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Histidyl Conformations and Short N—H···N Hydrogen Bonds: Structure of D,L-Histidyl-L,D-histidine Pentahydrate

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Abstract

D,L-Histidyl-L,D-histidine pentahydrate, $C_{12}H_{16}N_6O_3.5H_2O$, $M_r = 382{\cdot}38$, $F(000) = 408$, crystallizes in the monoclinic space group Pc with the cell dimensions $a = 9{\cdot}971\ (2)$, $b = 4{\cdot}745\ (2)$, $c = 19{\cdot}572\ (3)$ Å and $\beta = 96{\cdot}08\ (1)°$, $V = 920{\cdot}6$ Å^3, $Z = 2$, $D_x = 1{\cdot}379$ g cm^{-3}, $\mu = 1{\cdot}083$ cm^{-1}, $T = 295$ K, Mo $K\alpha$, $\lambda = 0{\cdot}71073$ Å. Final R (on F) = 0·040 for 1658 observed reflections with $I \geq 3\sigma(I)$. This dipeptide crystallizes in a zwitterionic form with protonation of the C-terminal imidazole ring. Both histidine units exist in the g^+ or 'closed' conformation with Cα—Cβ torsion angles of 67·2 (3) and 63·6 (3)°. Principal torsion angles, $\omega = 176{\cdot}8\ (2)$, $\psi_1 = 161{\cdot}8\ (3)$ and $\varphi_2 = -152{\cdot}1\ (3)°$, are indicative of a highly extended *trans* conformation. Intramolecular hydrogen bonding occurs between the imidazole rings [N2*D*—H2*D*1···N1*D* = 2·724 (4) Å]. Intermolecular hydrogen bonding occurs between symmetry-related histidine molecules forming chains along the y axis and includes another short [2·764 (4) Å] N—H···N interaction. The five water molecules occupy channels between adjacent histidine layers.

Introduction

Histidine, an important constituent of proteins which is frequently encountered in the active site of enzymes, has been studied extensively because of the ability of the imidazole moiety to act as a proton donor, proton acceptor or nucleophilic agent (Madden, McGandy & Seeman, 1972). Secondly, the histidine unit has been observed to exist in two molecular conformations, termed 'open' or 'closed' (Kistenmacher, Hunt & Marsh, 1972).

Conformational aspects of histidine are of interest since several conformations are possible for this residue in peptides and proteins. Here, we report the molecular structure of the racemic dipeptide, D,L-histidyl-L,D-histidine pentahydrate (His-His).

Experimental

D,L-Histidyl-L,D-histidine was kindly supplied by Dr K. Kopple (SmithKline Beecham Pharmaceuticals). Colorless plates were grown by slow evaporation of an aqueous ethanol solution.

For X-ray examination and data collection, a crystal of approximate dimensions 0·40 × 0·08 × 0·20 mm was mounted on a glass fiber with epoxy resin. Intensity data were collected at room temperature on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromated Mo $K\alpha$ radiation. Lattice parameters were obtained by least-squares refinement of the angular settings for 25 reflections lying in the 2θ range 30–34°. Intensity data (2624 reflections) were collected using variable speed ω–2θ scans with $2 \leq 2\theta \leq 56°$ under the following conditions: $0 \leq h \leq 13$, $0 \leq k \leq 6$, $-25 \leq l \leq 25$. Three standard reflections ($\bar{5}33$, $2,\bar{1},13$, $\bar{2}3\bar{9}$) monitored every 3 h of X-ray exposure time showed non-systematic intensity changes of −2·1%; no correction for deterioration was made. Symmetry-equivalent data were averaged, $R_{int} = 2{\cdot}7\%$ (on I), the 2222 unique reflections were corrected for Lorentz and polarization effects.

The structure was solved by a combination of direct methods with *SHELXS*86 (Sheldrick, 1985)

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Table 1. *Positional parameters and e.s.d.'s for histidylhistidine*

Anisotropically refined atoms are given in the form of the equivalent isotropic displacement parameter defined as $(8\pi^2/3) \times \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	B (Å^2)
O1	0·144	0·3803 (5)	0·380	2·57 (4)
O′	−0·1544 (3)	0·8568 (6)	0·5414 (1)	3·18 (5)
O″	−0·1373 (2)	1·0786 (5)	0·4431 (1)	2·71 (4)
N1	0·2632 (3)	0·6042 (6)	0·2719 (1)	2·54 (5)
N2	0·0931 (2)	0·8056 (5)	0·4221 (1)	1·82 (4)
N1*D*	0·4449 (3)	0·6127 (7)	0·4689 (1)	2·85 (6)
N2*D*	0·2971 (3)	0·8363 (7)	0·5649 (1)	2·70 (5)
N1*E*	0·6194 (3)	0·3892 (7)	0·4352 (2)	2·79 (6)
N2*E*	0·2542 (3)	1·0647 (7)	0·6553 (2)	3·13 (6)
C1′	0·1542 (3)	0·6388 (6)	0·3796 (2)	1·58 (5)
C2′	−0·1035 (3)	0·8923 (7)	0·4865 (2)	1·94 (5)
C1*A*	0·2373 (3)	0·7886 (6)	0·3293 (2)	1·75 (5)
C2*A*	0·0057 (3)	0·6827 (7)	0·4696 (2)	1·77 (5)
C1*B*	0·3704 (3)	0·9080 (7)	0·3650 (2)	2·23 (6)
C2*B*	0·0871 (3)	0·5540 (7)	0·5331 (2)	2·19 (6)
C1*D*	0·5703 (3)	0·5593 (8)	0·3815 (2)	2·65 (6)
C2*D*	0·1416 (4)	0·9048 (8)	0·6343 (2)	2·78 (6)
C1*E*	0·5419 (4)	0·428 (1)	0·4858 (2)	3·27 (8)
C2*E*	0·3441 (4)	1·018 (1)	0·6128 (2)	3·46 (8)
C1*G*	0·4621 (3)	0·6973 (7)	0·4021 (2)	1·98 (5)
C2*G*	0·1686 (3)	0·7582 (7)	0·5773 (2)	2·11 (6)
O*W*1	0·5935 (3)	0·0769 (7)	0·2467 (2)	4·76 (7)
O*W*2	−0·2002 (3)	1·3612 (6)	0·6098 (1)	3·64 (6)
O*W*3	−0·1361 (3)	0·1125 (8)	0·3019 (2)	4·79 (7)
O*W*4	−0·0507 (3)	0·6130 (7)	0·2406 (2)	4·68 (7)
O*W*5	0·5683 (3)	1·4282 (7)	0·6749 (2)	5·04 (8)

and the difference Fourier technique, and refined by full-matrix least squares. Non-H atoms were refined with isotropic displacement parameters, then with anisotropic displacement parameters. H-atom positions, including those for the waters, were located from difference Fourier maps. H-atom coordinates were fixed at their located positions along with isotropic displacement parameters assigned as $1{\cdot}3U$. The refinement converged $[(\Delta/\sigma)_{max} < 0{\cdot}005]$ to values of the standard crystallographic agreement factors of $R = 0{\cdot}040$, $wR = 0{\cdot}051$ and $S = 1{\cdot}140$ for 1658 observations with $I \geq 3\sigma(I)$ and 233 parameters. Weights were assigned to the data as $w = 1/s^2(F)$ with $s^2F = [\sigma^2(I_c) + (0{\cdot}06F_o)^2]$. Scattering factors were from *International Tables for X-ray Crystallography* (1974, Vol. IV) except for H atoms (Stewart, Davidson & Simpson, 1965). The effects of anomalous dispersion for non-H atoms were included. A final difference map showed $(\Delta\rho)_{max} = 0{\cdot}220$, $(\Delta\rho)_{min} = -0{\cdot}194$ e Å^{-3}. Final atomic positional and equivalent isotropic thermal parameters for the non-H atoms are collected in Table 1.* All programs used were from the locally modified Enraf–Nonius (1979) *SDP*.

* Lists of H-atom positions, anisotropic displacement parameters, torsion angles, least-squares planes and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53909 (24 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion

The molecular structure of D,L-histidyl-L,D-histidine pentahydrate is shown in Fig. 1. The unit-cell packing diagram is given in Fig. 2. Principal bond distances and bond angles are collected in Tables 2 and 3, respectively.

D,L-Histidyl-L,D-histidine pentahydrate crystallizes in a zwitterionic form with protonation of the C-terminal imidazole ring. An intramolecular hydrogen bond exists between the two imidazole rings, N2*D*—H2*D*1···N1*D* = 2·724 (4) Å and 168°, and is consistent with the study by Gorbitz (1989) on hydrogen bonding in amino acids and peptides [for hydrogen bonding of the type His-N(π)···H—N: N···N = 2·886–3·045, N···H = 1·73–2·15 Å, N—H···N = 161·3–177·5°]. The shorter N···N distance observed here results from the involvement of protonated

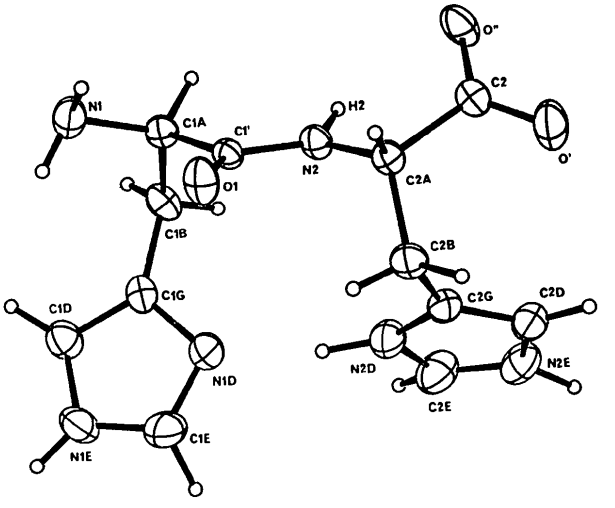

Fig. 1. *ORTEP* drawing of histidylhistidine showing 50% thermal ellipsoid probability for the non-H atoms, H atoms as small spheres of arbitrary size and atomic labeling scheme.

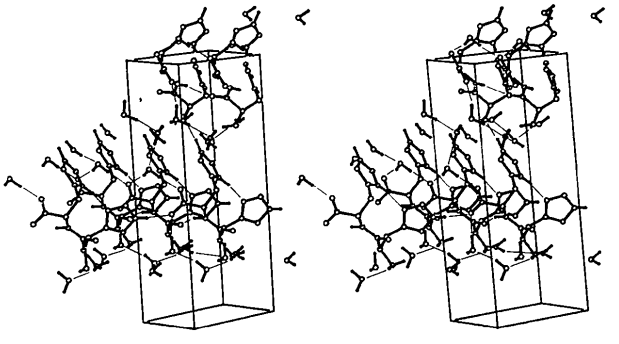

Fig. 2. Stereo unit-cell drawing of histidylhistidine indicating both intra- and intermolecular hydrogen bonding. Hydrogen bonding interactions are indicated by single lines. The *a* axis is along the horizontal at a rotation of 50° while the *c* axis runs vertically.

Table 2. *Principal bond distances* (Å) *for histidylhistidine with e.s.d.'s in parentheses*

O1—C1′	1·231 (4)	N1*E*—C1*E*	1·333 (5)
O′—C2′	1·247 (4)	N2*E*—C2*D*	1·381 (5)
O″—C2′	1·247 (4)	N2*E*—C2*E*	1·305 (5)
N1—C1*A*	1·467 (4)	C1′—C1*A*	1·527 (4)
N2—C1′	1·342 (4)	C2′—C2*A*	1·536 (4)
N2—C2*A*	1·461 (4)	C1*A*—C1*B*	1·542 (4)
N1*D*—C1*E*	1·322 (5)	C2*A*—C2*B*	1·537 (4)
N1*D*—C1*G*	1·394 (4)	C1*B*—C1*G*	1·490 (5)
N2*D*—C2*E*	1·322 (5)	C2*B*—C2*G*	1·482 (5)
N2*D*—C2*G*	1·380 (4)	C1*D*—C1*G*	1·360 (4)
N1*E*—C1*D*	1·374 (5)	C2*D*—C2*G*	1·365 (5)

Table 3. *Principal bond angles* (°) *for histidylhistidine with e.s.d.'s in parentheses*

C1′—N2—C2*A*	120·0 (2)	N2—C2*A*—C2*B*	111·9 (2)
C1*E*—N1*D*—C1*G*	105·5 (3)	C2′—C2*A*—C2*B*	114·2 (2)
C2*E*—N2*D*—C2*G*	108·4 (3)	C1*A*—C1*B*—C1*G*	115·4 (3)
C1*D*—N1*E*—C1*E*	107·5 (3)	C2*A*—C2*B*—C2*G*	114·9 (3)
C2*D*—N2*E*—C2*E*	108·0 (3)	N1*E*—C1*D*—C1*G*	106·6 (3)
O1—C1′—N2	122·5 (3)	N2*E*—C2*D*—C2*G*	107·4 (3)
O1—C1′—C1*A*	121·5 (3)	N1*D*—C1*E*—N1*E*	111·8 (3)
N2—C1′—C1*A*	116·0 (2)	N2*D*—C2*E*—N2*E*	110·3 (3)
O′—C2′—O″	125·2 (3)	N1*D*—C1*G*—C1*B*	121·3 (3)
O′—C2′—C2*A*	117·4 (3)	N1*D*—C1*G*—C1*D*	108·7 (3)
O″—C2′—C2*A*	117·3 (3)	C1*B*—C1*G*—C1*D*	130·1 (3)
N1—C1*A*—C1′	111·5 (2)	N2*D*—C2*G*—C2*B*	122·3 (3)
N1—C1*A*—C1*B*	110·7 (3)	N2*D*—C2*G*—C2*D*	105·9 (3)
C1′—C1*A*—C1*B*	112·2 (2)	C2*B*—C2*G*—C2*D*	131·8 (3)
N2—C2*A*—C2′	111·2 (2)		

histidine. The carboxyl group is ionized with C2′—O′ = 1·247 (4), C2′—O″ = 1·247 (4) Å and O′—C2′—O″ = 125·3 (3)°. These values are consistent with other terminal histidine residues (average values C—O′ = 1·243, C—O″ = 1·252 Å and O′—C—O″ = 126·3°) (Averbuch-Pouchot, Durif & Guitel, 1988; Edington & Harding, 1974; Kistenmacher, Hunt & Marsh, 1972; Lehmann, Koetzle & Hamilton, 1972; Madden, McGandy & Seeman, 1972; Madden, McGandy, Seeman, Harding & Hoy, 1972; Oda & Koyama, 1972; Bennett, Davidson, Harding & Morelle, 1970).

The bond distances and angles for the protonated imidazole ring are comparable to those found in the imidazolium cation (Blessing, 1986) or other histidinium cations (Averbuch-Pouchot, Durif & Guitel, 1988; Roman, Gutierrez-Zorrilla, Luque & Vegas, 1987; Blessing, 1986; Herbstein & Kapon, 1979; Fuess, Hohlwein & Mason, 1977; Oda & Koyama, 1972; Bennett, Davidson, Harding & Morelle, 1970; Donohue & Caron, 1964). The non-protonated imidazole ring has distances and angles comparable to imidazole (Martinez-Carrera, 1966) or other neutral histidine residues (Edington & Harding, 1974; Lehmann, Koetzle & Hamilton, 1972; Madden, McGandy & Seeman, 1972; Madden, McGandy, Seeman, Harding & Hoy, 1972). The differences observed in the Nε—Cε bonds [N1*E*—C1*E* = 1·333 (4) and N2*E*—C2*E* = 1·305 (4) Å] and the Nδ, Cε and Cγ angles [C1*E*—N1*D*—C1*G* = 105·5 (3), C2*E*—N2*D*—C2*G* = 108·4 (3), N1*D*—C1*E*—N1*E* = 111·8 (3), N2*D*—C2*E*—N2*E* = 110·3 (3), N1*D*—C1*G*—C1*D* = 108·7 (3) and N2*D*—C2*G*—C2*D* = 105·9 (3)°] between the protonated and the non-protonated rings reflect the aromaticity of the former. Both imidazole rings are planar.

The main chain of D,L-histidyl-L,D-histidine may be described as a highly extended *trans* conformation. The principal torsion angles as defined by the IUPAC–IUB Commission on Biochemical Nomenclature (1970) are $\omega = 176{\cdot}8\ (2)$, $\psi_1 = 161{\cdot}8\ (3)$ and $\varphi_2 = -152{\cdot}1\ (3)°$. The side-chain torsion angles are 67·2 (3) and 63·6 (3)° for the N- and C-terminal residues, respectively, for χ^1 defined as N—Cα—Cβ—Cγ.

Conformational aspects of the imidazole side chain are of interest since several low-energy conformations are possible; however, statistical studies (Ashida, Tsunogae, Tanaka & Yamane, 1987; Ponder & Richards, 1987; Benedetti, Morelli, Nemethy & Scheraga, 1983; Bhat, Sasisekharan & Vijayan, 1979; Janin, Wodak, Levitt & Maigret, 1978; Finkelstein & Ptitsyn, 1977) indicate that all histidine residues may be classified in three distinct groups depending on the interactions between the Cγ methylene and the neighboring peptide groups. Side-chain conformations are denoted as g^+, t and g^- (Fig. 3) corresponding to $\chi^1 = +60$, 180 and $-60°$,

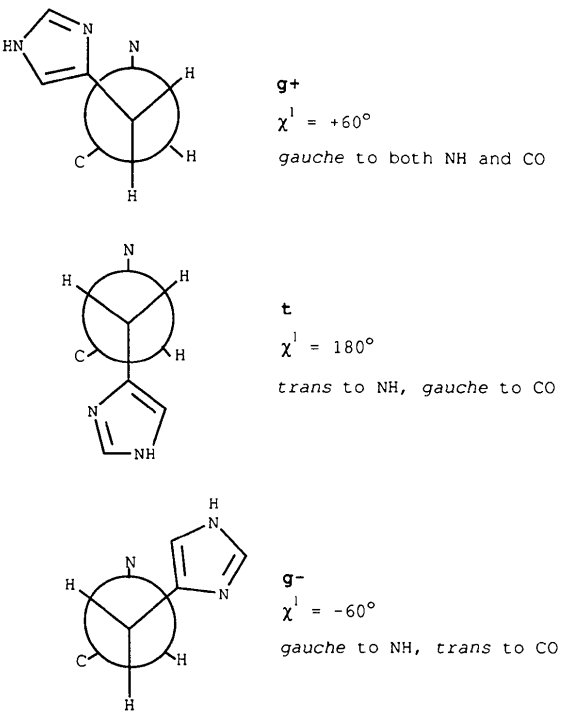

Fig. 3. Newman projections down the Cβ—Cα bond of the side-chain conformations g^+, t and g^+ corresponding to $\chi_1 = +60$, 180 and $-60°$, respectively.

Table 4. *Comparison of torsion angles* (°) *for various histidines*

χ^1 = N—Cα—Cβ—Cγ, χ = C′—Cα—Cβ—Cγ, χ^{21} = Cα—Cβ—Cγ—Nδ, χ^{22} = Cα—Cβ—Cγ—Cδ.

Compound		ω	ψ	φ	χ^1	χ	χ^{21}	χ^{22}
D,L-His-L,D-His[a]	(N-terminal)	176·9 (2)	161·8 (3)	−152·1 (3)	67·2 (3)	−58·1 (4)	83·4 (4)	−97·0 (4)
	(C-terminal)				63·6 (3)	−63·9 (3)	−86·0 (4)	93·8 (4)
L-*N*-Ac-His.H_2O[b]	(*A*)	172·2	−19·2	−152·0	79·6	−44·0	−75·6	97·6
	(*B*)	−174·8	−14·9	−80·2	−62·6	172·3	−87·0	92·1
L-His.L-Asp.H_2O[c]	(*A*)		−25·7		167·0	47·5	76·4	−99·4
	(*AS*)		−32·0		167·6	49·7	77·7	−100·5
	(*B*)		−8·0		64·7	−61·2	−120·4	58·2
	(*BS*)		−12·1		60·9	−68·0	−119·6	63·4
L-Met-Glu-His-Phe.H_2O[d]		174·5	171·2	−171·7	55·8	−62·4	73·8	−103·3
L-Pyro-Glu-L-His[e]		173·3	138·7	−80·6	−177·9	61·7	56·7	−127·6
L-His-L-Ser:Gly-L-Gln.$6H_2O$[f]		173·5	128·1	−135·9	−70·9	169·0	77·8	−100·2
N-Ac-L-His-NHMe[g]		175·2 (ω_1)	155·6	−71·6	−58·5	179·1	−55·5	124·6
N-Ac-His-NH_2[h]		177·1	153·2	−70·9	−60·0	177·3	−54·2	126·8
β-Ala-His[i]		174·9	130·5	−92·9	−178·7	60·7	62·3	−119·1
Boc-Pro-His-NHMe[j]		176·8 (ω_1)	−19·6	−70·4	59·9		−86·1	94·6
Boc-Pro-His(π-Me)NHMe[j]		−178·4 (ω_1)	29·8	−118·3	−46·0	−171·2	−72·7	103·1
Boc-Pro-His(τ-Me)NHMe[j]		−179·8 (ω_1)	7·4	−90·8	58·8	−68·5	−48·6	136·4
[Boc-Pro-His-NHMe][PF_6][j]		176·6 (ω_1)	159·5	131·0	−74·4	168·9	69·6	
L-His(orthorhombic)[k]			155·1 (ψ_2)		−59·2	179·8	56·8	−123·2
L-His(monoclinic)[l]			154·4 (ψ_2)		−61·7	179·8	58·0	−122·9
DL-His[m]			170·7 (ψ_2)		−86·7	150·9	−68·1	114·1
L-His.HCl.H_2O[n]			179·5 (ψ_2)		71·5	−52·1		61·1
DL-His.HCl.$2H_2O$[o]			162·6 (ψ_2)		−61·9	179·4	−70·6	107·7
L-His.H_3PO_4[p]			158·4 (ψ_2)		−68·0	172·7	−75·6	104·2
L-His.TMA[q]			150·5 (ψ_2)		−63·3	177·5	87·6	−89·6
L-His.$HClO_4$[r]			161·6 (ψ_2)		−60·4	176·8	−49·7	132·2

Notes: (*a*) This work. For comparison purposes, all torsion angles have been referred to a common L-configuration. (*b*) Kistenmacher, Hunt & Marsh (1972). (*c*) Bhat & Vijayan (1978). (*d*) Admiraal & Vos (1983). (*e*) Cotrait & Allard (1973). (*f*) Suresh & Vijayan (1985). (*g*) Harada & Iitaka (1977). (*h*) Pfeiffer, Reck & Oehlke (1985). (*i*) Itoh, Yamane, Ashida & Kakudo (1977). (*j*) Aubry, Vlassi & Marraud (1986). (*k*) Madden, McGandy & Seeman (1972). (*l*) Madden, McGandy, Seeman, Harding & Hoy (1972). (*m*) Edington & Harding (1974). (*n*) Donohue & Caron (1964). (*o*) Bennett, Davidson, Harding & Morelle (1970). (*p*) Blessing (1986). (*q*) Herbstein & Kapon (1979). (*r*) Roman, Gutierrez-Zorrilla, Luque & Vegas (1987).

respectively, with g^- corresponding to the sterically most favored and g^+ the sterically least favored conformation. In the nomenclature proposed by Bhat & Vijayan (1978) these conformations are termed 'closed', 'open II' and 'open I', respectively, based on the torsion angle N—Cα—Cβ—Cγ denoted here as χ^1. In Table 4 several histidine-containing structures are compared according to torsion angles and indeed the structures fall into these three distinct conformations. Both side chains of histidylhistidine exist in the 'closed' or g^+ conformation which places the imidazole ring *gauche* to both the carbonyl and amino groups. This otherwise energetically unfavorable juxtaposition may be facilitated through formation of the intramolecular N—H···N hydrogen bond (see above). It should be noted that in nomenclature first proposed by Kistenmacher, Hunt & Marsh (1972) they use the torsion angle C′—Cα—Cβ—Cγ to describe their 'closed' ($\chi = \pm 60°$) and 'open' ($\chi = 180°$) conformations. This designation does not change the classification of the histidylhistidine presented here; however, it would change the classification of several histidines as listed in Table 4. It is recommended that the g^+, t, g^- designations based on the N—Cα—Cβ—Cγ torsion angle be used exclusively, rather than the 'open/closed' designations based on either χ^1 or χ, to avoid future discrepancies in histidine classifications.

Bhat, Sasisekharan & Vijayan (1979) and Benedetti, Morelli, Nemethy & Scheraga (1983) have also suggested, based on the χ^2 angles of a combined set of phenylalanine, tyrosine, tryptophan and histidine structures, assuming twofold symmetry about the Cβ—Cγ bond and neglecting any hydrogen-bonding interactions, that the magnitude of the torsion angle χ^2 is correlated with χ^1 as follows: when $\chi^1 = +60°$ then χ^2 is centered around 90°, for $\chi^1 = 180$ or $-60°$ then χ^2 is either less than 90 or greater than 90°, respectively. The side-chain torsion angles of histidylhistidine [$\chi^1 = 67·2$ (3), $\chi^{21} = 83·4$ (4), $\chi^{22} = -97·0$ (4)° for the N-terminal residue and $\chi^1 = 63·6$ (3), $\chi^{21} = -86·0$ (4), $\chi^{22} = 93·8$ (4)° for the C-terminal residue] are consistent with the correlation. It is not surprising that the torsion angles are clustered around ±90° since this is a minimum-energy conformation. In this conformation the ring is perpendicular to the plane defined by the Cα, Cβ and Cγ atoms and is parallel to the plane defined by the main-chain atoms N, Cα and C′.

The generalization inherent in previous surveys may mask differences in the range of values adopted by χ^{21} and χ^{22} which arise as a result of the type of ring bonded to Cβ. Examination of the torsion angles in the histidine-containing structures collected in Table 4 indicates a wider range of values for χ^{21} (−48·6 to −120·4 and 56·7 to 87·6°) and χ^{22} (−89·6 to −123·2 and 58·2 to 136·4°) as compared to χ^1 (−46·0 to −86·7, 55·8 to 79·6 and 167·0 to 178·7°). Greater scatter in the χ^2 angles arises from decreased steric interactions of the ring as a result of its increased distance from the main chain. Differences occurring between χ^{21} and χ^{22} may be attributed to

Table 5. *Intermolecular hydrogen-bonding interactions* (Å, °)

				Symmetry operation
N1···O*W*4	3·124 (4)	N1—H12···O*W*4	136	1, 000
H12···O*W*4	2·36			
N2···O1	2·907 (3)	N2—H2···O1	146	1, 0−10
H2···O1	2·08			
N1*E*···O″	2·828 (3)	N1*E*—H1*E*1···O″	172	1, 1−10
H1*E*1···O″	1·96			
N2*E*···N1	2·764 (4)	N2*E*—H2*E*2···1	171	2, 020
H2*E*2···N1	1·76			
O*W*1···O*W*3	2·801 (4)	O*W*1—H*W*11···O*W*3	176	1, 100
H*W*11···O*W*3	1·77			
O*W*1···O*W*5	2·777 (4)	O*W*1—H*W*12···O*W*5	162	2, 01−1
H*W*12···O*W*5	1·99			
O*W*2···O′	2·768 (4)	O*W*2—H*W*21···O′	166	1, 0−10
H*W*21···O′	1·91			
O*W*2···O′	2·803 (4)	O*W*2—H*W*22···O′	169	1, 000
H*W*22···O′	1·88			
O*W*3···O″	2·769 (4)	O*W*3—H*W*31···O″	167	1, 010
H*W*31···O″	1·82			
O*W*3···O*W*4	2·832 (4)	O*W*3—H*W*32···O*W*4	171	1, 000
H*W*32···O*W*4	1·86			
O*W*4···O*W*2	2·826 (4)	O*W*4—H*W*41···O*W*2	175	2, 020
H*W*41···O*W*2	1·95			
O*W*4···O*W*3	2·827 (4)	O*W*4—H*W*42···O*W*3	163	1, 010
H*W*42···O*W*3	1·96			
O*W*5···O*W*2	2·770 (4)	O*W*5—H*W*51···O*W*2	174	1, 100
H*W*51···O*W*2	1·85			
O*W*5···O*W*1	2·735 (5)	O*W*5—H*W*52···O*W*1	167	2, 020
H*W*52···O*W*1	1·84			

the geometry of the imidazole ring, which lacks twofold symmetry, to the smaller size of the imidazole ring as compared to phenyl, and to the hydrogen-bonding interactions of the nitrogen atoms (Benedetti, Morelli, Nemethy & Scheraga, 1983).

Intermolecular hydrogen bonding (Table 5) occurs between the amide group of symmetry-related molecules [N2—H2···O1 = 2·907 (3) Å and 146°] along the *y* axis and between the imidazole nitrogen, N1*E*, and the carboxyl oxygen, O″ [N1*E*—H1*E*1···O″ = 2·828 (4) Å and 172°]. The imidazole ring also participates in an N—H···N hydrogen bond with the amine nitrogen, N1 [N2*E*—H2*E*2···N1 = 2·764 (4) Å and 171°]. The N—H···N hydrogen bond in histidylhistidine is similar to that in 5-fluorouracil-9-ethylhypoxanthine (N—H···N = 2·73 Å) (Kim & Rich, 1967) but is rather short when compared to other N—H···N interactions (2·90–3·0 Å) (Voet & Rich, 1970; Prasad & Govil, 1980). This short distance indicates a strong interaction on the same order as N—H···O or O—H···O interactions, even though it is generally thought that N—H···N bonds are weaker. In addition, hydrogen-bonding interactions occur between the carboxyl oxygen, O′, and O*W*2 [O*W*2—H*W*21···O′ = 2·768 (4) Å and 166°; O*W*2—H*W*22···O′ = 2·803 (4) Å and 169°] and also between the amine nitrogen, N1, and O*W*4 [N1—H12···O*W*4 = 3·124 (4) Å and 136°].

An extensive network of hydrogen-bonding interactions also exists between the five water molecules which occupy channels in the *xy* plane of the crystal lattice as indicated in Fig. 2. Closer examination of the hydrogen-bonding patterns of the water molecules indicates that bonding in the *x* direction occurs between O*W*3—O*W*1—O*W*5—O*W*2—O*W*4 and in the *y* direction between O*W*4—O*W*3—O*W*1 and O*W*5—O*W*1—O*W*2 to form sheets in the *xy* plane. The bonding with respect to the individual water molecules may be classified as type I*A* and type II*A* according to Jeffrey & Maluszynska (1990). Type I*A* water participates in a three-center bond (an acceptor for one hydrogen bond and a donor for two hydrogen bonds), whereas type II*A* has water in a four-center bond (two acceptor hydrogen bonds and two donor hydrogen bonds). In this structure, O*W*1 and O*W*5 both participate in type I*A* while O*W*2, O*W*3 and O*W*4 participate in type II*A* bonding. The bond distances and angles observed range from 2·735–2·832 Å and 163–176°, respectively, and fall within normal ranges for O—H···O interactions (Mitra & Ramakrishnan, 1977). It has generally been observed that water molecules which accept one hydrogen bond (type I*A*) are more common than those that accept two hydrogen bonds (type II*A*) by a factor of 1·4 (Jeffrey & Maluszynska, 1990). It is interesting to note that in histidylhistidine type II*A* hydrogen bonds favor type I*A* hydrogen bonds by a factor of 1·3.

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Structural Comparison of a *gem*-Dichlorodiarylcyclopropane Antiestrogen and Three of its Derivatives

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Abstract

The pure antiestrogenic activity of compound (1) gave the impetus to synthesize a series of its derivatives (2)–(4). Structural features of these compounds are compared. Compound (1): 1,1-dichloro-*cis*-2,3-diphenylcyclopropane, $C_{15}H_{12}Cl_2$, $M_r = 263{\cdot}2$, orthorhombic, *Pbca*, $a = 19{\cdot}627$ (7), $b = 19{\cdot}460$ (6), $c = 6{\cdot}670$ (2) Å, $V = 2547{\cdot}5$ Å^3, $Z = 8$, $D_x = 1{\cdot}372$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, μ(Mo $K\alpha$) = 4·3 cm^{-1}, $F(000) = 1088$, $T = 138$ K, $R = 0{\cdot}026$ for 1923 observed reflections. Compound (2): 1,1-dichloro-*cis*-2,3-bis(4-methoxyphenyl)cyclopropane, $C_{17}H_{16}Cl_2O_2$, $M_r = 323{\cdot}2$, monoclinic, $P2_1/c$, $a = 16{\cdot}540$ (1), $b = 7{\cdot}4749$ (7), $c = 12{\cdot}333$ (3) Å, $\beta = 91{\cdot}53$ (2)°, $V = 1524{\cdot}2$ Å^3, $Z = 4$, $D_x = 1{\cdot}408$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, μ(Cu $K\alpha$) = 37·0 cm^{-1}, $F(000) = 672$, $T = 163$ K, $R = 0{\cdot}031$ for 2919 observed reflections. Compound (3): 1,1-dichloro-*cis*-2-(4-benzyloxyphenyl)-3-phenylcyclopropane, $C_{22}H_{18}Cl_2O$, $M_r = 369{\cdot}3$, monoclinic, $P2_1/a$, $a = 21{\cdot}064$ (3), $b = 14{\cdot}749$ (2), $c = 5{\cdot}8222$ (8) Å, $\beta = 95{\cdot}48$ (2)°, $V = 1800{\cdot}5$ Å^3, $Z = 4$, $D_x = 1{\cdot}362$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, μ(Cu $K\alpha$) = 31·5 cm^{-1}, $F(000) = 768$, $T = 163$ K, $R = 0{\cdot}032$ for 3256 observed reflections. Compound (4): 1,1-dichloro-*trans*-2-(4-acetoxyphenyl)-3-phenylcyclopropane, $C_{17}H_{14}Cl_2O_2$, $M_r = 321{\cdot}2$, monoclinc, $P2_1/n$, $a = 16{\cdot}555$ (4), $b = 12{\cdot}297$ (2), $c = 7{\cdot}439$ (1) Å, $\beta = 98{\cdot}31$ (2)°, $V = 1498{\cdot}5$ Å^3, $Z = 4$, $D_x = 1{\cdot}423$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, μ(Mo $K\alpha$) = 3·8 cm^{-1}, $F(000) = 664$, $T = 163$ K, $R = 0{\cdot}034$ for 2474 observed reflections. The crystal structure determinations show that the relative conformation of the two aryl rings in all four structures are quite similar. In this conformation one of the phenyl rings is in a

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