http://www.e-journals.in
DOI:10.7598/cst2014.764

Chemical Science Transactions
2014, **3(2),** 624-633

RESEARCH ARTICLE

Experimental and Theoretical Investigation and NBO Analysis on the Structure of Pregabalin

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Received 30 October 2013, Accepted 22 November 2013

Abstract: A systematic vibrational spectroscopic assignment and analysis of pregabalin has been carried out by using FTIR, FT-Raman spectral data. The vibrational analysis were aided by electronic structure calculations-hybrid density functional methods (B3LYP) performed with 6-31G(d,p) basis set. Molecular equilibrium geometries, electronic energies, natural bond order analysis, IR intensities, and harmonic vibrational frequencies have been computed. The assignments proposed based on the experimental IR and Raman spectra have been reviewed and selected assignment of the observed spectra have been proposed. The electronic properties, such as HOMO and LUMO energies and λ_{max} were determined by time-dependent DFT (TD-DFT) method. The thermodynamic functions of the title molecule were also performed using DFT method.

Keywords: Pregabalin, Vibrational spectra, DFT

Introduction

Pregabalin is an anticonvulsant drug used for neuropathic pain and as an adjunct therapy for partial seizures with or without secondary generalization in adults[1]. It has also been found effective for generalized anxiety disorder and is (as of 2007) approved for this use in the European Union and Russia[1]. It was designed as a more potent successor to gabapentin. Pregabalin is marketed by Pfizer under the trade name Lyrica. Pfizer described in an SEC filing that the drug could be used to treat epilepsy, post-herpetic neuralgia, diabetic peripheral neuropathy and fibromyalgia. Sales reached a record $3.063 billion in 2010[2]. It is effective at treating some causes of chronic pain such as fibromyalgia but not others. It is considered to have a low potential for abuse, and a limited dependence liability if misused, but is classified as a Schedule V drug in the U.S[3].

In our present work, an attempt has been made to interpret the vibrational spectra of pregabalin by applying density functional theory calculations based on Becke3- Lee-Yang-Parr (B3LYP) level using 6-31G(d,p) basis set. Further, the calculation of electronic excitations, particularly for valence-like transitions and oscillator strength of pregabalin, were calculated employing the all valence electron TD-DFT methods. In addition to these atomic charges calculated at the B3LYP/6-31G(d,p) level. Experimentally observed spectral data of the title compound is found to be well comparable with the data obtained by quantum mechanical methods.

Experimental

The solid phase FTIR spectrum was recorded in the region 4000-400 cm^{-1} in evacuation mode on Nexus 670 DTGS using KBr pellet technique with 4.0 cm^{-1} resolution. The FT-Raman spectrum was recorded using 1064 nm line of Nd:YAG laser as excitation wavelength in the region 5000-100 cm^{-1} on Bruker IFS 66V spectrometer equipped with FRA 106 Raman module was used as an accessory.

Computational details

To provide complete information regarding the structural characteristics and the fundamental vibrational modes of pregabalin the DFT-B3LYP correlation functional calculations have been carried out. The calculations of geometrical parameters in the ground state were performed using the Gaussian 03[4] programs, invoking gradient geometry optimization[5] on Intel core i3/2.93 GHZ processor. The geometry optimization was carried out using the initial geometry generated from standard geometrical parameters at DFT-B3LYP methods adopting 6-31G(d,p) basis set to characterize all stationary points as minima. The optimized structural parameters of the compound pregabalin were used for harmonic vibrational frequency calculations resulting in IR and Raman frequencies together with intensities. In DFT methods, Becke's three parameter exchange-functional (B3)[6,7] combined with gradient-corrected correlation functional of Lee, Yang and Parr (LYP)[8] by implementing the split-valence polarized 6-31G(d,p) basis set[9,10] have been utilized for the computation of molecular structure optimization, vibrational frequencies, thermodynamic properties and energies of the optimized structures.

Results and Discussion

Molecular geometry

The molecular structure of pregabalin belongs to C_1 point group symmetry. All vibrations are active in both IR and Raman. The optimized structure parameters of pregabalin calculated by DFT-B3LYP levels are listed in the Table 1 in accordance with the given Figure 1 atom numbering scheme of pregabalin. Table 1 compares the calculated bond lengths and angles for pregabalin with those experimentally available data[11]. From the theoretical values, we can find that most of the optimized bond angles are slightly larger than the experimental values due to the theoretical calculations belonging to isolated molecules in gaseous phase and the experimental results belonging to the molecule in the solid state. In spite of the differences, calculated geometric parameters represent a good approximation and they are the basis for calculating other parameters, such as vibrational frequencies and thermodynamic properties.

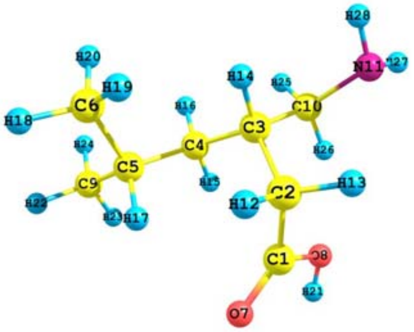

Figure 1. Atom numbering scheme of pregabalin

Table 1. Structural parameters of pregabalin

Structural parameters	Pregabalin	
	B3LYP/6-31G(d,p)	Experimental[11]
Internuclear distance (A˚)		
R(1-2)	1.46	1.51
R(1-7)	1.21	1.21
R(1-8)	1.34	1.34
R(2-3)	1.46	1.52
R(2-12)	1.10	1.11
R(2-13)	1.09	1.11
R(3-4)	1.52	1.52
R(3-10)	1.52	1.52
R(3-14)	1.10	1.11
R(4-5)	1.55	1.52
R(4-15)	1.10	1.11
R(4-16)	1.11	1.11
R(5-6)	1.54	1.52
R(5-9)	1.55	1.52
R(5-17)	1.10	1.11
R(6-18)	1.09	1.11
R(6-19)	1.10	1.11
R(6-20)	1.10	1.11
R(8-21)	1.02	1.00
R(9-22)	1.09	1.11
R(9-23)	1.09	1.11
R(9-24)	1.10	1.11
R(10-11)	1.46	1.44
R(10-25)	1.10	1.11
R(10-26)	1.11	1.11
R(11-27)	1.02	1.02
R(11-28)	1.02	1.02
BOND ANGLE(Å)		
A(2-1-7)	128.2	120.00
A(2-1-8)	114.3	120.00
A(1-2-3)	111.2	109.50
A(1-2-12)	107.1	109.40
A(1-2-13)	109.0	109.4
A(7-1-8)	116.3	119.9
A(1-8-21)	99.7	120.0
A(3-2-12)	110.9	109.4
A(3-2-13)	109.6	109.4
A(2-3-4)	114.8	109.5
A(2-3-10)	113.5	109.4
A(2-3-14)	105.6	109.4
A(12-2-13)	108.9	109.5
A(4-3-10)	110.1	109.4

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A(4-3-14)	107.5	109.4
A(3-4-5)	118.8	109.4
A(3-4-15)	111.0	109.4
A(3-4-16)	104.6	109.4
A(10-3-14)	104.5	109.5
A(3-10-11)	113.0	109.4
A(3-10-25)	104.4	109.4
A(3-10-26)	111.3	109.4
A(5-4-15)	109.1	109.4
A(5-4-16)	106.7	109.4
A(4-5-6)	113.2	109.4
A(4-5-9)	111.1	109.4
A(4-5-17)	108.3	109.4
A(15-4-16)	105.9	109.5
A(6-5-9)	110.4	109.4
A(6-5-17)	107.7	109.4
A(5-6-18)	110.3	109.4
A(5-6-19)	112.4	109.4
A(5-6-20)	111.7	109.4
A(9-5-17)	105.7	109.4
A(5-9-22)	109.9	109.4
A(5-9-23)	111.2	109.4
A(5-9-24)	112.1	109.4
A(18-6-19)	107.0	109.4
A(18-6-20)	107.7	109.4
A(19-6-20)	107.4	109.4
A(22-9-23)	107.7	109.4
A(22-9-24)	107.6	109.4
A(23-9-24)	108.1	109.4
A(11-10-25)	106.6	109.4
A(11-10-26)	114.6	109.4
A(10-11-27)	108.1	120.0
A(10-11-28)	110.2	119.9
A(25-10-26)	106.1	109.4
A(27-11-28)	106.2	119.9

Electronic properties

The energies of four important molecular orbitals of pregabalin: the highest and second highest occupied MO's (HOMO and HOMO-1), the lowest and the second lowest unoccupied MO's (LUMO and LUMO+1) were calculated and are presented in Table 2. The lowest singlet→singlet spin-allowed excited states of pregabalin were taken into account for the TD-DFT calculation in order to investigate the properties of electronic absorption. The calculations were also performed with methanol solvent effect. The calculated absorption wavelengths λ_{max}, oscillator strength, excitation energies and the experimental wavelengths are also given in Table 2. The energy gap between HOMO and LUMO is a critical parameter in determining molecular electrical transport properties[12]. TD-DFT calculations using B3LYP/6-31G(d,p), predict three intense electronic transitions at λ_{max} = 247.56 nm, f = 0.0120; λ_{max} = 226.81 nm, f = 0.0002 and λ_{max} = 198.79 nm, f = 0.0100 are in agreement with the experimental electronic transitions at λ_{max} 198.79 nm. The experimental λ_{max} values are obtained from the UV/Visible spectra recorded as reported earlier[13]. In the electronic absorption spectrum of pregabalin, there are three absorption bands with a maximum 247.56 nm. The strong absorption band 247.56 nm is caused by the $n \rightarrow \pi^*$ and the other two calculated value moderately intense bands are due to $\pi \rightarrow \pi^*$ transitions. The $\pi \rightarrow \pi^*$ transitions are expected to occur relatively at lower wavelength, due to the consequence of the extended aromaticity of the structure. The HOMO and LUMO diagram as shown in Figure 2.

Table 2. Experimental and calculated absorption wavelenght(λ), excitation energies(E), oscillator strength(f) and frontier orbital energies of Pregabalin by TD-DFT method

λ Expt.;nm	λ Cal.;nm	E, eV	f	Assignment	E_{HOMO}, eV	E_{LUMO}, eV	E_{HOMO-1}, eV	E_{LUMO+1} (eV)
	247.56	5.0083	0.0120	$n \rightarrow \pi^*$	-5.3718	0.3298	-7.0152	1.6488
	226.81	5.4664	0.0002	$n \rightarrow \pi^{-*}$				
196.2	198.79	6.2368	0.0100	$n \rightarrow \pi^*$				

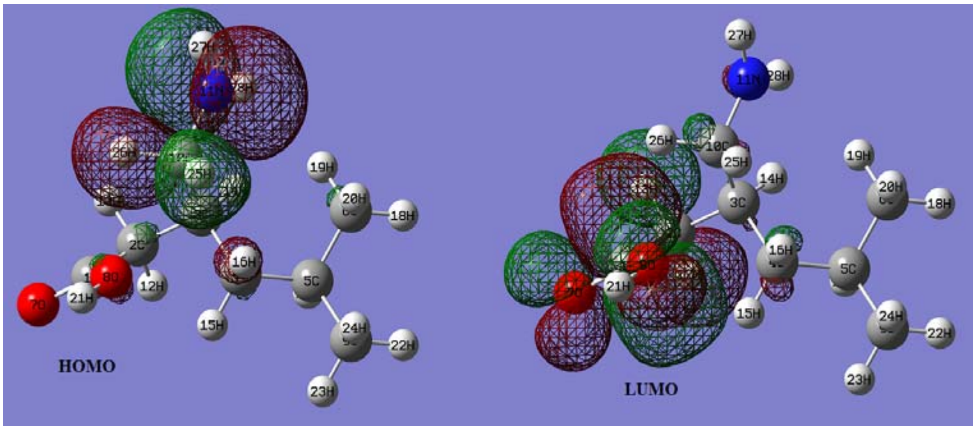

Figure 2. The HOMO and LUMO of pregabalin

Natural population analysis

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 (DFT-B3LYP/6-31G(d.p)) to describe the electron distribution in pregabalin as broadly as possible and to assess the sensitivity of the calculated charges to changes in the choice of the quantum chemical method. The calculated natural atomic charge values from the natural population analysis (NPA) and Mulliken population analysis (MPA) procedures using the DFT-B3LYP/6-31G(d,p) method are listed in Table 3. The NPA from the natural bonding orbital (NBO) method is better than the MPA scheme. Table 3 compares the atomic charge site of pregabalin from both MPA and NPA methods. The NPA of pregabalin shows that the presence of two oxygen atoms [O7= -0.600; O8= -0.735] imposes large positive charges on the carbon atom [C1 = 0.818]. However, the nitrogen atom N11 possess large negative charges, resulting in the positive charges on the hydrogen atoms H27 and H28. Moreover, there is no difference in charge distribution observed on all hydrogen atoms except the H21, H27 and H28 hydrogen atoms respectively. The large positive charge on H22 is due to the large negative charge accumulated on the O8 atom.

Table 3. Natural atomic charges of pregabalin

Atom	MPA	NPA
	B3LYP/6-31G(d,p)	B3LYP/6-31G(d,p)
C1	0.579	0.818
C2	-0.271	-0.553
C3	-0.080	-0.272
C4	-0.126	-0.457
C5	-0.076	-0.253
C6	-0.284	-0.681
O7	-0.471	-0.600
O8	-0.484	-0.735
C9	-0.298	-0.682
C10	0.052	-0.242
N11	-0.670	-0.951
H12	0.135	0.271
H13	0.142	0.276
H14	0.079	0.239
H15	0.078	0.232
H16	0.092	0.239
H17	0.076	0.235
H18	0.091	0.234
H19	0.082	0.220
H20	0.100	0.231
H21	0.329	0.522
H22	0.092	0.233
H23	0.093	0.233
H24	0.096	0.228
H25	0.084	0.213
H26	0.073	0.205
H27	0.242	0.401
H28	0.245	0.395

Vibrational analysis

The FTIR and FT-Raman spectra of pregabalin are shown in Figures 3 and 4. The observed and calculated frequencies using B3LYP/6-31G(d,p) method along with their relative intensities and assignments of pregabalin are summarised in Table 4. The maximum number of values determined by DFT method is well agreed with the experimental values. Therefore, this method is considered to be more reliable and taken for discussion. The calculated (B3LYP) vibrational spectra were shown in Figure 5. Comparison of the frequencies calculated at B3LYP/6-31G(d,p) with experimental values.

The CH, NH and OH stretching modes are expected to be observed at the high wave number region. The CH stretching bands are observed between 3073-3049 cm^{-1} in DFT methods. A very weak band at 3581 cm^{-1} in DFT was attributed to NH_2 asymmetric stretching vibration. The CH_2 wagging mode was also identified. Let us start considering the contribution of theoretical methods B3LYP, the OH stretching mode is predicted at 3744 cm^{-1} in B3LYP. This OH stretching mode is affected in the presence of water molecules. The OH stretching vibrational wave number is decreasing in DFT polarization effect inclusion in DFT method.

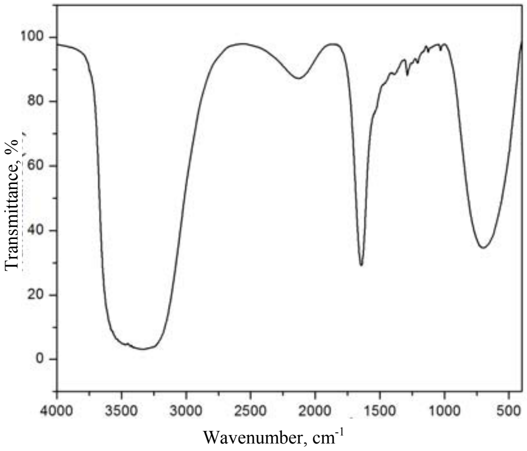

Figure 3. FTIR spectrum of pregabalin

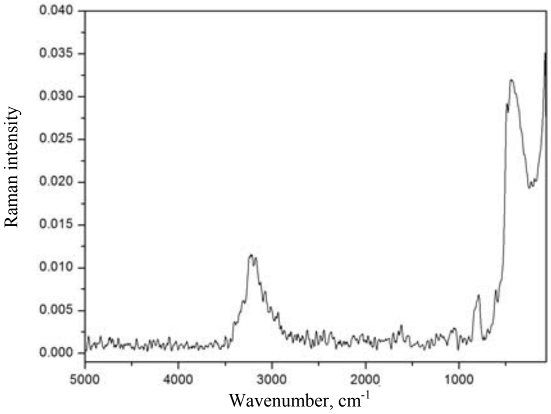

Figure 4. FT-Raman spectrum of pregabalin

Table 4. Selected observed and calculated vibrational assignments of Pregabalin

Observed wavenumber cm^{-1}		B3LYP/6-31G(d,p) calculated wavenumber, cm^{-1}		Assignments
TIR	FT-Raman	Theoretical	IR intensity	
700	788	742	42.5	CH out of plane
1030	1052	1042	30.7	CH out of plane
		1071	15.0	CH out of plane
		1113	57.5	CH inplane
1125		1127	41.4	CH inplane
1207		1204	78.0	NH_2 wagging
1288		1286	1.7	CH_2 wagging
1387		1382	9.5	CH_2 wagging
1642	1614	1678	29.0	NH_2 scissoring
		1839	238.0	C=O stretching
2135		2960	55.2	CH_3 symmetric stretching

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		3010	23.1	CH_3 asymmetric stretching
		3029	28.5	CH_3 stretching
		3034	17.2	CH_3 stretching
		3044	6.8	CH_3 stretching
		3049	11.4	CH stretching
		3062	17.1	CH stretching
		3073	65.3	CH stretching
		3092	7.5	CH_2 symmetric stretching
		3096	6.0	CH_2 symmetric stretching
		3104	73.4	CH_2 symmetric stretching
		3109	24.7	CH_2 asymmetric stretching
		3112	57.6	CH_2 asymmetric stretching
		3144	8.0	CH_2 asymmetric stretching
3339	3225	3499	2.8	NH_2 symmetric stretching
		3581	1.8	NH_2 asymmetric stretching
		3744	50.3	OH stretching

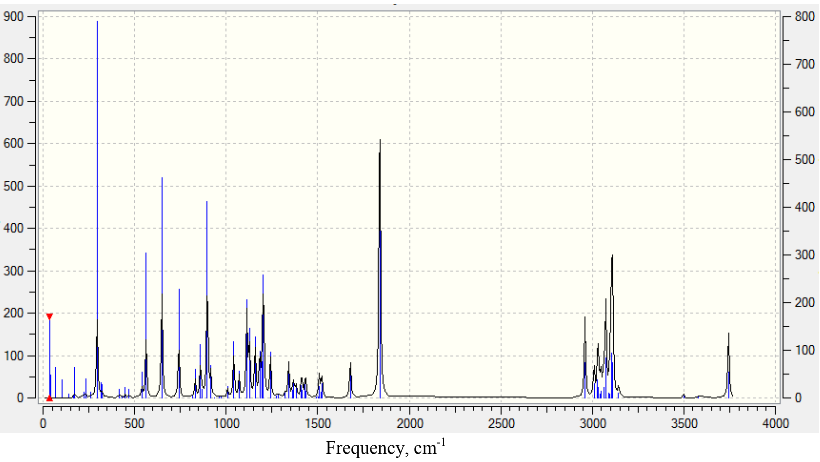

Figure 5. DFT calculated IR spectrum of pregabalin

The NH_2 symmetric and asymmetric stretching vibrations in the range 3200–3400 cm^{-1} are in good agreement with the experimental spectrum. The computed NH_2 scissoring vibration at 1678 cm^{-1} in DFT is excellent agreement with the expected characteristic value 1642 cm^{-1} in FTIR and 1614 cm^{-1} in FT-Raman[14]. In the presence of water molecules in the pregabalin, the NH stretching vibrations were red shifted by 10 cm^{-1}. But however, the NH_2 scissoring mode was not affected. Also, the C=O stretching modes have been assigned at 1839 cm^{-1} in DFT method. The assumption that the compound group plays very important role in stabilizing the structure of pregabalin.

Methyl group vibrations

The title molecule pregabalin under consideration possesses one CH_3 unit which lies in the terminal group of molecule. For the assignments of CH_3 group frequencies, nine fundamentals can be associated to each CH_3 group[15]. The C–H stretching in CH_3 occurs at lower frequencies than those of aromatic ring (3100-3000 cm^{-1}). Moreover, the asymmetric stretch is usually at higher wave number than the symmetric stretch. Methyl group vibrations system, the antisymmetric C–H stretching mode of CH_3 is expected around 3029 cm^{-1} and CH_3 symmetric stretching is expected[16,17] at 2960 cm^{-1}. The antisymmetric C–H stretching mode of CH_3 identified at 3010 cm^{-1} in DFT spectrum.

Thermodynamic properties

Several calculated thermodynamic parameters are presented in Table 5. Scale factors have been recommended[18] for an accurate prediction in determining the zero-point vibrational energies and the entropy S. The variation in the ZPVEs seems to be insignificant. The total energies found to decrease with increase of the basis sets dimension. The changes in the total entropy of pregabalin at room temperature at different basis sets are only marginal.

Table 5. The calculated thermodynamic parameters of pregabalin

Parameter	B3LYP/6-31G(d,p)
Total Energy(a.u)	-520.08
Zero point energy(kcal/mol)	157.715
Rotational Constants(GHz)	1.408
	0.695
	0.546
Entropy	
Translational	41.103
Rotational	30.776
Vibrational	42.674
Dipole moment(Debye)	1.8161

Conclusion

The geometry of pregabalin was optimized with DFT-B3LYP method using 6-31G(d,p) basis set. The complete molecular structural parameters and thermodynamic properties of the optimized geometry of the compound have been obtained from DFT calculations. The NBO analysis of the title compound has been studied by DFT methods. The vibrational frequencies of the compound have been precisely assigned and analysed and the theoretical results were compared with the experimental vibrations. The energies of important MO's, absorption wavelength (λ_{max}), oscillator strength and excitation energies of the compound were also determined from TD-DFT method and compared with the experimental values. Thus the present investigation provides selected vibrational assignments, structural information and electronic properties of the compound which may be useful to upgrade the knowledge on pregabalin.

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