Theoretical study of γ-aminobutyric acid conformers: Intramolecular interactions and ionization energies*

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Allowing for all combinations of internal single-bond rotamers, 1,296 unique trial structures of γ-Aminobutyric acid (GABA) are obtained. All of these structures are optimized at the M06-2X level of theory and a total of 68 local minimal conformers are found. The nine low-lying conformers are used for further studies. According to the calculated relative Gibbs free energies at M06-2X level of theory, we find that the dispersion is important for the relative energy of GABA. The intramolecular hydrogen bonds and hyperconjugative interaction and their effects on the conformational stability are studied. The results show that both of them have great influence on the conformers. The vertical ionization energies (VIE) are calculated and match the experimental data well. The results show that the neutral GABA in the gas phase is a multi-conformer system and at least four conformations exist.

Keywords: conformation, hydrogen bond, hyperconjugative interaction, ionization energy

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1. Introduction

γ-Aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the brain and brainstem/spinal cord. It plays a significant role in controlling the neuronal activity in a mammalian central nervous system.[1] The importance of GABA has attracted the attention of experimental and theoretical researchers. Due to the highly flexible backbone of GABA, it has a large number of low-energy conformations. Considerable experimental and theoretical studies have been carried out to investigate the conformational preferences of GABA.[2–5] Allison *et al.*[2] studied the structures of GABA in the monoclinic phase. They found that the hydrogen bond (HB) involving the H atoms bound to the N atom is an important stabilizing factor for the gauche conformation. Crittenden *et al.*[3] studied the stabilization of the zwitterionic GABA at the HF/6-31+G(d), B3LYP/6-31+G(d), and MP2/6-31+G(d) levels of theory in different aqueous solutions. They found 18 stable forms including 9 neutral and 9 zwitterionic stable ones both in GABA.5H_2O and GABA.2H_2O. Recently, many conformational studies of GABA were carried out in the gas phase. In 2010, Blanco *et al.*[4] measured the rotational spectrum of GABA by using LAMB–FTMW experiment in the gas phase. In their work, 30 feasible conformations with relative energies below 900 cm^{-1} were calculated at the MP2/6-311++G (d, p) level of theory and 9 conformations were experimentally observed. They also studied the role of the n–π* interaction between the nonbonding electron pair of the nitrogen and the π* orbital at the carbonyl group in the most stable conformation. Song and Kang[5] investigated GABA at the M06-2X/cc-pVTZ level of theory in the gas phase and the solvation model based on density M06-2X/cc-pVTZ level of theory in water. Sixty-eight neutral (including eight enantiomers) were obtained through optimizing the ninety initial structures of GABA in the gas phase. In this search of GABA conformers, some rotational degrees of freedom are ignored, which might be a serious limitation. On the other hand, the key factors affecting the stabilities of these conformers, such as HBs and hyperconjugative interactions, have not been discussed. Because of their importance for understanding the molecular characteristics, it is necessary to study the HBs and hyperconjugative interactions.

In the present work, we report a comprehensive study of the conformations of gaseous GABA and the relevant properties. The purpose of this investigation is to locate all possible gaseous GABA conformers, to obtain precise knowledge about the relative stabilities of different conformers on the energy surface, to discuss the intramolecular interactions and their effects on the conformational stabilities and to gain the conformation-dependent vertical ionization energies (VIEs).

2. Theoretical method

The planar structure of GABA is shown in Fig. 1. In principle, the full conformational space of GABA can be explored through a systematic variation of all rotational degrees of freedom. As a dihedral angle can change from 0° to 360°, typically, 60° increments for asymmetrical dihedral angles and 120° increments for symmetrical dihedral angles are required to ensure a complete scan of the potential energy surface.[6,7]

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As a result, the numbers of trial structures obtained by allowing for all combinations of every internal bond rotamers are $2 \times 6 \times 6 \times 6 \times 3 = 1296$.

To avoid losing important low-energy conformers, all of the 1,296 trial structures are optimized with M06-2X/6-311++G** method and 68 local minima are obtained. All the calculations are carried out using the Gaussian 09 package.[8] The final energies for the 17 conformers of interest are determined at the coupled-cluster level of theory with single and double excitations (CCSD(T))[9] and the aug-cc-pVTZ basis set at the optimal M06-2X geometries, for M06-2X is usually preferable to treat hydrogen-bonded systems.[10,11] With the M06-2X optimized geometries, the VIE is calculated in the P3 electron propagator approximation, which has been shown to give excellent agreement with experimental photoelectron spectra (PES) for nucleic acid bases[12,13] and some organic molecules.[13,14]

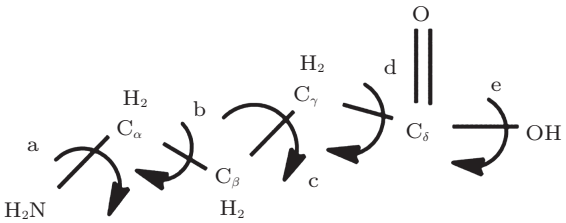


Fig. 1. Planar structure of GABA. (a), (b), (c), (d) and (e) refer to various internal single-bond rotamers. a 3-fold: –120, 0, 120; b 6-fold: –120, –60, 0, 60, 120, 180; c 3-fold: –120, –60, 0, 60, 120, 180; d 6-fold: –120, –60, 0, 60, 120, 180; e 2-fold: 0, 180.

Many conformational studies of GABA have indicated the presence of the intramolecular interactions such as HBs and the associated internal strains. Here, atoms in molecules (AIM)[15] and the natural bond orbital (NBO)[16] analysis are employed to study the HBs and hyperconjugative interactions in different conformers of GABA. NBO theory has been successfully used to analyze intermolecular[17] and intramolecular interactions.[18,19] The energy lowering due to the delocalization caused by the intramolecular HBs and hyperconjugative interactions can be treated by the second-order perturbation energy $E(2)$ in the NBO theory, $E(2) = -n_\sigma F_{ij}^2/\Delta\varepsilon$, where n_σ is the population of the lone pair (n) orbital, F_{ij} is the Fock matrix (or Kohn–Sham matrix in density functional theory) element between the NBOs $i(n)$ and $j(\sigma^*)$, and $\Delta\varepsilon$ is the energy level differences between these two orbitals.

3. Results and discussion

3.1. Conformers and energy

Table 1 lists the dihedral angles, bond angles, rotational constants and relative energies of the 17 local minima conformers of GABA. According to our calculated rotational constant, we find that the nine conformers contribute to the experimental rotational spectra measured by Blanco *et al.*[4] The nine conformers are shown in Fig. 2. Our result is in agreement with their result. The stable order based on Gibbs free energies at M06-2X level predicted by us and Song and Kang[5] are also

Table 1. Properties of GABA calculated at M06-2x/6-311++G** level of theory in the gas phase.

		Dihedral angles/(°)			Bond angles/(°)		Rotational constants/MHz			ΔE	ΔG^1	ΔG^2	ΔG^3	Abound
		D_1	D_2	D_3	J_1	J_2	A	B	C					
m5	e(GG1)	61.70	72.66	–177.00	110.13	111.64	4.928	1.461	1.401	0.59	0	0	0.21	0.22
m10	a(gG1)	–50.36	79.07	–154.43	110.29	112.08	4.188	1.854	1.679	0.00	0.09	0.15	0.40	0.19
m17	g(gt2)	–178.96	71.15	–169.64	115.41	111.66	6.141	1.287	1.181	1.53	0.54	0.88	0.90	0.09
m19	i(tt3)	–177.80	–177.10	–176.47	109.98	111.56	8.256	1.057	0.956	2.05	0.65	0.62	1.06	0.07
m26		–57.58	–66.64	168.14	110.77	111.71	4.577	1.534	1.475	1.62	0.77	0.87		0.06
m18		–62.21	177.01	–58.88	110.18	111.88	6.317	1.213	1.145	1.87	0.85	0.66		0.05
m15		55.99	–80.46	150.09	116.37	112.06	4.095	1.792	1.631	1.82	0.85	1.11		0.05
m21	h(tG1)	–60.22	174.13	178.18	110.95	111.54	6.430	1.214	1.074	1.86	0.98	0.92	0.00	0.04
m27	f(GG2)	53.49	50.88	75.22	116.44	112.23	4.104	1.883	1.592	1.44	1.03	1.4	0.86	0.04
m16		178.07	60.20	53.51	109.86	111.83	4.946	1.356	1.344	1.94	1.05	1.19		0.04
m1	b(gG2)	–65.47	94.41	–55.28	111.18	116.37	4.852	1.758	1.381	0.55	1.06	1.04	1.22	0.04
m9		–60.54	178.91	79.43	110.43	111.91	6.245	1.235	1.113	1.93	1.16	0.88		0.03
m14	d(gg)	45.31	52.21	–78.65	110.70	115.26	4.360	1.948	1.581	0.20	1.21	1.33	1.46	0.03
m35		64.03	–71.44	–66.51	111.33	111.84	3.853	1.963	1.678	1.51	1.48	1.51		0.02
m32		179.20	–179.14	–61.72	109.93	111.71	7.236	1.078	1.008	2.53	1.51	1.65		0.02
m20	c(gG6)	–56.24	71.50	40.51	110.02	112.47	4.003	1.912	1.725	1.49	1.58	1.43	1.90	0.02
m33		–179.50	–178.34	–71.88	109.92	111.76	7.043	1.075	1.022	2.47	1.75	1.94		0.01

D_1: dihedral angle N–C_α–C_β–C_γ; D_2: dihedral angle C_α–C_β–C_γ–C_δ; D_3: dihedral angle O–C_δ–C_γ–C_β; J_1: bond angle N–C_α–C_β; J_2: bond angle O–C_δ–C_γ; Abound: calculate at 298 K by ΔG. ΔE: relative energies of GABA calculated at CCSD(T)/aug-cc-pVTZ level of theory. ΔG_1 and ΔG_2: relative Gibbs free energies calculated at M06-2X/aug-cc-pVTZ and M06-2X/6-311++G** level of theory respectively. ΔG_3: Gibbs free energies calculated at M06-2X/cc-pVTZ in Ref. [6].

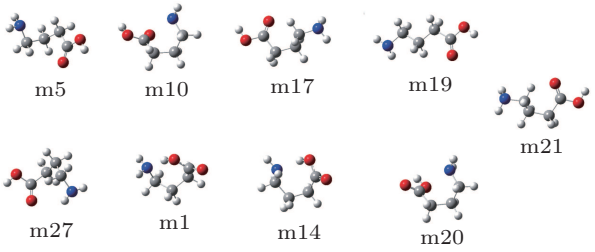


Fig. 2. (color online) Local minima observed in experiment for the neutral GABA optimized at M06-2X/6-311++G**level.

shown in Table 1. We find that our predicted stable order is different from their result. The most stable conformer is m5 according to our M06-2X/aug-cc-pVTZ result. But Song and Kang[5] predicted that m5 is the fifth stablest and m21 is the most stable according to their M06-2X/cc-pVTZ result. What is more, the stable orders of conformers m17, m27, and m19 also have great changes. Through careful analysis, we find these differences are caused by the different basis sets used in the calculations. The result indicates that the dispersion is important for the relative energy of GABA. We also calculate the relative energy with the smaller basis set 6-311++G** including dispersion function, which also predicts a similar stable order as shown in Table 1. This further supports the conclusion that the dispersion is important for the relative energy of GABA.

Blanco *et al.*[4] have studied the n–π^* hyperconjugative interaction of the most stable conformer m10. Song and Kang[5] also studied the hyperconjugative interactions of m10, m5, and m9. But none of them analyzed the influence of hyperconjugation interaction on the stable order of GABA. Here, we perform an NBO analysis of the nine conformers. The energies of the hyperconjugative interaction are listed in Table 2. As seen from Table 2, the main interactions between orbitals are $n(N) \rightarrow \pi^*$ (C_δ=O) or $\sigma^*(C_\alpha$–$C_\beta)$ and $\pi(C_\delta$=O) $\rightarrow \sigma^*(C_\gamma$–H). The present M06-2X/aug-cc-pVTZ calculation including all the hyperconjugation predicts the stable order: m5 > m10 > m1 > m14 > m20. When n(N) $\rightarrow \pi^*(C_\delta$=O) or $\sigma^*(C_\alpha$–$C_\beta)$ interactions are removed, m14 has the lowest energy, and the stable order changes completely. When $\pi(C_\delta$=O)$\rightarrow \sigma^*(C_\gamma$–H) interactions are removed, the most stable conformer is also m5, but the order changes greatly. After all of the hyperconjugative interactions are removed, the result shows dramatic changes and the stable order is m14 > m5 > m10 > m20 > m1. Therefore we can draw a conclusion that the hyperconjugative interactions have a great influence on the stable order of these conformers.

The previous studies[2,4,5] have predicted the existence of HBs in GABA, but they did not calculate HBs of GABA in detail. In order to study the HBs of GABA, we perform AIM and NBO analysis for the stable conformers of GABA at the M06-2X/6-311++G(d, p) level of theory. The results are listed in Table 3. As shown in Table 3, all HBs are subjected to typical close-shell interactions, for the value of $\nabla^2\rho$ falls in the proposed range of 0.014 a.u.–0.139 a.u.[20] ρ and $\nabla^2\rho$ are bigger in the OH–N HBs than in O–HN. The intramolecular HBs between the carboxylic O–H group and the lone electron pair of the amine nitrogen atom group are strong HBs with the distances (OH–N) = 1.88 and 1.75 Å in conformers m14 and m1, respectively. This suggests that the OH–N HB is the strongest in all the types of HBs and the N atom is the best HB acceptor. This kind of HB makes a great contribution to lowering the relative electronic energies in the two conformers. According to the data of ρ and $\nabla^2\rho$ in Table 2, the O–HN HB is weak, and the HB in m9 is slightly stronger than in m20. The HBs

Table 2. Favored second-order hyperconjugative interaction energies (kcal/mol), based on the M06-2X/6-311++G (d, p) geometries.

	n(N) $\rightarrow \pi^*(C_\delta$=O)	n(N) $\rightarrow \sigma^*(C_\alpha$–$C_\beta)$	$\pi(C_\delta$=O)$\rightarrow \sigma^*(C_\gamma$–H)	total[a]	Del$_{n\mathrm{N}}$	Del$_{n\mathrm{C=O}}$	Del$_{\mathrm{all}}$
m5	0	2.78	1.92	0	0.20	0.00	0.99
m10	1.01	2.22	1.89	0.09	0.74	0.06	1.5
m1	0	3.74	1.8	1.06	2.22	0.94	2.89
m14	0	1.37	1.13	1.21	0.00	0.42	0
m20	0	3.85	1.08	1.58	2.85	0.74	2.8

[a] Relative Gibbs free energies (kcal/mol) of the most stable conformers of GABA, calculated M06-2x/aug-cc-pVTZ level based on M06-2X structures.

Table 3. Property analysis of the bond critical points (BCPs) about HBs of the ten most stable GABA conformers at M06-2X/6-311++G(d, p) level, based on the M06-2X/6-31++G (d, p) geometries.

	Type	ρ	$\nabla^2\rho$	λ_1	λ_2	λ_3	Bond length/Å	$E(2)$/(kcal/mol)
m14	N–HO	0.0346	0.0245	–0.0493	–0.0474	0.1947	1.86	34.42
m20	O–HN	0.0097	0.0081	–0.0087	–0.0076	0.0487	2.53	1.01
m1	N–HO	0.0469	0.0267	–0.0762	–0.0740	0.2568	1.75	52.82
m9	O–HO	0.0042	0.0060	–1.1219	–1.0438	2.189	2.28	1.45

ρ and $\nabla^2\rho$ (in atomic units a.u.): the electron density and its Laplacian at the BCP. λ_1, λ_2, and λ_3 (in atomic units): the eigenvalues of the Hessian matrix of the electron density, $E(2)$: the strength of HBs by NBO.

in m9 and m20 are so weak that they might contribute to stabilizing these conformers but are not strong enough to lower the relative energies. As a result, we can draw a conclusion that the interaction between HBs are more important than the hyperconjugative interactions in m14 and m1, and the former has a greater influence on their energies.

3.2. Ionization energy

The values of VIEs for the five most stable conformers of GABA are determined at the P3/aug-cc-pVTZ level of theory, based on the M06-2X/6-311++G (d, p) geometries, and the results are reported in Table 4. The pole strengths for P3 VIEs are ≥ 0.89, which validates the approximations used by the P3 method.

Table 4. Ionization energies (in eV) of GABA.

m5	m10	m17	m19	m26	Exp[a]
9.63	9.56	9.44	9.65	9.58	9.6
10.74	10.61	10.97	10.87	10.92	10.65
11.97	11.83	12.09	12.19	12.18	11.9
12.58	12.47	12.68	12.56	12.51	12.6
13.85	13.93	13.78	13.84	12.82	14.0
14.17	14.18	14.37	14.46	14.18	16.5
16.50	16.72	16.65	16.57	16.14	

[a] Ref. [21]

The PES of GABA reported by Cannington and Ham[21] using HeI radiation source are shown in Fig. 3(a), in which five diffuse bands are observed. The VIEs predicted by P3 are presented with short vertical bars. As shown in Fig. 3(a), although the predicted IEs of the stablest conformer m5 accord better with the PES than with the other ones, there is a disagreement between the predicted IE (10.74 eV) of m5 and the position of the experimental peak at 10.65 eV. There is a weak peak at 13.90 eV in the PES. This weak peak is regarded as being from the contribution of m10 with the perfected value of 13.93 eV. A little platform at about 12.60 eV in the PES comes from the contribution of the conformer m17, which has a peak value of 12.68 eV. The relative intensity between 11.9 eV and 12.6 eV in the PES is very high. We regard it as being from the contribution of m19 for this conformer with a suitable IE value of 12.18 eV. The predicted IEs of the conformer m26 are overlapped with those of the other conformers. We cannot elucidate whether m26 exists in the experiment. So we can draw a conclusion that there are at least four conformations existing in the gas-phase experiment. m5 and m10 are the main components in the gas-phase experiment and the contributions from m17 and m19 are not negligible.

By considering the relative abundances of the most stable five conformers at 298 K, as shown in Table 1, we simply simulate the theoretical PES with an energy resolution of about 50 meV[22] by using the P3 values of the IEs. The intensity is the pole strength for the relevant molecular orbital.[23,24] As shown in Fig. 3(b), despite the fact that none of the five conformers can match the experimental peaks perfectly, the peak positions in the simulated PES generally match the observed ones very well. This also indicates that the neutral GABA in the gas phase is a multi-conformer system and at least four conformers exist: m5, m10, m17, and m19.

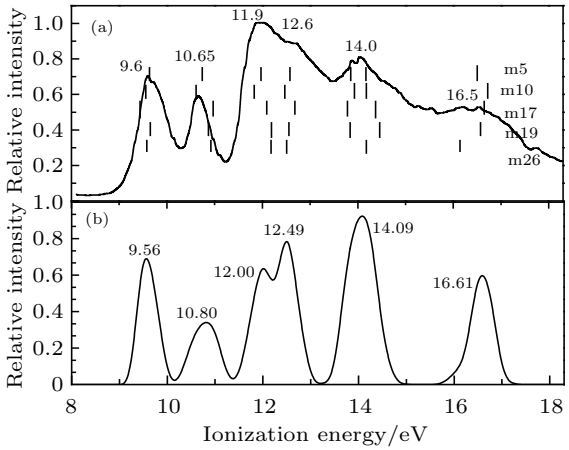


Fig. 3. Comparison between (a) the experimental spectra adopted from Ref. [21] and (b) the simulated spectra of GABA. The short vertical bars represent the P3 values of the IEs for the five low-lying conformers.

4. Summary

The conformations of GABA in the gas phase are investigated. By a structural search based on the M06-2X/6-311++G** geometry optimizations, 68 stable conformers are obtained. Nine low-lying conformers are used for further studies. According to the relative Gibbs free energies at M06-2X level of theory, we find the dispersion is important for the relative energy of GABA. AIM and NBO analysis are performed to analyze intramolecular HBs and hyperconjugative interaction energies. The results indicate that hyperconjugative interactions lower the relative energies in all of the stablest five conformers and intramolecular HB interactions are more important than the hyperconjugative interactions in both m1 and m14 conformers. The theoretical PESs simulated with the P3 calculated results match the experimental data well. Combining the conformational distributions with the theoretical PESs, we can draw a conclusion that the neutral GABA in the gas phase is a multi-conformer system and at least four conformers exist: m5, m10, m17, and m19.

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