ν(CO), ν(NC), ν(NH), δ(CH)
14		1485		77	1500	1483	3	8	δ(CH_2)
15	1478		70		1493	1475	1	9	δ(CH_2
16	1443	1444	100	60	1457	1438	1	8	δ(CH_2)
17	1420	1421	72	45	1438	1434	17	3	ν(CC), ν(NC), δ(CH)
18	1413	1408	63	44	1407	1398	2	3	ω(CH_2), δ(CH_2), δ(CH)
19	1390	1390	86	46	1396	1391	5	3	ω(CH_2, ν(CC), δ(NH), δ(CH)
20	1376	1381	89	41	1388	1388	8	1	ω(CH_2), δ(CH), ν(CC), ν(NC)
21	1274	1271	86	42	1280	1273	9	21	δ(NH), δ(CH), ω(CH_2), ν(NC), ν(CC), ν(CO)
22	1244	1244	43	45	1261	1246	1	7	ν(CC), δ(CH), τ($C19H_2$)
23	1192	1188	70	48	1200	1192	0	5	τ(CH_2), δ(CH)
24	1167		99		1179	1176	39	2	δ(CH), δ(CH), τ(CH_2), ν(CN), ν(CC)
25	1078	1084	46	38	1079	1078	2	1	δ(CH), ρ(CH_2), τ(CH_2), ν(NC), ν(CC)
26	1062	1055	49	56	1068	1068	2	5	ω(CH_2), ν(CC), δ(CH_2), δ(CH), ρ(CH_2), ν(CC), ν(OC)
27	997	1001	40	48	1007	1010	0	4	ρ(CH_2), ω(CH_2), ν(NC), ν(CC), ν(OC), δ(CH)
28	967	968	42	46	977	979	10	0	ρ(CH_2), ω(CH_2), ν(CC), ν(CN)
29	816	825	38	45	818	823	6	1	δ(CH)
30	795	793	65	52	805	799	1	0	ρ(CH_2), δ(CH)
31	756	758	38	55	759	765	2	4	δ(CH), ν(CCl), ν(CN)
32	743	744	41	53	753	753	1	3	ρ(CH_2), δ(CH), δ(NH), ν(CC)
33	667	673	54	43	675	674	1	1	ρ(CH_2), δ(CH), δ(NH)
34		540		88	546	542	4	1	ρ(CH_2), δ(NH), δ(CH), ω(CH_2)
35		469		71	477	473	0	1	δ(CH), ρ(CH), ρ(CH_2)
36		447		54	446	446	0	2	δ(CH)
37		359		56	356	355	0	2	ρ(CH_2), δ(CH), ω(CH_2)
38		335		59	325	323	0	2	ρ(CH_2), δ(NH), δ(CH)
39		294		52	298	297	0	1	δ(CH), δ(NH), ω(CH_2), ρ(CH_2)
40		171		74	186	184	1	1	ρ(CH_2), δ(CH)
41		155		81	164	162	0	1	ρ(CH_2), δ(CH), τ(CH_2)
42		135		100	142	141	0	0	δ(CH), δ(CH_2), ρ(CH_2), ω(CH_2)

* scaled values

** ν-stretching, δ-in-plane bending, ω-wagging, ρ-rocking, τ-twisting

We will base our discussion of the vibrational bands mainly on the results obtained by B3LYP/6-31G(d) method because it has already been proved [7,24] as an excellent compromise between accuracy and computational efficiency. First we will give some general characteristics of the calculated vibrational spectrum. The mean deviation in reproducing the whole Raman spectrum of Aripriprazole is 13.0 cm^{-1} and 20.7 cm^{-1} by B3LYP and BLYP method, respectively. BLYP method is known to be able to provide accurate vibrational frequencies without

the need for scaling the calculated wavenumbers. However, for Aripriprazole molecule, the BLYP/6-31G(d) calculation does not offer a better agreement between the experimental and theory, neither for higher frequencies nor for the lower ones. The calculations reveal that BLYP exchange-correlation functional performs better than B3LYP for few exceptions: the normal modes seen in the experimental Raman spectrum at 758 cm^{-1}, 1408 cm^{-1} and 1719 cm^{-1} in the IR spectrum. The first mode involves a δ(CH) and ν(CCl) vibrations, the second has dominant out-of-plane vibrations of CH and CH_2 groups in the aromatic rings, including also out-of-plane bending vibrations and the third involves has a dominant ν(CO) vibration. BLYP method provides an improvement of the agreement between the experiment and theory of 6cm^{-1}, 9cm^{-1} and 14cm^{-1} for the three modes, respectively.

The experimental band at 3200 cm^{-1} in the IR spectrum corresponds to the ν(NH) stretching vibration. The corresponding theoretical value for the gas-phase molecule was found at 3453 cm^{-1} (using the B3LYP functional) and 3470 cm^{-1} (using the BLYP functional), a significantly larger value than the experimental one. This discrepancy is due to the intermolecular interactions involving the NH group [23].The asymmetric and symmetric vibrations of the CH_2 group are seen at 3014 cm^{-1} to 2895 cm^{-1}(IR) and 3016 cm^{-1} to 2891 cm^{-1} (Raman), very well reproduced by B3LYP calculations at 3013 and 2894 cm^{-1}, respectively.

The experimental bands at 1719 cm^{-1} and 1663 cm^{-1} correspond to the C-O vibrations The C-O stretching normal mode give rise to the most intense IR calculated band at 1740 cm^{-1}, attributed to the experimental value at 1719 cm^{-1}.

The most intense calculated Raman activity (2926 cm^{-1}) corresponds to the ν(CH) ring vibrations. FTIR experimental spectrum shows the most intense band at 1443cm^{-1}, assigned to in plane CH bending, while the theory predicts it at 1740 cm^{-1}, corresponding to a complex vibrational mode involving in plane NH vibrations, ring bending, CO, CN, CC and CH stretching vibrations. C-C stretching vibrations coupled with C-H bendings give rise to the experimental bands in the 1580-1517 cm^{-1} range. Also in this range there is a very good agreement between the experiment and theory, the deviation being less than 10 cm^{-1}. The most intense band in the experimental IR spectrum is located at 1443 cm^{-1} and it is assigned to a δ(CH_2) mode whose the calculated wavenumber is 1438 cm^{-1}. C-N stretching vibrations in the 1381-1322 cm^{-1} are strongly coupled with CH_2 wagging vibrations and with stretching C-C modes.

The most intense band in the low wave number region correspond to the C-Cl stretching whose experimental and B3LYP calculated value is 496 cm^{-1}.

Molecular electrostatic potential (MEP) is related to the electronic density and is a very useful descriptor in understanding sites for electrophilic attack and nucleophilic reactions as well as hydrogen bonding interactions [14-17]. It can be used for interpreting and predicting the reactive behavior of a wide variety of chemical systems in both electrophilic and nucleophilic reactions, the study of biological recognition processes and hydrogen bonding interactions [18].

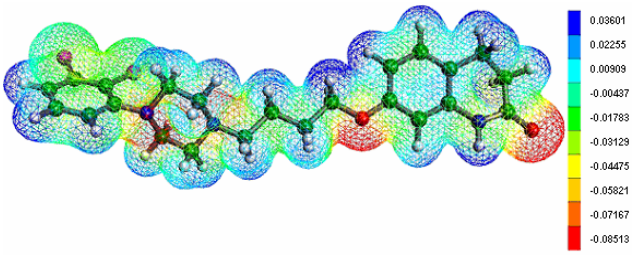

Fig. 3. Calculated 3D molecular electrostatic potential contour map of Aripriprazole molecule in a.u. The electron density isosurface is 0.02 a.u.

Unlike many of the other quantities used at present and earlier as indices of reactivity, molecular electrostatic potential (MEP) is a real physical property [19]. To predict reactive sites for electrophilic and nucleophilic attack for the investigated molecule, MEP was calculated for the B3LYP/6-31G(d) optimized geometries using the same method**.** Fig. 3 shows the calculated 3D electrostatic potential contour map of Aripriprazole in [au], the electron density isosurface being 0.02a.u.

The negative regions of *V(r)* are related to electrophilic reactivity and the positive ones to nucleophilic reactivity. As easily can be seen in Fig. 3, this molecule has several possible sites for electrophilic attack in which *V*(*r*) calculations have provided insights. Negative regions of V(r) are associated with O11 and O12 atoms (see Fig. 1 for atom numbering scheme). The most negative V(r) value is associated with O11 and O12 with a value around –0.08513 a.u. while the corresponding value associated with CH, CH_2 and NH groups is about 0.03601 au.

Chemical shifts associated with the ^{1}H and ^{13}C nuclei in the Aripriprazole molecule have been obtained experimentally and they have also been calculated using the hybrid B3LYP functional in conjunction with the 6-31G(d) and cc-pVDZ basis sets. The experimental and calculated chemical shifts are collected in Table 2.

As seen in Table 2, the largest discrepancies between the experimental and calculated ^{13}C chemical shifts are noted for C7 and C14 nuclei. Most probably, this can be related to the ability of this groups for the participation in intermolecular hydrogen bonds and this conclusion is sustained by the MEP which shows large positive values in these regions. CH_2 protons have chemical shifts in the 1.5-3.8 ppm, depending on their specific place in the molecule. The ring protons have chemical shifts in the 6.4 and 7.2 ppm, in very good agreement with the calculated

values. Another large difference reported in Table 2 is related to the H53 proton from the NH group. We assigned the experimental value of 10.0 ppm to this proton based on the assumption that this it manifests a large possibility to be involved in intermolecular hydrogen bonds with the solvent molecules. In such a case, the proton becomes significantly deshielded as it was previously reported in other studies [23].

Table 2. Experimental and calculated chemical shifts for Aripriprazole molecule.

Nucleus	Calculated (ppm)	Experimental (ppm)
C(3)	132.4	132.7
C(4)	109.7	107.6
C(5)	27.3	26.0
C(6)	31.1	30.8
C(7)	122.6	115.7
C(8)	97.6	101.0
C(9)	150.6	149.6
C(10)	97.2	101.0
C(13)	66.3	66.7
C(14)	29.2	24.0
C(15)	25.6	23.9
C(16)	58.6	51.0
C(18)	50.9	51.0
C(19)	48.3	47.6
C(21)	48.8	47.6
C(22)	55.4	55.1
C(23)	144.5	149.5
C(24)	138.1	139.2
C(25)	136.1	139.2
C(26)	122.6	119.8
C(27)	120.2	119.7
C(28)	126.2	126.0
H(31)	7.1	7.1
H(32)	6.9	7.0
H(33)	7.0	7.2
H(34)	2.3	2.5
H(35)	3.7	2.5
H(36)	2.1	2.4
H(37)	2.6	2.4
H(38)	2.5	2.4
H(39)	2.4	2.4
H(40)	2.3	2.5
H(41)	3.7	2.5
H(42)	2.3	2.4
H(43)	2.3	2.4
H(44)	1.5	1.7
H(45)	1.4	1.7
H(46)	3.7	2.5
H(47)	3.7	2.5
H(48)	1.8	1.9
H(49)	1.8	1.9
H(50)	5.7	6.4
H(51)	5.9	6.4
H(52)	6.7	7.2
H(53)	5.6	10.0
H(54)	2.3	2.7
H(55)	2.1	2.7
H(56)	2.4	2.7
H(57)	2.8	2.7

5. Conclusions

The very good match between the experimental and calculated normal modes wave-numbers of Aripriprazole molecule allow us to safely assign the vibrational spectrum of the molecule. BLYP combination of exchange-correlation functional offers a minor improvement with respect to the hybrid B3LYP functional for few exceptions.

Molecular electrostatic potential calculations indicate that the most suitable atomic sites for electrophilic attack or for metal coordination are O11 and O12 atoms, while the most probable sites which could be involved in nucleophilic processes are CH_2 and NH groups.

The correlation consistent cc-pVDZ basis set performs much better than the standard 6-31G(d) basis set for predicting the chemical shifts associated with carbon nuclei. NMR spectrum of the molecule is well reproduced, with few exceptions which are attributable to intermolecular interactions.

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