Acta Cryst. (1972). B28, 2377

The Crystal Structure of the Orthorhombic Form of L-(+)-Histidine

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(*Received* 23 *August* 1971)

L-(+)-Histidine ($C_6N_3O_2H_9$) crystallizes in the orthorhombic space group $P2_12_12_1$, with $a=5{\cdot}177$, $b=7{\cdot}322$, $c=18{\cdot}87$ Å, and $Z=4$. Data were collected with Mo $K\alpha$ radiation, using balanced filters. The structure was solved by direct phasing methods and refined to a final agreement index of 0·034 for all reflections. The conformation of the molecule is that of the open, extended form, and is stabilized principally by an intramolecular hydrogen bond between the amino nitrogen atom and the adjacent imidazole nitrogen atom. Where this conformation is found in proteins, it is likely to reduce the chemical reactivity of that imidazole group, because one of the imidazole nitrogen atoms is sterically hindered by the peptide backbone.

Introduction

The amino acid L-histidine (Fig. 1) has been extensively studied because of the ability of its imidazole moiety to act as a proton donor, a proton acceptor, and a nucleophilic reagent. As the free amino acid, histidine catalyzes the degradation of various esters (Rohling & Fox, 1967), while in polypeptides, histidine has been implicated in the mechanism of a number of enzymes, most notably bovine pancreatic ribonuclease (Meadows, Roberts & Jardetsky, 1969) and α-chymotrypsin (Schoellman, Schoellman & Shaw, 1963). In an effort to relate the conformation of histidine to its reactivity in these systems, its structure has been studied by X-ray crystallography in several metal complexes (Freeman, 1967) and as the protonated hydrochloride (Donohue, Lavine & Rollett, 1956; Donohue & Caron, 1964; Bennett, Davidson, Harding & Morelle, 1970). We have investigated the free base form of L-histidine by X-ray crystallography to determine the conformation of the molecule in the absence of ionic ligands.

Experimental

Preparation of the crystals

Crystals of histidine were prepared by slow evaporation of an aqueous solution of L-histidine (Nutritional Biochemical Corporation), and were then dried over calcium chloride. A large number of the crystals were either twinned or warped, as judged by visual inspection. Of those of acceptable size for data collection, only one was untwinned as determined by precession and Weissenberg photographs. This crystal was cleaved into a plate (0·3×0·3×0·1 mm), and mounted on a 0·05 mm glass fiber along its [121] axis with epoxy resin.

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Data collection and processing

Table 1 lists the unit-cell parameters, space group, and density as measured on the crystal used for data collection. Intensity data were collected on a Picker four-circle FACS I diffractometer, using ω scans of 0·7° taken at a scan rate of 0·25° min^{-1} to a 2θ value of 55°. Molybdenum radiation (Mo $K\alpha_{avg}=0{\cdot}71068$ Å) was used with balanced zirconium and yttrium filters. A bandpass intensity correction (Young, 1966; McGandy, 1969) was applied. 992 independent reflections, excluding systematic absences, were measured, of which 927 were observed and 65 unobserved. A reflection was considered to be unobserved if its measured intensity was less than $2{\cdot}50\sigma$ (with $\sigma^2=N_T+N_{BG1}+N_{BG2}$, where N_T = total peak count, and N_{BG1} and N_{BG2} = the background counts on either side of the peak). The intensity for unobserved reflections was set arbitrarily to $1{\cdot}25\sigma$, and these reflections were given a weight of zero in the least-squares refinement procedure.

Table 1. *Crystal data*

L-Histidine $C_6N_3O_2H_9$. M.W. 155·2 dalton
Space group: orthorhombic, $P2_12_12_1$
Systematically absent reflections: $h00$, $h=2n+1$; $0k0$, $k=2n+1$; $00l$, $l=2n+1$
$a=5{\cdot}177$ (5) Å
$b=7{\cdot}322$ (7)
$c=18{\cdot}87$ (2)
$\alpha=\beta=\gamma=90{\cdot}00°$
$Z=4$
$d_{calc}=1{\cdot}446$ (7) g.cm^{-3}
$d_{obs}=1{\cdot}428$ (7) g.cm^{-3}

Solution of the structure

The structure was solved using direct-method programs (Maslen & Hall, 1967) for generating triple products (*DP*3) and for tangent refinement (*DP*5), and a program (Main, 1968) for the selection of origin- and enantiomorph-determining reflections. Normalized structure amplitudes (E's) were determined from scale and temperature factors, estimated from a Wilson plot

(Shiono, 1966), and were renormalized on parity, sin θ, and HKL groupings. The 117 highest E reflections were used as input to the $DP3$ program and the Main program.

The Main program generated three linearly independent reflections to determine an origin, one reflection to fix the enantiomorph, and an arbitrary fifth reflection, which was necessary to generate phases for all of the other reflections. Phases were generated and refined by program $DP5$, and an E Fourier map was calculated. This map contained five major peaks, which could not be attributed to any particular group in histidine, but which were used to calculate structure factors for the high E reflections. The 10 reflections which gave the best agreement with the observed structure factors and which contained three origin-determining reflections and an enantiomorphic one, were recycled into $DP5$, and the resultant E Fourier map calculated. This map contained the 11 nonhydrogen atoms of histidine and gave an initial R of 0·27 ($R=\sum||F_o|-|F_c||/|F_o|$).

After six cycles of isotropic full-matrix least-squares refinement (Busing, Martin & Levy, 1962), the parameter shifts had converged and the R value was 0·07 for all reflections. A difference Fourier map revealed four peaks, corresponding to four of the hydrogen atoms. Structure factors were recalculated, including these four hydrogen atoms, and a second difference Fourier map was computed. The highest five peaks corresponded to the remaining hydrogen atoms. Two cycles of least-squares refinement, using isotropic temperature factors for the hydrogen atoms and anisotropic ones for the nonhydrogen atoms, reduced the unweighted R to 0·032 for all reflections and 0·030 for all observed reflections. To improve the agreement between F_o and F_c for both the low- and high-angle (θ) reflections, a weighting scheme (Snyder, 1968) was derived such that $\Delta F/\sigma$ was equal to 1·0 for 15 sin θ groups of F_o containing equal numbers of reflections. Two cycles of full-matrix least-squares refinement, using this weighting scheme, yielded an R of 0·034 for all reflections and gave the parameters and molecular dimensions shown in Tables 2 to 8. The atomic positions calculated with this empirical weighting scheme were not significantly different from those calculated without a weighting scheme, while the thermal parameters showed slight variations between the two weighting schemes.

Table 2. *Positional parameters of* L-*histidine*

The x, y, and z coordinates for one of the four molecules in the unit cell are given, along with an estimate of the accuracy of each. The three symmetry-related molecules have the coordinates: $0{\cdot}5-x$, $-y$, $0{\cdot}5+z$; $0{\cdot}5+x$, $0{\cdot}5-y$, $-z$; and $-x$, $0{\cdot}5+y$, $0{\cdot}5-z$.

The values for the nonhydrogen atoms are multiplied by 10^4, those for the hydrogen atoms by 10^3.

	X	Y	Z
O(1)	2249 (3)	47 (2)	1982 (1)
O(2)	−1759 (3)	90 (2)	2419 (1)
N(1)	4120 (3)	−1788 (2)	3107 (1)
N(2)	5331 (3)	−605 (2)	4470 (1)
N(3)	3743 (3)	−5 (2)	5534 (1)
C(1)	622 (3)	−170 (2)	2463 (1)
C(2)	1647 (3)	−765 (2)	3197 (1)
C(3)	2089 (4)	907 (3)	3674 (1)
C(4)	3082 (4)	398 (2)	4397 (1)
C(5)	5629 (4)	−816 (3)	5163 (1)
C(6)	2092 (4)	774 (3)	5050 (1)
H(1N1)	487 (4)	−186 (3)	353 (1)
H(2N1)	374 (5)	−295 (4)	296 (1)
H(3N1)	524 (5)	−123 (3)	281 (1)
H(N3)	349 (5)	0 (4)	603 (1)
H(C2)	41 (4)	−162 (3)	342 (1)
H(1C3)	44 (5)	152 (3)	371 (1)
H(2C3)	320 (5)	184 (4)	345 (1)
H(C5)	704 (5)	−146 (4)	536 (1)
H(C6)	53 (5)	146 (4)	517 (1)

Discussion

The distances and valence angles in the orthorhombic form of L-histidine (Table 5) are not significantly

Table 3. *Thermal parameters for* L-*histidine*

The anisotropic coefficients are derived from the expression: $T=\exp[-(h^2\beta_{11}+k^2\beta_{22}+l^2\beta_{33}+2hk\beta_{12}+2hl\beta_{13}+2kl\beta_{23})]$

β and $\sigma\beta\times 10^5$.

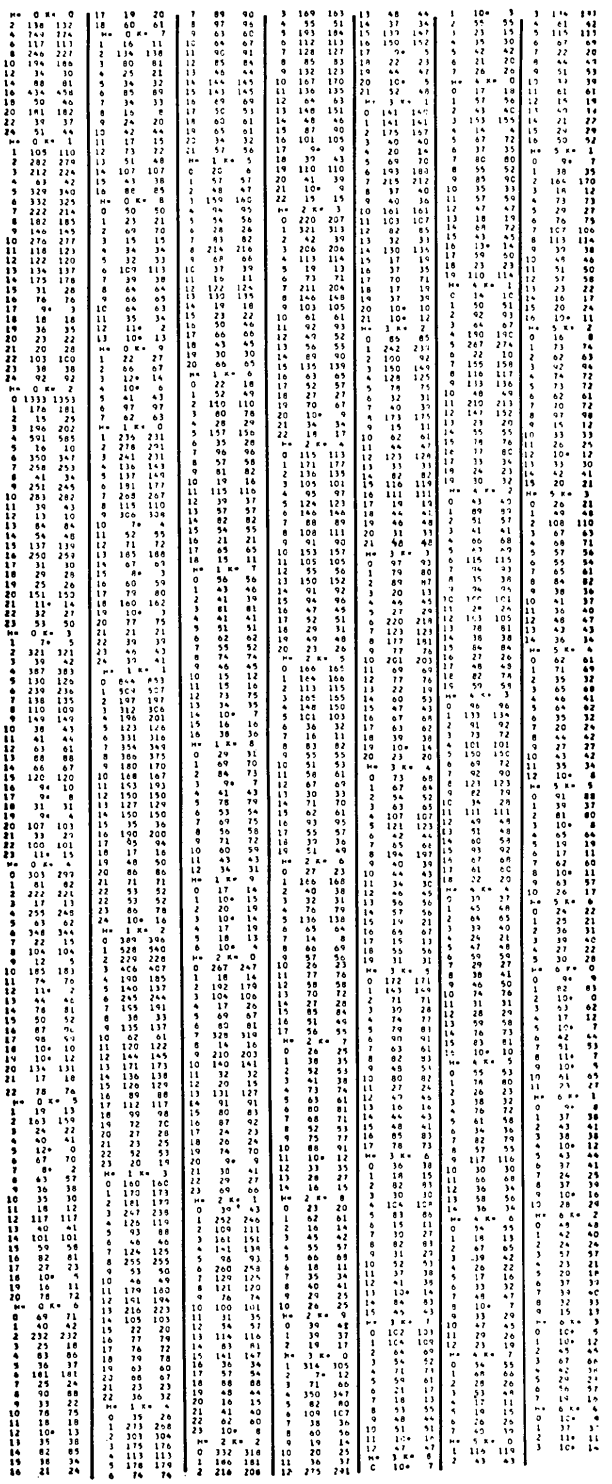
	β_{11} (σB or $\sigma\beta_{11}$)	β_{22} ($\sigma\beta_{22}$)	β_{33} ($\sigma\beta_{33}$)	β_{12} ($\sigma\beta_{12}$)	β_{13} ($\sigma\beta_{13}$)	β_{23} ($\sigma\beta_{23}$)
O(1)	2424 (15)	2236 (14)	115 (2)	−207 (2)	− 15 (1)	125 (1)
O(2)	1870 (11)	1552 (9)	226 (4)	71 (1)	−104 (2)	187 (4)
N(1)	1961 (12)	950 (6)	115 (2)	223 (4)	−7 (1)	1 (1)
N(2)	2430 (16)	1411 (9)	128 (2)	315 (5)	− 59 (1)	−6 (1)
N(3)	2932 (18)	1319 (8)	107 (1)	−211 (4)	− 23 (1)	− 13 (1)
C(1)	2035 (12)	855 (6)	116 (2)	−197 (4)	−105 (2)	24 (1)
C(2)	1615 (9)	848 (6)	105 (2)	57 (1)	−3 (1)	32 (1)
C(3)	2993 (19)	884 (6)	126 (2)	392 (6)	−111 (2)	− 21 (1)
C(4)	2316 (14)	816 (5)	121 (2)	26 (1)	− 67 (2)	− 28 (1)
C(5)	2544 (15)	1375 (8)	141 (3)	179 (4)	−135 (2)	36 (1)
C(6)	2439 (15)	1159 (7)	147 (3)	36 (1)	− 11 (1)	− 84 (2)

Isotropic temperature factors B for hydrogen atoms

H(1N1)	H(2N1)	H(3N1)	H(N3)	H(C2)	H(1C3)	H(2C3)	H(C5)	H(C6)
1·65 (5)	3·18 (4)	2·81 (9)	4·27 (10)	1·48 (4)	2·59 (7)	2·69 (8)	3·01 (9)	3·56 (9)

Table 4. *Structure factor table for orthorhombic* L-*histidine*

The various columns listed are l, F_{obs}, and F_{calc}. Unobserved reflections are designated with an asterisk after the F_{obs}.



different from those of the other crystalline histidine forms of the free base that have been solved by X-ray analysis (Madden, McGandy, Seeman, Harding &

Table 5. *Comparison of the bond lengths in orthorhombic* L-*histidine with those in* L-*histidine hydrochloride monohydrate (Donohue & Caron, 1964)*

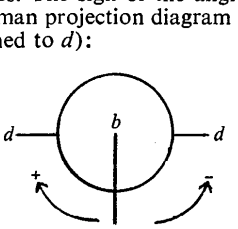
	L-Histidine	L-His-HCl.H_2O
O(1)–C(1)	1·247 (2) Å	1·240 Å
O(2)–C(1)	1·250 (2)	1·265
C(2)–C(1)	1·545 (2)	1·530
C(2)–N(1)	1·493 (2)	1·495
C(2)–C(3)	1·536 (3)	1·527
C(4)–C(3)	1·505 (3)	1·508
C(4)–N(2)	1·382 (2)	1·386
C(5)–N(2)	1·327 (3)	1·319
C(5)–N(3)	1·339 (3)	1·314
C(6)–N(3)	1·374 (3)	1·359
C(6)–C(4)	1·361 (3)	1·358
N(1)–H(1N1)	0·89 (2)	
N(1)–H(2N1)	0·91 (3)	
N(1)–H(3N1)	0·90 (2)	
C(2)–H(C2)	1·00 (2)	
C(3)–H(1C3)	0·97 (3)	
C(3)–H(2C3)	0·97 (2)	
C(5)–H(C5)	0·95 (3)	
C(6)–H(C6)	0·98 (3)	
N(3)–H(N3)	0·96 (3)	

Table 6. *Comparison of the bond angles in* L-*histidine with those in* L-*histidine hydrochloride monohydrate and conformation angles of* L-*histidine*

Comparison of bond angles. The angles are given in the form $\angle ABC$, where B is the vertex of the angle.

A	B	C	L-Histidine	L-His-HCl.H_2O
O(1)	C(1)	O(2)	126·7 (2)°	125·8°
O(1)	C(1)	C(2)	117·1 (2)	114·2
O(2)	C(1)	C(2)	116·3 (2)	120·0
C(1)	C(2)	C(3)	110·6 (1)	113·3
N(1)	C(2)	C(3)	109·8 (1)	111·1
N(1)	C(2)	C(1)	109·5 (1)	109·4
C(2)	C(3)	C(4)	112·7 (2)	114·9
C(3)	C(4)	C(6)	129·9 (2)	131·6
C(3)	C(4)	N(2)	120·5 (2)	122·1
C(6)	C(4)	N(2)	109·6 (2)	106·2
C(4)	N(2)	C(5)	104·9 (2)	108·5
N(2)	C(5)	N(3)	112·2 (2)	108·7
C(5)	N(3)	C(6)	106·9 (2)	109·6
N(3)	C(6)	C(4)	106·4 (2)	106·9

Conformation angles. The sign of the angle is designated according to the Newman projection diagram below (c is directly behind b and attached to d):



a–b–c–d	
O(1)–C(1)–C(2)–C(3)	−26·8°
C(1)–C(2)–C(3)–C(4)	179·9
N(1)–C(2)–C(3)–C(4)	−59·3
C(2)–C(3)–C(4)–C(5)	−123·2
C(2)–C(3)–C(4)–N(2)	56·8

Hoy, 1972; Edington, 1969). There are, however, significant differences between the neutral histidines and the protonated forms, *e.g.* L-histidine.HCl.H_2O (Donohue & Caron, 1964) and DL-histidine.HCl.$2H_2O$ (Bennett *et al.*, 1970). Orthorhombic L-histidine has an extended alanine backbone as does the DL hydrochloride salt, while the L hydrochloride salt folds back on itself around C(2)–C(3). This folding causes the imidazole residue to be *gauche* to both the carboxyl and primary amino groups, while in the extended conformation the imidazole is *gauche* only to the amino group, and *trans* to the carboxyl. Thus, as noted by Bennett *et al.* (1970), the angles C(1)–C(2)–C(3), C(2)–C(3)–C(4), and to a lesser extent N(1)–C(2)–C(3), are significantly larger in L-histidine hydrochloride than in the orthorhombic free base and the DL-hydrochloride (Table 6).

The angles around the N(2), C(5) and N(3) atoms in the imidazole residue are also significantly different in the protonated and unprotonated forms. In the protonated hydrochloride salts, the three angles centered on these atoms are approximately equal to 109°, a fact indicative of the aromaticity of the ring. In the unprotonated orthorhombic compound, the ring angles at N(2) and N(3) are both significantly compressed

Table 7. *Hydrogen bonding distances and angles in* L-*histidine*

Atom *A* is covalently bonded to the hydrogen (H) and *B* is hydrogen-bonded to atom *A*. The number in parentheses after the atom name refers to the unit cell and symmetry operation relating this atom to the atoms listed in Table 2. 555 refers to the origin cell (as per the *ORTEP* conventions), while 1, 2, 3, and 4 refer to the symmetry operators listed in Table 2. If no such information is listed, the atom is in the origin unit cell, with a symmetry operation of 1 Johnson 1965).

Atom *A*	Atom *B*	Distances and angles *A–B*	*B–H*	∠*AHB*
N(1)	N(2)	2·783 Å	1·990 Å	143·8°
N(1)	O(2) (545,4)	2·773	1·925	159·2
N(1)	O(2) (655,1)	2·851	1·981	167·6
N(3)	O(1) (555,2)	2·781	1·866	176·5
Close contacts				
N(1)	O(1)	2·693		
N(1)	O(1) (645,4)	2·988		

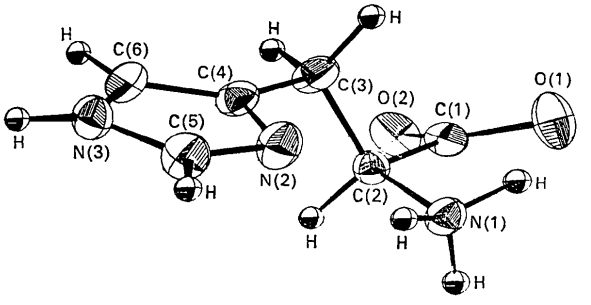


Fig. 1. An *ORTEP* plot (Johnson 1965) of L-histidine, as found in this study, demonstrating the numbering system used.

Table 8. *Planarity of the imidazole ring plus the adjacent carbon* C(3)

The plane calculated for the imidazole ring plus the carbon C(3) by least-squares analysis is given by the equation:

$$0{\cdot}5317A + 0{\cdot}8463B + 0{\cdot}0324C = 1{\cdot}3633.$$

	Distance from plane
N(2)	0·0015 Å
N(3)	0·0012
C(3)	−0·0004
C(4)	0·0002
C(5)	−0·0004
C(6)	−0·0020

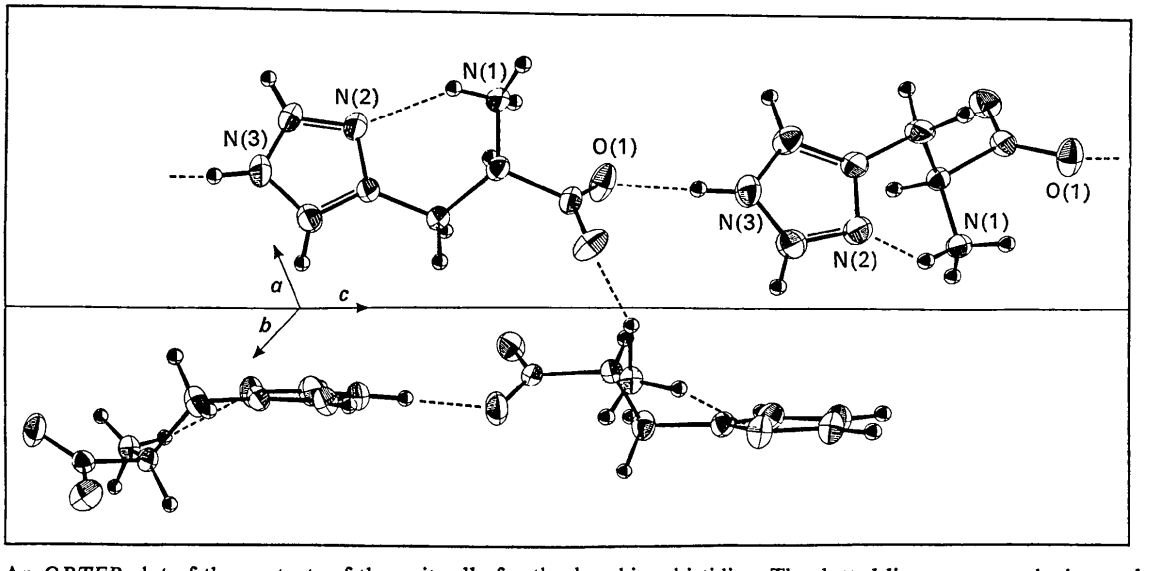


Fig. 2. An *ORTEP* plot of the contents of the unit cell of orthorhombic L-histidine. The dotted lines represent hydrogen bonds found in this structure.

(104·9 and 106·9° respectively) while the N(2)–C(5)–N(3) angle is widened to 112°, which is consistent with an increase in the sp^2 character of the bond hybridization at the ring carbon, C(5).

A series of three intermolecular hydrogen bonds determines the packing of the carboxyl and amino groups, and links the head of one molecule [N(3)] to the tail of the next [O(1)] (Fig. 2). A weak intramolecular hydrogen bond with an NH---N distance of 1·99 Å also occurs between the N(1) and N(2) atoms, contrary to the assertion of Kier (1968) that this type of bond could probably not form in a similar compound (histamine). N(1) also approaches O(1) of the same molecule to a distance of 2·69 Å, but none of the N(1) hydrogen atoms is closer than 2·42 Å to O(1), so that there is no hydrogen bond formed (Table 7). This type of interaction is identical to the electrostatic interaction described by Sasisekharan (1971) for free amino acids.

The charge density of each of the atoms in histidine was estimated using an INDO approximation (Pople, Beveridge & Dobosh, 1967), giving the results shown in Table 9. The unprotonated nitrogen atom of histidine has a large negative charge, as is the case for the unprotonated nitrogen atom of β-(pyrazolyl3-)-L-alanine (Seeman, 1970) with which it is compared. These ring charges can be explained by postulating the resonance forms shown in Fig. 3. The contributions of resonance form (II), in which the unprotonated nitrogen atoms have formal negative charges, is further confirmed by the fact that the N(3)–C(5) bond in histidine and the N(3)–C(5) bond in pyrazole–alanine are considerably shortened (1·339 and 1·332 Å respectively) compared to the expected N–C single bond length (about 1·47 Å), and even shorter than those of N(2)–C(4) and N(3)–C(6) (1·382 and 1·374 Å, respectively) of the histidine imidazole.

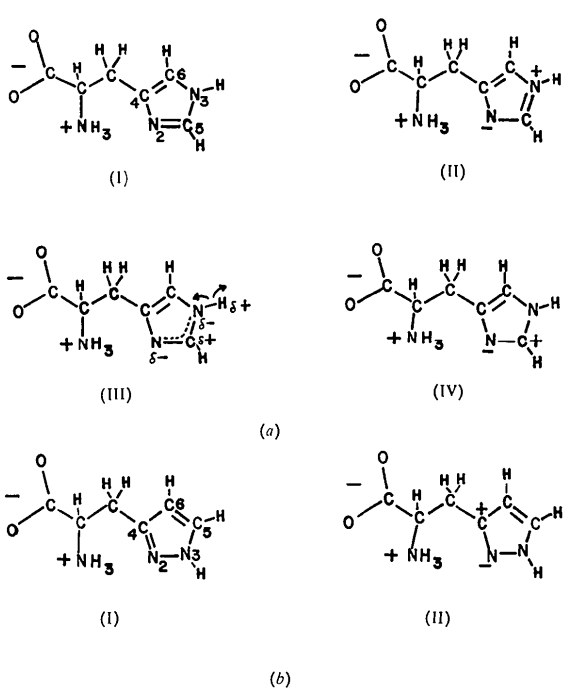


Fig. 3. The primary resonance contributors to the structures of (*a*) L-histidine and (*b*) β(pyrazolyl-3)-alanine (Seeman, 1970).

Table 9. *Charge density on the nonhydrogen atoms of* L-*histidine and β(pyrazolyl-3)-*L-*alanine* (*Seeman*, 1970) *as determined by INDO* (*Pople et al.*, 1967)

The numbers given represent the number of electrons found on each atom, such that a charge of 7·00 would be neutral for nitrogen, highly negative for carbon, and highly positive for oxygen.

	Electronic charge	
	L-Histidine	β (Pyrazolyl-3)-L-alanine
O(1)	8·58	8·58
O(2)	8·54	8·54
N(1)	6·95	7·16
N(2)	7·31	7·25
N(3)	7·05	6·95
C(1)	5·53	5·51
C(2)	5·99	5·97
C(3)	5·96	5·98
C(4)	5·93	5·89
C(5)	5·79	5·92
C(6)	5·99	6·06

While the *trans* conformation about C(2)–C(3) places the bulkiest groups (carboxyl and imidazole) on opposite sides of the molecule, thereby reducing steric interference, there are several other conformations of equally low energy (Kistenmacher & Marsh, 1971). More stability of the type described by Ponnuswamy & Sasisekharan (1970), is obtained by the intramolecular, zwitterionic interaction between the O(1) and N(1) atoms, and also from the intramolecular hydrogen bond between the N(1) and N(2) atoms. In this conformation, N(2), the unprotonated nitrogen atom, is sterically hindered so that it cannot be approached by an electrophilic reagent without first a rotation of 120° around either C(2)–C(3) or C(3)–C(4). While such a rotation is energetically allowed for the free amino acid in solution, in a polypeptide, steric hindrance from spatially neighboring groups could prevent such a rotation, thereby chemically inactivating the imidazole residue.

We wish to thank Professor G. A. Jeffrey for the use of the facilities of the Crystallography Department. Thanks also go to Dr R. Shiono for programming assistance and to the University of Pittsburgh Computing Center for the use of its IBM 7090. We also thank Dr Robert Stewart, of Carnegie-Mellon U., for helping one of us (NCS) to perform the INDO calculations. This research is supported by Training Grant No. GM-01728 of the U.S. Public Health Service, National Institutes of Health, and by Grant Number L-71 of the Pittsburgh Health Research and Services Foundation.

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Acta Cryst. (1972). B**28**, 2382

The Crystal Structure of the Monoclinic Form of L-Histidine

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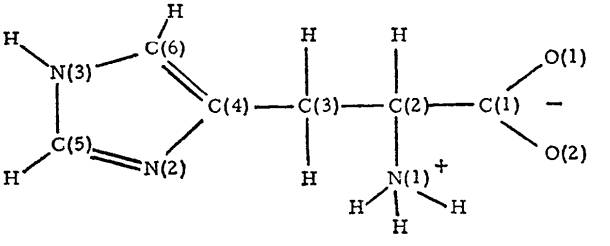
(*Received* 4 *October* 1971)

L-Histidine ($C_6N_3O_2H$) crystallizes from ethanol in the monoclinic space group $P2_1$, with $a=5{\cdot}172$, $b=7{\cdot}384$, $c=9{\cdot}474$ Å, $\beta=97{\cdot}162°$ and $Z=2$. The structure was solved simultaneously by independent investigations using the tangent formula and from a trial solution based on the structure of the orthorhombic form. The crystals show lamellar twinning, which arises from faults in the stacking of the imidazole residues such that there are two possible orientations of the unit cells. The structures could not be refined below an $R=0{\cdot}10$, but a comparison of the bond distances and angles with those of other free-base histidines shows no significant differences.

Introduction

Histidine, pictured below, and some of its isostructural analogs, have now been examined as free bases in a series of compounds which includes orthorhombic L-histidine (Madden, McGandy & Seeman, 1972), D,L-histidine (Edington, 1970), β-(pyrazoyl-3)-L-alanine (Seeman, McGandy & Rosenstein, 1972), and monoclinic L-histidine which is described in this paper and was studied independently and simultaneously at Edinburgh and Pittsburgh.



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