The Crystal and Molecular Structure of γ-Guanidinobutyric Acid Monohydrate

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The crystal structure of γ-guanidinobutyric acid (GGBA) monohydrate, $C_5H_{11}O_2N_3 \cdot H_2O$, was determined by X-ray diffraction. The crystals are monoclinic, space group $P2_1/a$, with cell dimensions, a = 7.72(2), b = 10.188(8), c = 10.686(3) Å, β = 96.62(5)° and Z = 4. The structure was refined to R = 0.057. The molecular conformation is characterized by an extended *trans* planar zig-zag conformation. The GGBA molecule is a zwitter-ion structure, $H_2N^+=C(NH_2)NH(CH_2)_3COO^-$, and the molecules are linked by N–H···O and O–H···O intermolecular hydrogen bonds.

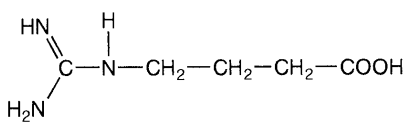
Key words γ-guanidinobutyric acid; GGBA; neurotransmitter; X-ray analysis; crystal structure

γ-Guanidinobutyric acid (GGBA, I) is a compound analogous to the well-known neurotransmitter, γ-aminobutyric acid (GABA), and has been found in brain as a complex of GABA with a basic amino acid.[1,2] It is known to act as a depressive neurotransmitter in mammalian brain like GABA,[3] is toxic enough to kill egg embryos following injection into chick eggs,[4] and is also found in various plant materials such as soybean, tea or citrus.[5] It is, therefore, important to elucidate the accurate molecular structure of GGBA in order to clarify its physiological function.

The crystal structures of GGBA hydrochloride and hydrobromide have already been reported by Maeda *et al.*[6] They refined the structure of GGBA hydrochloride with rather high *R*-index values of 0.143 and large standard deviations for the geometric parameters. However, they found that GGBA hydrochloride has the form, $H_2N^+=C(NH_2)NH(CH_2)_3COOH \cdot Cl^-$, and proposed that GGBA has probably a zwitter-ion structure in the free state. In this study we wished to determine the structure of GGBA in the free state which may be predominant under physiological conditions.

Experimental

Colorless crystalline platelets of GGBA monohydrate were obtained by slow evaporation of an aqueous solution at room temperature . A single crystal with the dimensions 0.3 × 0.3 × 0.1 mm³ was used for X-ray diffraction data collection. The crystal density was measured by the floatation method using a C_6H_6/CCl_4 mixture. The intensities were measured with a Rigaku AFC 5R automated four circle diffractometer with graphite-monochromated MoK_α radiation (λ = 0.71069 Å) at 50 kV–180 mA using the $\omega/2\theta$ scan mode. Lattice parameters were determined from 2θ angles of 31 reflections ranging $9.67° < 2\theta < 32.8°$. The linear absorption coefficient μ(MoK_α) was 0.10 mm^{-1}. Three standard reflections which were measured after every 150 reflections declined by 0.92%. A linear correction factor was applied to the data to account for this phenomena. The data were corrected for Lorenz, polarization and absorption factors. An empirical absorption correction using the program DIFABS[7] resulted in minimum and maximum transmission factors of 0.82 and 1.10, respectively. A total of 2162 reflections within $2\theta = 55°$ were collected with the ω–2θ scan method with a peak range of $(1.37 + 0.30 \tan\theta)°$ and a scan speed of 32.0° min^{-1} in ω; the ratio of peak counting time to background counting time was 2 : 1. The scan speed was slightly high because of the unstability of the crystal during the intensity measurements. Of the 2020 unique reflections (R_{int} = 0.023), 769 reflections with $I > 3\sigma(I)$ were used for structure determination and refinement. The structure was solved by direct methods with SHELXS[8] and DIRDIF[9] and refined by full-matrix least-squares methods with anisotropic displacement factors for all non-H atoms using the program TEXSAN.[10] The positions of the hydrogen atoms of the GGBA were obtained from a difference Fourier map and were included for refinement with isotropic displacement factors. The hydrogen atoms of the water molecule were not located. At final convergence, R = 0.057, R_w = 0.071, with $w = 4F_o^2/\sigma^2(F_o^2)$, goodness of fit indicator = 1.90 and $(\Delta/\sigma)_{max}$ = 0.02 for 100 parameters. The minimum and maximum peaks in the final difference Fourier map were −0.33 and 0.29 eÅ^{-3}. The crystal data are given in Table 1 and the final atomic coordinates are listed in Table 2.[11] The atomic scattering factors were taken from International Tables for X-Ray Crystallography.[12]



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Results and Discussion

The crystal data shown in Table 1 differ from those of the GGBA hydrochloride and/or hydrobromide forms,[6] in which the space group and crystal system are $P1$ and triclinic. A perspective view of GGBA (I) is shown in Fig. 1. GGBA has a zwitter-ion structure in the free state, in which the guanidyl group is protonated and the carboxylate group deprotonated. This zwitter-ion structure was suggested by Maeda *et al.*,[6] although they did not find it in the crystal structure of GGBA hydrochloride

Table 1. Crystal Data of γ-Guanidinobutyric Acid

Chemical formula	$C_5H_{11}N_3O_2 \cdot H_2O$
Molecular weight	163.18
Space group	$P2_1/a$
a (Å)	7.72 (2)
b (Å)	10.188 (8)
c (Å)	10.686 (3)
β (°)	96.62 (5)
V (Å^3)	835 (2)
Z	4
D (mesd) (g·cm^{-3})	1.302 (1)
D (Calcd) (g·cm^{-3})	1.298
μ (MoK_α) (cm^{-1})	1.00
F (000)	352
T (K)	296

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determined in their own study. The molecule has the *trans* planar zig-zag carbon-skeletal conformation as indicated by the torsion angles shown in Table 3. The planar zig-zag conformation was also found in GGBA hydrochloride. Tomita[13] stated from the crystallographic data of GABA and its derivatives determined by him and his collaborators

Table 2. Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters (Å^2)

Atom	x	y	z	B_{eq} (Å^2)
O(1)	0.9415 (6)	−0.3292 (3)	0.5867 (3)	4.8 (2)
O(2)	0.9052 (5)	−0.2804 (3)	0.7840 (3)	3.7 (2)
O(3)	0.3173 (6)	0.2440 (4)	0.0366 (3)	5.6 (2)
N(1)	0.8661 (7)	0.4462 (4)	0.8399 (4)	4.1 (2)
N(2)	0.9317 (6)	0.4036 (4)	0.6404 (4)	3.5 (2)
N(3)	0.8837 (6)	0.2326 (4)	0.7749 (4)	3.2 (2)
C(1)	0.8967 (7)	0.3605 (5)	0.7515 (5)	2.9 (2)
C(2)	0.9158 (7)	0.1318 (5)	0.6829 (5)	3.1 (2)
C(3)	0.8986 (7)	−0.0051 (4)	0.7370 (5)	3.2 (2)
C(4)	0.9400 (7)	−0.1045 (4)	0.6386 (5)	3.2 (2)
C(5)	0.9264 (7)	−0.2477 (5)	0.6723 (5)	3.1 (2)

$B_{eq} = (\frac{8}{3}\pi^2)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i \cdot a_j$.

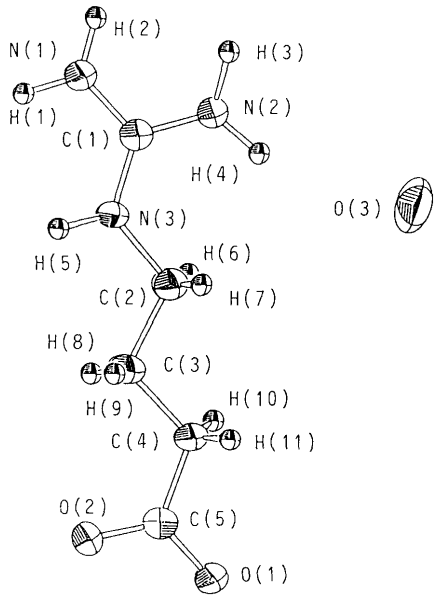

Fig. 1. A Perspective View of γ-Guanidinobutyric Acid Monohydrate Showing the Labelling of the Atoms

Thermal ellipsoids are shown at 50% probability levels.

Table 3. Bond Lengths (Å), Angles (°), Hydrogen-Bond Distances (Å) and Torsion Angles (°)

Bond lengths Bond	Distance (Å)	Bond lengths Bond	Distance (Å)
O(1)–C(5)	1.250 (5)	N(3)–C(2)	1.462 (6)
O(2)–C(5)	1.269 (6)	C(2)–C(3)	1.522 (6)
N(1)–C(1)	1.327 (6)	C(3)–C(4)	1.520 (6)
N(2)–C(1)	1.323 (6)	C(4)–C(5)	1.509 (7)
N(3)–C(1)	1.333 (6)		

Bond angles Bond	Angle (°)	Bond angles Bond	Angle (°)
C(1)–N(3)–C(2)	122.6 (4)	C(2)–C(3)–C(4)	108.3 (4)
N(1)–C(1)–N(2)	119.5 (4)	C(3)–C(4)–C(5)	116.9 (4)
N(1)–C(1)–N(3)	119.1 (4)	O(1)–C(5)–O(2)	123.2 (5)
N(2)–C(1)–N(3)	121.3 (4)	O(1)–C(5)–C(4)	116.9 (4)
N(3)–C(2)–C(3)	111.1 (4)	O(2)–C(5)–C(4)	119.8 (4)

Hydrogen-bond distances

Donor (D) at x, y, x	Acceptor (A)	at symmetry operation	Distance (Å) D---A
N(1)	O(3)	$1/2+x$, $1/2-y$, $1+z$	2.915 (6)
N(1)	O(2)	x, $1+y$, z	2.872 (5)
N(2)	O(1)	x, $1+y$, z	2.785 (5)
N(2)	O(1)	$2-x$, $-y$, $1-z$	2.824 (5)
N(3)	O(3)	$1/2+x$, $1/2-y$, $1+z$	2.910 (5)
O(3)	O(2)	$3/2-x$, $1/2+y$, $1-z$	2.717 (7)
O(3)	O(2)	$1-x$, $-y$, $1-z$	2.743 (6)

Torsion angles

Bond sequence	Angle (°)
O(1)–C(5)–C(4)–C(3)	172.3 (5)
O(2)–C(5)–C(4)–C(3)	−9.5 (8)
N(1)–C(1)–N(3)–C(2)	−179.8 (5)
N(2)–C(1)–N(3)–C(2)	3.2 (9)
N(3)–C(2)–C(3)–C(4)	−177.9 (5)
C(1)–N(3)–C(2)–C(3)	177.8 (5)
C(2)–C(3)–C(4)–C(5)	−178.6 (5)

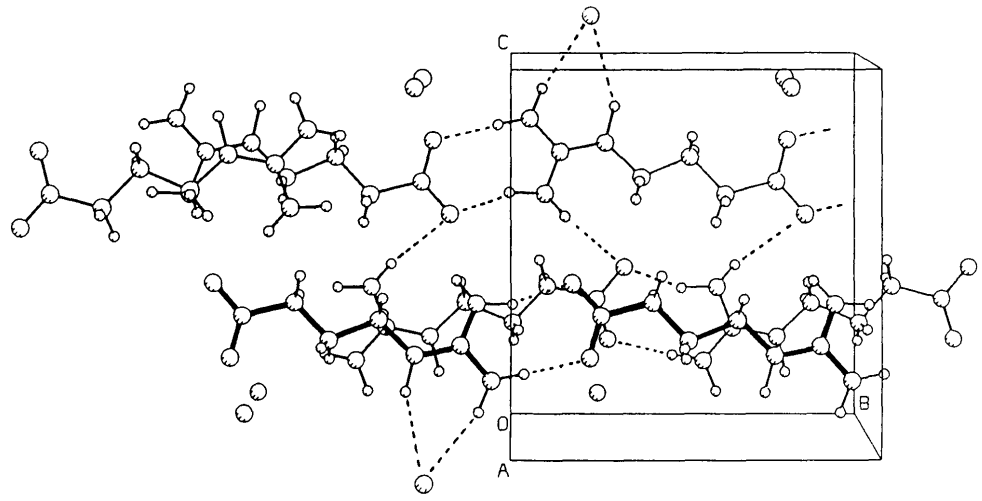

Fig. 2. Crystal Structure of γ-Guanidinobutyric Acid Monohydrate with the Hydrogen Bonding Scheme, Viewed along the *a*-Axis

that those compounds have some common features: (1) the molecule has a zwitter-ion structure in the crystalline state as in α-amino acids; (2) it has a planar carbon skeletal conformation in most of the compounds so far investigated.

In this study, these features were also found in the crystal structure of GGBA in the free state. The bond lengths and angles involving the non-hydrogen atoms are also shown in Table 3. The dimensions are comparable with those of the protonated guanidyl and deprotonated α-carboxylate groups of L-arginine,[14-17] although the dimensions of the protonated guanidyl group could not be closely compared with those of GGBA hydrochloride having some large standard deviations around 0.015 Å.[6] The molecular packing of the crystal structure is shown in Fig. 2. The crystal structure is stabilized by ionic interaction and hydrogen bonds between the guanidyl and carboxylate groups in a "head-to-tail" arrangement. These stabilizing forces may be important as possible binding forces for the GGBA molecule in the binding pocket on its receptor under physiological conditions.

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