A Refinement of the Crystal Structure of Histidine Hydrochloride Monohydrate

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The crystal structure of histidine hydrochloride monohydrate has been refined. The crystals are orthorhombic $P2_12_12_1$, $a = 15\cdot301$ (3), $b = 8\cdot921$ (2), $c = 6\cdot846$ (2) Å, $Z = 4$. The intensities were measured with an automatic four-circle diffractometer using Mo $K\alpha$ radiation. The structure was solved by the program *SEARCHER*, for the automatic heavy-atom analysis, and refined by full-matrix least-squares calculations to a final R of 0·037 for 1079 independent observed reflexions.

Introduction

The crystal structure of histidine hydrochloride monohydrate, $C_6H_9O_2N_3 \cdot HCl \cdot H_2O$, was first determined by Donohue, Lavine & Rollett (1956), and the structure including hydrogen atoms was further refined by Donohue & Caron (1964) on the basis of the original data. In the present study, the crystal structure of the same compound was further refined on the basis of the intensity data collected by the diffractometer method. This is a part of a series of automatic structure analyses of organic compounds by the heavy atom method. The authors' interest lies in the accurate determination of the shape and the size of an organic molecule and in the detection of their changes in different molecular environments.

Experimental

The crystals used, kindly supplied by Dr Yoshiharu Wakisaka, were obtained by slow evaporation of an aqueous solution. Precession and Weissenberg photographs were taken with Cu $K\alpha$ ($\lambda = 1\cdot5418$ Å) radiation in order to determine the space group and the unit-cell dimensions. More accurate cell dimensions were determined by the least-squares method using data obtained from an automatic diffractometer.

Crystal data

$C_6H_9O_2N_3 \cdot HCl \cdot H_2O$, M.W. 209·63.

Orthorhombic

$a = 15\cdot301 \pm 0\cdot003, b = 8\cdot921 \pm 0\cdot002, c = 6\cdot846 \pm 0\cdot002$ Å,

$U = 934\cdot5$ Å^3, $D_m = 1\cdot483$ g.cm^{-3} (by flotation),

$D_x = 1\cdot489$ g.cm^{-3}, $Z = 4$, $F(000) = 440$,

μ(Mo $K\alpha$) = 3·94 cm^{-1}.

Absent reflexions: $h00$ when h is odd, $0k0$ when k is odd, $00l$ when l is odd,

Space group: $P2_12_12_1$ (D_2^4, No. 19).

Three-dimensional intensity data were collected on a Hilger and Watts automatic four-circle diffractometer Y-290 controlled by a PDP-8 computer. Integrated intensities were measured for $\theta \le 27\cdot5°$ by the $\theta-2\theta$ scan technique using Mo $K\alpha$ radiation and a scintillation counter (with a zirconium filter and pulse-height analyser). Each reflexion was integrated in eighty steps at an interval of 0·01°. In total 1262 independent reflexions were recorded, of which 1168 were sufficiently above the background. All the intensities were corrected for Lorentz and polarization factors. No absorption correction was applied in view of the small size of the specimen used, $0\cdot25 \times 0\cdot30 \times 0\cdot35$ mm, and the small value of μ(Mo $K\alpha$), 3·94 cm^{-1}.

Table 1. *Final fractional atomic coordinates and anisotropic thermal parameters,* with estimated standard deviations in parentheses (all quantities $\times 10^4$)*

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl$^-$	1758 (0)	2274 (0)	302 (1)	34 (0)	70 (0)	109 (1)	7 (0)	−3 (0)	1 (0)
O(1)	2854 (1)	1839 (2)	5389 (3)	26 (0)	78 (2)	161 (5)	−1 (1)	18 (1)	−23 (3)
O(2)	4208 (1)	2629 (3)	6058 (3)	33 (1)	142 (4)	104 (4)	−21 (2)	2 (1)	−34 (3)
N(1)	3303 (1)	378 (3)	2179 (4)	26 (1)	59 (2)	94 (5)	0 (1)	2 (2)	−13 (3)
N(2)	3834 (1)	3958 (3)	−609 (4)	32 (1)	69 (3)	90 (5)	−6 (1)	3 (2)	3 (3)
N(3)	3304 (2)	5754 (3)	1117 (5)	32 (1)	62 (3)	172 (7)	2 (1)	0 (2)	9 (3)
C(1)	3642 (2)	1925 (3)	5067 (4)	25 (1)	62 (3)	88 (6)	2 (1)	6 (2)	9 (3)
C(2)	4016 (1)	1157 (3)	3233 (4)	21 (1)	62 (3)	93 (5)	4 (1)	0 (2)	0 (3)
C(3)	4509 (1)	2245 (3)	1895 (4)	23 (1)	62 (3)	118 (6)	3 (1)	9 (2)	−10 (4)
C(4)	4012 (1)	3617 (3)	1321 (4)	19 (1)	60 (3)	95 (6)	−6 (1)	1 (2)	5 (4)
C(5)	3398 (2)	5260 (4)	−678 (5)	38 (1)	84 (4)	144 (8)	0 (2)	−9 (2)	29 (4)
C(6)	3679 (2)	4756 (3)	2402 (5)	28 (1)	62 (3)	117 (6)	−1 (1)	7 (2)	0 (4)
O′	807 (2)	970 (4)	4094 (4)	34 (1)	193 (5)	191 (7)	22 (2)	9 (2)	102 (5)

* In the form: $T = \exp \{ -(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl) \}$.

Structure determination and refinement

The structure was solved by the *SEARCHER* program (Koyama & Okada, 1970), written for the CDC 6600 computer. Initial coordinates for the chloride ion were easily derived from three Harker sections of the three-dimensional Patterson synthesis. They were: $x=0.175$, $y=0.230$, $z=0.030$. The atomic coordinates of 11 light atoms, which were treated as carbon atoms, were found from the first cycle of the *SEARCHER* program (see Fig. 1). The time of the automatic heavy-atom analysis was only 270 sec.

The coordinates of the 12 atoms from the *SEARCHER* cycle were refined by a program *ORFLS* (Busing, Martin & Levy, 1962). After two cycles, with isotropic temperature factors, the R value became 0.093. At this stage a three-dimensional difference Fourier synthesis was calculated, and the positions of the ten hydrogen atoms and the water molecule were found (see Fig. 2).

Table 2. *Final fractional hydrogen atom coordinates* ($\times 10^3$) *with their standard deviations in parentheses and isotropic temperature factors*

	x	y	z	B
H(N1)a	280 (2)	108 (3)	177 (5)	1·255
H(N1)b	345 (2)	−6 (4)	130 (5)	1·255
H(N1)c	306 (2)	−29 (4)	296 (5)	1·255
H(N2)	398 (2)	332 (4)	−154 (5)	1·255
H(N3)	300 (2)	668 (4)	130 (5)	1·255
H(C2)	446 (2)	37 (3)	375 (5)	1·255
H(C3)a	468 (2)	174 (3)	75 (5)	1·255
H(C3)b	502 (2)	254 (3)	253 (5)	1·255
H(C5)	318 (2)	571 (3)	−192 (5)	1·255
H(C6)	367 (2)	496 (4)	387 (5)	1·255
H(O′)a	105 (2)	120 (4)	308 (5)	1·255
H(O′)b	29 (2)	150 (4)	405 (5)	1·255

The final five cycles of full-matrix least-squares refinement with anisotropic temperature factors reduced R to 0.037 for the 1079 reflexions, where those with inten-

Table 3. *Comparison of bond lengths, bond angles and dihedral angles in the histidine molecule*

(a) Bond lengths

	I	II	IIIa	IIIb	IV	V	VI	VII
C(1)–C(2)	1·540 Å	1·515 Å	1·50 Å	1·51 Å	1·45 Å	1·530 Å	1·537 Å	1·519 Å
C(2)–C(3)	1·532	1·545	1·56	1·51	1·60	1·527	1·553	1·539
C(3)–C(4)	1·493	1·487	1·48	1·49	1·46	1·508	1·400	1·486
C(4)–C(6)	1·355	1·355	1·38	1·33	1·35	1·358	1·332	1·369
N(1)–C(2)	1·481	1·504	1·49	1·49	1·51	1·495	1·487	1·473
N(2)–C(4)	1·384	1·403	1·37	1·38	–	1·386	1·404	1·417
N(2)–C(5)	1·340	1·306	1·32	1·30	1·43	1·319	1·278	1·329
N(3)–C(5)	1·313	1·331	1·33	1·34	1·43	1·314	1·290	1·324
N(3)–C(6)	1·377	1·381	1·37	1·37	1·37	1·359	1·368	1·374
O(1)–C(1)	1·228	1·235	1·26	1·29	1·16	1·240	1·193	1·243
O(2)–C(1)	1·266	1·262	1·26	1·23	1·29	1·265	1·231	1·260
R(%)	3·7	10·8	11·0		15·7	7·6	–	10·5
σ { C–C	0·004 Å	0·010 Å	0·015 Å		–	0·011 Å	0·025 Å	0·020 Å
N–C	0·004	0·010	0·015		–	0·011	0·023	0·020
O–C	0·004	0·010	0·015		–	0·010	0·021	0·020

(b) Bond angles

	I	II	IIIa	IIIb	IV	V	VI	VII
O(1)–C(1)–O(2)	127·3°	126·3°	125·4°	124·2°	127°	125·8°	125·0°	123°
O(1)–C(1)–C(2)	118·8	118·3	116·1	118·6	111	120·0	118·6	119
O(2)–C(1)–C(2)	113·7	115·4	118·4	117·2	120	114·2	116·6	117
N(1)–C(2)–C(1)	109·3	109·1	111·5	109·7	120	109·4	108·9	111
N(1)–C(2)–C(3)	111·6	109·2	110·6	110·2	111	111·1	111·9	110
C(1)–C(2)–C(3)	112·8	108·3	106·7	112·3	110	113·3	109·4	110
C(2)–C(3)–C(4)	115·2	111·8	113·7	114·3	121	114·9	114·6	114
N(2)–C(4)–C(3)	122·1	123·1	123·0	121·7	122	122·1	128·0	124
N(2)–C(4)–C(6)	106·4	107·5	109·8	111·2	112	106·2	105·6	107
C(3)–C(4)–C(6)	131·4	129·4	127·1	127·1	126	131·6	127·3	129
N(2)–C(5)–N(3)	108·1	108·3	112·1	111·3	105	108·7	111·6	110
N(3)–C(6)–C(4)	106·9	105·1	105·2	105·0	107	106·9	107·6	107
C(4)–N(2)–C(5)	108·7	108·6	105·1	104·6	106	108·5	107·2	107
C(5)–N(3)–C(6)	109·6	110·5	107·7	108·0	109	109·6	107·5	109
σ(angles)	0·2	0·4–0·6	0·6		–	–	2·0	1·3

(c) Dihedral angles

	I	II	IIIa	IIIb	IV	V	VI	VII
O(1)–C(1)–C(2)–N(1)	−1·7°	16·7°	15·8°	−15·3°	87·4°	0·4°	11·8°	−3·6°
O(1)–C(1)–C(2)–C(3)	123·2	−102·1	−105·0	107·5	−143·5	125·0	−111·1	118·5
O(2)–C(1)–C(2)–N(1)	−179·7	−162·6	−167·3	167·1	−76·0	179·5	−170·9	176·1
O(2)–C(1)–C(2)–C(3)	−54·8	78·6	71·8	−70·0	53·2	−55·9	66·2	−61·9
C(1)–C(2)–C(3)–C(4)	−52·8	−179·4	50·7	−58·2	−173·5	−52·1	50·2	−49·2
N(1)–C(2)–C(3)–C(4)	70·9	61·9	−70·7	64·4	−39·5	71·5	−70·9	73·2
C(2)–C(3)–C(4)–N(2)	−120·3	70·6	36·1	−18·6	87·4	−120·5	45·2	−42·1
C(2)–C(3)–C(4)–C(6)	62·0	−107·7	−139·4	164·9	−94·5	61·1	−134·4	139·8

I: This paper, II: DL-Histidine hydrochloride dihydrate, III: D-Histidino-L-histidinocobalt(II) dihydrate, IV: Complex of mercury(II) chloride and histidine hydrochloride, V: Histidine hydrochloride monohydrate, VI: Di(L histidino) zinc(II) dihydrate, VII: Di(histidino)zinc pentahydrate.

sites less than three times the standard deviation of the total counts were rejected. For the final stage of the refinement a weight given by Cruickshank's (1965)
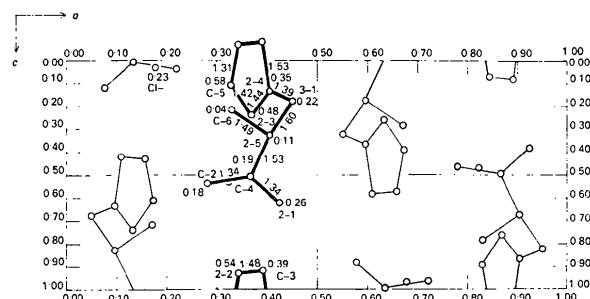

Fig. 1. Projection of the structure of histidine hydrochloride, viewed along the b axis, which were printed from output (after 1st cycle) of the program *SEARCHER*.
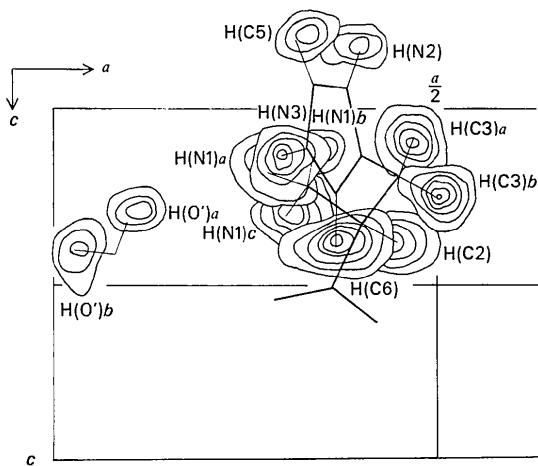
Fig. 2. Difference electron density map showing the hydrogen atoms. Contours are drawn on an arbitrary scale.

weighting scheme was employed,

$$\omega = (a + |F_{obs}| + c|F_{obs}|^2)^{-1} ,$$

where $a = 4.00$, $c = 0.0166$.

All hydrogen atoms were included in the final refinement with isotropic temperature factors. The atomic scattering-factors used in all calculations are those of Doyle & Turner (1968) for non-hydrogen atoms and those of Stewart, Davidson & Simpson (1965) for hydrogen atoms. The final positional and thermal parameters with their estimated standard deviations are given in Tables 1 and 2.*

Crystal structure

The configuration of the molecule is illustrated in the stereodiagram (Johnson, 1965) in Fig. 3 where each atom is represented as an ellipsoid corresponding to the thermal parameters listed in Table 1. Mostly the corresponding bond lengths and angles are not significantly different from expected values. Table 3 summarizes the bond lengths, angles and the dihedral angles of this paper and, for comparison, of di(histidino)zinc pentahydrate (Harding & Cole, 1963), of di(L-histidino)zinc(II) dihydrate (Kretsinger, Cotton & Bryan, 1963), of histidine hydrochloride monohydrate (Donohue & Caron, 1964), of DL-histidine hydrochloride dihydrate (Bennett, Davidson, Harding & Morelle, 1970), of D-histidino-L-histidinocobalt(II) dihydrate (Candlin & Harding, 1970), and of a complex of mercury(II) chloride and histidine hydrochloride (Adams, Hodgkin & Raeburn, 1970). Some of the differences in bond lengths and angles observed among crystals III, IV, and VI seem to be due to different molecular environments in respective crystal structures.

* A list of structure factors is available on request from our laboratory.

Table 4. *Bond distances and angles to hydrogen, with standard deviations in parentheses*

(a) Bond distances

C(2)–H(C2)	1·04 (3) Å	N(1)–H(N1)c	0·88 (3) Å
C(3)–H(C3)a	0·93 (3)	N(2)–H(N2)	0·88 (3)
C(3)–H(C3)b	0·93 (3)	N(3)–H(N3)	0·95 (3)
C(5)–H(C5)	0·99 (3)		
C(6)–H(C6)	1·02 (3)		
N(1)–H(N1)a	1·02 (3)	O'——H(O')a	0·81 (3)
N(1)–H(N1)b	0·75 (3)	O'——H(O')b	0·91 (3)

(b) Bond angles

C(1)——C(2)–H(C2)	105 (1)°	C(2)——N(1)–H(N1)a	113 (1)°
C(3)——C(2)–H(C2)	107 (1)	C(2)——N(1)–H(N1)b	114 (2)
N(1)——C(2)–H(C2)	109 (1)	C(2)——N(1)–H(N1)c	109 (2)
C(2)——C(3)–H(C3)a	109 (2)	H(N1)a–N(1)–H(N1)b	109 (3)
C(2)——C(3)–H(C3)b	107 (2)	H(N1)a–N(1)–H(N1)c	105 (2)
C(4)——C(3)–H(C3)a	108 (2)	H(N1)b–N(1)–H(N1)c	104 (3)
C(4)——C(3)–H(C3)b	108 (2)	C(4)——N(2)–H(N2)	120 (2)
H(C3)a–C(3)–H(C3)b	106 (3)	C(5)——N(2)–H(N2)	131 (2)
N(2)——C(5)–H(C5)	122 (2)	C(5)——N(3)–H(N3)	117 (2)
N(3)——C(5)–H(C5)	128 (2)	C(6)——N(3)–H(N3)	132 (2)
C(4)——C(6)–H(C6)	132 (1)		
N(3)——C(6)–H(C6)	120 (1)	H(O')a–O'——H(O')b	104 (3)

The C–H bond lengths and angles are given in Table 4, together with their standard deviations computed from the least-squares residuals. The imidazole ring is perfectly planar. The β-carbon C(3) is slightly displaced by 0·02 Å from the imidazole ring. The atoms of the carboxyl group and the α-carbon C(2) and amino nitrogen N(1) are also planar. The displacements of the atoms from the planes are shown in Table 5. The dihedral angle between the planes is ca. 72·4°. All intermolecular distances were calculated, and the most significant contacts ($< 3·6$ Å) are given in Table 6.

Table 5. *Equations of planes and displacements of the atoms from mean planes*

X, Y and Z are orthogonal coordinates (Å)

(a) Imidazole ring

$$0·8686X + 0·4902Y - 0·0708Z = 6·8537$$

N(2)	0·00 Å	H(N2)	−0·02 Å
N(3)	0·00	H(N3)	0·00
C(4)	0·00	H(C5)	−0·02
C(5)	0·00	H(C6)	0·01
C(6)	0·00		

(b) Carboxyl group and α-carbon

$$-0·1632X + 0·8278Y - 0·5367Z = -1·3392$$

O(1)	0·00 Å	C(1)	−0·01 Å
O(2)	0·00	C(2)	0·00
N(1)	0·00		
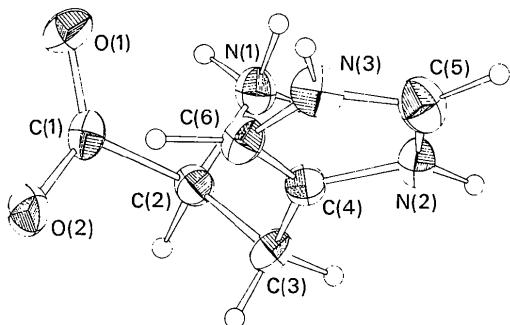
Fig. 3. A stereodiagram of the histidine hydrochloride molecule.

Table 6. *Intermolecular distances* ($< 3·6$ Å)

Cl⁻---N(1ᵛ)	3·191 Å	N(1)-O′ᵛ	2·785 Å
Cl⁻---N(3ᵛⁱⁱ)	3·363	N(2)-C(1ⁱⁱ)	3·485
Cl⁻---C(2ᵛ)	3·576	N(3)-C(5ᵛⁱ)	3·524
Cl⁻---C(5ᵛⁱ)	3·530	N(3)-O′ᵛⁱⁱ	3·506
Cl⁻---C(6ᵛⁱⁱ)	3·377	C(2)-O′ᵛ	3·421
O(1)-N(1ⁱᵛ)	2·924	C(3)-C(6ᵛⁱⁱⁱ)	3·583
O(1)-N(3ᵛⁱ)	2·828	C(3)-O′ᵛ	3·484
O(1)-C(5ᵛⁱ)	3·301	C(5)-C(6ᵛⁱⁱ)	3·439
O(2)-N(2ⁱ)	2·633	C(5)-O′ᵛⁱⁱ	3·578
O(2)-C(5ⁱ)	3·470	O′---O(1)	3·346
O(2)-O′ⁱⁱⁱ	2·748	O′---Cl	3·195

The roman numerals as superscripts refer to the equivalent position relative to the reference molecule at x, y, z:

i	$x, y, 1+z$	v	$\frac{1}{2}-x, -y, -1+(\frac{1}{2}+z)$
ii	$x, y, -1+z$	vi	$\frac{1}{2}-x, 1+(-y), \frac{1}{2}+z$
iii	$\frac{1}{2}+x, \frac{1}{2}-y, 1+(-z)$	vii	$\frac{1}{2}-x, 1+(-y), -1+(\frac{1}{2}+z)$
iv	$\frac{1}{2}-x, -y, \frac{1}{2}+z$	viii	$1+(-x), -1+(\frac{1}{2}+y), \frac{1}{2}-z$

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