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Crystal and Molecular Structure of ω-Amino Acids, ω-Aminosulfonic Acids and Their Derivatives. I. The Crystal and Molecular Structure of γ-Guanidinobutyric Acid Hydrochloride and Hydrobromide

Tomie MAEDA, Takaji FUJIWARA, and Ken-ichi TOMITA

Faculty of Pharmaceutical Sciences, Osaka University, Toneyama, Toyonaka, Osaka

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The crystals of γ-guanidinobutyric acid (GGBA) hydrochloride and hydrobromide, $C_5H_{12}O_2N_3Cl$ and $C_5H_{12}O_2N_3Br$, are both triclinic, space group $P\bar{1}$, with two molecules in a unit cell with the following dimensions; hydrochloride: $a=7.41$, $b=9.12$, $c=7.25$ Å, $\alpha=101.5°$, $\beta=112.4°$, $\gamma=65.2°$; hydrobromide: $a=7.94$, $b=9.36$, $c=7.78$ Å, $\alpha=103.2°$, $\beta=115.5°$, $\gamma=61.5°$. The X-ray structure analysis was carried out by the application of heavy atom method and refined by three dimensional least-squares method. Since GGBA hydrochloride and hydrobromide are isomorphous, the structure analysis was started by using of X-ray data of the hydrobromide to determine the rough atomic coordinates of its molecule, and the data of hydrochloride were used for the further refinement. The positions of the involved twelve hydrogen atoms were located by a three dimensional difference Fourier analysis. GGBA cation, $^{+}NH_2(NH_2)CNH(CH_2)_3COOH$, and Cl^- ion were almost perfectly on the $(20\bar{1})$ plane and formed a pararell sheet structure with six hydrogen bonds. The possible resonance structures were also discussed.

γ-Guanidinobutyric acid (GGBA) is one of the amino acids related to γ-aminobutyric acid (GABA), which was first discovered in mammalian brain by Roberts and Frenkel[1] and others,[2-3] and was also found in *Crustacea* as a depressive transmitter by Elliott *et al.*,[4,5] or in cerebral cortex of mammalian brain as an anti-convulsive substance by Hayashi and Nagai.[6] Since then, the significance of GABA has been widely studied from the physiological and biological standpoints. On the other hand, GGBA has been found in

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brain as a complex of GABA with basic amino acid,[7,8] and it acts as a depressive substance in peripheral nervous system of *Crustacea*,[9] as a stimulant in mammalian brain,[10,11] and as a convulsive substance in cerebrum of rabbit.[12]

The crystal and molecular structure of GGBA, therefore, is of most interest in order to elucidate the correlation between its structural specificity and pharmacological action of GABA, GGBA and other related ω-amino acids. Preliminary structural feature of these compounds has been discussed,[13] and this paper deals with the precise structure analysis of GGBA hydrochloride and hydrobromide.

Experimental

GGBA was synthesized from GABA and methyl-isothiourea sulfate, confirmed by Sakaguchi's and ninhydrin reactions, and recrystallized from aqueous solution at room temperature.

The crystals of GGBA were dissolved in concentrated solution of hydrochloric acid or hydrobromic acid and the crystals of GGBA hydrochloride or hydrobromide were obtained after staying for about three days. They are both colorless needles and the marked cleavage plane is parallel to $(20\bar{1})$. Intensity data were collected by the multiplefilm method of the equi-inclination Weissenberg photographs with Ni-filtered Cu-$K\alpha$ radiation and estimated by visual comparison with a calibrated scale. Lorentz-polarization and spot-shape correction were applied, but no correction for absorption.

Weissenberg photographs around the *a*- and *b*- axes demonstrated that almost all the crystals of hydrochloride and hydrobromide were twins consisting of two components, in which *a**- and *b**- axes have the opposite directions for each component in the reciprocal lattice.

The two-dimensional intensity data for (*h*0*l*) and (0*kl*) reflections of hydrobromide were collected, in which almost all the reflections of each component were separable except a few overlapped reflections. A single crystal of hydrochloride was incidentally obtained and the three-dimensional intensity data around the *a*- and *b*- axes were collected and totally 1435 independent reflections were used for the refinement.

Unit cell parameters of GGBA hydrochloride and hydrobromide were determined by Weissenberg and precession photographs and the space group $P\bar{1}$ was confirmed by statistical method. Densities were measured by floatation method with benzene and carbon tetrachloride mixture. Crystallographic data so obtained are listed in Table 1.

Structure Determination

GGBA hydrochloride and hydrobromide seem to be isomorphous, as shown in Table 1. The Patterson projections on (010) and (100) planes of hydrochloride and hydrobromide are similar and, therefore, the molecular structure and packing in the crystal lattice should be similar in both crystals.

Table 1. Crystal data

γ-Guanidinobutyric acid
Hydrobromide $C_5H_{12}O_2N_3Br$ (M.w=226.13)
Hydrochloride $C_5H_{12}O_2N_3Cl$ (M.w=181.73)

Cell constant	Hydrobromide	Hydrochloride
a (Å)	7.94±0.03	7.41±0.04
b (Å)	9.36±0.01	9.12±0.02
c (Å)	7.78±0.02	7.25±0.03
α (°)	103.2±0.2	101.5±0.3
β (°)	115.5±0.3	112.4±0.5
γ (°)	61.5±0.3	65.2±0.3
Space group	$P\bar{1}$	$P\bar{1}$
Crystal system	Triclinic	Triclinic
Z	2	2
V (Å^3)	459.08	410.80
D_o (g·cm^{-3})	1.664	1.429
D_c (g·cm^{-3})	1.654	1.433

The structure determination was carried out by the usual heavy atom method. To determine the coordinates of heavy atoms, bromine and chlorine, in the unit cell, the Patterson projections along the *a*- and *b*-axes were calculated. The coordinates of light atoms except hydrogen atoms in GGBA hydrobromide could be determined from the Fourier projections on (010) and (100) planes of GGBA hydrobromide with the phase based on the coordinate of heavy atom.

In the following stage, the three-dimensional full data of hydrochloride were used. Since GGBA molecule itself has pseudo center of symmetry at the midpoint of C_β–C_γ bond and the both end groups of the molecule occupied by oxygen or nitrogen atoms have similar scattering power for X-ray, it is difficult to distinguish which end group is carboxyl or guanidyl group.

In Fig. 1, model (1) shows the Fourier map calculated with one chlorine and ten carbon atoms on the supposition that GGBA molecule is constituted by carbon atom alone, and model (2) and (3) give both Fourier maps calculated from two models in which the former has guanidyl group as the left terminal group and the latter as the right terminal group of GGBA molecular chain. From these Fourier maps, overall feature of peak heights in (1) is similar to that in (2) and the peak corresponding to N(3) in (2) has reasonable height but the peak in (3) is too high to assume it as a carbon atom. Therefore, Fourier map by the model (2) was thought to show the most probable electron density distribution of this compound, and it was also confirmed by the following least-squares refinement.

Table 2 lists up the isotropic temperature factors for each atoms, the scale factors for F_o, k, and R-index, $R=\Sigma||F_o|-|F_c||/\Sigma|F_o|$, for two models, (2) and (3), after five cycles of block-diagonal least-squares refinement. In this table, several features will be

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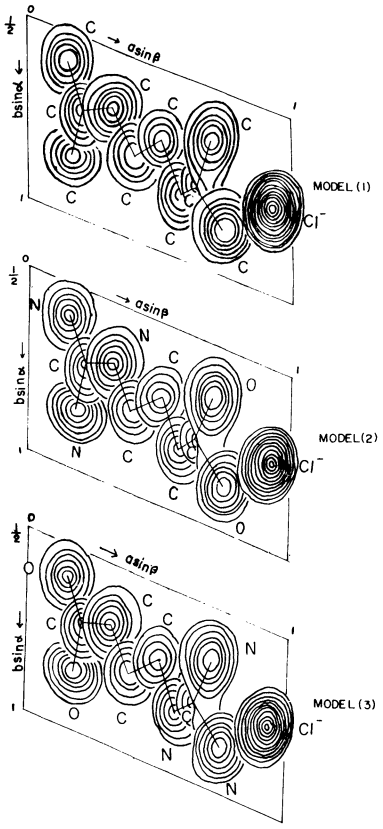

Fig. 1. The electron density maps for three models, viewed down along the c-axis.

TABLE 2. THE ISOTROPIC TEMPERATURE FACTORS ($Å^{-2}$)

Model (2)		Model (3)	
Cl^-	3.13	Cl^-	3.15
N(1)	3.22	O(1)	5.34
N(2)	3.00	O(2)	5.09
C(1)	2.72	C(1)	2.31
N(3)	2.72	C(2)	1.33
C(2)	3.77	C(3)	3.38
C(3)	3.46	C(4)	3.59
C(4)	3.72	N(1)	4.88
C(5)	3.72	C(5)	3.02
O(1)	3.53	N(2)	1.87
O(2)	4.24	N(3)	2.75
$R=0.299$		$R=0.324$	
$k=0.961$		$k=0.974$	

noted. For example, in comparison of N(1) in model (2) with O(1) in model(3), the temperature factor of O(1) is found to be larger than that of N(1). Considering that all atoms of GGBA molecule are covalently bonded with each other, it seems reasonable that the temperature factors of all atoms might be nearly equal as found in model (2) in Table 2. Therefore, if the resultant scale factor, k, is equal for two models and the model(2) is correct, the temperature factor of the oxygen atom assigned improperly in model(3) might become larger and that of nitrogen atom should be much smaller for the minimizing of the difference between $|F_o|$ and $|F_c|$.

The block-diagonal least-squares refinement was then carried out on the structure corresponding to the model (2). After five cycles of refinement with isotropic temperature factors to all the non-hydrogen atoms, the R-index value reduced to 0.254. Further five cycles of refinement with anisotropic temperature factor to chlorine atom and isotropic temperature factors to other ten atoms dropped the R-index to 0.195.

At this stage, a difference Fourier synthesis was computed in order to find the hydrogen atoms and all twelve hydrogen atoms could be located. After several cycles of refinement with anisotropic temperature factors to all non-hydrogen atoms, the R-index dropped to 0.153. One more refinement with all the twenty-three atoms including hydrogen atoms with isotropic temperature factors was performed to reduce the R-factor to 0.143 (0.129 except $F_o=0$). The agreement between the observed and calculated struc-

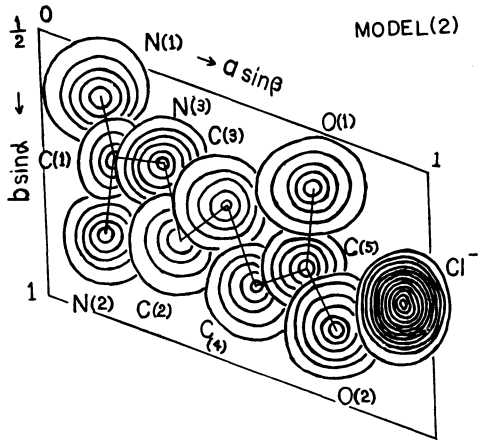

Fig. 2. A view of sections of final electron density map along the c-axis. Contours are at intervals of $2\,eÅ^{-3}$, starting with the contour of $1\,eÅ^{-3}$.

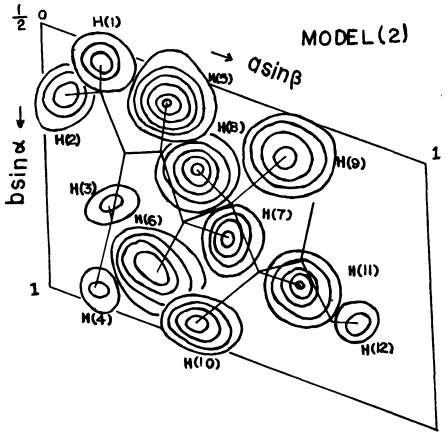

Fig. 3. A view of sections of a difference map for the location of hydrogen atoms along the c-axis. Contours are at intervals of $0.2\,eÅ^{-3}$, starting with the contour of $0.1\,eÅ^{-3}$.

Table 3. Final fractional coordinates and their standard deviations (in Å) of GGBA hydrochloride

	x	$\sigma(x)$	y	$\sigma(y)$	z	$\sigma(z)$
Cl^-	0.9370	0.003	0.7677	0.003	1.8913	0.002
N(1)	0.1428	0.010	0.5894	0.008	0.3033	0.007
N(2)	0.1739	0.011	0.8349	0.007	0.3635	0.007
C(1)	0.2078	0.011	0.6963	0.009	0.4314	0.007
N(3)	0.3049	0.010	0.6679	0.008	0.6227	0.007
C(2)	0.3781	0.013	0.7835	0.009	0.7746	0.007
C(3)	0.4862	0.012	0.7049	0.010	0.9762	0.008
C(4)	0.5608	0.013	0.8288	0.009	1.1345	0.008
C(5)	0.6658	0.011	0.7654	0.009	1.3420	0.008
O(1)	0.6845	0.010	0.6410	0.007	1.3844	0.006
O(2)	0.7394	0.009	0.8666	0.007	1.4747	0.005

Final anisotropic temperature factors and their standard deviations ($\times 10^4$).
The anisotropic temperature factors are in the form of
$\exp\{-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)\}$

	B_{11}	σB_{11}	B_{22}	σB_{22}	B_{33}	σB_{33}	B_{12}	σB_{12}	B_{13}	σB_{13}	B_{23}	σB_{23}
Cl^-	280	7	170	4	43	3	−173	9	10	8	49	6
N(1)	276	25	80	11	67	13	−135	28	46	29	−13	19
N(2)	370	30	48	10	95	15	−137	29	80	34	6	19
C(1)	219	26	81	12	25	13	16	29	41	29	63	20
N(3)	280	25	90	11	44	12	−129	29	−4	28	4	19
C(2)	359	34	79	13	14	13	−131	35	9	34	17	20
C(3)	304	32	86	13	30	14	−144	34	−8	33	31	21
C(4)	358	34	72	13	23	13	−122	34	19	34	2	20
C(5)	238	28	75	13	48	15	−24	31	56	32	25	21
O(1)	450	29	91	10	70	12	−229	28	0	29	53	17
O(2)	409	26	83	9	32	10	−200	26	31	26	−9	15

Table 4. The atomic coordinates for the hydrogen atoms of GGBA hydrochloride

Atom	Bonded to	x	y	z
H(1)	N(1)	0.198	0.502	0.399
H(2)	N(1)	0.067	0.631	0.175
H(3)	N(2)	0.090	0.842	0.204
H(4)	N(2)	0.203	0.938	0.420
H(5)	N(3)	0.308	0.554	0.626
H(6)	C(2)	0.228	0.901	0.773
H(7)	C(2)	0.483	0.815	0.725
H(8)	C(3)	0.381	0.676	1.016
H(9)	C(3)	0.627	0.592	0.974
H(10)	C(4)	0.420	0.943	1.130
H(11)	C(4)	0.672	0.858	1.100
H(12)	O(2)	0.810	0.839	1.601

ture amplitudes is reasonable.[14]

The final electron density map and the difference map indicating the locations of the twelve hydrogen atoms are shown in Figs. 2 and 3, respectively. The final atomic coordinates and anisotropic temperature factors are listed in Table 3, and the coordinates for hydrogen atoms are given in Table 4.

All the numerical computations were carried out on the NEAC 2203, the NEAC 2200—500 computers of this University, and the HITAC 5020E of the Computer Centre, University of Tokyo. The programs used for the correction of X-ray data, three-dimensional Patterson and Fourier syntheses and difference Fourier synthesis are written by one of the authors (T.F) and that for the block-diagonal least-squares refinement of the structure is written by Dr. Tamaichi Ashida.

Results and Discussion

The bond lengths and angles are shown in Fig. 4 (a) and (b), and also listed in Table 5 with their esti-

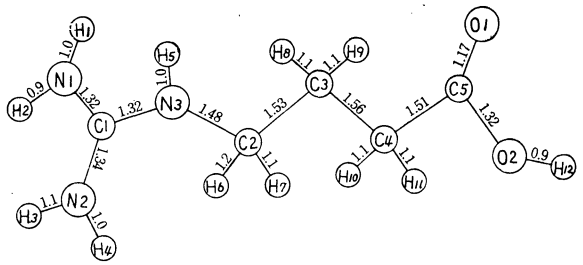

Fig. 4. (a) Bond distances (in Å) of GGBA hydrochloride.

14) A complete list of the observed and calculated structure factors has been submitted to, and is kept as Document No. 7212 at the office of the Bulletin of the Chemical Society of Japan, 1-5 Kanda-Surugadai, Chiyodaku, Tokyo. A copy may be secured by citing the Document number. Pay by check or money order payable to: The Chemical Society of Japan.

TABLE 5. BOND DISTANCES AND ANGLES OF GGBA HYDROCHLORIDE

N(1)-C(1)	1.318±0.015 (Å)	N(1)-C(1)-N(2)	118.7±1.0 (°)
N(2)-C(1)	1.338±0.015	N(2)-C(1)-N(3)	120.3±1.0
N(3)-C(1)	1.317±0.014	N(1)-C(1)-N(3)	120.9±1.0
C(2)-N(3)	1.477±0.016		
C(2)-C(3)	1.528±0.017	C(1)-N(3)-C(2)	123.7±1.0
C(3)-C(4)	1.557±0.016	N(3)-C(2)-C(3)	107.8±1.0
C(4)-C(5)	1.510±0.017	C(2)-C(3)-C(4)	107.1±1.0
C(5)-O(1)	1.173±0.015	C(3)-C(4)-C(5)	111.8±1.0
C(5)-O(2)	1.320±0.014		
		C(4)-C(5)-O(2)	111.9±1.0
		O(2)-C(5)-O(1)	122.7±1.1
		C(4)-C(5)-O(1)	125.5±1.1

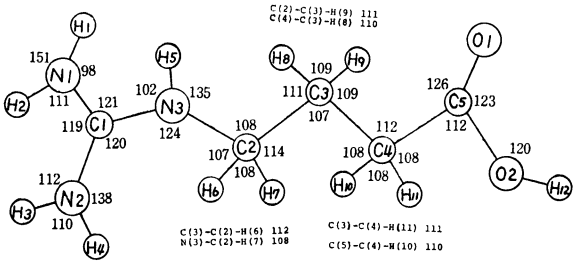

Fig. 4. (b) Bond angles (in degree) of GGBA hydrochloride.

mated standard deviations.

In guanidyl group, the average of three C–N bond lengths; 1.32, 1.32 and 1.34 Å, is 1.33 Å. These values are very similar to those reported so far in other compounds[15–19] with guanidyl group. However, these C–N bond distances are halfway between the normal C–N single bond length (1.47 Å) and the pure double bond distance (1.24 Å) proposed by Shomaker *et al.*[20]

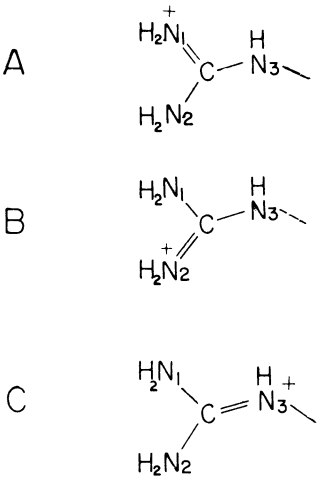

Fig. 5. Resonance of the guanidyl group in GGBA molecule.

Therefore, three C–N bonds of GGBA molecule have somewhat double bond character and the calculation by Pauling's method[21] indicated that the double bond characters of C(1)–N(1), C(1)–N(2) and C(1)–N(3) bonds are about 35%, 29% and 36% respectively. The major three resonance structures, A, B and C of the guanidyl group in GGBA cation, are shown in Fig. 5.

Three N–C–N angles, 119°, 120° and 121°, are not different with each other within the standard deviation. Similar bond angles are reported in guanidium chloride[17] and L-arginine dihydrate.[19]

The guanidyl group is attached to the carbon chain by a normal C–N bond of 1.48 Å. The average of the three C–C bond lengths is 1.53 Å and the C(3)–C(4)–C(5) angle of 112° is significantly larger than the other two angles, 107° and 108°.

The skeletal conformation of GGBA molecule is the 'trans-zigzag' form which is also found in GABA hydrochloride.[22]

In carboxyl group, C(5)–O(1) and C(5)–O(2) bond lengths are 1.17 and 1.32 Å respectively, and the three angles around the C(5) atom are 123°, 125° and 112° respectively. These values are not particularly different from those reported for α-amino acids so far investigated. However, C(5)–O(1) bond length is significantly shorter than C(5)–O(2) bond distance, and the angle of C(4)–C(5)–O(2) is smaller than that of C(4)–C(5)–O(1). Therefore, a hydrogen atom attaches to O(2) atom, which is confirmed by the difference Fourier synthesis, and GGBA hydrochloride is of the form, $^{+}NH_2(NH_2)CNH(CH_2)_3COOH\cdot Cl^{-}$, and GGBA molecule has probably zwitter-ion structure in free state. A similar conclusion is also reported in GABA hydrochloride[22] and L-leucine hydrobromide.[23]

The molecule of GGBA hydrochloride is almost perfectly planar and lies nearly on the $(20\bar{1})$ plane as shown in Fig. 6. The deviations of individual atoms from a least-squares plane are listed in Table 6. Six hydrogen atoms attached to nitrogen and oxygen

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Table 6. The equation of a least-squares plane and deviations of the individual atoms from this plane

$0.89028X-0.43109Y-0.14687Z+0.17068=0$,

Cl^-	−0.03 (Å)	C(3)	+0.04 (Å)
N(1)	+0.01	C(4)	−0.02
N(2)	−0.02	C(5)	+0.00
C(1)	+0.00	O(1)	+0.00
N(3)	+0.01	O(2)	+0.03
C(2)	−0.02		

Table 7. The hydrogen bond distances

N(1)−H···O(1)	2.934±0.016 (Å)
N(2)−H···O(2)	2.970±0.014
N(3)−H···O(1)	2.775±0.017
N(1)−H···Cl^-	3.206±0.010
N(2)−H···Cl^-	3.266±0.009
O(2)−H···Cl^-	2.947±0.012

atoms lie also on the plane, but the other six hydrogen atoms attaching to the carbon atoms are situated above and below this plane.

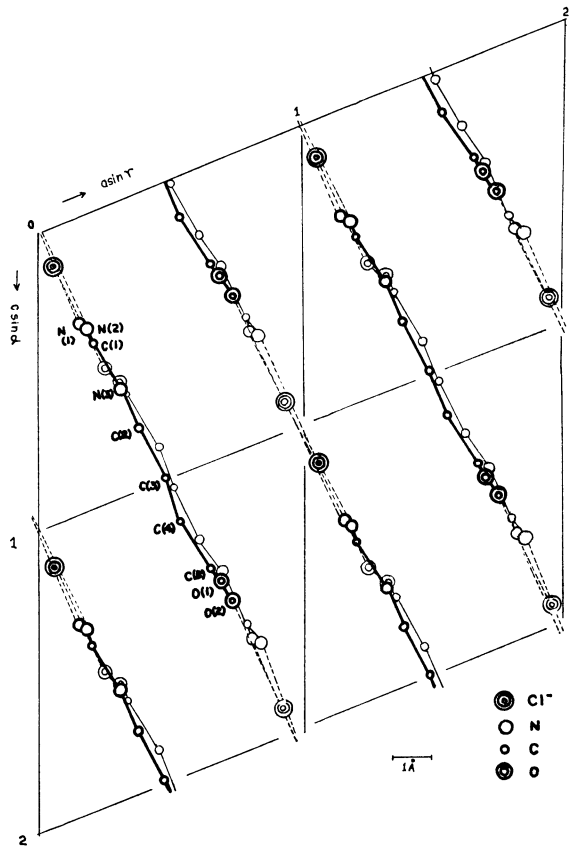

Fig. 6. A drawing of the structure of GGBA hydrochloride viewed down along the *b*-axis. The dashed lines indicate the hydrogen bonding.

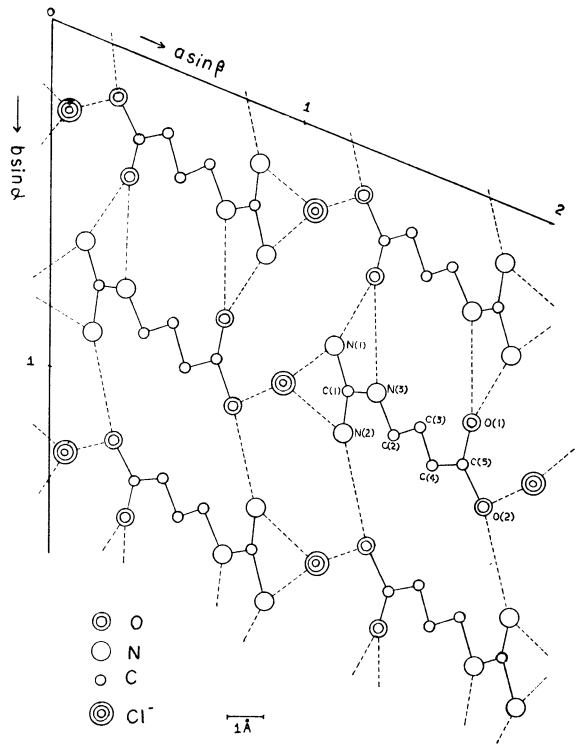

Fig. 7. A drawing of the structure of GGBA hydrochloride viewed down along the *c*-axis. The dashed lines indicate the hydrogen bonding.

The structure as viewed down the *c*-axis is shown in Fig. 7 and the hydrogen bond lengths are listed in Table 7. In guanidyl group, five hydrogen atoms attached to nitrogen atoms are used to form three N–H···O hydrogen bonds, 2.78 Å, 2.93 Å and 2.97 Å, and two N–H···Cl^- hydrogen bonds, 3.21 Å and 3.27 Å. One hydrogen atom attached to O(2) forms O–H···Cl^- hydrogen bond, 2.95 Å in length. Similar hydrogen bond lengths are reported in L-arginine dihydrate[19], L-tryptophan hydrochloride[24] and L-cystine hydrochloride.[25] All hydrogen bonds hold molecules together to form parallel sheets along $(20\bar{1})$ plane and no interaction except van der Waals force acts between the adjacent molecular planes as shown in Fig. 6 which is viewed down along the *b*-axis. This result explains the existence of the marked cleavage on $(20\bar{1})$ plane in the crystal.

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