Acta Cryst. (1977). B33, 3902–3904

Cyclo-L-leucyl-L-histidyl Monohydrate

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(*Received* 6 *June* 1977; *accepted* 18 *July* 1977)

Abstract. $C_{12}H_{18}N_4O_2.H_2O$, orthorhombic, $P2_12_12_1$; $a = 29{\cdot}074$ (1), $b = 6{\cdot}017$ (1), $c = 8{\cdot}306$ (1) Å; $Z = 4$, D_m (flotation) = 1·225, $D_x = 1{\cdot}227$ g cm^{-3}; $R = 0{\cdot}039$ for 1185 non-zero reflections. The diketopiperazine ring deviates slightly from planarity, and has a flagpole boat form. The molecule is in a folded conformation with the imidazole ring facing the diketopiperazine ring.

Introduction. In view of the hydrolytic activities of the title compound and its isomer toward some hydrophobic esters, *e.g.* *p*-nitrophenyl laurate, the present study was undertaken in order to ascertain the molecular conformation, which had been suggested by an NMR study (Imanishi, Sugihara, Tanihara & Higashimura, 1975).

The rod-shaped crystal elongated along the *b* axis showed a clear cleavage perpendicular to the *a* axis. The intensity data were collected on a Hilger & Watts four-circle diffractometer with Ni-filtered Cu $K\alpha$ radiation. 1185 non-zero reflections for $\theta < 57°$ were collected in the ω–2θ scan mode. The specimen size was 0·3 × 0·1 × 0·1 mm. Lp corrections were made, but absorption was neglected [μ(Cu $K\alpha$) = 7·6 cm^{-1}].

The structure was solved by *MULTAN* (Germain, Main & Woolfson, 1971), and refinement was by the block-diagonal least-squares method with *HBLS* V (Ashida, 1973). All the H atoms were found on a difference map, and were included in the refinement with isotropic temperature factors; the non-hydrogen atoms were refined with anisotropic temperature factors. The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The weighting scheme was: $w = 0$ for $F_o = 0$, $w = 1$ for $|F_o| < 8$, and $w = (8/|F_o|)^2$ for $|F_o| > 8$. All the calculations were carried out on a FACOM 230-75 computer in Nagoya University. The final atomic coordinates are listed in Tables 1 and 2.*

* Lists of the temperature factors and structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32880 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *The atomic positional parameters with their e.s.d.'s in parentheses* (×10^4)

	x	*y*	*z*
C(1α)	640 (1)	3118 (4)	−1923 (3)
C(1β)	749 (1)	3132 (5)	−106 (3)
C(1γ)	643 (1)	944 (6)	745 (4)
C(1δ1)	837 (1)	1018 (9)	2466 (4)
C(1δ2)	136 (1)	368 (7)	750 (4)
C(1)	754 (1)	5349 (4)	−2620 (3)
N(1)	882 (1)	1319 (3)	−2747 (3)
O(1)	520 (1)	6993 (3)	−2221 (3)
C(2α)	1428 (1)	3799 (4)	−4078 (3)
C(2β)	1910 (1)	4298 (5)	−3413 (4)
C(2γ)	1933 (1)	4589 (5)	−1631 (4)
C(2δ2)	1881 (1)	6469 (5)	−749 (4)
C(2ε1)	2011 (1)	3668 (6)	854 (4)
C(2)	1257 (1)	1507 (4)	−3636 (3)
N(2)	1098 (1)	5520 (3)	−3671 (3)
N(2δ1)	2018 (1)	2827 (4)	−603 (3)
H(2ε2)	1929 (1)	5877 (5)	832 (3)
O(2)	1464 (1)	−134 (3)	−4166 (2)
O(*W*)	2099 (1)	9032 (5)	3352 (3)

Table 2. *Hydrogen positional parameters with their e.s.d.'s in parentheses* (×10^3)

	x	*y*	*z*	Bonded to
H(1)	78 (1)	−42 (7)	306 (5)	C(1δ1)
H(2)	118 (1)	119 (6)	228 (4)	
H(3)	68 (1)	237 (5)	308 (4)	
H(4)	6 (1)	−105 (7)	140 (4)	C(1δ2)
H(5)	−3 (1)	176 (6)	130 (4)	
H(6)	0 (1)	34 (6)	−33 (4)	
H(7)	85 (1)	−43 (7)	21 (4)	C(1γ)
H(8)	110 (1)	345 (5)	0 (4)	C(1β)
H(9)	55 (1)	436 (6)	37 (4)	
H(10)	31 (1)	285 (5)	−203 (3)	C(1α)
H(11)	77 (1)	−5 (6)	−257 (4)	N(1)
H(12)	119 (1)	688 (6)	−381 (4)	N(2)
H(13)	147 (1)	373 (5)	530 (3)	C(2α)
H(14)	212 (1)	306 (6)	−379 (4)	C(2β)
H(15)	201 (1)	577 (6)	−390 (4)	
H(16)	181 (1)	802 (6)	−109 (4)	C(2δ2)
H(17)	198 (1)	678 (6)	179 (4)	N(2ε2)
H(18)	209 (1)	296 (6)	189 (4)	C(2ε1)
H(19)	236 (1)	882 (6)	374 (4)	O(*W*)
H(20)	192 (1)	945 (6)	415 (4)	

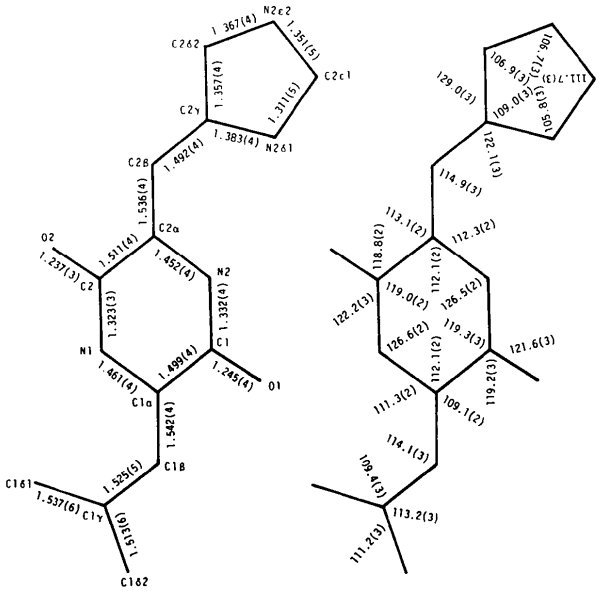

Fig. 1. Bond distances (Å) and angles (°).

Discussion. The bond distances and angles are shown in Fig. 1. The torsion angles are listed in Table 3, where the convention of the IUPAC–IUB Commission on Biochemical Nomenclature (1970) is used. An *ORTEP* (Johnson, 1965) drawing of the molecule is shown in Fig. 2. The crystal structure is shown in Fig. 3.

The imidazole ring is protonated at $N^{\varepsilon 2}$, and this tautomer is stabilized by the hydrogen-bond network in which water plays a part. The hydrogen bonds are listed in Table 4.

The diketopiperazine (DKP) ring has a rather flattened boat conformation, C(1α), and C(2α) lying 0·21 and 0·15 Å above the plane of N(1), N(2), C(1) and C(2). The two C^{β} atoms occupy the quasi-axial positions. Thus the conformation is described as 'flagpole boat' (Gawne, Kenner, Rogerts, Sheppard & Titlestad, 1968). The deviation of the DKP ring from planarity is one of the largest found among cyclic dipeptides with an arylmethyl side chain, such as *cyclo*(-L-Pro-L-Phe-) (Ramani, Venkatesan, Marsh & Kung, 1976), *cyclo*(-L-Thr-L-His-) (Cotrait, Ptak,

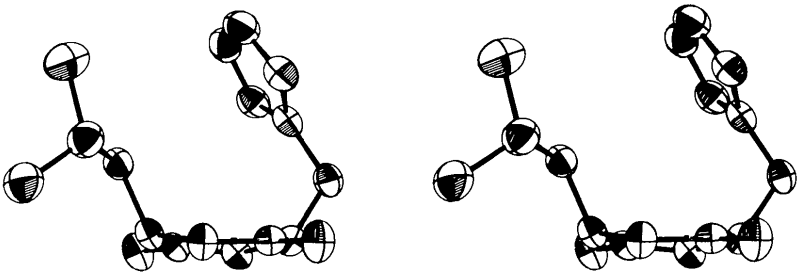

Fig. 2. A stereodrawing of one molecule.

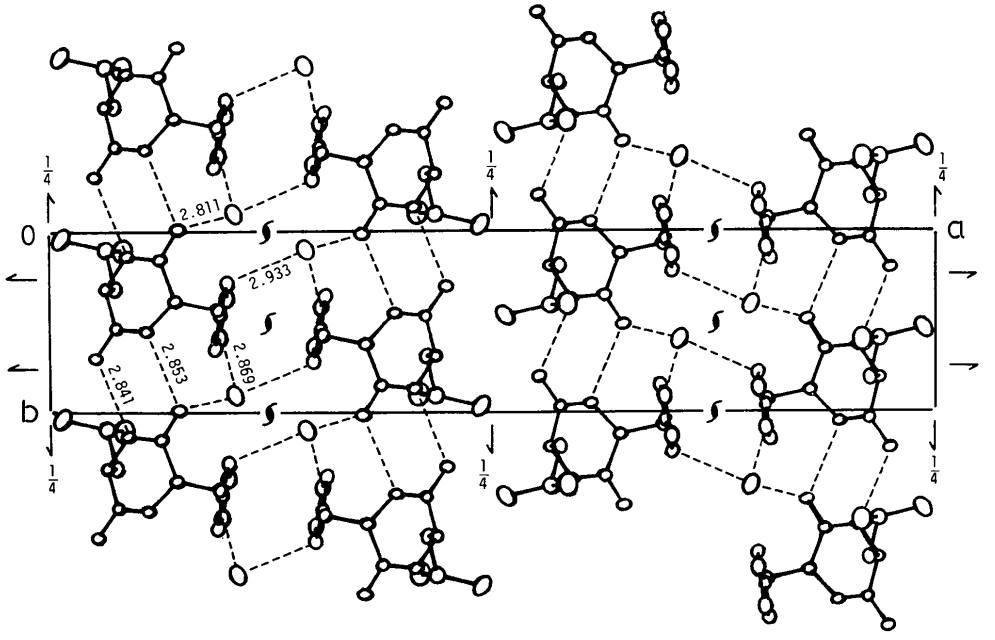

Fig. 3. Crystal structure viewed along the *c* axis.

Table 3. *Torsion angles*

φ_1	C(2)–N(1)–C(1α)–C(1)	20·2°
ψ_1	N(1)–C(1α)–C(1)–N(2)	−10·4
ω_1	C(1α)–C(1)–N(2)–C(2α)	−9·2
φ_2	C(1)–N(2)–C(2α)–C(2)	19·8
ψ_2	N(2)–C(2α)–C(2)–N(1)	−10·1
ω_2	C(2α)–C(2)–N(1)–C(1α)	−9·5
χ_1^1	N(1)–C(1α)–C(1β)–C(1γ)	−56·1
$\chi_1^{2,1}$	C(1α)–C(1β)–C(1γ)–C(1δ1)	170·8
$\chi_1^{2,2}$	C(1α)–C(1β)–C(1γ)–C(1δ2)	−64·6
χ_2^1	N(2)–C(2α)–C(2β)–C(2γ)	58·0
$\chi_2^{2,1}$	C(2α)–C(2β)–C(2γ)–N(2δ1)	90·9
$\chi_2^{2,2}$	C(2α)–C(2β)–C(2γ)–C(2δ2)	−89·3

Table 4. *Hydrogen bonds*

Donor Acceptor	$D\cdots A$	$H\cdots A$	$\angle DHA$
N(1)···O(1^{i})	2·841 Å	1·95 Å	177°
N(2)···O(2^{ii})	2·853	1·98	176
N(2ε2)···O(W)	2·869	1·91	168
O(W)···N(2δ1^{iii})	2·933	2·12	159
O(W)···O(2^{iv})	2·811	1·96	168

Symmetry code

(i)	$x, -1+y, z$	(iii)	$0{\cdot}5-x, 1-y, 0{\cdot}5+z$
(ii)	$x, 1+y, z$	(iv)	$x, 1+y, 1+z$

Busetta & Heitz, 1976), *cyclo*(-Gly-L-Tyr-) and *cyclo*-(-L-Ser-L-Tyr-) (Lin & Webb, 1973). The twisting of the two *cis* peptide bonds from planarity is also of significance.

The imidazole ring is folded over the DKP ring, the dihedral angle between the two ring planes being 57°. Such a conformation is common to several cyclic dipeptides containing Tyr or Phe residues. The maximum DKP–imidazole ring interaction has no unusual structural features and this is brought about by the torsion angles C^{α}–C^{β} and C^{β}–C^{γ} of His being close to the ideal values 60° and ±90° respectively. This structural feature is essentially the same as has been suggested by the NMR study (Imanishi, Sugihara, Tanihara & Higashimura, 1975). On the other hand, the torsion angle C^{α}–C^{β} of Leu, −56·1°, shows that the side chain is kept away from either DKP or the imidazole ring. This suggests that the DKP–imidazole ring attractive interaction is stronger than the hydrophobic DKP–Leu side-chain interaction.

The present conformation is essentially different from that of *cyclo*(-L-Thr-L-His-) (Cotrait *et al.*, 1976), in which a water links O^{γ} of Thr to $N^{\delta 1}$ of His *via* hydrogen bonds and plays a key role in determining the molecular conformation. Owing to the presence of this water bridge, both the Thr and His side chains are kept away from the DKP ring, and no direct DKP–imidazole ring contact is observed.

The authors express their sincere thanks to Professors T. Higashimura and Y. Imanishi of Kyoto University for their helpful advice and discussions. We also thank Professor J. Tanaka of Nagoya University for the use of a diffractometer.

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