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The Neutron Structure of and Thermal Motion in γ -Aminobutyric Acid (GABA) at 122 K

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Abstract

At 122 K, γ -aminobutyric acid ($C_4H_9NO_2$) is monoclinic, space group $P2_1/a$, with $a = 8.214(2)$, $b = 10.000(2)$, $c = 7.208(2)$ Å, $\beta = 110.59(2)^\circ$. A structure refinement by full-matrix least squares based on 1686 neutron reflections ($\sin \theta/\lambda < 0.78$ Å $^{-1}$) has converged with $R_w(F^2) = 0.044$. Bond lengths and angles involving nuclear thermal centroids have e.s.d.'s less than 0.002 Å and 0.2° respectively, including those with H atoms. Because of marked anisotropy in atomic and molecular vibrations, thermal corrections to the bond lengths are important. These have been determined taking intramolecular modes of vibration into account. A novel aspect of the thermal-motion analysis is the inclusion of anharmonic thermal-motion corrections for the C–H bonds. They are found to be similar in magnitude and opposite to the harmonic corrections (~ 0.02 Å). The six C–H bond lengths before and after correction lie within the range 1.093–1.099 Å and 1.099–1.103 Å respectively. The C(trig.)–C(tetr.) bond may be longer (1.534 Å) than the C(tetr.)–C(tetr.) bonds (mean value 1.527 Å). There are three strong N–H \cdots O hydrogen bonds with similar geometries (H \cdots O distances: 1.69, 1.71, 1.74 Å; uncorrected).

Introduction

The detailed structure of γ -aminobutyric acid (GABA, Fig. 1) is of biological interest because this molecule is

believed to function as a neurotransmitter in the mammalian central nervous system (Davidson, 1976). We have carried out a neutron crystal structure determination at low temperature in conjunction with an X-ray study of the electronic charge density distribution in the molecule (Craven & Weber, 1983). The neutron structure is necessary for determining the nuclear positional and thermal parameters, including H atoms, without bias due to the electronic charge density distribution.

This crystal structure provides a good example of the importance of a detailed analysis of anisotropic thermal motion in order to derive corrected bond lengths and angles. The non-rigid behavior of the molecule was found to be highly significant. For the neutron C–H bond lengths, satisfactory agreement with spectro-

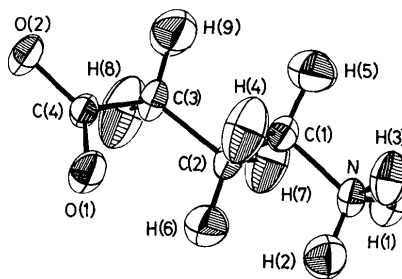


Fig. 1. γ -Aminobutyric acid. Atomic nomenclature and thermal ellipsoids at 90% probability (Johnson, 1976).

scopic values was obtained only by applying corrections for anharmonic motion ($\sim 0.02 \text{ \AA}$) which are almost equal and opposite to the harmonic corrections. In general, the bond-length corrections in GABA at 122 K are an order of magnitude greater than the experimental error in the nuclear positions.

The X-ray crystal structure of GABA at 138 K has already been accurately determined by Steward, Player & Warner (1973)[†] using Cu $K\alpha$ X-ray diffraction data with $\sin \theta/\lambda \leq 0.62 \text{ \AA}^{-1}$. They showed that the molecule exists as the zwitterion. However, their data were not sufficiently extensive for a detailed charge density analysis.

Experimental

In aqueous solution, crystals of GABA commonly grow as monoclinic prisms. The crystal selected for data collection was elongated on c bounded by the forms $\{110\}$ and $\{001\}$. The crystal volume was 13.6 mm^3 as determined from measurements of edges and corners. The weight was 16.29 mg , giving a density of 1.20 g cm^{-3} in agreement with the value calculated from the unit-cell data. The crystal was glued on a hollow Al pin, which was fastened at the bottom of an Al can filled with helium gas and the can was attached to the cold tip of a closed-cycle refrigerator.[‡] The whole assembly was then mounted onto a four-circle diffractometer at the Brookhaven High Flux Beam Reactor, such that the c^* axis was aligned approximately parallel to the ϕ axis of the diffractometer. The cell parameters of GABA at 122 K were obtained by a least-squares fit to $\sin^2 \theta$ values for 32 accurately centered reflections ($34^\circ \leq 2\theta \leq 53^\circ$). The wavelength of the incident neutron beam had previously been determined by a similar least-squares fit to $\sin^2 \theta$ data for a standard KBr crystal ($a_0 = 6.600 \text{ \AA}$ at 298 K). The sample temperature measured inside the cryostat was corrected by 2.6 K , due to a prior calibration based on the magnetic phase transition of FeF_2 at 78.4 K (Hutchings, Shulhof & Guggenheim, 1972). Neutron values for the cell parameters are in good agreement with X-ray values which were also obtained at a measured temperature of 122 K (Table 1). Table 2 lists other experimental conditions for the neutron data collection.

Reflections were collected in the θ - 2θ step-scan mode for one quadrant in reciprocal space ($\pm hkl$). Some reflections were measured in other quadrants as well so as to confirm the diffraction symmetry ($2/m$) and to check the adequacy of the subsequent neutron absorption correction. Every third reflection profile was

[†] Their choice of space group $P2_1/a$ has presently been retained for convenience in comparison of results.

[‡] Air Products and Chemicals, Inc., DISPLEX[®] Model CS-202.

Table 1. *Crystal lattice parameters for γ -aminobutyric acid*

Temperature (K)	a (Å)	b (Å)	c (Å)	β (°)	V (Å ³)
295*	8.285 (5)	10.224 (12)	7.203 (5)	110.79 (9)	570.4 (5)
294†	8.265 (2)	10.143 (2)	7.186 (1)	110.92 (2)	562.7 (4)
138*	8.228 (5)	10.036 (9)	7.210 (4)	110.63 (5)	557.2 (6)
122‡	8.214 (2)	10.000 (2)	7.208 (2)	110.59 (2)	554.2 (4)
122‡	8.217 (3)	10.005 (5)	7.210 (4)	110.60 (4)	554.8 (7)

* X-ray data (Steward, Player & Warner, 1973).

† X-ray data (Mo $K\alpha_1$, $\lambda = 0.7093 \text{ \AA}$; Craven & Weber, 1983).

‡ Neutron data, this work.

Table 2. *Experimental conditions*

Monochromator	Be (002), reflection geometry
Scan mode	θ - 2θ steps
Average scan rate	11.5 reflections h^{-1}
Scan range	$\Delta 2\theta^\circ = 1.76 + 1.23 \tan \theta$
Reference reflections	413, 163
($\sin \theta/\lambda$) _{max}	0.782 \AA^{-1}
Wavelength	$1.0470 (1) \text{ \AA}$
Linear absorption coefficient	0.270 mm^{-1}
Crystal transmission factors for neutrons	0.57 – 0.68
Number of reflections measured	1938
Number of unique reflections used in refinement	1686

Table 3. *Nuclear parameters for γ -aminobutyric acid*

Values of scattering lengths other than N [9.34 (2)], were taken from Koester (1977). They are 6.648, 5.803, -3.741 fm for C, O and H nuclei, respectively. The fractional positional parameters are multiplied by 10^5 . E.s.d.'s (in parentheses) refer to the last digit given. U_{eq} is the equivalent isotropic temperature factor defined by Hamilton (1959). Extinction coefficients ($\text{rad}^{-1} \times 10^{-4}$) are $g_{11} = 156 (8)$, $g_{22} = 26 (5)$, $g_{33} = 69 (2)$, $g_{12} = 18 (5)$, $g_{13} = -49 (4)$ and $g_{23} = -19 (4)$.

	x	y	z	U_{eq}^* ($\text{Å}^2 \times 10^4$)
N	7062 (6)	84072 (6)	-31876 (7)	176
C(1)	16511 (10)	80162 (8)	-10953 (11)	177
C(2)	29478 (9)	90863 (8)	-238 (10)	178
C(3)	38391 (9)	87744 (8)	21739 (10)	192
C(4)	26795 (9)	89446 (8)	34121 (10)	169
O(1)	12245 (13)	94783 (12)	26550 (14)	316
O(2)	32774 (11)	85316 (10)	51826 (12)	224
H(1)	16037 (20)	85584 (18)	-39201 (22)	300
H(2)	-45 (22)	92722 (18)	-32222 (23)	324
H(3)	-1811 (20)	76569 (18)	-39321 (24)	315
H(4)	6947 (25)	78716 (22)	-3748 (25)	422
H(5)	23066 (26)	70674 (18)	-11043 (27)	407
H(6)	22515 (27)	100379 (18)	-1966 (26)	395
H(7)	39231 (23)	91831 (22)	-7384 (25)	399
H(8)	49518 (23)	94433 (24)	28353 (26)	466
H(9)	43705 (25)	77571 (21)	23958 (26)	405

* E.s.d.'s are 0.0005 \AA^2 .

plotted to determine the necessary background limits. The integrated intensities were corrected for absorption by the analytical method (de Meulenaer & Tompa, 1965; Templeton & Templeton, 1973). The mass-absorption coefficient of H, $23.9 \times 10^{-4} \text{ m}^2 \text{ g}^{-1}$, which had been determined experimentally for barbital II (McMullan, Fox & Craven, 1978) was assumed to

apply to GABA as well and scaled to the slightly different wavelength used in the present experiment. The agreement factor between symmetry-equivalent reflections was $R = \sum |F_o^2 - \langle F_o^2 \rangle| / \sum \langle F_o^2 \rangle = 0.020$.

The refinement of the structure was carried out with a modified version of the full-matrix least-squares program of Busing, Martin & Levy (1962) so as to minimize the function $\sum w(F_o^2 - F_c^2)^2$. The weights were assumed to be $w = \sigma^{-2}(F^2)$ where $\sigma^2(F^2) = \sigma^2(F^2)_{\text{counts}} + bF^4 + cF^{-4}$, where $b = 10^{-4}$ and $c = 3.5 \times 10^5$. Initial values for the atomic parameters were assumed to be those of Steward *et al.* (1973). Neutron coherent scattering lengths were taken from Koester (1977). In the final cycle of refinement, the variables consisted of a scale factor, components g_{ij} of an extinction tensor (type I crystal, Lorentzian distribution of mosaicity; Becker & Coppens, 1974), the coherent scattering length for N, and the nuclear positional and aniso-

Table 4. *Anisotropic thermal parameters and analysis of molecular thermal motion*

(a) Anisotropic thermal parameters for γ -aminobutyric acid

The temperature factor has the form

$$\exp(-2\pi^2 \sum_i \sum_j h_i h_j a_i^* a_j^* U_{ij})$$

with U_{ij} in units of $\text{\AA}^2 \times 10^4$. For each parameter, values are for the neutron refinement (above) and for the assumed harmonic molecular motion (below).

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}	σ
N	158	230	126	-5	45	-20	2
	157	232	125	-8	44	-18	
C(1)	200	177	136	-36	49	4	3
	198	168	136	-30	48	0	
C(2)	199	204	117	-50	47	-2	3
	200	196	119	-44	44	-3	
C(3)	154	294	118	-1	45	-1	3
	151	297	121	-10	44	4	
C(4)	164	210	116	41	43	7	3
	166	215	127	43	49	15	
O(1)	277	475	179	229	74	51	4
	267	481	168	211	63	44	
O(2)	189	347	133	66	64	52	4
	196	343	139	81	68	56	
H(1)†	299	377	218	-8	115	5	7
	233	181	123	-43	40	-9	
H(2)†	310	368	265	93	80	13	7
	276	414	135	117	15	20	
H(3)†	267	411	227	-63	47	-60	7
	296	437	156	-185	43	-43	
H(4)	372	617	284	-177	160	5	9
	309	632	267	-131	117	-9	
H(5)	526	246	357	69	50	2	10
	613	270	303	97	113	-18	
H(6)	587	237	280	31	67	4	9
	594	244	282	41	97	-1	
H(7)	342	591	271	-161	149	-21	9
	346	626	253	-165	138	-37	
H(8)	307	770	268	-210	50	-49	10
	357	739	256	-245	87	-68	
H(9)	416	510	301	219	148	79	9
	397	501	288	204	131	57	

† The ammonium H atoms H(1), H(2) and H(3) were not included in the analysis of molecular thermal motion. To obtain U_{calc} values, it was assumed that these atoms are riding rigidly on the N atom.

Table 4 (cont.)

(b) Analysis of molecular thermal motion

The ammonium H atoms are omitted from the analysis. The six methylene H atoms are assumed to have C-H bond stretching, and CH_2 scissors and wagging motion as described in the text. A small carboxylate scissors motion is also included. The remaining molecular parameters are determined with these non-rigid modes considered as fixed contributions to the atomic thermal parameters. The molecular model consists of three fragments ($\text{N}-\text{CH}_2$)-(CH_2CH_2)-(COO) with all these atoms included in determining the rigid-body motion. Only the terminal fragments are used to determine the two internal librations with respect to the central reference fragment.

(i) Rigid-body motion

Tensor components are with respect to the orthogonal axes a , b , c^* with origin at the molecular center of mass.

Translation T ($\text{\AA}^2 \times 10^4$)

158 (5)	16 (5)	-4 (12)
	171 (7)	12 (4)
		126 (3)

Libration L (deg^2)

3.0 (5)	-0.1 (4)	-6.1 (8)
	1.8 (5)	1.2 (8)
		43.3 (1.6)

Cross tensor S ($\text{\AA} \text{ deg}$)

-0.02 (3)	-0.03 (1)	-0.02 (1)
-0.03 (1)	0.03 (3)	0.03 (1)
-0.18 (2)	-0.14 (2)	-0.01

(ii) Principal values of L and their direction cosines with respect to a , b , c^*

L_1 2.1 deg^2	(0.951	0.279	0.132)
L_2 1.7	(-0.272	0.960	-0.067)
L_3 44.2	(-0.146	0.028	0.989)

The principal moments of inertia of the GABA molecule are 391.7, 427.8 and 81.5 daltons \AA^2 . The minimum moment of inertia and L_3 are in directions making an angle 5.8° .

(iii) Internal librations

$$\Omega(\text{N}-\text{CH}_2) = -15 (3) \text{ deg}^2; \Omega(\text{COO}) = +25 (5) \text{ deg}^2$$

tropic thermal parameters for all atoms. Final values are in Tables 3 and 4.* The final agreement index was $R_w(F^2) = (\sum w|F_o^2 - F_c^2|^2 / \sum wF_o^4)^{1/2} = 0.044$ (unweighted: 0.043) and the goodness of fit $S = [\sum w|F_o^2 - F_c^2|^2 / (n_{\text{obs}} - n_{\text{param}})]^{1/2}$ had the value 1.308. The extinction was significantly anisotropic but was not severe. The reflection most affected ($0.75F_c^2$) was 120. The scattering length obtained for N [9.34 (3) fm] is consistent with the value 9.36 fm given by Koester (1977), and may be marginally larger than values 9.24 to 9.30 fm obtained in other recent structure refinements (Weber, Craven & McMullan, 1980).

* Observed and calculated F^2 values [including $\sigma(F^2)$ and calculated extinction factors] have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38183 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Analysis of anisotropic thermal parameters

The thermal vibrations of the molecule were analyzed in terms of overall rigid-body motion (Schomaker & Trueblood, 1968), together with non-rigid librations of molecular fragments about various bonds as axes (Dunitz & White, 1973). A full-matrix least-squares procedure programmed for minicomputer (Craven & He, 1982) was used to minimize the residual $\sum_k w_k \Delta_k^2$. In this expression, $\Delta_k = [(U_{ij})_o - (U_{ij})_c]_k$ where $(U_{ij})_o$ is the neutron value for an anisotropic thermal parameter for the k th atom, referred to the Cartesian crystal axial system a , b , c^* , and $(U_{ij})_c$ is the corresponding value calculated for the assumed molecular motion. The weights $w_k = \sigma^{-2}(U_k)$ were obtained from the mean variances in U_{ij} for the k th atom in the neutron refinement.

A poor fit was obtained by assuming simple rigid-body motion for the complete molecule. This model gave $R_w = [\sum w \Delta^2 / \sum w (U_{ij})_o^2]^{1/2} = 0.187$ and $S = [(\sum w \Delta^2) / (m - n)]^{1/2} = 8.74$. In the expression for S , $m = 96$ is the number of atomic thermal parameters and $n = 20$ is the number of variables, consisting of the components of the rigid-body librational, translational and cross tensors. The fit was considerably better when H atoms were omitted ($R_w = 0.079$, $S = 5.49$). However, there were some highly significant discrepancies, the largest (13σ) being ΔU_{33} for atom O(1).

The use of more elaborate models for the molecular motion was found to be justified when mean-square (m.s.) vibrational amplitudes for intramolecular pairs of atoms A and B were calculated along the direction of the interatomic vector $A \cdots B$. A difference $\Delta = \langle u_A^2 \rangle - \langle u_B^2 \rangle$ which is significant indicates that atoms A and B are non-rigidly connected.† Several pairs of atoms within the GABA molecule show such differences, notably $N \cdots O(1)$ with $\Delta = 0.0103$ (4) \AA^2 and $C(1) \cdots O(1)$ with $\Delta = 0.0030$ (5) \AA^2 .

Consequently, the molecular motion (omitting H atoms) was assumed to be non-rigid with internal librations about each of the covalent bonds of the backbone. Librations about the central C(2)–C(3) bond and the wagging of atom O(1) about the C(4)–O(2) bond were found to be negligible, with m.s. values of -4 (4) deg^2 and 5 (13) deg^2 respectively. Subsequently, both librations were excluded as variables. The best agreement ($R_w = 0.032$, $S = 2.34$) was obtained for a model having three segments [N–C(1)]–[C(2)–C(3)]–[C(4)O(1)O(2)] with intramolecular librations about the two connecting bonds, C(1)–C(2) and C(3)–C(4). Thus the framework appears to be rigid except for the terminal N atom which has an m.s. libration of -23 (3) deg^2 and the carboxylate O atoms for which the value is $+26$ (4)

deg^2 .* The model gives satisfactory agreement for thermal parameters of the framework atoms; the most significant residuals being -4.2σ for ΔU_{33} of C(4) and 2.9σ for ΔU_{12} of C(3). However, there is very poor agreement for the H atoms when they are included to form rigid methylene and ammonium groups. Estimates of non-rigid motion of the H atoms were obtained by comparing their residual ΔU_{ij} values calculated with respect to a molecular axial system. There were notable similarities in these residuals among the methylene H atoms. These were interpreted as non-rigid thermal motion having m.s. amplitudes of 0.0063 (11) \AA^2 for C–H bond stretching, 0.0225 (59) \AA^2 for in-plane CH_2 scissors motion and 0.0142 (31) \AA^2 for out-of-plane CH_2 wagging. Here the e.s.d.'s come from the distribution of values for the six H atoms. The m.s. amplitudes from GABA are similar to the average values of 0.0061 \AA^2 for CH stretching and 0.0182 \AA^2 for methylene H \cdots H motion derived from spectroscopic studies (Morino, Kuchitsu, Takahashi & Maeda, 1953). However, the GABA ammonium H atoms have ΔU_{ij} values which are not consistent with such simple motions relative to the molecular framework. The greater complexity for these H atoms probably arises because each is hydrogen-bonded with a different neighbor molecule (Fig. 2) and has motion influenced by intermolecular coupling.

In the subsequent analysis of molecular thermal motion, the methylene H atoms were included in the model, assuming them to have the above fixed contributions due to non-rigid motion. The ammonium H atoms were omitted. This model gave $R_w = 0.069$, $S = 3.52$. Further study of ΔU_{ij} values indicated that the scissors motion of the methylene groups was greater for C(1) than for C(2) and C(3), having values

* The difference in sign means that if the central C(2)–C(3) reference segment is assumed to make no contribution to the internal librations, then the motion of the N atom is damped with respect to the overall rigid-body motion, whereas the motion of the O atoms is enhanced.

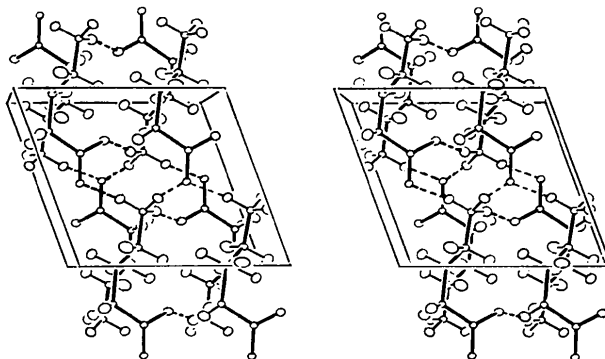


Fig. 2. Stereoview of the crystal structure of γ -aminobutyric acid viewed along the $-b$ axis. The unit cell is bounded by solid lines with the a axis directed from left to right and the c^* axis up the page; the dashed lines represent the hydrogen bonds.

† This observation is attributed to K. N. Trueblood (see Johnson, 1980).

Table 5. Bond lengths (Å) and angles ($^{\circ}$)

(a) Values for non-H atoms

Successive columns are (1) Steward *et al.* (1973), X-ray analysis with no thermal corrections, (2) present neutron results before thermal corrections, (3) present results corrected for harmonic librational motion. The anharmonic corrections are negligible.

	(1)	(2)	(3)
N—C(1)	1.497 (4)	1.486 (1)	1.486 (1)
C(1)—C(2)	1.520 (5)	1.516 (1)	1.525 (1)
C(2)—C(3)	1.528 (5)	1.526 (1)	1.528 (1)
C(3)—C(4)	1.522 (6)	1.527 (1)	1.534 (1)
C(4)—O(1)	1.249 (4)	1.246 (1)	1.258 (1)
C(4)—O(2)	1.268 (4)	1.265 (1)	1.271 (1)
N—C(1)—O(2)	110.1 (3)	110.7 (1)	110.5 (1)
C(1)—C(2)—C(3)	112.0 (3)	112.3 (1)	112.1 (1)
C(2)—C(3)—C(4)	114.3 (3)	114.5 (1)	114.1 (1)
C(3)—C(4)—O(1)	119.5 (3)	119.4 (1)	119.7 (1)
C(3)—C(4)—O(2)	116.6 (3)	116.9 (1)	116.6 (1)
O(1)—C(4)—O(2)	124.0 (4)	123.7 (1)	123.7 (1)

(b) Values involving methylene H atoms

Successive columns for bond lengths are (1) neutron values before thermal correction, (2) correction due to rigid and non-rigid harmonic thermal motion, (3) correction due to anharmonic motion and (4) thermally corrected value. Bond angles are uncorrected values. The corrections are all within the range $\pm 0.3^{\circ}$.

	(1)	(2)	(3)	(4)
C(1)—H(4)	1.093 (2)	0.024 (2)	-0.016 (1)	1.101 (3)
C(1)—H(5)	1.093 (2)	0.026 (2)	-0.016 (1)	1.103 (3)
C(2)—H(6)	1.095 (2)	0.023 (4)	-0.017 (1)	1.101 (4)
C(2)—H(7)	1.099 (2)	0.021 (4)	-0.018 (1)	1.102 (4)
C(3)—H(8)	1.098 (2)	0.022 (4)	-0.020 (1)	1.100 (4)
C(3)—H(9)	1.097 (2)	0.023 (4)	-0.021 (1)	1.099 (4)
N—C(1)—H(4)	108.1 (1)		C(2)—C(3)—H(8)	110.4 (1)
N—C(1)—H(5)	107.8 (1)		C(2)—C(3)—H(9)	111.2 (1)
C(2)—C(1)—H(4)	110.2 (1)		C(4)—C(3)—H(8)	105.9 (1)
C(2)—C(1)—H(5)	110.9 (1)		C(4)—C(3)—H(9)	108.4 (1)
C(1)—C(2)—H(6)	108.1 (1)			
C(1)—C(2)—H(7)	108.7 (1)		H(4)—C(1)—H(5)	110.9 (2)
C(3)—C(2)—H(6)	109.7 (1)		H(6)—C(2)—H(7)	107.9 (2)
C(3)—C(2)—H(7)	110.0 (1)		H(8)—C(3)—H(9)	105.9 (2)

(c) Values involving ammonium H atoms

The bond-length values in successive columns are (1) uncorrected for thermal motion, (2) with minimum possible correction, (3) corrected for each H atom riding independently on the N atom, (4) corrected for uncorrelated thermal motion, (5) with maximum possible correction, and (6) the anharmonic correction. Values (2) through (5) were calculated according to Busing & Levy (1964); and (6) was obtained as described in the text, assuming $\alpha = 2.0$ (1 \AA^{-1}). Bond angles are uncorrected values.

	(1)	(2)	(3)	(4)	(5)	(6)
N—H(1)	1.058 (2)	1.060 (2)	1.071 (2)	1.105 (2)	1.151 (2)	-0.018 (2)
N—H(2)	1.039 (2)	1.043 (2)	1.057 (2)	1.087 (2)	1.131 (2)	-0.022 (2)
N—H(3)	1.053 (2)	1.055 (2)	1.069 (2)	1.101 (2)	1.147 (2)	-0.022 (2)
C(1)—N—H(1)		109.7 (1)		H(1)—N—H(2)		110.7 (2)
C(1)—N—H(2)		109.4 (1)		H(1)—N—H(3)		107.4 (2)
C(1)—N—H(3)		110.5 (1)		H(2)—N—H(3)		107.4 (2)

of 0.0312 (10) and 0.0191 (32) \AA^2 . A scissors motion of the carboxylate O atoms with m.s. amplitude 0.0019 (7) \AA^2 was also indicated. With these revisions the final molecular model gave $R_w = 0.060$ and $S = 3.10$, with $(m - n) = 56$. The librations about the bonds C(1)—C(2) and C(3)—C(4) have values -15 (3)

and 25 (5) deg^2 , similar to those determined before the methylene H atoms were included. Observed and calculated anisotropic thermal parameters are in Table 4.

The bond lengths and angles are given in Table 5 both before and after corrections for thermal motion (Schomaker & Trueblood, 1968; Cruickshank, 1956; Busing & Levy, 1964). For the C—H and N—H bond lengths, an anharmonic thermal-motion correction δd has also been estimated using an expression which was first developed for application in molecular spectroscopy and gas electron diffraction (Kuchitsu & Bartell, 1961). This correction is $\delta d = 3a\Delta/2$ where the constant a expresses the asymmetry of the Morse potential function for C—H stretching and $\Delta = \langle u_C^2 \rangle - \langle u_H^2 \rangle$ is the relative m.s. amplitude for harmonic motion along the C—H bond. The value $a = 2.0$ (1 \AA^{-1}) was assumed (Kuchitsu & Morino, 1965). Values for Δ were calculated from the neutron anisotropic thermal parameters.

Discussion

There is good agreement between neutron bond lengths and angles and the corresponding X-ray values of Steward *et al.* (1973). However, the appropriate corrections for anisotropic thermal motion must be considered in order to give meaning to the greater accuracy for the neutron structure. This is well illustrated by considering the three C—C neutron bond lengths (Table 5a). The uncorrected distance C(1)—C(2) is significantly shorter than the others (10σ), whereas after corrections according to the assumed model for molecular thermal motion, the conclusion is different, with C(3)—C(4) being significantly longer than the others (6σ).

In GABA, the corrected bond lengths of 1.525 , 1.528 (1) \AA between tetrahedral C atoms agree with the corresponding values of 1.526 (2) \AA for propane obtained from the microwave spectrum (Lide, 1960) and 1.531 (2) \AA for *n*-butane obtained by gas electron diffraction (Bradford, Fitzwater & Bartell, 1977). By comparison, the C(3)—C(4) bond involving a trigonal C atom may be slightly longer [1.534 (1) \AA], as was found for C^α — C^β and C — C^α neutron bond lengths [1.532 (2) vs 1.535 (1) \AA] in a series of α -amino acid zwitterions (Koetzle & Lehmann, 1976).

The carboxylate C—O bond lengths are significantly different (0.013 \AA). The longer bond involves atom O(2) which forms two hydrogen bonds, whereas atom O(1) forms only one.

The six C—H bond lengths uncorrected for thermal motion fall within a narrow range, 1.093 to 1.099 (2) \AA . As noted by others, most recently by Srinivasan & Jagannathan (1982) and by Jeffrey, Ruble, McMullan, DeFrees & Pople (1981), the correction for harmonic thermal librations results in

neutron diffraction values which are systematically longer (~ 0.02 Å) than C—H bond lengths determined spectroscopically. Jeffrey *et al.* (1981) suggested that this may be due to the neglect of anharmonic thermal motion. Indeed, when such a correction was estimated as described in the previous section, it was found to be similar in magnitude and opposite in sign to the harmonic correction (Table 5*b*). For GABA, the average of six corrected C—H bond lengths is 1.101 Å with $\sigma = 0.001$ Å estimated from the distribution. This agrees satisfactorily with the value $1.096(2)$ Å which was obtained for the methylene C—H distances in propane from a microwave study (Lide, 1960). Similar corrected C—H bond lengths have since been obtained from a re-examination of other neutron structure determinations (B. M. Craven & S. Swaminathan, unpublished). On this basis, we conclude that for most crystal structures, the uncorrected neutron C—H distances are likely to be more reliable than those which have been corrected only for harmonic thermal motion.

There are small but highly significant irregularities in the chemically equivalent bond lengths and angles of the ammonium group (Table 5*c*). In particular, the uncorrected N—H(2) bond is shorter by $0.019(3)$ Å than the equivalent N—H(1) bond. It is also shorter by $0.014(3)$ Å than the N—H(3) bond which is distinct because it occurs in the C—C—N plane (Table 6). Thermal-motion corrections are appreciable and may well account for these differences (Table 5*c*). However, the riding model and other simple assumptions based on rigid and non-rigid molecular behavior were unsatisfactory in this respect. These all assume that the GABA molecules are vibrating harmonically without being coupled to each other. Since the molecules are hydrogen-bonded in a three-dimensional network (Fig. 2), a more complex model may well be required. When the upper and lower bounds for the N—H bond lengths are calculated (Busing & Levy, 1964), and corrections for anharmonic motion are taken into account (Table 5*c*), then the three N—H bond lengths could be equal if they have a value in the range 1.04 to 1.11 Å. This variation is orders of magnitude greater than the e.s.d. in the uncorrected N—H bond lengths. Thus we emphasize that care should be taken in the interpretation of apparent neutron bond lengths involving H atoms, because these are strongly dependent on the nature of the molecular thermal motion. Difficulties in determining an appropriate bond-length correction are likely to be most severe for H atoms involved in hydrogen bonding.

The most notable feature in the conformation of the GABA zwitterion is the twist which occurs at the carboxylate end of the central trimethylene chain (Fig. 1). The torsion angle C(4)—C(3)—C(2)—C(1) is $-72.6(1)^\circ$ (see Table 6). This introduces the following short intramolecular non-bonded distances involving the carboxylate group: C(4)···C(1), 3.19 ; O(1)···

Table 6. *Torsion angles* ($^\circ$)

Torsion angles are given for the molecule shown in Fig. 1, having the atomic coordinates given in Table 3. The crystal structure also contains zwitterions with conformations of the opposite chirality, for which the torsion angles all have the opposite sign.

O(1)—C(4)—C(3)—C(2)	$-9.4(1)$	C(4)—C(3)—C(2)—H(6)	$47.6(1)$
O(2)—C(4)—C(3)—C(2)	$170.9(1)$	C(3)—C(2)—C(1)—H(5)	$-65.1(1)$
C(4)—C(3)—C(2)—C(1)	$-72.6(1)$	C(3)—C(2)—C(1)—H(4)	$55.8(1)$
C(3)—C(2)—C(1)—N	$175.3(1)$	C(2)—C(1)—N—H(3)	$179.3(1)$
O(2)—C(4)—C(3)—H(9)	$46.1(2)$	C(2)—C(1)—N—H(2)	$-62.7(1)$
O(2)—C(4)—C(3)—H(8)	$-67.2(2)$	C(2)—C(1)—N—H(1)	$58.9(1)$
C(4)—C(3)—C(2)—H(7)	$166.2(1)$		

Table 7. *Intermolecular interactions involving H atoms*

(a) Hydrogen-bond distances and angles (uncorrected for thermal motion)

N—H···O	N—H (Å)	H···O (Å)	N···O (Å)	N—H···O ($^\circ$)
N—H(1)···O(2)	$1.058(2)$	$1.712(2)$	$2.756(2)$	$168.2(2)$
N—H(2)···O(1)	$1.039(2)$	$1.737(2)$	$2.749(2)$	$163.4(2)$
N—H(3)···O(2)	$1.052(2)$	$1.690(2)$	$2.733(3)$	$170.7(2)$

(b) Those non-bonded distances which are short in terms of assumed van der Waals distances (H···H, 2.4 Å; H···O, 2.6 Å)

H(4)···H(7)	$[\frac{1}{2} + x, \frac{3}{2} - y, z]$	2.48 Å
H(5)···H(6)	$[\frac{1}{2} - x, -\frac{1}{2} + y, 1 - z]$	2.21
H(7)···H(7)	$[1 - x, 2 - y, -z]$	2.36
H(8)···O(2)	$[1 - x, 2 - y, 1 - z]$	2.61

C(2), 2.79 ; O(1)···C(1), 3.20 ; O(1)···H(6), 2.54 ;
O(1)···H(4), 2.62 Å. Possible strain from intramolecular interactions may also be responsible for the larger C—C—C bond angle at atom C(3) compared with C(2) [114.1 vs 112.1°] and the larger C—C—O bond angle involving O(1) [119.7 vs 116.6°].

The GABA zwitterions are arranged in sheets parallel to (001), with non-polar trimethylene groups near $z = 0$ and the polar groups near $z = \frac{1}{2}$ (Fig. 2). The sheets are cross-linked by a three-dimensional network of strong N—H···O hydrogen bonds in which the three distinct hydrogen bonds have similar distances and angles (Table 7*a*). The N···O distances are short (2.73 to 2.76 Å), but this is usual for hydrogen bonds involving formally charged ammonium and carboxylate groups, *e.g.* those in α -glycylglycine (Griffen & Coppens, 1975). There are no unusually short van der Waals interactions involving the C—H groups (Table 7*b*).

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* In the X-ray study of GABA (Craven & Weber, 1983), the methylene atom H(6) is found to be unusually deficient in electronic charge. There may be an intramolecular O(1)···H(6)···N bridging interaction which helps to stabilize the observed twisted conformation.

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Location of Guest Molecules in Inclusion Compounds of Deoxycholic Acid by Means of van der Waals Energy Calculations

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Abstract

The crystal structures of the inclusion compounds of deoxycholic acid with phenanthrene and (*E*)-*p*-dimethylaminoazobenzene (hereafter abbreviated to DCAPHE and DCADAB respectively) have been investigated by means of van der Waals energy calculations in order to locate the guest molecules and to establish if more than one arrangement is allowed, since the standard X-ray methods were unsuccessful. Two possible packings have been found for DCAPHE and only one for DCADAB. The main interactions stabilizing the crystal packings have been identified, and discussed on the basis of measurements of the

enthalpy change due to the releasing of the guest molecule from the canals of the crystals. Strong host-guest interactions between the π charge cloud of the guest molecule and the C(18) methyl group or the H(5) atom of deoxycholic acid characterize these types of inclusion compounds.

Introduction

A major problem in solving the crystal structure of an inclusion compound is the location of the guest molecules, which, generally, contribute much less than the host molecules to the Fourier transform of the crystal. This occurs mainly for the following reasons: