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X-ray studies on crystalline complexes involving amino acids and peptides. XXXIX. Crystal structures of malonic acid complexes of DL- and L-histidine. Preservation of aggregation pattern on reversal of chirality

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The malonic acid complexes of DL- and L-histidine are made up of zwitterionic positively charged histidinium ions and semimalonate (hydrogen malonate) ions. They crystallise in space groups $P2_1/n$ and $P2_1$, respectively, with nearly the same unit-cell parameters. The molecules aggregate in the two complexes in a remarkably similar manner. The two sets of crystallographically independent molecules are related by a pseudo-glide plane. This pseudo-symmetry is almost exact except in the case of the α-carboxylate group and, to some extent, the α-C and the α-N atoms. Preservation of the aggregation pattern to such an extent on the reversal of chirality of half the amino-acid molecules is observed for the first time in amino-acid complexes. This is achieved at the cost of considerable conformational strain in one of the two histidinium ions in the L-histidine complex.

1. Introduction

The programme on crystalline complexes involving amino acids and peptides being pursued in this laboratory (Saraswathi & Vijayan, 2001, and references therein) was originally meant for elucidating the geometrical features of biologically relevant interactions at atomic resolution. It was subsequently realised that the results of the work on the complexes have implications for chemical evolution and the origin of life as well (Vijayan, 1980, 1988). Since then, the approach involving the complexes has provided interesting insights into the role of molecular interactions and aggregation in prebiotic polymerisation, chiral discrimination and self-assembly. The current focus of the programme is on complexes of amino acids and peptides with carboxylic acids believed to have existed in the prebiotic milieu or those similar to them. Several such complexes involving formic (Suresh & Vijayan, 1995), acetic (Suresh, Prasad & Vijayan, 1994), succinic (Prasad & Vijayan, 1993), glycolic (Suresh & Vijayan, 1996), oxalic (Manoj & Vijayan, 2000), maleic (Pratap *et al.*, 2000) and glutaric (Saraswathi *et al.*, 2001) acids have already been prepared and X-ray analysed. Here we report the crystal structures of yet another dicarboxylic acid, namely, malonic acid, with DL- and L-histidine. The structures are particularly interesting in relation to the effect of chirality on molecular aggregation and that of aggregation on molecular conformation.

2. Materials and methods

Crystals of the L-histine complex were obtained by the diffusion of isopropyl alcohol into an aqueous solution of L-histi-

Table 1
Experimental details.

	DL	L
Crystal data		
Chemical formula	$C_6H_{10}N_3O_2^+\cdot C_3H_3O_4^-$	$C_6H_{10}N_3O_2^+\cdot C_3H_3O_4^-$
Chemical formula weight	259.1	259.1
Cell setting, space group	Monoclinic, $P2_1/n$	Monoclinic, $P2_1$
a, b, c (Å)	5.3643 (10), 25.3538 (6), 8.3043 (14)	5.3287 (15), 25.534 (3), 8.2421 (15)
β (°)	96.202 (15)	97.00 (2)
V (Å^3)	1122.8 (3)	1113.1 (4)
Z	4	4
D_x (Mg m^{-3})	1.533	1.547
Radiation type	Cu $K\alpha$	Cu $K\alpha$
No. of reflections for cell parameters	25	25
θ range (°)	18–30	18–30
μ (mm^{-1})	1.126	1.136
Temperature (K)	293 (2)	293 (2)
Crystal form, colour	Plate-like, colourless	Plate-like, colourless
Crystal size (mm)	0.30 × 0.08 × 0.05	0.28 × 0.04 × 0.03
Data collection		
Diffractometer	CAD-4	CAD-4
Data collection method	ω–2θ scans	ω–2θ scans
Absorption correction	Empirical (North *et al.*, 1968)	Empirical (North *et al.*, 1968)
T_{min}	0.9038	0.9412
T_{max}	0.9991	0.9968
No. of measured, independent and observed reflections	2364, 2135, 1760	2376, 2147, 1657
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0243	0.0226
θ_{max} (°)	69.92	69.90
Range of h, k, l	$0 \rightarrow h \rightarrow 6$ $0 \rightarrow k \rightarrow 30$ $-10 \rightarrow l \rightarrow 10$	$-6 \rightarrow h \rightarrow 6$ $-19 \rightarrow k \rightarrow 31$ $-10 \rightarrow l \rightarrow 9$
No. and frequency of standard reflections	2 every 60 min	2 every 60 min
Refinement		
Refinement on	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0367, 0.1061, 1.05	0.0517, 0.1365, 1.032
No. of reflections, restraints and parameters used in refinement	2135, 0, 169	2147, 1, 336
H-atom treatment	Mixed	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0514P)^2 + 0.4527P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0641P)^2 + 0.6228P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.000	0.003
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.244, −0.203	0.227, −0.212
Extinction method	*SHELXL*97	*SHELXL*97
Extinction coefficient	0.0025 (5)	0.0033 (7)

Computer programs used: *CAD*-4 (Enraf–Nonius, 1989), *Molen* (Fair, 1990), *SHELXS*97 (Sheldrick, 1997), *SHELXL*97 (Sheldrick, 1997), *Microsoft Word*.

dine (Sigma) and malonic acid (AR, E-Merck) mixed in a 1:2.5 molar ratio. DL-Histidine (Sigma) and malonic acid mixed in a 1:6 molar ratio were used for growing the crystals of the DL-histidine complex with ethanol as the precipitant. Crystal data, details of data collection and refinement statistics are given in Table 1. The H atoms belonging to the carboxyl group of the semimalonate ion were refined isotropically, while the other H atoms were fixed using geometrical considerations and refined using the 'riding-model' method. The non-H atoms were refined anisotropically. The positional and thermal parameters of the atoms in the two structures are given as supplementary material.[1]

Table 2
Torsion angles (°) that define molecular conformation in the two histidine complexes.

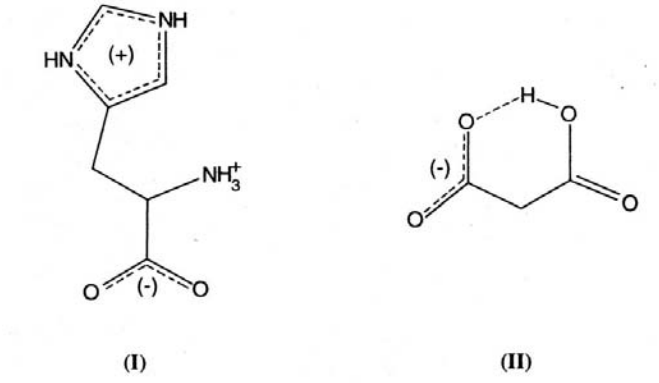
The angles in the DL-histidine complex correspond to the L-isomer.

DL-Histidine complex	N1—C2—C1—O1 (ψ^1)	−12.9 (2)
	N1—C2—C3—C4 (χ^1)	−169.9 (1)
	C2—C3—C4—N5 (χ^{21})	−112.0 (2)
	O31—C33—C34—C35	4.0 (3)
	C33—C34—C35—O36	−5.9 (3)
L-Histidine complex		
His A	N1—C2—C1—O1(ψ^1)	−12.7 (7)
	N1—C2—C3—C4 (χ^1)	−171.8 (5)
	C2—C3—C4—N5 (χ^{21})	−111.0 (7)
His B	N11—C12—C11—O11(ψ^1)	−6.4 (7)
	N11—C12—C13—C14 (χ^1)	−139.5 (5)
	C12—C13—C14—N15(χ^{21})	145.8 (6)
Mal A	O21—C23—C24—C25	1.1 (10)
	C23—C24—C25—O26	−4.1 (10)
Mal B	O31—C33—C34—C35	−3.4 (10)
	C33—C34—C35—C36	5.8 (10)

3. Results and discussion

3.1. Molecular structure

In both the complexes, the amino-acid molecules are zwitterionic with protonated positively charged amino and imidazole groups and deprotonated negatively charged carboxylate groups. The net positive charge on each histidinium ion (I) is compensated by a singly negatively charged



semimalonate (hydrogen malonate) ion (II). Perspective views of the ions in the structures are shown in Fig. 1, while the torsion angles that define their conformation are listed in Table 2. The amino-acid molecules in the DL-histidine complex have open conformation II (Bhat & Vijayan, 1978), with the

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE0016). Services for accessing these data are described at the back of the journal.

Table 3
Hydrogen bonds (Å, °) in the DL-histidine complex.

D—H···A	d(H···A)	d(D···A)	∠DHA
N1—H1A···O2^{ii}	1.96	2.815 (2)	161
N1—H1B···O1^{iii}	1.86	2.733 (2)	168
N1—H1C···O37^{iv}	1.99	2.839 (2)	158
N5—H5···O37^{v}	2.00	2.859 (2)	178
N7—H7···O32^{vi}	1.91	2.761 (2)	170
O31—H31···O36^{i}	1.38 (3)	2.420 (2)	163 (3)

Symmetry codes: (i) x, y, z; (ii) $x-\frac{1}{2}, -y+\frac{1}{2}, z-\frac{1}{2}$; (iii) $x-1, y, z$; (iv) $x+\frac{1}{2}, -y+\frac{1}{2}, z+\frac{1}{2}$; (v) $x+1, y, z$; (vi) $x, y, z+1$.

Table 4
Hydrogen bonds (Å,°) in the L-histidine complex.

D—H···A	d(H···A)	d(D···A)	∠DHA
N1—H1A···O12^{ii}	1.98	2.862 (6)	170
N1—H1B···O1^{iii}	1.82	2.703 (6)	172
N1—H1C···O37^{vii}	1.99	2.827 (7)	157
N5—H5···O27^{ii}	1.94	2.798 (8)	176
N7—H7···O22^{v}	1.90	2.751 (8)	170
N11—H11A ···O2^{vi}	1.97	2.768 (6)	149
N11—H11B···O11^{ii}	1.84	2.725 (7)	177
N11—H11C ···O27^{i}	1.99	2.848 (7)	162
N15—H15···O37^{ii}	2.01	2.866 (8)	176
N17—H17···O32^{v}	1.91	2.760 (8)	173
O21—H21···O26^{i}	1.33 (9)	2.427 (8)	169 (9)
O31—H31···O36^{i}	1.55 (6)	2.427 (8)	148 (6)

Symmetry codes: (i) x, y, z; (ii) $x+1, y, z$; (iii) $x-1, y, z$; (iv) $x+1, y, z-1$; (v) $x, y, z+1$; (vi) $x-1, y, z-1$; (vii) $x+1, y, z+1$.

side chain *trans* to the α-amino group. χ^{21}, which defines the orientation of the imidazole ring, is close to one of the two possible idealised values (90° and −90°). The same description applies to the conformation of molecule *A* (His A) in the L complex. The other molecule (His B) in this complex, however, has a very strained conformation. χ^{1} has a value close to that corresponding to an eclipsed arrangement. The same is true of χ^{21}. As discussed later, requirements of favourable aggregation with good hydrogen bonds appear to lead to this strained conformation.

The three crystallographically independent semimalonate ions in the structures have nearly the same closed planar conformation stabilised by a strong intramolecular O—H···O hydrogen bond (Tables 3 and 4). The O···O distances are close to that for a symmetrical hydrogen bond (Gilli *et al.*, 1994), but the refined H-atom positions still indicate them to be asymmetric. Conformations similar to those observed in the present complexes have been observed for several structures containing the semimalonate ion (Briggman & Oskarsson, 1978; Djinović *et al.*, 1990; Kalsbeek, 1992; Barnes & Weakley, 2000).

3.2. Hydrogen bonding and crystal structure

The crystal structures of the two complexes are given in Figs. 2 and 3. The parameters of the hydrogen bonds present in them are listed in Tables 3 and 4. As in the case of most of the crystal structures of amino acids and their complexes, both the structures can be described in terms of planar features.

The structure of the DL-histidine complex can be described as slabs of molecules, stabilised by hydrogen bonds, stacked along the crystallographic *b* axis. Central to each slab is a layer of amino-acid molecules interconnected by hydrogen bonds giving rise to head-to-tail sequences. According to the nomenclature used in this laboratory to describe amino-acid aggregation, a linear array of translationally related molecules stabilised by an N1···O1 hydrogen bond between adjacent molecules is called an S1 (straight involving O1) type head-to-tail sequence (Suresh & Vijayan, 1983; Vijayan, 1988). When the adjacent molecules are related by a glide plane and the O atom involved in the hydrogen bond is O2, then a DL2 head-to-tail sequence results. The arrangement of molecules in the layer may be described as S1DL2 (Fig. 4). The side chains stick out on either side of the planar hydrogen-bonded network involving amino and carboxylate groups. Each amino-acid layer is flanked by semi-

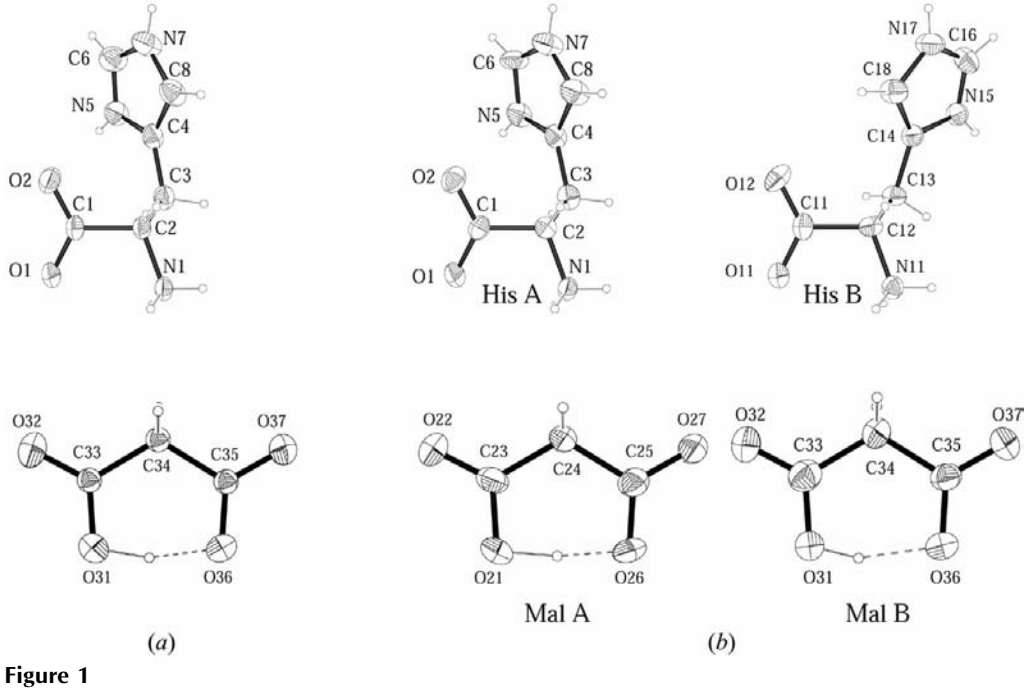


Figure 1
ORTEP diagrams of histidinium and semimalonate ions in (*a*) the DL-histidine complex and (*b*) the L-histidine complex. The displacement ellipsoids are at the 50% probability level. The numbering scheme is indicated. All figures were generated using *ORTEP*3 (Farrugia, 1998).

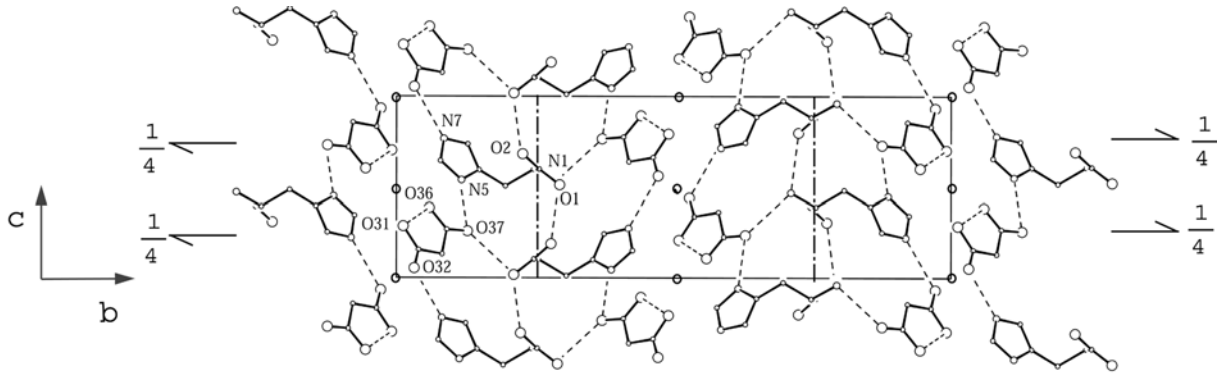


Figure 2
Crystal structure of the DL-histidine complex.

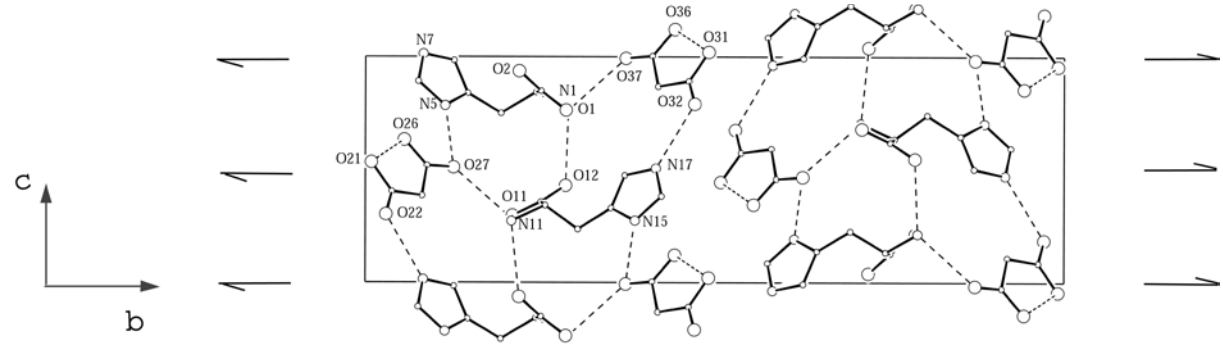


Figure 3
Crystal structure of the L-histidine complex.

malonate ions. Each ion is hydrogen bonded to imidazole groups of two histidinium ions related by an $a + c$ translation. It is also hydrogen bonded to the amino group of a histidinium ion of opposite chirality, situated between the two. Interestingly, adjacent slabs, related by a 2_1 screw, are not connected by hydrogen bonds.

DL2 sequences frequently occur in crystal structures containing amino acids of mixed chirality. (However, DL1 sequences with O1 instead of O2 involved in the hydrogen bond do not appear to have been observed so far.) They also occur in combination with S2, Z1 and Z2 sequences (Suresh & Vijayan, 1983; Soman *et al.*, 1989; Suresh & Vijayan, 1995). A combination of S1 and DL2 sequences has been observed for the first time in the present structures.

As the unit-cell parameters indicate, the arrangement of molecules in the L-histidine complex is remarkably similar to that in the DL complex. This similarity is facilitated by a pseudo-glide plane that relates the two sets of crystallographically independent molecules. This pseudo-glide is almost exact for all atoms except the main chain atoms of His B. The histidinium ion related to the reference molecule by the *n*-glide in the DL complex corresponds to His B in the L complex. The only major difference between the two structures is the change in the orientation of the α-carboxylate group in His B (an L isomer) with respect to that in the histidinium ion (a D isomer) in the DL complex. That leads to some readjustments in the positions of C^{α} and the amino N atom as well, in addition to major differences in the positions of atoms in the carboxylate group. The rest of the atoms in the structure overlap with an r.m.s. deviation of 0.07 Å. Even the reorientation of the carboxylate group is such that the O atoms in the L complex are within 1 Å of those in the DL complex related by an a translation.

While the packing arrangements in the two complexes are essentially the same, there are differences in detail, particularly in relation to the direction of adjacent S1 sequences, as illustrated in Fig. 4, which shows the arrangements of the main chain component of the histidinium ions in the amino-acid layer. All the S1 sequences have the same direction in the DL complex, while adjacent sequences run in opposite directions in the L complex. The similarity in the arrangements extends to the disposition and the interactions of the side chains as well. In both the complexes, the imidazole groups interact exclusively with semimalonate ions. The linear arrangement of alternating imidazole groups and semimalonate ions (Fig. 5) has the same geometry in the two complexes.

As indicated earlier, the side chain of His B in the L complex almost exactly superposes on that of a D-histidinium ion in the DL complex, while the main chain atoms have somewhat different positions on account of the difference in chirality. That appears to be the reason for the unusual conformation of His B. The advantage in substantially retaining in the L

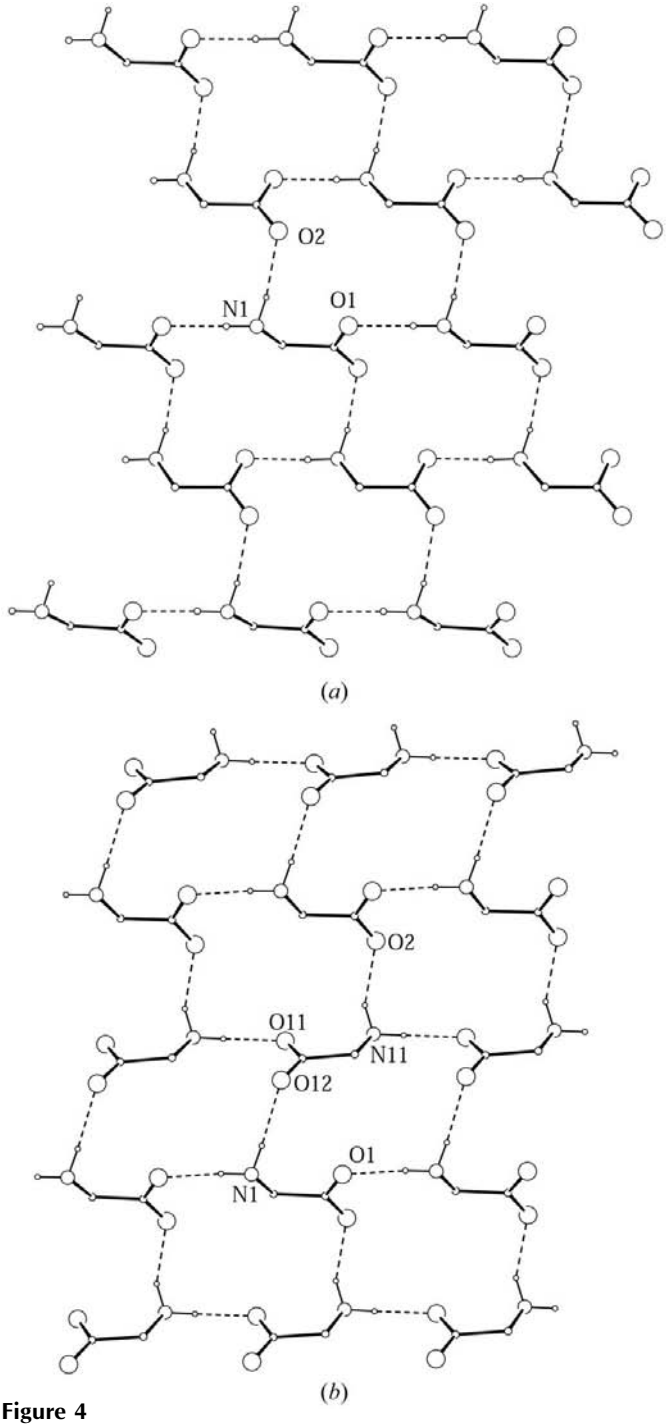


Figure 4
Comparable views of the basic element of aggregation in (*a*) the DL-histidine complex and (*b*) the L-histidine complex.

complex the packing arrangement in the DL complex apparently more than compensates for the disadvantage involved in a strained conformation for His B.

3.3. Effect of chirality on amino-acid aggregation

The effect of chirality on amino-acid aggregation has been a recurring theme of our work on complexes, partly on account of its relevance to chemical evolution and the origin of life. There are situations where the reversal of chirality of half the amino-acid molecules in the structure, as in the comparision between the crystals containing L amino acids and DL amino acids, leads to a fundamentally different aggregation pattern (Suresh *et al.*, 1986; Soman *et al.*, 1990; Suresh, Padmanabhan & Vijayan, 1994; Venkataraman *et al.*, 1997; Chandra *et al.*, 1998; Saraswathi *et al.*, 2001). On the other hand, in many cases the aggregation pattern is essentially maintained with suitable small adjustments in the crystal and molecular structure (Soman *et al.*, 1988, 1989; Soman & Vijayan, 1989, and references therein). The latter situation prevails in a majority of amino-acid structures, while fundamental changes in the aggregation pattern occur on reversal of chirality of half the amino-acid molecules in a majority of amino-acid complexes (Soman & Vijayan, 1989). The structures reported here present a rare case where the DL- and L-amino-acid complexes have essentially the same aggregation pattern. Similarity between the patterns to the extent of retaining nearly the same unit-cell parameters, as in the present case, is rare indeed. The structures of DL- and L-alanine (Nandhini *et al.*, 2001) and the Cu^{II}-phen complexes of DL- and L-leucine (Hu *et al.*, 1989) constitute other instances where the same situation occurs. Thus, the present work again demonstrates that the effect of chirality on molecular aggregation covers a wide range and is not easily predictable.

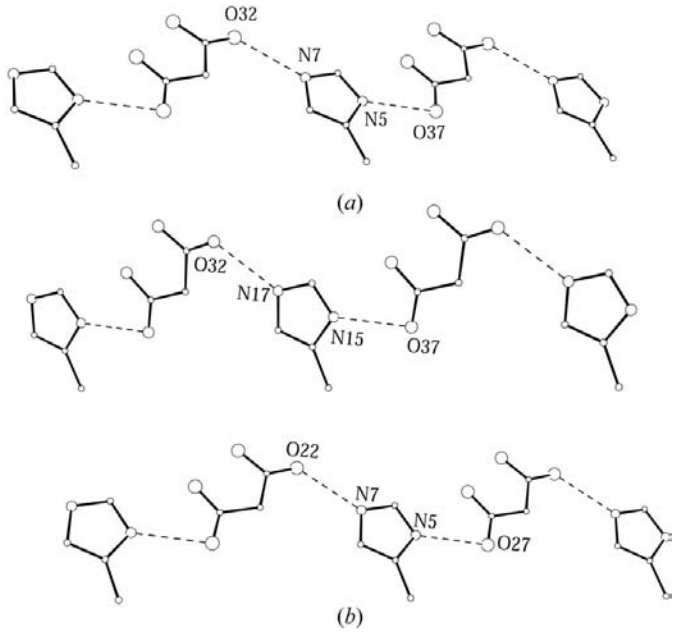


Figure 5
Characteristic interaction pattern observed in (*a*) the DL-histidine complex and (*b*) the L-histine complex.

The diffraction data were collected at the Regional Sophisticated Instrumentation Centre, Indian Institute of Technology, Chennai. The computations were performed at the Supercomputer Education and Research Centre at this institute. Financial support from the Indian Space Research Organization through their RESPOND programme is acknowledged.

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