

Studies in molecular structure, symmetry and conformation— Part XIV. Crystal and molecular structure of L-isoleucine hydrochloride monohydrate form II*

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Abstract. The crystal structure of a new form of L-isoleucine hydrochloride monohydrate $C_6H_{13}O_2NHClH_2O$ (termed form II) has been determined using three-dimensional photographic data. This differs conformationally from the hydrochloride derivative (termed form I, Trommel and Bijvoet 1954) reported earlier. The crystal belongs to the orthorhombic space group $P2_12_12_1$ with cell dimensions, $a = 5.87 \pm 0.01$, $b = 24.77 \pm 0.02$ and $c = 6.85 \pm 0.01$ Å and four molecules per cell, $\rho_{obs} = 1.240$ g/cm³, $\rho_{cal} = 1.238$ g/cm³, μ for $CuK\alpha = 32.6$ cm⁻¹.

Keywords. L-isoleucine; crystal structure

1. Introduction

As a continuation of our studies on the isomers of isoleucine, the structure of a new form of L-isoleucine HCl H₂O (termed hereafter as form II) is reported here. The crystal structures of D-alloisoleucine and D-alloisoleucine hydrochloride monohydrate have been reported elsewhere (Varughese and Srinivasan 1975 *a, b*). The crystal of L-isoleucine HCl H₂O form II was accidentally met with while trying to crystallize t-BOC-L-isoleucine as a hydrochloride. The structures of hydrochloride and hydrobromide derivative of D (—) isoleucine were reported earlier by Trommel and Bijvoet (1954) (hereafter TB). We arbitrarily call the hydrochloride derivative reported earlier (TB) as form I and the hydrobromide derivative as form II. It turns out that the enantiomorph† of the structure reported presently is non-isomorphous with the form I but is isomorphous with the hydrobromide derivative. Forms I and II differ conformationally and are non-isomorphous.

2. Experimental

Some t-BOC-L-isoleucine was dissolved in dilute hydrochloric acid and small crystals were obtained by slow evaporation. The molecular weight estimated

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† Trommel and Bijvoet (1954) reported the D-isomers while we deal with the L-isomer. Excepting when the absolute configuration is involved the difference in isomers is inconsequential structurally. However, for purposes of precise comparison, it is necessary to take this into account and hence we reckon the enantiomer of the present compound.

from the density did not agree with the formula of t-BOC-L-isoleucine HCl and suggested that crystals might be L-isoleucine HCl \cdot H₂O. But the cell dimensions were significantly different from those of form I. This raised the possibility of the present crystals being different from form I. It turned out to be so and the enantiomorph of the present crystal is isomorphous with the hydrobromide derivative of D (—) isoleucine and is hence termed form II.

A later attempt to crystallize D-isoleucine from dilute hydrochloric acid by slow evaporation yielded crystals of form II. TB obtained crystals of form I by adding concentrated hydrochloric acid to a suspension of D-isoleucine in acetone and allowing the solution to evaporate slowly over soda lime *in vacuo*. They also accidentally found that the crystals of hydrochloride obtained by 96% alcoholic solution was isomorphous with hydrobromide derivative and the crystals were unstable.

The three-dimensional intensity data were collected from multiple film equi-inclination Weissenberg photographs. Layers 0 to 3 were collected about both *a* and *c* axes with CuK α radiation. Intensities were estimated visually and were corrected for Lorentz, polarisation and spot shape (Phillips 1954) factors. Absorption corrections were neglected ($\mu t \sim 0.3$). A total of 776 reflections were observed which is about 57% of the total reflections accessible to the copper sphere. The two sets of data were brought to a single scale by correlating the data using 360 common reflections by the method of Rollett and Sparks (1960) and the discrepancy factor for *F*'s for the two sets of data is 0.11.

3. Determination and refinement of the structure

The isomorphism of the present structure with D-isoleucine HBr \cdot H₂O (TB) was not detected in the beginning and hence the structure was determined by the heavy atom method. At this stage the comparison of the coordinates with those of D-isoleucine HBr \cdot H₂O (TB) showed the two are isomorphous. However, the work was continued since the accuracy of the present structure determination may be expected to be higher as the earlier work on the hydrobromide derivative was done with two-dimensional data and consequently standard deviations in bond lengths (0.05 Å) and angles (10°) were reported to be large.

Three cycles of least squares full matrix refinement with isotropic temperature factors using the program of Gantzel, Sparks and Trueblood (1961) brought the R factor to 0.14. Though the hydrogens were located from a difference electron density map, the hydrogens H (8), H (10) and H (13) were fixed from stereochemical consideration (see table 2 for symbols of hydrogens) as they did not appear in the difference electron density map. Hydrogens were not refined but were included in the structure factor for further refinement. They were assigned the isotropic temperature factors of the atoms to which they are bonded.

For further refinements anomalous dispersion correction factors for chlorine ($\Delta f' = 0.348$ and $\Delta f'' = 0.702$, Cromer and Liberman 1970) were taken into account. Three cycles of anisotropic refinement brought the R factor to 0.096. Shifts in the parameters in the last cycle were less than 1/5th the standard deviations. Hughes (1941) weighting scheme with $F_{\text{min}} = 10$ was employed in the refinements.

Even though the absolute configuration was known to be L and the appropriate precaution had been taken during indexing (Peerdeman and Bijvoet, 1956; Vaidya and Ramaseshan, 1963) another set of refinement with $\Delta f''$ sign reversed was carried out for the opposite configuration which gave an R factor of 0.099. The difference in R factor is significant at 0.005 level according to the Hamilton's (1965) statistical test. The final positional and thermal parameters are given in table 1 *a*. Table 1 *b* gives the positional and thermal parameters of hydrogen atoms. The scattering factors for Cl⁻, O, N, C and H were taken from International Tables for X-ray Crystallography (1962). Observed and calculated structure factors are available from the authors on request.

4. Description of the structure

4.1 Bond lengths and angles

The bond lengths and angles with their standard deviations are listed in figure 1. The average standard deviation of the various bonds involving C, N, O is about 0.016 Å and that for bond angles is 1.1°. In general, there are no abnormalities in bond lengths and angles.

4.2 Conformation of the molecule

The deviation of the amino nitrogen from the mean plane defined by the carboxyl and C^α atoms is 0.310 Å. The ψ_1 and ψ_2 angles (Lakshminarayanan, Sasisekharan and Ramachandran 1967) are 167.1° (12) and -11.8° (15). The torsion angles χ_{11} and χ_{12} are 190.8° (12) and 64.5° (10) respectively. The corresponding angles in L-isoleucine HCl H₂O form I are 48.4° and 287.5° respectively. Thus it can

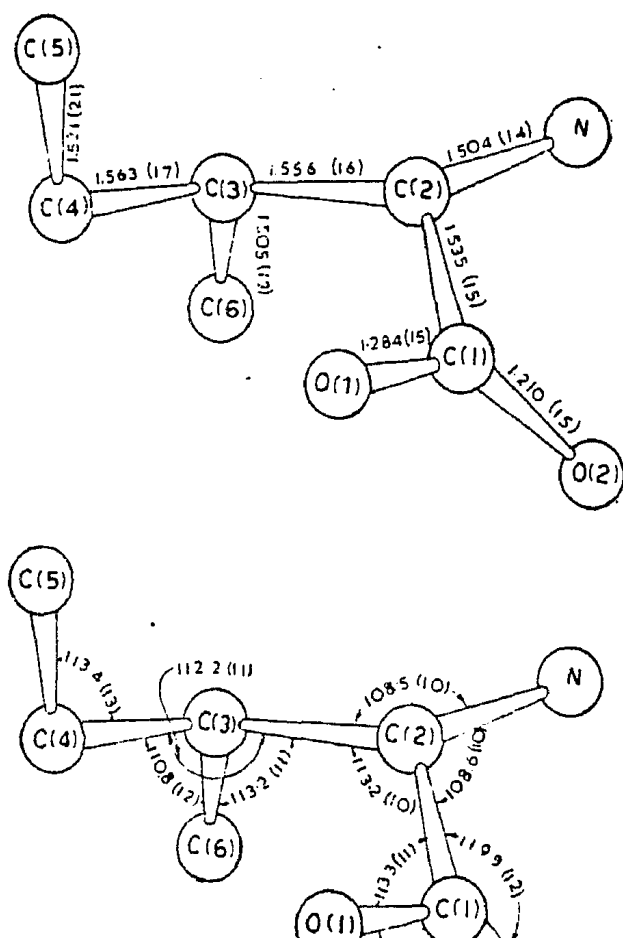


Figure 1. Bond lengths and angles.

Table 1a. The final positional (fractional) and thermal parameters of non-hydrogen atoms with standard deviations. Thermal parameter values multiplied by 10^3 . Temperature factor is of the form $T = \exp -(B_{11}a^{*2}h^2 + B_{22}b^{*2}k^2 + B_{33}c^{*2}l^2 + B_{12}a^*b^*hk + B_{13}a^*c^*hl + B_{23}b^*c^*kl)$.

Atom	Positional			Thermal					
	X	Y	Z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	0.1979 (5)	0.1649 (1)	0.0672 (4)	369 (11)	395 (10)	341 (10)	18 (25)	-137 (23)	64 (21)
O _w	0.8103 (17)	0.2415 (3)	0.2292 (14)	489 (39)	371 (40)	414 (43)	195 (69)	12 (90)	56 (63)
O (1)	0.8010 (18)	0.1253 (4)	0.8324 (14)	524 (40)	441 (46)	472 (47)	-226 (81)	-316 (96)	329 (71)
O (2)	0.8715 (17)	0.1943 (4)	0.6323 (15)	580 (50)	557 (48)	582 (57)	-592 (88)	-584 (90)	539 (84)
C (1)	0.7558 (20)	0.1571 (4)	0.6896 (18)	433 (65)	209 (52)	342 (45)	-50 (75)	190 (89)	42 (70)
C (2)	0.5266 (18)	0.1449 (4)	0.5911 (16)	365 (46)	256 (46)	270 (49)	-195 (75)	-28 (85)	126 (77)
C (3)	0.5299 (21)	0.0923 (4)	0.4670 (18)	483 (56)	186 (43)	392 (59)	-95 (82)	39 (82)	-168 (75)
C (4)	0.5458 (23)	0.0405 (4)	0.5965 (23)	543 (63)	209 (50)	666 (88)	-31 (81)	-144 (144)	98 (105)
C (5)	0.3466 (31)	0.0341 (6)	0.7365 (25)	909 (108)	348 (49)	299 (85)	-195 (130)	343 (179)	364 (112)
C (6)	0.7125 (31)	0.0922 (5)	0.3128 (21)	817 (82)	394 (55)	370 (57)	75 (132)	135 (138)	-273 (91)
N	0.4662 (16)	0.1914 (3)	0.4598 (15)	358 (39)	232 (28)	415 (51)	18 (62)	-201 (84)	-35 (71)

be seen that the main difference between the two structures is in the rotational angles about $C^{\alpha} - C^{\beta}$. The χ_{21} angle in form II is $60.5(14)$ and the C^{δ} atom is trans to C^{γ} .

4.3 Crystal packing and hydrogen bonding

The packing of the structure viewed down the c axis is shown in figure 2. The structure is stabilized by a three-dimensional net work of hydrogen bonds. The relevant hydrogen bond lengths and angles are given in table 2.

The hydroxyl oxygen O (1) donates the hydrogen attached to it to form a fairly strong hydrogen bond O (1) ... Cl(V) (2.996 \AA). The water oxygen O_w gets hydrogen bonded to Cl(iii) and Cl(iv) and the hydrogen bond distances are 3.152 \AA and 3.163 \AA respectively. The water molecule accepts two protons in the direction of the lone pairs. The amino nitrogen N has four neighbours Cl, O_w , O_w (ii) and O (2) (ii) at distances of 3.185 \AA , 2.847 \AA , 2.853 \AA and 2.945 \AA respectively. The possibility of O (2) (ii) and O_w (ii) forming a bifurcated hydrogen bond was investigated. However the angles C (2)-N ... O (2) (ii) (155.0), H (8)-N ... O (2) (ii) (46°) and the distance H (8) ... O (2) (ii) of 2.37 \AA are not within acceptable limits of hydrogen bond and hence N ... O (2) (ii) can be considered to be an ionic contact. The molecules are arranged in hydrogen bonded double layers perpendicular to the b axis. Between the doublet layers only Van der Waals forces exist. Intermolecular contacts between the side chains less than 4.2 \AA were examined and there are no abnormal short contacts.

Table 1*b*. Positional (fractional) parameters of hydrogen atoms and their peak heights as obtained from the difference electron density map

Atom	Bonded to	X	Y	Z	B (\AA^2)
H (1)	C (2)	0.411	0.135	0.717	3.34
H (2)	C (3)	0.342 (0.375)	0.088 (0.090)	0.350 (0.382)	3.02
H (3)	C (4)	0.572	0.013	0.506	2.50
H (4)	C (4)	0.717	0.042	0.689	2.50
H (5)	O (1)	0.972	0.139	0.892	4.92
H (6)	N	0.622 (0.587)	0.194 (0.196)	0.400 (0.358)	2.00
H (7)	N	0.356 (0.317)	0.181 (0.184)	0.400 (0.395)	2.00
H (8)	N	(0.454)	(0.225)	(0.539)	2.00
H (9)	C (6)	0.911	0.083	0.381	5.92
H (10)	C (6)	(0.706)	(0.055)	(0.234)	5.92
H (11)	C (6)	0.669	0.131	0.197	5.92
H (12)	C (5)	0.200	0.050	0.639	6.22
H (13)	C (5)	(0.368)	(-0.002)	(0.821)	6.22
H (14)	C (5)	0.322	0.075	0.833	6.22
H (15)	O_w	0.817	0.272	0.133	4.25
H (16)	O_w	0.939	0.228	0.200	4.25

Values within the brackets correspond to geometrically assumed positions.

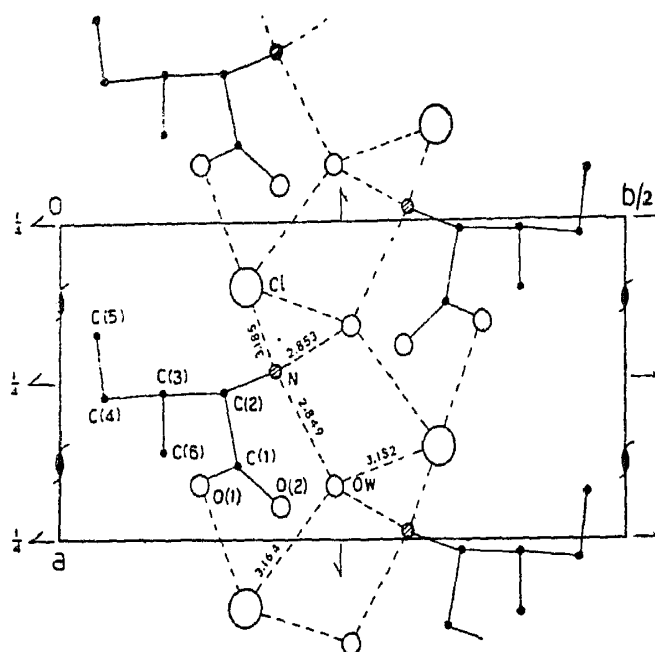


Figure 2. Packing diagram of the structure.

Table 2. Hydrogen bond lengths and angles

Donor	Acceptor	D...A (Å)	H...A (Å)	D-H...A (°)	C-D...A (°)	H-D...A (°)
C(2)-N-H(7)	Cl	3.185	2.49 (2.40)	144 (135)	117.6	27 (32)
C(2)-N-H(6)	O _w	2.847	1.99 (1.94)	142 (149)	119.8	25 (2)
C(2)-N-H(8)	O _w (II)	2.853	(1.98)	(145)	94.3	(24)
C(2)-N-H(8)	O(2)* (II)	2.954	(2.37)	(117)	155.0	(46)
OW-H(15)	Cl (III)	3.152	2.19	159	..	14
OW-H(16)	Cl (IV)	3.163	2.36	157	..	17
C(1)-O(1)-H(5)	Cl (V)	2.996	1.90	161	111.6	13

$$\text{Cl (III)-O}_w\text{-Cl (IV)} = 111.5.$$

Values within the brackets correspond to the geometrical positions of hydrogen.

* Ionic contact.

Table 2 (Contd.)

Symmetry Code			
(I)	$1/2 - X$	$- Y$	$Z - 1/2$
(II)	$X - 1/2$	$1/2 - Y$	$1 - Z$
(III)	$1/2 + X$	$1/2 - Y$	$- Z$
(IV)	$1 + X$	Y	Z
(V)	$1 + X$	Y	$1 + Z$
(VI)	$3/2 - X$	$- Y$	$1/2 + Z$
(VII)	$1/2 - X$	$- Y$	$1/2 + Z$
(VIII)	$X - 1/2$	$1/2 - Y$	$- Z$
(IX)	$Y - 1$	Y	Z
(X)	$X - 1$	Y	$Z - 1$
(XI)	$Y + 1/2$	$1/2 - Y$	$1 - Z$

References

- Cromer D T and Liberman D 1970 Los Alamos Scientific Laboratory *University of California Report LA 4403, UC 34*.
- Gantzel P K, Sparks R A and Trueblood K N 1961 *University of California Program, UCLALS I*
- Hamilton W C 1965 *Acta Cryst.* **18** 502
- Hughes I W 1941 *J. Am. Chem. Soc.* **63** 1737
- International Tables for X-ray Crystallography Vol. III 1962 Birmingham; Kynoch Press
- Lakshminarayanan A V, Sasisekharan V and Ramachandran G N 1967 in *Conformation of Biopolymers*, Vol. 1 ed G N Ramachandran London Academic Press p. 61
- Peerdeeman A F and Bijvoet J M 1956 *Acta Cryst.* **9** 1012
- Phillips D C 1954 *Acta Cryst.* **7** 746
- Collett J S and Sparks R A 1960 *Acta Cryst.* **13** 273
- Trommel J and Bijvoet J M 1954 *Acta Cryst.* **7** 703
- Vaidya S N and Ramaseshan S 1963 in "Crystallography and Crystal Perfection" ed G N Ramachandran London Academic Press p. 243
- Varughese K I and Srinivasan R 1975a *J. Cryst. Mol. Struct.* (In Press)
- Varughese K I and Srinivasan R 1975b *Acta Cryst.* (In Press)