Force field calculation of GABA using *ab-initio* methods and Raman spectroscopy

BOUTASTA Amel[1*], BENOSMAN Abdelhakim[1], CHERIET Mouna[2], KHELLAF Ammar[3]

[1] Department of physics, Theoretical Physics Laboratory, University of Tlemcen, Tlemcen 13000, Algeria
[2] Center for Biotechnology Research (CRBT), Constantine, Algeria.
[3] École Nationale Polytechnique de Constantine, Laboratoire des Mathématiques Appliquées, *Algeria.*

*Corresponding author: amel.boutasta@univ-tlemcen.dz

Abstract

In this paper, we study in a theoretical way the γ-Aminobutyric acid GABA, which has many important biological functions. The optimized molecular structure was studied by the DFT/B3LYP method with a 6-31 G (d, p) basis set, we used the software Gaussian 09. we are considering the vibrational spectra of the molecule. The Raman spectrum of GABA was recorded in the 4000-40 cm^{-1} region. This spectrum constitutes the experimental support that allows the theoretical reproduction of the vibrational frequencies. Good agreements were obtained between the observed and calculated frequencies. The scale factors are adjusted to obtain a good agreement between the calculated and observed frequencies. The results obtained reproduce the experimental frequencies.

Keywords: *γ-Aminobutyric acid, DFT, vibrational spectra, Gaussian,*

I. Introduction

Drug design can be made rational when the three-dimensional structure of the receptor is known. In the majority of cases, the structure of the receptor is not known. To do this, we model the site of action of the receptor by the knowledge of biologically active molecules thanks to the methodologies of molecular mechanics and dynamics coupled with molecular graphics. γ-Aminobutyric acid (GABA), $C_4H_9NO_2$, is a nonprotein amino acid that works as a neurotransmitter in the mammalian central nervous system, as well as plants [1].

It works as an inhibitory neurotransmitter in the neuronal excitability control, it blocks, or inhibits, certain brain signals and decreases activity in the nervous system [2-7], being of high pharmaceutical relevance due to its physiological activities in cognition, learning, and memory. [8-11]. Since the concept of receptors was introduced, molecular pharmacology has been interested in the question of interactions between compounds.

The spectra in these systems are difficult to interpret because the presence of many oscillators creates modes that span much of the spectral range. To solve this problem, we use analysis in normal coordinates. More precisely, to determine the structure of the active molecule, we start from crystallographic data. A molecular force field is determined by comparison between the calculation of the normal modes of vibration of the isolated molecule and the

experimental Raman spectra. More precisely, to determine the structure of the active molecule, and the vibrational properties of the GABA molecule, crystallographic data are used. A molecular force field is determined by comparison between the calculation of the normal modes of vibration of the isolated molecule and the experimental Raman spectra. The theoretical calculation is performed by the ab-initio quantum mechanical method based on the DFT (density functional theory) [12]. This theory is an excellent method to calculate molecular geometries and vibrational frequencies, etc. [13,14].

II. The geometry

The structure of γ-aminobutyric acid (GABA) derived from X-ray diffraction was first determined by Steward in 1973 [15] Figure 1.

In 1983 Weber et al. [16] studied the structure of GABA at low temperature (122 K) by neutron diffraction. This technique is necessary to determine the position of hydrogen atoms more accurately.

Fig. 1 Atomic numbering of GABA

The compound crystallizes in a monoclinic system with four molecules per cell. The positions of the four molecules, according to the crystallographic data are as follows: (x, y, z) (-x, -y, -z) (+1/2x, -1/2y, z) and (-1/2x, +1/2+y, -z).

At 122 K, the GABA crystal is monoclinic with space group P2$_1$/a with Z = 4 (4 molecules/cell). [16] The parameters of the unit cell for GABA are: a = 8.2140 Å, b = 10.0000, c = 7.2008 Å, β= 110.5900°.

III. Internal and symmetry coordinates

The internal coordinates related to the elongations, angular deformations and torsions are 46 in number which are used in the Redong program for the calculation of the matrix of the constants of force [17]. They are shown in the table 2.

Table 2. Internal coordinates for GABA

In plane		Out of plane	
Internal coordinate	Assignment	internal coordinate	Assignment
R1	O4−C2	R24	C2−C1−C7
R2	O3−C2	R25	C1−C7−H10
R3	C2−C1	R26	C9−C7−H10
R4	C1−C7	R27	C1−C7−H8
R5	C7−C9	R28	C9−C7−H8
R6	C9−N13	R29	H10−C7−H8
R7	C1−H6	R30	C1−C7−C9
R8	C1−H5	R31	C7−C9−H12
R9	C7−H10	R32	N13−C9−H12
R10	C7−H8	R33	C7−C9−H11
R11	C9−H12	R34	N13−C9−H11
R12	C9−H11	R35	H12−C9−H11
R13	O3−H14	R36	C7−C9−N13
R14	N13−H15	R37	C9−N13−H15
R15	N13−H16	R38	C9−N13−H16
R16	O4−C2−O3	R39	H15−N13−H16
R17	O4−C2−C1	R40	C2−O3−H14
R18	O3−C2−C1	R41	Bal C2−O3
R19	C2−C1−H6	R42	Tor C2−C1
R20	C7−C1−H6	R43	Tor C1−C7
R21	C2−C1−H5	R44	Tor C7−C9
R22	C7−C1−H5	R45	Tor C9−N13
R23	H6−C1−H5	R46	Tor C2−O3

The factor group C$_{2h}$ and the optical vibrations of the grating will be classified according to the following irreducible representation (1):

$$\Gamma_{vr} = 6Ag + 6Bg + 5Au + 4Bu \qquad (1)$$

The molecule has 16 atoms, so we expect 42 (3N-6) internal vibrations, which will couple according to the symmetry elements of the C_{2h} group. Then, the irreducible representation is given by the following equation (2)

$$\Gamma_{vr} = 42Ag + 42Bg + 42Au + 42Bu \quad (2)$$

The molecule has only 42 degrees of freedom. Thus, we have 4 tree-type redundancy relations. Also, we add the 3 rotations and 3 translations of the whole (table3) from these 46 coordinates of local symmetry

Table 3: Symmetry coordinates of GABA

Symmetry coordinate	Assignment
Internal vibrations	
S1=R1	AS CO2
S2=R2	St C2C1
S3=R3	St C1C7
S4=R4	St C7C9
S5=R5	St CN
S6=R6	Tor C2O3
S7=R46	SS C1H2
S8=R8+R7	SS C7H2
S9=R9+R10	SS C9H2
S10=R11+R12	AS C1H2
S11=R7-R8	AS C7H2
S12=R9-R10	AS C9H2
S13=R11-R12	SS NH2
S14=R14+R15	AS NH2
S15=R14-R15	St OH
S16=R13	Bend CO2
S17=2.R16-R17-R18	Ipb CO2
S18=R17-R18	Sci C1H2
S19=4.R23-R19-R20-R21-R22	Sci C7H2
S20=4.R29-R25-R26-R27-R28	Sci C9H2
S21=4.R29-R35-R32-R23-R34	Sci NH2
S22=2.R39-R37-R38	Wag C1H2
S23=R19-R20+R21-R22	Wag C7H2
S24=R25-R26+R27-R28	Wag C9H2
S25=R39+R37+R38	Wag NH2
S26=R31-R32+R33-R34	Twi C1H2
S27=R19-R20-R21+R22	Twi C7H2
S28=R25-R26-R27+R28	Twi C9H2
S29=R31-R32-R33+R34	Twi NH2
S30=R37-R38	Roc C1H2
S31=R19-R20-R21-R22	Roc C7H2

Symmetry coordinate	Assignment
S32=R25+R26-R27-R28	Roc C9H2
S33=R31-R32-R33-R34	Bend CCC
S34=-R23-R19-R20-R21-R22+5R34	Bend CCC
S35=-R29-R25-R26-R27-R28+5R30	Bend CCN
S36=-R35-R31-R32-R33-R34+5R36	Bend COH
S37=2.R40-R16-R18	Opb CO2
S38=R41	Tor C2C1
S39=R42	Tor C1C7
S40=R43	Tor C7C9
S41=R44	Tor CN
S42=R45	AS CO2
External vibrations	
S43=Tx	
S44=Ty	
S45=Tz	
S46=Ra	
S47=Rb	
S48=Rc	

AS: anti-symmetric stretching mode; **SS**: symmetric stretching mode; **Sci**: scissoring mode; Wag: wagging mode; **Twi**: twisting mode; **Roc**: rocking mode; **Tor**: torsional modes; **Bend**: deformation mode; *R*a, *R*b and *R*c are rotational lattice modes around the principal axes *a*, *b*, *c*, of the molecule, respectively. *Tx*, *Ty*, and *Tz* are translational latice modes along *x*, *y* and *z* crystallographic axes, respectivly.

IV. Computation method

The quantum chemical, the optimization and the force field calculations of GABA are performed using *ab-initio* calculation methods based on the density functional theory (DFT). Using Becke's exchange functional [18] and B3LYP (Lee-Yang-Parr) level of theory [19,20], associated with the basis of atomic functions of Gaussian Double-Zeta types containing orbitals of polarization (6-31 G (d, p)) [21,22], so the purpose is to calculate the normal vibration modes and using the Gaussian 09 program [23].

V. Results and discussion

The Raman spectra of the molecule were recorded from 3000 to 40 cm^{-1}. This spectrum was used to adjust the scaling

factors of the molecule. The values obtained are given in Table 3.

The theoretical vibrations have been calculated according to the method described above, each mode is calculated with the contributions to the potential energy distribution (PED). These results are presented in Table 5 from which there is a very good agreement between the calculated frequencies and the observed data.

VI.I. Scale Factors

First, we choose 22 scale factors, each one is related to a type of internal coordinate. After bringing the calculated frequencies as close as possible to the experimental frequencies, and to refine the force constants, only 16 factors were kept. These factors range between 0.89 and 1.00. The scale factors they have given in table 4.

Table 4: Scaling factors for GABA from DFT calculations

Internal coordinates	Scaling factors
ν OC	0.98
ν CH	0.98
δ HOC	0.99
δ CCH	0.90
δ HNH	0.94
δ HCH	0.99
Bal OCOC	0.89
Tor CN	0.90
ν O=C, ν CC, ν CN, ν OH, ν NH, δ OC=O, δ O=CC, δ OCC, δ CCC, δ HCN, δ CCN, δ CNH, δ HOC, Tor CC, Tor CO	1.00

ν: stretching, δ: in plane bending, **Tor**: Torsion, **Bal**: Balancement.

VI.II. Vibrational analysis

The NH stretching modes, symmetric and anti-symmetric are calculated 3498 and 3583 cm^{-1} respectively. We find an OH stretching mode linked to the hydroxymethyl group calculated at 3362 cm^{-1}. This is in agreement with previous studies [24-26]. The PEDs show that the NH and the OH stretching modes are almost pure modes.

The CH stretching modes are calculated between 2910 and 3129 cm^{-1}for GABA, they are in agreement with the experimental data. The symmetric modes coupled with the anti-symmetric stretching mode of the methylene group are calculated at 2910, 2921 and 3085 cm^{-1} and observed at 2911 and 2938 cm^{-1}. However, the anti-symmetric modes of the methylene group coupled with the NH symmetric stretching mode is calculated at 2963 cm^{-1} and observed at 2953 cm^{-1}. The intensity of these bands is very strong in Raman.

This region between 1700 and 700 cm^{-1} is characterized by many strongly coupled modes involving HCO, HCH and CCH deformations.

Table 5. The observed and calculated vibrational frequencies (cm^{-1}) and the potential energy distribution for GABA

Calc.	Exp.	Assignements (%)
71	75	70 (Tor C2C1)
97	96	54 (Tor C1C7) +10 (Tor C7C9)
183	*	47 (Tor C1C7) +39 (Tor C7C9)
254	*	48 (Bend CCC)
301	291	22 (Bend CCC) +22 (Tor C1C7)
328	324	39 (Tor CN) + 30 (Tor C2O3)
433	*	33 (Ipb CO2) +30 (Tor C1C7)
474	483	21 (Bend CCN) +18 (Bend CCC)
576	581	38 (Bend CO2) +18 (St C2C1)
688	*	27 (Opb CO2) +16 (Tor C1C7)
792	792	18 (Roc C7H2) +14 (Bend CO2)
873	963	30 (Roc C9H2) + 18 (RocC1H2)
889	882	25 (St C7C9) +24 (St C2C1)
922	*	28 (Roc C1H2) +19 (Roc C7H2)
966	*	20 (Roc C7H2) +20 (Tor C2O3)
999	998	27 (Wag NH2) +26 (St C1C7)
1036	1030	40 (Tor C2O3) +18 (Roc C7H2)
1061	1070	17 (Roc C9H2) +16 (St CN)
1105	1104	28 (Twi C1H2) +13(St CN)
1135	1130	22 (Twi C1H2) +20 (Twi C7H2)
1227	*	28 (Twi C1H2) +19 (AS CO2)
1286	1292	22 (Twi C7H2) +20 (Twi C9H2)
1315	1316	31 (AS CO2) +16 (Twi C1H2)
1342	1341	32 (Twi C9H2) +14 (Twi NH2)
1364	*	41 (Wag C1H2) +26 (Twi C7H2)
1385	1404	62 (Wag C7H2)
1422	1426	62 (Wag C9H2)
1482	1473	68 (Bend COH)
1503	1500	91 (Sci C1H2)
1518	*	80 (Sci C7H2)
1530	*	90 (Sci C9H2)
1663	1664	95 (Sci NH2)
1851	*	74 (SS C2O4)
2910	2911	74 (SS C9H2) +21 (AS C9H2)
2921	2926	60 (SS C1H2) +25 (AS C1H2)
2931	2938	78 (SS C7H2)
2963	2953	42 (AS C9H2+40 (SS NH2)
3085	*	50 (AS C7H2) +35 (AS C9H2)
3129	*	72 (AS C1H2)
3247	*	99 (St OH)
3498	*	98 (SS NH2)
3583	*	98 (AS NH2)

The scissoring modes are calculated between 1700 and 1500 cm^{-1} with a potential energy distribution (PED) of not less than 80%. These deformation bands show weak bands in Raman.

However, the deformation bands which present intense bands in Raman correspond to the wagging mode, which contribute to different frequencies calculated at 1364, 1385 and 1422 cm^{-1} and observed at 1404 and 1426 cm^{-1}.

There are other bands corresponding to the contribution of the C-O torsion modes coupled to the rocking mode of methylene group and due to the small contributions of the COC, CCH and OCH deformation modes are calculated in the range of 1100 and 900 cm^{-1}.

The bands calculated at 1105, 1135, 1225 and 1286 assigned to the angular torsion mode of the methylene group are observed at 1104, 1130 and 1292 cm^{-1}.

Strong couplings of the vibrations are found in the region below 700 cm^{-1}. According to the PED, the normal modes of vibration in this region is assigned to of angular deformations of the heavy atoms) coupled with torsions around the C-O and C-C bonds, which is in agreement with the previous works [24-26].

VII. Conclusion

In this work we have performed our calculations by ab initio methods based on DFT using exchange and correlation functions of type B3LYP using the Gaussian 09 program. On the other hand, these theoretical data (partial charges, force constants) can be used to constitute a force field in the modeling of the dynamic properties and the structure of GABA. We use the Redong program which is based on the transformation of the constants to the space of Cartesian coordinates to the space of internal coordinates. Then, we refine the force constants. Hence, we apply the least squares method and a normal mode decomposition for the determination of the non-redundant coordinates. Thus, this calculation provides access to the harmonic force constants and calculates in the harmonic approximation the vibration modes. Vibration spectroscopy allows as to verify the validity

of the geometrical calculations and to advance in the problem of band allocation. Thus, it is possible to make between theoretical and experimental approaches. From the results obtained, are quite correct, but it is however very often limited to the determination of frequencies.

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