

X-Ray Studies on Crystalline Complexes Involving Amino Acids and Peptides. XXIV. Different Ionization States and Novel Aggregation Patterns in the Complexes of Succinic Acid with DL- and L-Histidine

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SYNOPSIS

Diffusion of acetonitrile into an aqueous solution of DL-histidine and succinic acid in 1 : 3 molar proportions results in the crystals of DL-histidine hemisuccinate dihydrate [triclinic, $P\bar{1}$, $a = 7.654(1)$, $b = 8.723(1)$, $c = 9.260(1)$ Å, $\alpha = 77.23(1)$, $\beta = 72.37(1)$ and $\gamma = 82.32(1)^\circ$]. The replacement of DL-histidine by L-histidine in the crystallization experiment under identical conditions leads to crystals of L-histidine semisuccinate trihydrate [orthorhombic, $P2_12_12_1$, $a = 7.030(1)$, $b = 8.773(1)$, and $c = 24.332(3)$ Å]. The structures were solved using counter data and refined to R values of 0.056 and 0.054 for 2356 and 1778 observed reflections, respectively. Histidine molecules in both the complexes exist in open conformation I. Succinate and semisuccinate ions in them are planar, and exactly or nearly centrosymmetric. In the DL-histidine complex, the amino acid molecules form double ribbons and the succinate ions occupy voids left behind when the double ribbons aggregate, as in inclusion compounds. In the L-histidine complex, the amino acid molecules form columns; so do the semisuccinate ions and water molecules. The two columns interdigitate to form the complex crystal. There are similarities between the molecular aggregation in the complexes and that in the crystals of L- and DL-histidine. However, the presence of succinic acid has the effect of disrupting, partially or totally, head-to-tail sequences involving amino acid molecules. © 1993 John Wiley & Sons, Inc.

INTRODUCTION

A major research program in this laboratory is concerned with biomolecular interactions, and consists primarily of the preparation and x-ray analysis of crystalline complexes involving amino acids and peptides, among themselves as well as with other molecules.¹⁻⁵ These studies, in addition to providing information on the noncovalent interactions that play a vital role in the structure, function, and assembly of proteins, have also resulted in a detailed understanding of the well-defined patterns of amino acid and peptide aggregation.^{6,7} These patterns with head-to-tail sequences in which the main-chain amino and carboxylate groups are brought into periodic hydrogen-bonded proximity in a polypeptide-

like arrangement have been shown to be relevant to prebiotic polymerization during chemical evolution.^{1,8,9} The effect of chirality on amino acid aggregation has also been explored through the analysis of complexes involving amino acids of mixed chirality.^{2,10,11} Yet another problem the program addresses is concerned with the elucidation of specific interactions¹² and characteristic interaction patterns,¹³ which might have been important in the self-assembly of primitive multimolecular systems. The current focus of the program is on the complexes of amino acids and peptides with other organic compounds that are believed to have existed in the prebiotic milieu.^{3-5,14} Succinic acid is one such important organic compound. Its complexes with the DL and the L forms of arginine and lysine have provided a wealth of interesting information pertaining to ionization states, conformation, effects of chirality, and molecular aggregation.^{4,5} Here we report the crystal

Table I Crystal Data and Experimental Information

	DL-Histidine Hemisuccinate Dihydrate	L-Histidine Semisuccinate Trihydrate
Formula unit	$C_6H_{10}N_3O_2^+ \cdot \frac{1}{2}C_4H_4O_4^{2-} \cdot 2H_2O$	$C_6H_{10}N_3O_2^+ \cdot C_4H_5O_4^- \cdot 3H_2O$
Formula weight	250.3	327.3
Crystal system	Triclinic	Orthorhombic
Space group	$P\bar{1}$	$P2_12_12_1$
<i>a</i>	7.654 (1) Å	7.030 (1) Å
<i>b</i>	8.723 (1)	8.773 (1) Å
<i>c</i>	9.260 (1)	24.322 (3) Å
α	77.23 (1)°	
β	72.37 (1)	
γ	82.32 (1)	
Unit cell volume	573.0 Å ³	1500.1 Å ³
<i>Z</i>	2	4
Density measured	1.44 (3) g cm ⁻³	1.41 (2) g cm ⁻³
Density calculated	1.45 g cm ⁻³	1.45 g cm ⁻³
μ (Mo K α)	0.80 cm ⁻¹	0.83 cm ⁻¹
<i>F</i> (000)	264	692
Radiation used	Mo K α	Mo K α
θ range of 25 standard reflections used for refining lattice parameters	8°–21°	8°–28°
Maximum Bragg angle	28°	28°
Crystal dimension	0.27 × 0.37 × 0.40 mm ³	0.18 × 0.22 × 0.27 mm ³
Unique reflections measured	3088	2217
Observed reflections [with $I > 2\sigma(I)$]	2356	1778
Ranges of <i>h</i>	0 to 10	0 to 9
<i>k</i>	–11 to 11	0 to 11
<i>l</i>	–12 to 12	0 to 32
ΔI for standard reflections	0.026	0.012
<i>R</i> _{int}	0.016	

structures of its complexes with the DL and the L forms of the less basic, but more versatile, amino acid histidine.

EXPERIMENTAL

Crystals of the DL- and the L-histidine complexes were readily obtained from concentrated aqueous solutions of the amino acid and succinic acid in 1 : 3 molar ratio by liquid diffusion using acetonitrile. The space groups and the unit cell dimensions of the crystals were determined from x-ray diffraction photographs, and the densities were measured by flotation in mixtures of benzene and carbon tetrachloride. The cell parameters were subsequently refined on a CAD-4 diffractometer. The crystal data and details of data collection are given in Table I.

The structures were solved using the direct

methods program MULTAN¹⁵ and refined using the full-matrix SFLS routine in SHELX.¹⁶ The hydrogen atoms were located from difference Fourier maps with the help of geometrical considerations. The nonhydrogen atoms were refined anisotropically and the hydrogen atoms (except the two discussed later) isotropically. Only reflections with $I > 2\sigma(I)$ were used in the refinement. The various indicators pertaining to the refinement are listed in Table II, while the refined positional parameters and equivalent isotropic temperature factors are given in Tables III and IV.

The only notable feature observed during the course of refinement was the abnormally high temperature factor of C(14) in the DL-histidine complex and the shortness of the central C—C bond in the succinate ion involving C(14) and its centrosymmetric equivalent. Careful examination of difference Fourier maps employing phases calculated using the

Table II Refinement Parameters

	DL-Histidine Hemisuccinate Dihydrate	L-Histidine Semisuccinate Trihydrate
<i>R</i>	0.056	0.054
<i>wR</i>	0.079	0.062
<i>S</i>	1.900	0.351
	[1.00/ $\sigma^2(F_0)$]	[1.00/ $\sigma^2(F_0)$]
Weighting function	+ 0.002207(F_0) ²]	+ 0.068842(F_0) ²]
(Δ/σ) _{max}	0.54	0.44
$\Delta\rho_{\text{max}}$	0.40 eÅ ⁻³	0.36 eÅ ⁻³
$\Delta\rho_{\text{min}}$	-0.62 eÅ ⁻³	-0.38 eÅ ⁻³

whole structure and those computed using all atoms except C(14) appeared to indicate disorder in the position of C(14). However, acceptable models using alternative positions could not be constructed despite repeated attempts. Also, the possible alternative positions were too close to each other to permit their meaningful refinement. Therefore, only a single position, albeit with high anisotropic thermal parameters, was used in the refinement. However, the two hydrogen atoms attached to C(14) were not refined, although they were included in structure factor calculations.

Table III Positional Parameters and Equivalent Isotropic Temperature Factors ($\times 10,000$) of Nonhydrogen Atoms in DL-Histidine Hemisuccinate Dihydrate (Estimated Standard Deviations Are Given in Parentheses)

Atom	<i>X</i>	<i>Y</i>	<i>Z</i>	Equivalent <i>U</i> (Å ²)
N (1)	7554 (3)	9305 (2)	467 (2)	288 (6)
O (1)	5891 (2)	9222 (2)	-1680 (2)	352 (6)
O (2)	6856 (3)	6720 (2)	-1776 (2)	473 (7)
C (1)	6604 (3)	7924 (3)	-1200 (2)	278 (7)
C (2)	7225 (3)	7729 (2)	268 (2)	253 (6)
C (3)	5719 (3)	6976 (3)	1673 (2)	283 (7)
C (4)	6210 (3)	6687 (2)	3158 (2)	257 (6)
N (5)	7198 (3)	5338 (2)	3644 (2)	298 (6)
C (6)	7380 (3)	5389 (3)	5016 (2)	325 (8)
N (7)	6555 (3)	6717 (2)	5422 (2)	341 (7)
C (8)	5811 (3)	7555 (3)	4285 (2)	311 (7)
O (11)	9662 (2)	9860 (2)	2340 (2)	319 (6)
O (12)	10961 (3)	7555 (2)	3162 (2)	557 (9)
C (13)	10206 (3)	8858 (3)	3363 (2)	300 (7)
C (14)	9867 (9)	9265 (4)	4926 (3)	967 (24)
W (1)	7809 (4)	12824 (3)	2303 (3)	599 (9)
W (2)	11430 (4)	6161 (3)	767 (3)	747 (12)

RESULTS AND DISCUSSION

Stoichiometry and Ionization State

The amino and the imidazole groups in the histidine molecules in the structures are protonated and the carboxylate groups deprotonated. Thus, the mole-

Table IV Positional Parameters and Equivalent Isotropic Temperature Factors ($\times 10,000$) of Nonhydrogen Atoms in L-Histidine Semisuccinate Trihydrate (Estimated Standard Deviations Are Given in Parentheses)

Atom	<i>X</i>	<i>Y</i>	<i>Z</i>	Equivalent <i>U</i> (Å ²)
N (1)	6970 (4)	8898 (3)	7050 (1)	221 (7)
O (1)	5640 (5)	9305 (3)	8056 (1)	326 (7)
O (2)	4472 (5)	6949 (3)	8131 (1)	326 (7)
C (1)	5177 (5)	8038 (4)	7871 (1)	211 (8)
C (2)	5513 (5)	7807 (3)	7252 (1)	193 (7)
C (3)	3649 (5)	8001 (4)	6927 (1)	263 (9)
C (4)	3950 (5)	7737 (4)	6327 (1)	244 (8)
N (5)	4364 (5)	6307 (3)	6119 (1)	258 (8)
C (6)	4636 (6)	6413 (5)	5574 (1)	297 (10)
N (7)	4361 (5)	7853 (4)	5432 (1)	319 (9)
C (8)	3923 (6)	8702 (4)	5890 (2)	308 (9)
O (11)	4848 (5)	9096 (3)	1673 (1)	378 (9)
O (12)	4857 (4)	7251 (4)	2283 (1)	366 (8)
C (13)	4935 (5)	7641 (4)	1803 (1)	272 (9)
C (14)	5093 (6)	6537 (4)	1329 (1)	297 (10)
C (15)	5649 (6)	4967 (4)	1492 (1)	304 (9)
C (16)	5763 (5)	3820 (4)	1018 (1)	242 (8)
O (17)	6394 (5)	2528 (3)	1124 (1)	347 (8)
O (18)	5221 (5)	4246 (3)	550 (1)	382 (8)
W (1)	9612 (6)	10084 (4)	5657 (1)	420 (10)
W (2)	4769 (6)	2787 (5)	5768 (2)	507 (10)
W (3)	8061 (5)	8590 (4)	9961 (1)	367 (9)

Table V Side-Chain Conformation Angles ($^{\circ}$) in Crystal Structures Containing Histidine. (The Signs of the Torsion Angles Correspond to L-Enantiomer)

Compound/Complex	χ^1	χ^{21}	Ref.
DL-histidine hemisuccinate dihydrate	-62	-86	Present study
L-histidine semisuccinate trihydrate	-59	-69	Present study
L-histidine L-aspartic acid monohydrate			24
Molecule 1	167	78	
Molecule 2	65	-120	
Molecule 3	168	78	
Molecule 4	61	-120	
L-histidine L-aspartate monohydrate (new form)	65	-118	25
L-histidine trimeisic acid .1/3 acetone	-60	88	26
L-histidine (monoclinic)	-57	53	27
L-histidine (orthorhombic)	-59	57	28
DL-histidine	-87	-68	29
L-histidine hydrochloride monohydrate	71	-120	30
DL-histidine hydrochloride dihydrate	-62	-71	31
L-histidine dihydrochloride	-53	-75	32
L-histidinium dihydrogen monophosphate monohydrate	-62	-77	33

cules are zwitterionic in both the structures. Bond lengths and angles, and hydrogen atom positions, indicate that the succinic acid exists in different ionization states in the two complexes. The asymmetric unit of the DL-histidine complex consists of one histidinium cation, half of a centrosymmetric doubly negatively charged succinate ion, and two water molecules. Hence the complex may be described as DL-histidine hemisuccinate dihydrate. The asymmetric unit in the L-histidine complex contains one histidinium cation, one singly negatively charged semisuccinate ion, and three water molecules. The complex could therefore be termed as L-histidine semisuccinate trihydrate.

Molecular Dimensions

The bond lengths and angles in the two structures, except the length of the central bond C(14)-C(14') of the succinate ion in the DL-histidine complex, are normal.¹⁷⁻²⁰ As mentioned earlier, C(14) and the centrosymmetrically related C(14') are probably disordered. The disorder expresses itself as high anisotropic thermal parameters. The component of the apparent thermal vibration is the highest along the direction of the bond, which is roughly parallel to the a axis.

As is well known, the conformation of the histidine molecule is defined by two torsional angles χ^1 and χ^{21} . (see Ref. 21). The values of these angles, along with those in the other crystal structures containing histidine, are given in Table V. The metal complexes of the amino acid are not included in the table as the conformation of the molecules in them are severely restricted by the requirements of metal coordination. It has been shown on the basis of steric

Table VI Torsion Angles ($^{\circ}$) of the Succinate and the Semisuccinate Ion in the Complexes (Estimated Standard Deviations Are Given in Parentheses)

Succinate ion	
O11-C13-C14-C14'	-44.6 (3)
O12-C13-C14-C14'	137.5 (5)
C13-C14-C14'-C13'	180.0 (6)
Semisuccinate ion	
O11-C13-C14-C15	166.0 (3)
O12-C13-C14-C15	-15.1 (5)
C13-C14-C15-C16	178.4 (3)
C14-C15-C16-O17	173.4 (3)
C14-C15-C16-O18	-6.4 (5)

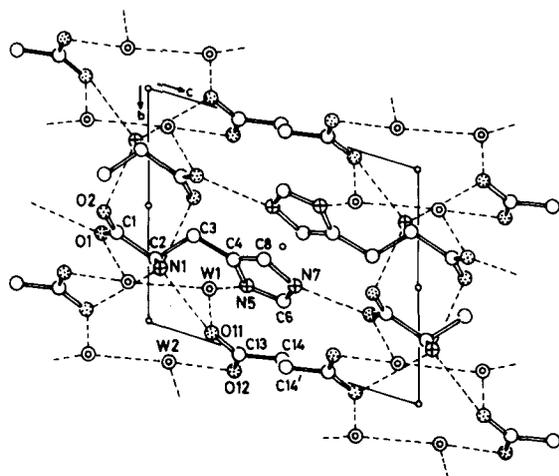


Figure 1. The crystal structure of DL-histidine hemisuccinate dihydrate as projected on to the ac plane. In this and in the subsequent figures hydrogen bonds are indicated by broken lines.

considerations and conformational and MO calculations that χ^{21} has preferred values in the neighborhood of $\pm 90^\circ$.^{22,23} The imidazole ring usually takes part in hydrogen bonds and, when protonated, electrostatic interactions, which often cause χ^{21} to deviate substantially from the two ideal values. The χ^1 , which defines the disposition of the side chain as a whole with respect to the rest of the molecule, can, as usual, have values in the neighborhood of

-60° , 180° , and 60° . As has been noted earlier,²⁴ $\chi^1 \sim -60^\circ$ corresponds to "open conformation I" with the imidazole ring *trans* to the α -carboxylate group while $\chi^1 \sim 180^\circ$ corresponds to "open conformation II" in which the ring is *trans* to the α -amino group. The molecule has a "closed conformation" when $\chi^1 \sim 60^\circ$. Thus, with three possible ranges for χ^1 and two for χ^{21} , the molecule can assume six unique conformations.

The histidine molecules in the two complexes exists in open conformation I with $\chi^{21} \sim -90^\circ$. In fact, as is to be expected on steric considerations, open conformation I is found in 9 of a total of 15 histidine molecules listed in Table V. Five of them have positive values for χ^{21} while 10 have negative values. Open conformation II occur only in 2 cases. The χ^{21} happens to be positive in both the cases. Surprisingly, sterically the least favorable closed conformation occurs in as many as 4 molecules. The χ^{21} is negative in all these cases. The imidazole ring is protonated and positively charged in all of them as indeed in the 2 cases where $\chi^1 \sim 180^\circ$.

The torsion angles that define the conformation of the succinate and the semisuccinate ions in the two complexes are given in Table VI. The ions are planar as in most other crystal structures containing succinic acid or its ions.^{4,5,17,18} The carboxyl hydrogen in the semisuccinate ion is *trans* with respect to the oxygen atom double bonded to the central carbon atom.

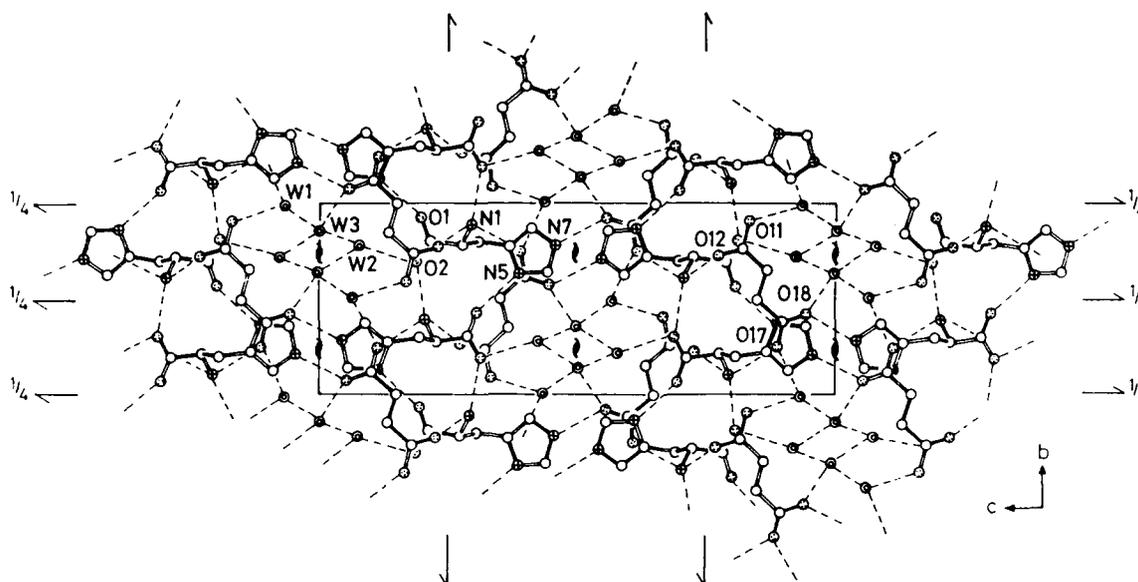


Figure 2. The crystal structure of L-histidine semisuccinate trihydrate as viewed down the a axis. The numbering scheme in the histidine molecule is the same as in the DL-histidine complex (Figure 1). The atoms in the carbon skeleton of the semisuccinate ion have numbers C(13) to C(16) starting with the atom to which O(11) and O(12) are bonded. In this and in the subsequent figures only O and N atoms are numbered.

Table VII Hydrogen-Bond Parameters in DL-Histidine Hemisuccinate Dihydrate (Estimated Standard Deviations Are Given in Parentheses)

A-H...B	A...B (Å)	H-A...B (°)	Symmetry of Atom B
N (1)-H1N (1)...O (11)	2.838 (2)	14 (2)	$-x + 2, -y + 2, -z$
N (1)-H2N (1)...O (11)	2.850 (3)	13 (2)	x, y, z
N (1)-H3N (1)...O (1)	2.793 (2)	10 (2)	$-x + 1, -y + 2, -z$
N (5)-HN (5)...W (1)	2.673 (4)	12 (2)	$x, y - 1, z$
N (7)-HN (7)...O (2)	2.674 (3)	16 (2)	$x, y, z + 1$
W (1)-H1W (1)...O (11)	2.777 (3)	10 (2)	x, y, z
W (1)-H2W (1)...W (2)	2.687 (4)	13 (3)	$-x + 2, -y + 2, -z$
W (2)-H1W (2)...O (12)	2.668 (4)	9 (3)	x, y, z
W (2)-H2W (2)...O (2)	2.781 (3)	4 (3)	$-x + 2, -y + 1, -z$

Hydrogen Bonding and Molecular Aggregation

The crystal structures of the two complexes are illustrated in Figures 1 and 2, while Tables VII and VIII lists the parameters of the hydrogen bonds that stabilize them. As can be seen from the figures, the aggregation patterns in the two complexes are very different.

The unlike molecules aggregate into separate alternating layers in the DL-histidine complex. In the histidine layer (Figure 3), the molecules form what may be described as double ribbons running parallel to the *c* axis. One strand in the ribbon is made up of L isomers and the other of D isomers. Each strand is stabilized by a hydrogen bond between N^ε and an α-carboxylate oxygen in the neighboring molecule, and its translational equivalents. The two strands are connected through hydrogen bonds across centers of symmetry; each pair of such hydrogen bonds give rise to a cyclic arrangement involving α-amino

and α-carboxylate groups of a L molecule and a D molecule. Adjacent double ribbons in the layer are not connected to each other. In each histidine molecule, the carboxylate oxygen O(2) is bridged to N^δ by two water molecules.

The arrangement of succinate ions in its layer in the DL-histidine complex is shown in Figure 4. Here again ribbons are formed parallel to *c*. Each ribbon consists of succinate ions bridged by water molecules. There are no interactions between adjacent ribbons.

The histidine layer in the DL-histidine complex lies between $x \sim 0.25$ and $x \sim 0.75$, while the succinate layer lies between $x \sim 0.90$ and $x \sim 1.10$. The two water molecules and their centrosymmetric equivalents have coordinates $x \sim 0.14$, $x \sim 0.22$, $x \sim 0.78$, and $x \sim 0.86$. They interact with the amino acid layer as well as the succinate layer. Indeed, it is the interactions involving water molecules and succinate ions that link histidine double ribbons.

Table VIII Hydrogen-Bond Parameters in L-Histidine Semisuccinate Trihydrate (Estimated Standard Deviations Are Given in Parentheses)

A-H...B	A...B (Å)	H-A...B (°)	Symmetry of Atom B
N (1)-H1N (1)...O (18)	2.822 (4)	3 (3)	$-x + 2, 0.5 + y - 1, 0.5 - z + 1$
N (1)-H2N (1)...O (11)	2.791 (4)	26 (4)	x, y, z
N (1)-H3N (1)...O (2)	2.896 (4)	4 (4)	$-x + 1, 0.5 + y, 0.5 - z + 1$
N (5)-HN (5)...O (1)	2.701 (4)	16 (2)	$-x + 1, 0.5 + y - 1, 0.5 - z + 1$
N (7)-HN (7)...O (17)	2.701 (4)	24 (4)	$0.5 - x + 1, -y + 2, 0.5 + z - 1$
O (12)-HO (12)...W (1)	2.601 (4)	6 (3)	$0.5 + x, 0.5 - y + 1, -z + 2$
W (1)-H1W (1)...O (18)	2.653 (4)	4 (7)	$0.5 + x - 1, 0.5 - y + 2, -z + 2$
W (1)-H2W (1)...W (3)	2.785 (5)	14 (4)	x, y, z
W (2)-H1W (2)...W (3)	2.761 (5)	9 (5)	$0.5 + x - 1, 0.5 - y + 1, -z + 2$
W (2)-H2W (2)...O (2)	2.826 (4)	10 (5)	x, y, z
W (3)-H1W (3)...O (17)	2.732 (4)	17 (5)	x, y, z
W (3)-H2W (3)...W (2)	2.761 (5)	9 (6)	x, y, z

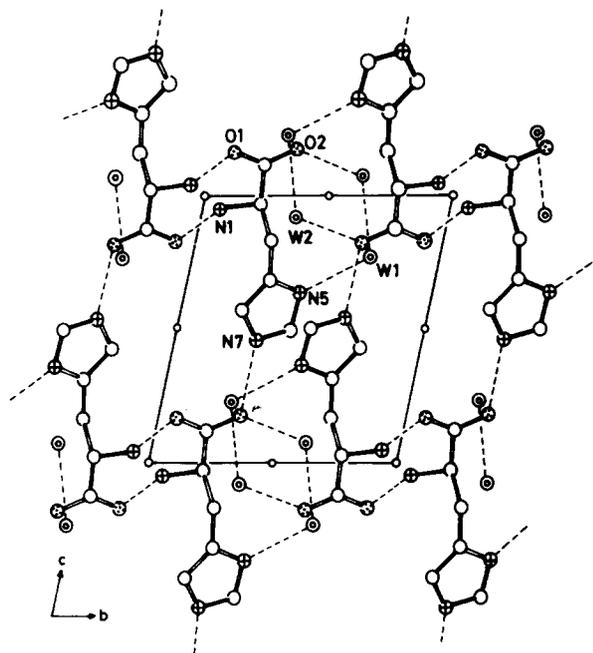


Figure 3. The arrangement of molecules in the histidine layer in DL-histidine hemisuccinate dihydrate.

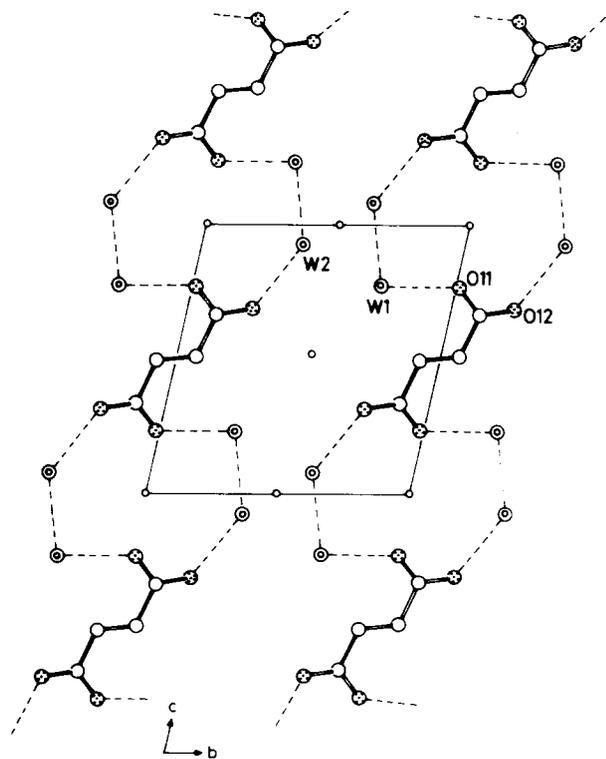


Figure 4. The layer of succinate ions in DL-histidine hemisuccinate dihydrate.

Likewise, succinate ions are linked among themselves through interactions involving water molecules and histidine molecules.

It can be clearly seen from Figure 3 that the histidine layer has a vacant space around $y = 0.0$ and $z = 0.5$. The succinate ion located on the center of inversion at $x = 0.0$, $y = 0.0$, and $z = 0.5$ is trapped between the vacant spaces around $x = -0.5$ and $x = 0.5$. This interesting arrangement is illustrated in Figure 5. The succinate ion then forms a hydrogen bond with the layer below as well as above, as illustrated in the Figure 5. The arrangement is reminiscent of those in some inclusion compounds.³⁴

The amino acid molecules in the L-histidine complex first aggregate into ribbons centered around 2_1 screw axes parallel to b . Such a ribbon is illustrated in Figure 6. Each ribbon is stabilized by hydrogen bonds appropriate for a Z2 head-to-tail sequence⁶ and a hydrogen bond between the carboxylate oxygen O(1) and N^δ, and its symmetry equivalents.

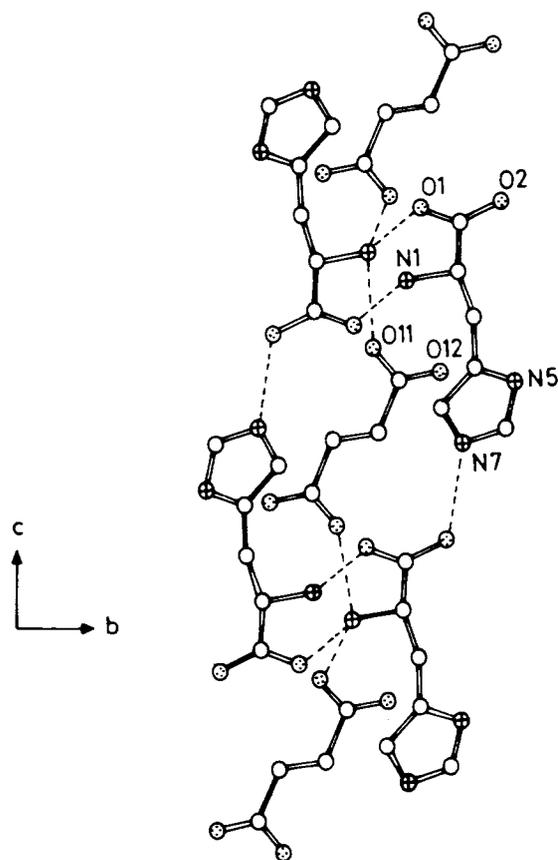


Figure 5. The arrangement illustrating the inclusion of the succinate ion in the DL-histidine complex in the vacant spaces left behind when the histidine molecules aggregate.

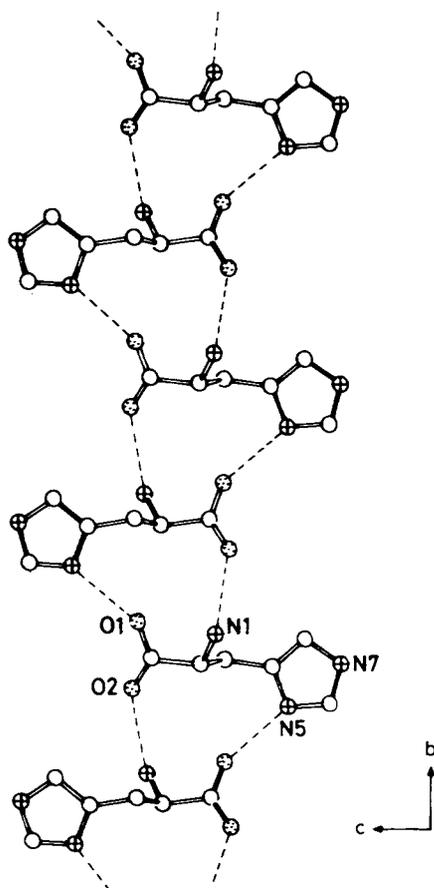


Figure 6. The arrangement of histidine molecules in L-histidine semisuccinate trihydrate.

The semisuccinate ions and the water molecules in the structure are also involved in a columnar arrangement, as shown in Figure 7, parallel to b . The interactions between the ions in these columns are through water molecules. In fact, the water molecules in the column can be described as sandwiched between semisuccinate ions. All the semisuccinate ions on one side of the column have an approximate x coordinate of 0.5 whereas those on the other side have approximate x coordinates of 0.0 (1.0). The columns are located at $z = 0.0$ and $z = 0.5$. The histidine ribbons are located at $z = 0.25$ and 0.75 . The molecules in the one at $z = 0.25$ are centered around $x = 0.5$ while those in the ribbon at $z = 0.75$ are centered around $x = 0.0(1.0)$. These locations are such that they permit efficient packing of histidine ribbons and semisuccinate/water columns, as shown in Figure 2 and illustrated schematically in Figure 8. The packing arrangement is then stabilized by several hydrogen-bonded interactions. These interactions include three direct hydrogen bonds be-

tween histidine and the semisuccinate ion, two with the α -amino nitrogen as the donor and one with N^{ϵ} as the donor. In addition, a water molecule W(2) in the semisuccinate/water column is hydrogen bonded to a carboxylate oxygen O(2) in histidine.

It is interesting to note that the water molecules in the structure and their symmetry equivalents form a water channel centered around the 2_1 screw axis parallel to a located at $b = 0.75$ and $c = 0.0$. Each water molecule forms three hydrogen bonds, two as donor and one as acceptor. W(1) accepts a proton from the carboxyl group of the semisuccinate ion and donates one to the carboxylate group of the ion. W(2) and W(3) are involved in hydrogen bonds as donors with the α -carboxylate group of histidine and the carboxylate group in the semisuccinate ion respectively. The remaining five hydrogen bonds are among water molecules themselves.

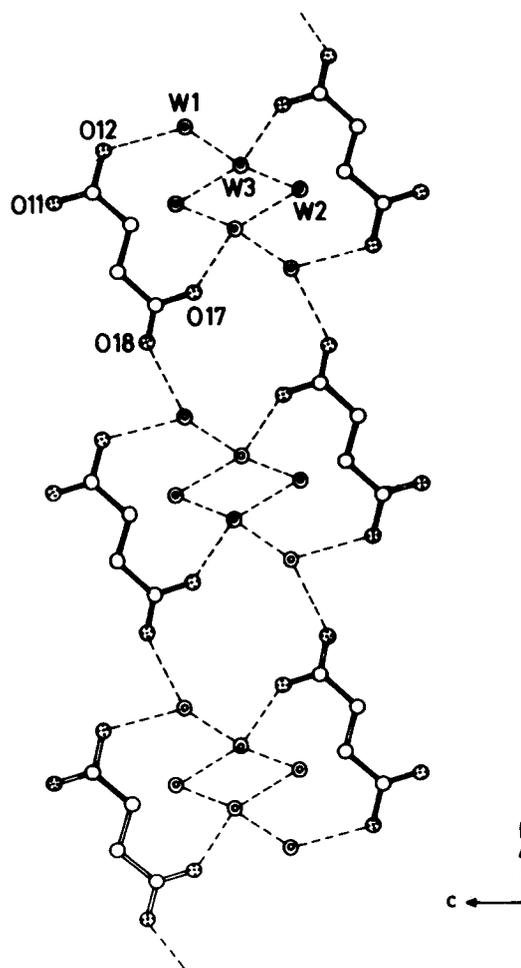


Figure 7. The columnar arrangement of semisuccinate ions and water molecules in L-histidine semisuccinate trihydrate.

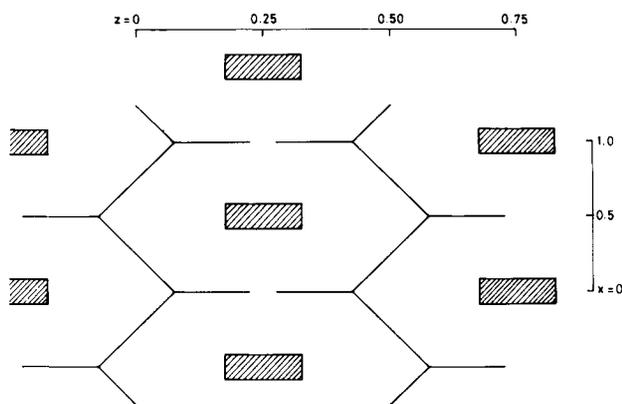


Figure 8. Schematic representation of the packing of histidine ribbons (hatched blocks) and semisuccinate/water columns (lines) in L-histidine semisuccinate trihydrate. The ribbons and columns run perpendicular to the plane of the figure.

It is of obvious interest to compare the aggregation patterns in the complexes with those in the crystals of the corresponding free amino acids. The central feature of the aggregation patterns in amino acid crystals is head-to-tail sequences.^{2,6} As indicated earlier, it has been suggested that such sequences could well have facilitated prebiotic polymerization.^{1,8} The patterns in the crystals of most hydrophilic L-amino acids, including L-histidine,^{27,28} is characterized and stabilized by two head-to-tail sequences, one of type S2 and the other of type Z2.⁶ The S2 sequence is disrupted in the complex while the Z2 sequence is preserved. It is interesting to note that the Z2 sequence in the crystals of L-histidine and that in the complex have nearly the same periodicity and similar structural characteristics. Substantial similarities exist between the aggregation of amino acids in the crystals of DL-histidine²⁹ and that in the DL-histidine succinate complex also. In both structures, the L- and D-amino acid molecules dimerize through hydrogen bonding across inversion centers and they form double ribbons through intermolecular interactions between imidazole and carboxylate groups. In DL-histidine, the double ribbons are interconnected through DL2 head-to-tail sequences.⁶ In the corresponding succinate complex, these sequences do not exist; instead the ribbons are interconnected through succinate ions and water molecules. As far as head-to-tail sequences are concerned, there are two in L-histidine while there is only one in the L-histidine complex; there is one in DL-histidine and none in the DL-histidine complex. Thus, the presence of succinic acid has the effect of

disrupting, partially or totally, the geometrical arrangement that is believed to facilitate nonenzymatic condensation of amino acids.

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REFERENCES

- Vijayan, M. (1988) *Prog. Biophys. Molec. Biol.* **52**, 71-99.
- Soman, J. & Vijayan, M. (1989) *J. Biosci.* **14**, 111-125.
- Soman, J., Rao, T., Radhakrishnan, R. & Vijayan, M. (1989) *J. Biomol. Struct. Dynam.* **7**, 269-277.
- Prasad, G. S. & Vijayan, M. (1990) *Int. J. Peptide Protein Res.* **35**, 357-364.
- Prasad, G. S. & Vijayan, M. (1991) *Acta Cryst.* **B47**, 927-935.
- Suresh, C. G. & Vijayan, M. (1983) *Int. J. Peptide Protein Res.* **22**, 129-143.
- Suresh, C. G. & Vijayan, M. (1985) *Int. J. Peptide Protein Res.* **26**, 311-328.
- Vijayan, M. (1980) *FEBS Lett.* **112**, 135-137.
- Vijayan, M. & Suresh, C. G. (1985) *Curr. Sci.* **54**, 771-780.
- Suresh, C. G., Ramaswamy, J. & Vijayan, M. (1986) *Acta Cryst.* **B42**, 473-478.
- Soman, J., Vijayan, M., Ramakrishnan, B. & Guru Row, T. N. (1990) *Biopolymers* **29**, 533-542.
- Salunke, D. M. & Vijayan, M. (1981) *Int. J. Peptide Protein Res.* **18**, 348-351.
- Soman, J., Suresh, C. G. & Vijayan, M. (1988) *Int. J. Peptide Protein Res.* **32**, 352-360.
- Miller, S. L. & Urey, H. C. (1959) *Science* **130**, 245-251.
- Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1984) *MULTAN84. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Universities of York, England, and Louvain, Belgium.
- Sheldrick, G. M. (1976) *SHELX76, Program for Crystal Structure Determination and Refinement.* University of Cambridge, England.
- Broadley, J. S., Cruickshank, D. W. J., Morrisson, J. D., Robertson, J. M. & Shearer, H. M. M. (1959) *Proc. Roy. Soc. London A* **251**, 441-457.
- Huang, C. M., Leiserowitz, L. & Schmitt, G. M. J. (1973) *J. Chem. Soc. Perkin Trans. II*, 503-508.
- Leviel, J.-L., Auvert, G. & Savariault, J.-M. (1981) *Acta Cryst.* **B37**, 2185-2189.
- Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1989) *J. Chem. Soc. Perkin Trans. II*, S1-S19.

21. IUPAC-IUB Commission on Biochemical Nomenclature. (1970) *J. Mol. Biol.* **52**, 1-17.
22. Ponnuswamy, P. K. & Sasishekar, V. (1971) *Int. J. Peptide Protein Res.* **3**, 9-18.
23. Ramani, R. & Boyd, J. R. (1981) *Can. J. Chem.* **59**, 3232-3236.
24. Bhat, T. N. & Vijayan, M. (1978) *Acta Cryst.* **B34**, 2556-2565.
25. Suresh, C. G. & Vijayan, M. (1987) *J. Biosci.* **12**, 13-21.
26. Herbstein, F. H. & Kapon, M. (1979) *Acta Cryst.* **B35**, 1614-1619.
27. Madden, J. J., McGandy, E. L., Seeman, N. C., Harding, M. M. & Hoy, A. (1972) *Acta Cryst.* **B28**, 2382-2389.
28. Madden, J. J., McGandy, E. L. & Seeman, N. C. (1972) *Acta Cryst.* **B28**, 2377-2382.
29. Edington, P. & Harding, M. M. (1974) *Acta Cryst.* **B30**, 204-206.
30. Oda, K. & Koyama, H. (1972) *Acta Cryst.* **B28**, 639-642.
31. Bennett, I., Davidson, A. G. H., Harding, M. M. & Morella, I. (1970) *Acta Cryst.* **B26**, 1722-1729.
32. Kistenmacher, T. J., Hunt, D. J. & Marsh, R. E. (1972) *Acta Cryst.* **B28**, 3352-3361.
33. Averbuch-Pouchot, M. T., Durif, A. & Guitel, J. C. (1988) *Acta Cryst.* **C44**, 890-892.
34. Goldberg, I. (1984) in *Inclusion Compounds*, Vol. 2, J. L. Atwood et al., Eds., Academic Press, London, pp. 261-335.

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