
7. Understanding the Interactions of α -, β - and γ -Aminobutyric Acids with Mg^{+2} Through Computational Investigations

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Abstract:

This study involves a computational analysis of the interaction of Mg^{+2} with the three isomeric forms of aminobutyric acid (ABA), namely α -ABA, β -ABA and γ -ABA. The interaction enthalpies (metal-binding affinities) and Gibbs energies, calculated vibrational spectra, along with several other molecular and electronic properties of the reaction species predicted in the gaseous and aqueous phases, are used to analyze the coordination features of α -, β - and γ -aminobutyric acids. The vibrational spectroscopic investigations provide insightful information in understanding how metal binding and the aqueous conditions affect the structural and molecular features of the metal complexes.

Keywords:

Aminobutyric acids, Metal complexes, Density functional theory, Vibrational frequencies, hydrogen bonding.

7.1 Introduction:

There are three isomeric forms of aminobutyric acid viz. α -aminobutyric acid (α -ABA), β -aminobutyric acid (β -ABA) and γ -aminobutyric acid (γ -ABA). α -ABA serves a key role in the biological synthesis of ophthalmic acid or ophthalmate, β -ABA is known to possess antifungal activities whereas γ -ABA is the main inhibitory neurotransmitter in the central nervous system of mammals (Watanabe et al., 2002). Because of their extensive biological importance, all the three isomeric forms of aminobutyric acid have been subjected to numerous thorough experimental and theoretical investigations in recent decades. Gas phase conformers of α -ABA have been characterized experimentally (Cocinero et al., 2006). β -ABA-induced pathogenic resistance in plants is well documented in the literature (Jakob et al., 2001). HF, B3LYP and MP2 methods have been applied for in silico investigation of the stabilization of γ -ABA zwitterions in aqueous solution (Crittender et al., 2004). However, as far as we are aware, literature review does not contain any references regarding computational investigation explaining the interaction the three aminobutyric acids with magnesium ion. Metal ion interactions with amino acids and nucleic acids are extremely important. Protein structure, enzyme catalysis, signal transduction, nitrogen fixation, photosynthesis, and respiration are all stabilised by metal cations. The biological

significance of the divalent metal cation of magnesium is well reported in literature (Pyle, 2002; Fawcett et al., 1999); Frausto, 1991; Bertini et al., 2001). Due to some limitations of experimental methodologies that have been noted in the literature, computational investigations are increasingly crucial in describing the structural details of proteins on an atomic scale (Wormald et al., 2002; Floppe et al., 2002). The aim of this study is to explore the coordination aspects of α -ABA, β -ABA and γ -ABA as possible metal-binding entities and to analyze the theoretical outcomes regarding interaction enthalpies (ΔH), Gibbs energies (ΔG), vibrational spectra, rotational constants, dipole moments, Wiberg bond indices and energy gaps of the complexes. The number and types of intramolecular H-bond interactions are thoroughly analysed since they may be crucial in defining the energetics and conformational characteristics of the complexes. Figure 7.1 and 7.2 schematically represents the structures and atom numbering given to α -ABA, β -ABA, γ -ABA and their divalent metal complexes with Mg^{+2} . This DFT study which was performed in the gaseous and aqueous phases taking both the non-ionic and zwitterionic forms is expected to provide an in-depth picture of the coordination aspects of the three aminobutyric acids at the atomic level.

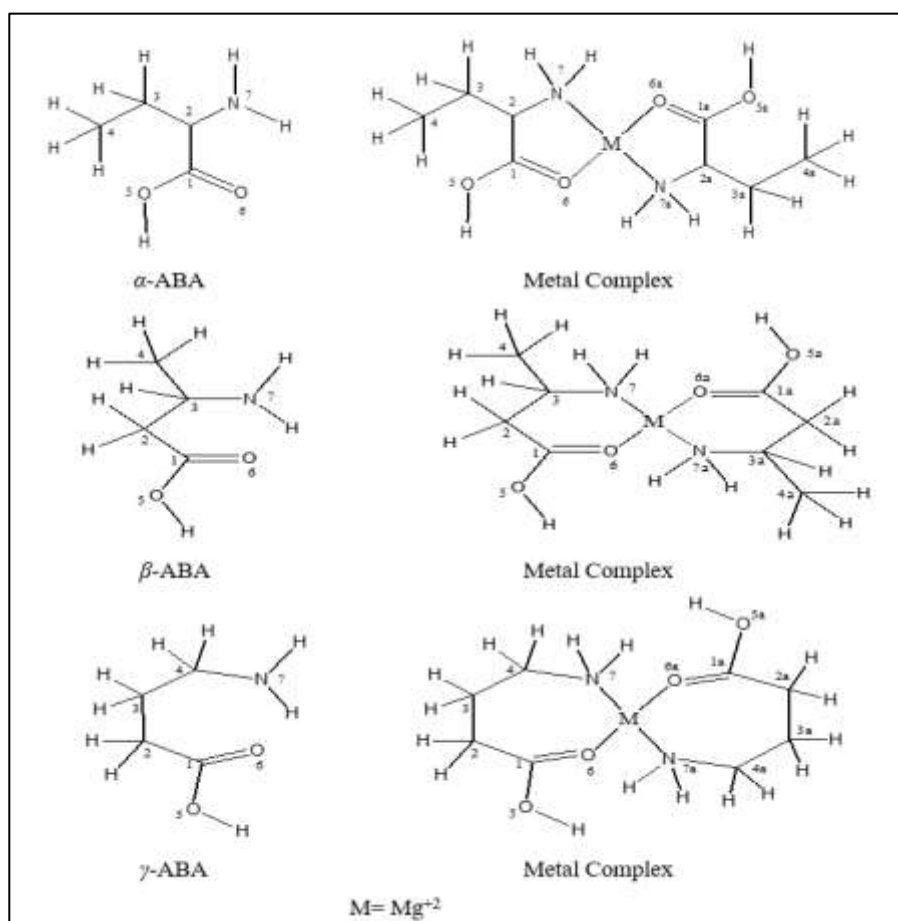


Figure 7.1: Schematic representation of the structures of α -ABA, β -ABA, γ -ABA and their metal complex with Mg^{+2} in gaseous phase

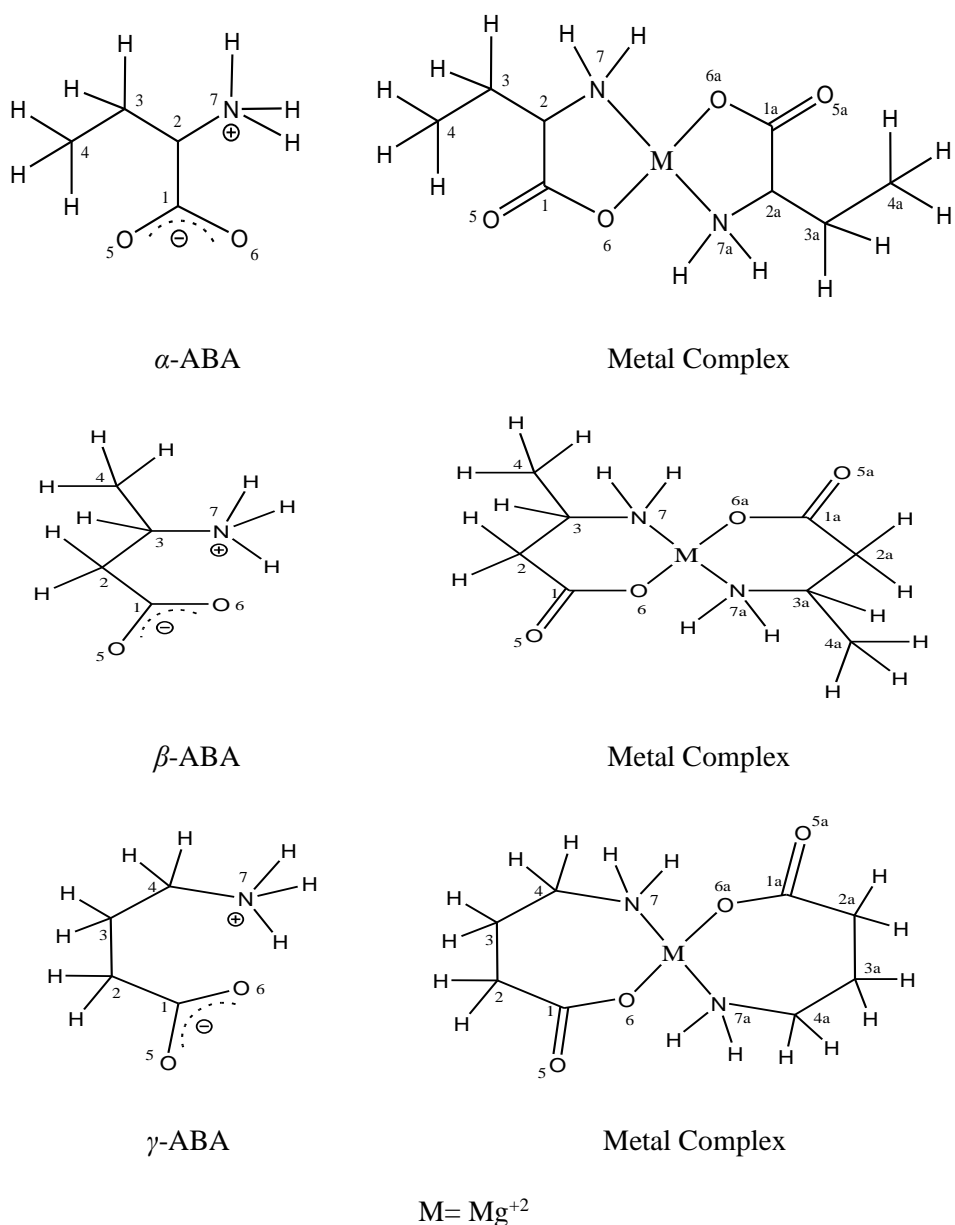


Figure 7.2: Schematic representation of the structures of α -ABA, β -ABA, γ -ABA and their metal complex with Mg^{+2} in aqueous phase

7.2 Computational Methodologies:

Full geometry optimization and vibrational frequency calculations in gaseous and aqueous phases were performed on the molecular geometries of α -ABA, β -ABA and γ -ABA as well as their metal complexes with Mg^{+2} ion, modeled in 1:2 molar ratio (Metal: Ligand) using a polarizable continuum model (PCM) (Miertus et al., 1981) at the B3LYP/6-311++G(d,p) level of theory (Becke, 1993; Lee et al., 1988) of Gaussian 16 programs (Frisch

et al., 2016). The study involves triplet state calculation for the metal complexes. The total energies of all the reaction species were corrected with zero-point energy (ZPE) using a correction factor of 0.9877. The vibrational frequencies of α -ABA, β -ABA, γ -ABA and their metal complexes were scaled using the proper correction factors; 0.9679 for $\nu(C-H)$ and $\nu(N-H)$ stretching frequencies while 1.01 for those vibrational modes that appear below 1800 cm^{-1} (Andersson and Uvdal, 2005). The interaction enthalpies ΔH (cation binding affinities) and Gibbs energies ΔG were calculated using the equations, (I) for gas phase and (II) for aqueous phase, mentioned below:



$$\text{Thus, } \Delta H \quad \text{or} \quad \Delta G = [Et_{\text{products}}] - [Et_{\text{reactants}}],$$

where, $M = Mg^{+2}$; $Et_{\text{reactants}}$ is the sum of the ZPE corrected total electronic or Gibbs energies of the starting chemical species and Et_{products} is same for the products.

7.3 Results and Discussion:

The gaseous and aqueous phase optimized structures of all the Mg^{+2} complexes of α -ABA, β -ABA and γ -ABA are depicted in Figure 7.3 and 7.4 respectively.

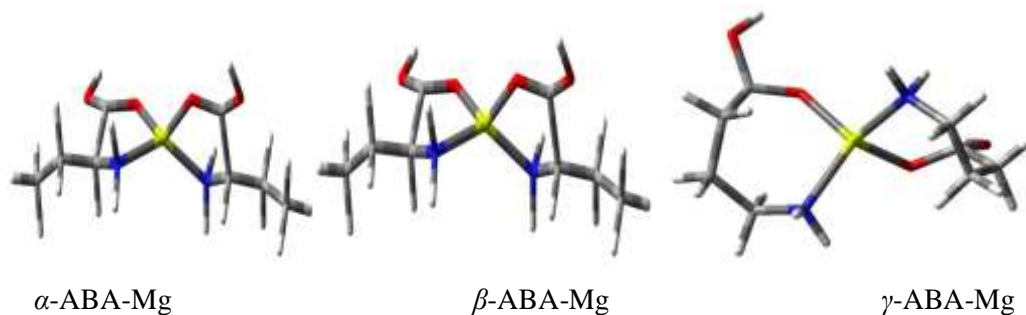


Figure 7.3: Optimized structures of the Mg^{+2} metal complexes of ABA (Gaseous phase)

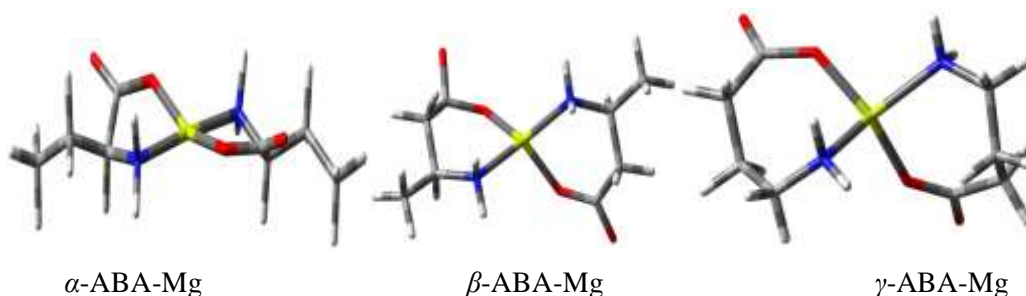


Figure 7.4: Optimized structures of the Mg^{+2} metal complexes of ABA (Aqueous phase)

7.3.1 Stability and Structural Features:

The Table 7.1 shows that the zwitterionic forms of all three aminobutyric acids are thermodynamically more stable than their non-ionic counterparts in the aqueous environment.

Table 7.1 Computed ZPVE values, total energy and Gibbs free energies^a for all the reaction species in gas and aqueous phase

Systems	Phases		ZPVE	Total Energy (E)	Gibbs Energy (G)
α -ABA	Gas phase	Non-ionic	0.135977	-363.1772296	-363.074261
	Aqueous phase	Non-ionic	0.135711	-363.1876907	-363.085010
	Aqueous phase	Zwitterion	0.137269	-363.1902874	-363.085734
$\text{Mg}(\alpha\text{-ABA})_2$	Gas phase		0.272710	-926.4771959	-926.253669
	Aqueous phase		0.249790	-925.3058644	-925.104537
β -ABA	Gas phase	Non-ionic	0.135839	-363.1804794	-363.077736
	Aqueous phase	Non-ionic	0.135671	-363.192352	-363.089879
	Aqueous phase	Zwitterion	0.136784	-363.1989208	-363.093830
$\text{Mg}(\beta\text{-ABA})_2$	Gas phase		0.272780	-926.482392	-926.258070
	Aqueous phase		0.250385	-925.3164901	-925.114800
γ -ABA	Gas phase	Non-ionic	0.136613	-363.1793029	-363.075905
	Aqueous phase	Non-ionic	0.136444	-363.1881539	-363.085364
	Aqueous phase	Zwitterion	0.136717	-363.1972128	-363.092480
$\text{Mg}(\gamma\text{-ABA})_2$	Gas phase		0.274979	-926.4727066	-926.245421
	Aqueous phase		0.252896	-925.3020402	-925.095294

^aenergies in Hartrees

The aminobutyric acids bind to the Mg^{+2} ion in bi-dentate form giving rise to five, six and seven membered rings for the α -, β - and γ -forms respectively (shown in Fig. 7.3 and 7.4). The Mg^{+2} complexes of α -ABA, β -ABA and γ -ABA assume nearly tetrahedral geometries around the metal cores. As listed in Table 2, the negative values of interaction enthalpies (-76.16 to -82.20 kcal/mol in gas and -59.13 to -72.83 kcal/mol in aqueous phase) and Gibbs energies (-53.56 to -61.42 kcal/mol in gaseous phase and -52.00 to -68.88 kcal/mol in aqueous phase) for all the three complexes indicate that the interactions of Mg^{+2} ion with α -ABA, β -ABA and γ -ABA leads to a decrease in the overall electronic energy of the complexes and are therefore thermodynamically stable. Among the three isomeric forms of aminobutyric acid, α -ABA produces the most stable complexes with Mg^{+2} studied here. Thus, in this study it is reasonable to assume that the metal-binding affinity order of the three isomeric forms of aminobutyric acid is α -ABA > β -ABA > γ -ABA. Details about the total dipole moments of the complexes in the gas and aqueous phases are provided in Table 7.2. The literature has explored how well the DFT approach predicts the rotational constants of various aliphatic amino acid conformers (Stepanian et al., 1998).

Future experimental scientists finding out the structural characteristics of these metal complexes using microwave and rotational spectroscopy may benefit from the theoretically anticipated gas and aqueous phase values of dipole moments and rotational constants. Table 8.2 includes the information of representative reaction species in the gaseous and aqueous phases regarding the energy gaps between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies. The predicted aqueous phase energy gaps for α -ABA, β -ABA and γ -ABA are 6.567, 6.530 and 6.420 eV respectively whereas those in the Mg^{+2} complexes are 3.648, 3.554 3.033 eV (lower in magnitude) respectively. The information provided by this DFT analysis also reveals that, in contrast to those in gas phase, the HOMO-LUMO energy gaps of all metal complexes increase in the environment of a solvent with a high dielectric constant, which is consistent with earlier theoretical observations (Das and Mandal, 2014; Bae et al., 2012).

According to Table 7.3, which lists the values of the different backbone dihedral angles for α -ABA, β -ABA, γ -ABA as well as their Mg^{+2} complexes, significant internal structural changes in the α -ABA, β -ABA, γ -ABA molecules may emerge from metal coordination.

The gaseous and aqueous phase values of the Wiberg bond indices (Wiberg, 1968) for the M-O and M-N bonds of the Mg^{+2} complexes are presented in Table 8.4. The bond order and, consequently, the bond strength between two chemically bound atoms can be estimated using the Wiberg bond indices.

Table 7.2: Calculated interaction enthalpies ΔH (kcal/mol) and Gibbs energies ΔG (kcal/mol), dipole moments (Debye), rotational constants (GHz), HOMO-LUMO energy gaps for all the reaction species in gas and aqueous phase (gas phase values are given in parentheses)

Systems	ΔH	ΔG	Dipole Moments	Rotational Constants			HOMO-LUMO Energy gaps
				A	B	C	
α -ABA	---	---	13.020 (2.143)	3.249 (2.984)	2.332 (2.348)	1.549 (1.656)	6.567 (6.447)
$Mg(\alpha$ -ABA) ₂	-72.83 (- 82.20)	-68.88 (- 61.42)	3.892 (3.776)	1.486 (1.420)	0.207 (0.204)	0.187 (0.196)	3.648 (2.636)
β -ABA	---	---	17.272 (2.471)	5.134 (4.856)	1.692 (1.500)	1.335 (1.465)	6.530 (6.415)
$Mg(\beta$ -ABA) ₂	-67.70 (- 81.17)	-64.19 (- 59.61)	14.678 (4.531)	0.798 (0.776)	0.281 (0.308)	0.251 (0.246)	3.554 (2.267)
γ -ABA	---	---	14.438 (2.913)	4.744 (4.502)	1.807 (1.527)	1.386 (1.383)	6.420 (6.377)
$Mg(\gamma$ -ABA) ₂	-59.13 (- 76.16)	-52.00 (- 53.56)	15.004 (5.442)	0.822 (0.856)	0.304 (0.291)	0.295 (0.283)	3.033 (2.224)

Table 7.3: Predicted dihedral angles (in degrees) of α -ABA, β -ABA, γ -ABA and their Mg^{+2} complexes in gas and aqueous phase (gas phase values are listed in parentheses)

Dihedral Angles	N ₇ -C ₂ -C ₁ -O ₅	N ₇ -C ₂ -C ₁ -O ₆	O ₅ -C ₁ -C ₂ -C ₃	O ₆ -C ₁ -C ₂ -C ₃	C ₁ -C ₂ -C ₃ -C ₄	H _a -N ₇ -C ₂ -C ₁	H _b -N ₇ -C ₂ -C ₁	N ₇ -C ₂ -C ₃ -C ₄
α -ABA	162.7 (134.7)	-18.1 (- 46.7)	-78.1 (- 100.3)	101.2 (78.2)	68.9 (63.6)	-98.0 (173.0)	138.6 (51.0)	-174.1 (-176.1)
Mg(α -ABA) ₂	163.0 (- 171.6)	38.5 (50.2)	-71.9 (- 46.8)	163.7 (175.0)	61.6 (79.2)	-164.1 (- 164.3)	79.8 (80.2)	-177.0 (-159.9)
Dihedral Angles	N ₇ -C ₃ -C ₂ -C ₁	C ₄ -C ₃ -C ₂ -C ₁	O ₅ -C ₁ -C ₂ -C ₃	O ₆ -C ₁ -C ₂ -C ₃	H _a -N ₇ -C ₃ -C ₂	H _b -N ₇ -C ₃ -C ₂	H _a -N ₇ -C ₃ -C ₄	H _b -N ₇ -C ₃ -C ₄
β -ABA	51.9 (63.6)	175.8 (- 169.9)	151.5 (- 128.8)	-30.2 (52.8)	-160.9 (- 168.2)	77.2 (72.2)	73.6 (67.3)	-48.3 (- 52.3)
Mg(β -ABA) ₂	77.8 (46.0)	-158.0 (171.8)	-173.4 (178.6)	-48.1 (40.3)	-174.3 (178.5)	72.1 (62.8)	61.1 (52.6)	-52.5 (- 63.0)
Dihedral Angles	N ₇ -C ₄ -C ₃ -C ₂	C ₁ -C ₂ -C ₃ -C ₄	O ₅ -C ₁ -C ₂ -C ₃	O ₆ -C ₁ -C ₂ -C ₃	H _a -N ₇ -C ₄ -C ₃	H _b -N ₇ -C ₄ -C ₃	-----	-----
γ -ABA	-73.3 (63.6)	73.7 (68.2)	148.8 (45.2)	-33.2 (- 136.3)	-79.7 (- 166.4)	160.2 (73.9)		
Mg(γ -ABA) ₂	-53.1 (62.0)	98.5 (45.6)	66.2 (178.7)	-58.8 (- 44.4)	-166.4 (168.1)	80.7 (49.5)		

Table 7.4: Wiberg bond indices for the M-N and M-O bonds of the Mg^{+2} complexes in gas and aqueous phase (gas phase data are listed in parentheses).

Complexes	M-O ₆	M-N ₇	M-O _{6a}	M-N _{7a}
Mg(α -ABA) ₂	0.1793 (0.2297)	0.1610 (0.1765)	0.1827 (0.2297)	0.1600 (0.1765)
Mg(β -ABA) ₂	0.2016 (0.2081)	0.1779 (0.1683)	0.1998 (0.2406)	0.1775 (0.1735)
Mg(γ -ABA) ₂	0.1980 (0.2483)	0.1729 (0.1658)	0.1994 (0.2203)	0.1730 (0.1712)

7.3.2 Intramolecular H-Bond Interactions:

This DFT study performed in gaseous phase along with aqueous phase predicts that three types of intramolecular H-bonding interactions, viz. O...H-O, O...H-N and O...H-C, play significant role on the energetics and preferred conformation of α -ABA, β -ABA, γ -ABA, and their complexes. Weak H-bonding interactions of the O...H-C type are important in many different biological systems. (Yerenko et al., 2011). Table 7.5 presents the gaseous and aqueous phase values of some structurally significant intramolecular H-bonds detected in α -ABA, β -ABA, γ -ABA and their metal complexes. Two geometrical criteria are used to determine the strength of the H-bonds: (a) the smaller the distance between A-H...B, more powerful the H-bond; and (b) the nearer the angle A-H...B to 180°, the more powerful the H-bond, here A is the donor and B is the acceptor of hydrogen bond (Arunan et al., 2011). The intramolecular H-bond interactions in the three isomeric forms of aminobutyric acid and associated metal complexes in the gas phase are clearly distinct from those in the

aqueous phase, as shown in Table 8.5. Compared to O...H-O or O...H-N, the relatively weaker O...H-C H-bonds seem to be the most predominant H-bonding interactions occurring in aminobutyric acids and their Mg^{+2} complexes in the aqueous environment.

Table 7.5 H-bond lengths^a (in angstrom) of the intramolecular hydrogen bond found in α -ABA, β -ABA, γ -ABA and their complexes in gas and aqueous phase (gas phase values are given in parentheses)

System	O ₆ ...H _b -N ₇	O ₆ ...H-O ₅	O ₅ ...H-C ₂	O ₆ ...H-C ₂	O ₅ ...H _a -C ₄
α -ABA	<i>abs</i> (2.503)	<i>abs</i> (2.293)	2.637 (2.419)	<i>abs</i> (<i>abs</i>)	<i>abs</i> (<i>abs</i>)
Mg(α -ABA) ₂	<i>abs</i> (<i>abs</i>)	<i>abs</i> (2.252)	2.658 (<i>abs</i>)	<i>abs</i> (2.726)	2.454 (2.410)
System	O ₆ ...H-O ₅	O ₅ ...H _a -C ₂	O ₅ ...H _b -C ₂	O ₆ ...H _a -C ₂	O ₆ ...H _a -C ₃
β -ABA	<i>abs</i> (2.286)	2.536 (<i>abs</i>)	<i>abs</i> (2.417)	<i>abs</i> (2.766)	<i>abs</i> (2.660)
Mg(β -ABA) ₂	<i>abs</i> (2.249)	2.747 (2.656)	2.681 (2.643)	<i>abs</i> (<i>abs</i>)	<i>abs</i> (2.738)
System	O ₆ ...H-O ₅	O ₅ ...H _a -C ₂	O ₅ ...H _b -C ₂	O ₆ ...H _b -C ₂	O ₆ ...H _a -C ₃
γ -ABA	<i>abs</i> (2.282)	2.481 (2.744)	<i>abs</i> (<i>abs</i>)	<i>abs</i> (2.550)	<i>abs</i> (<i>abs</i>)
Mg(γ -ABA) ₂	<i>abs</i> (2.267)	2.666 (2.603)	<i>abs</i> (2.647)	<i>abs</i> (<i>abs</i>)	<i>abs</i> (2.718)

^aOnly the (B...H) distances are presented. Here B is the acceptor of hydrogen bond and *abs* refers to absent.

7.3.3 Predicted Harmonic Frequencies:

Table 7.6 provides some of the vibrational frequencies for α -ABA, β -ABA, γ -ABA, and the complexes determined in gaseous and aqueous phase, along with their intensity values. It has been found that the frequent disparities among computed and experimental frequencies are due to repeated dereliction of the anharmonicity effects in theoretical treatments, the insufficient inclusion of electron correlation, and the utilization of finite basis sets (Hehre, 1976).

Nonetheless, in addition to describing the existence and nature of several forms of intramolecular H-bond interactions in the molecular geometries of α -ABA, β -ABA, and γ -ABA and their metal complexes, this study provides important information that will aid in understanding the impacts of metal binding.

Table 7.6 shows that the $\nu_{as}(N-H)$ and $\nu_s(N-H)$ modes of zwitterionic aminobutyric acids, which are observed in the regions of 3417-3427 cm^{-1} and 3358-3366 cm^{-1} , respectively, are blue-shifted in the complexes, which are noted to be falling within the sweep of 3424-3435 cm^{-1} and 3372-3376 cm^{-1} , respectively, in the aqueous phase. Again the aqueous phase $\nu_{as}(COO^-)$ stretching frequencies of the aminobutyric acids appearing at 1601-1639 cm^{-1} are shifted to higher frequency at 1627-1662 cm^{-1} in the complexes while the $\nu_s(COO^-)$ stretching modes (seen at 1393-1408 cm^{-1}) shift to lower frequency in the complexes (1375-1385 cm^{-1}). The geometric alterations surrounding the α -atom brought on by Mg^{+2} binding can be explained by the fact that the $\nu(C_2-H)$ stretching frequencies of the complex and the free α -

ABA molecule differ noticeably. The vibrational frequencies of the $\nu(\text{M-O})$ and $\nu(\text{M-N})$ modes of the complexes, $\nu(\text{M-O})$ span a scale of 631-687 cm^{-1} in gas phase and 573-602 cm^{-1} in aqueous phase whereas $\nu(\text{M-N})$ range from 436-491 cm^{-1} in gas phase and 477-537 cm^{-1} in aqueous phase.

7.4 Conclusions:

This study presents the interactions of α -ABA, β -ABA and γ -ABA with the divalent metal ion Mg^{+2} through computation. The results on the thermodynamic parameters provide a metal-binding affinity order of α -ABA> β -ABA> γ -ABA for the three aminobutyric acids.

The solvation effects due to aqueous environment seem to display a crucial role in determining intramolecular H-bond combinations as well as the energy profiles of the complexes of α -ABA, β -ABA and γ -ABA. The vibrational spectroscopic analysis provides vital information pertaining to the ramifications of the aqueous setting.

Table 7.6 Data on harmonic frequencies for α -ABA, β -ABA, γ -ABA and their Mg^{2+} complexes (intensities given in parentheses) determined in gas and aqueous. When scaling frequencies below 1800 cm^{-1} , 1.01 is used, while when scaling frequencies over 1800 cm^{-1} , 0.9679 is used as a correction factor.; ν =stretching; ν_{as} =asymmetric; ν_{s} =symmetric; δ =scissoring

Systems	Phases	$\nu(\text{O-H})$	$\nu_{\text{as}}(\text{N-H})$	$\nu_{\text{s}}(\text{N-H})$	$\nu_{\text{as}}(\text{COO-})$	$\nu_{\text{s}}(\text{COO-})$	$\nu(\text{C=O})$	$\nu(\text{C2-H})$	$\delta(\text{N-H})$	$\nu(\text{C-O})$	$\nu(\text{C-N})$	$\nu(\text{M-O})$	$\nu(\text{M-N})$	$\Delta\delta$
α -ABA	Aqueous	----	3417 (105)	3360 (82)	1639 (141)	1408 (84)	----	3015 (41)	1681 (245)	1125 (20)	1048 (31)	----	----	231
	Gas	3622 (62)	3466 (6)	3384 (3)	----	----	1752 (279)	2966 (18)	1659 (61)	1149 (140)	1078 (10)	----	----	----
$\text{Mg}(\alpha\text{-ABA})_2$	Aqueous	----	3424 (33)	3376 (7)	1662 (890)	1375 (102)	----	2848 (116)	1643 (70)	1254 (103)	1018 (120)	602 (97)	477 (45)	287
	Gas	3682 (45)	3410 (3)	3331 (6)	----	----	1443 (232)	2794 (107)	1638 (25)	1270 (304)	984 (114)	658 (13)	481 (0.4)	----
β -ABA	Aqueous	----	3424 (78)	3358 (56)	1626 (247)	1393 (34)	----	2973 (9)	1626 (247)	1247 (54)	1111 (50)	----	----	233
	Gas	3630 (60)	3460 (2)	3377 (0.8)	----	----	1752 (319)	2952 (3)	1673 (30)	1215 (130)	1182 (22)	----	----	----
$\text{Mg}(\beta\text{-ABA})_2$	Aqueous	----	3432 (27)	3372 (9)	1637 (1045)	1380 (356)	----	2930 (30)	1658 (69)	1336 (304)	1014 (69)	602 (97)	537 (46)	257
	Gas	3669 (34)	3407 (5)	3342 (0.8)	----	----	1420 (167)	2952 (7)	1657 (36)	1219 (116)	1126 (43)	687 (160)	491 (6)	----
γ -ABA	Aqueous	----	3427 (72)	3366 (53)	1601 (137)	1407 (107)	----	2988 (31)	1627 (95)	1258 (1272)	1088 (13)	----	----	194
	Gas	3638 (61)	3466 (2)	3387 (0.4)	----	----	1746 (289)	2945 (14)	1675 (31)	1132 (240)	1089 (10)	----	----	----
$\text{Mg}(\gamma\text{-ABA})_2$	Aqueous	----	3435 (24)	3373 (11)	1627 (1001)	1385 (309)	----	2968 (31)	1663 (86)	1309 (151)	1026 (32)	573 (228)	486 (131)	242
	Gas	3686 (43)	3392 (5)	3353 (82)	----	----	1425 (209)	2808 (120)	1656 (67)	1120 (90)	1086 (134)	631 (35)	436 (35)	----

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7.5 References:

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