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X-ray studies on crystalline complexes involving amino acids and peptides. XXXVIII. Crystal structures of the complexes of L-arginine and L-histidine with glutaric acid and a comparative study of amino acid–glutaric acid complexes

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The complexes of glutaric acid with L-arginine and L-histidine (two crystal forms) exhibit different stoichiometries and ionization states. The aggregation patterns in two of the crystals are remarkably similar to those observed earlier in similar structures, while the pattern in the remaining one has not been seen earlier. The variability in the ionization state and stoichiometry observed in amino acid–dicarboxylic acid complexes appears to represent subtle differences in the response of a molecule to the presence in its neighbourhood of another type of molecule. The glutaric acid molecules (or glutarate or semiglutarate ions) in their complexes and in other crystals favour a fully extended conformation, albeit with frequent departures from it. The change in the chirality of the component molecules in the complex could lead to drastic changes in the aggregation pattern; alternatively, the effects of the change are accommodated through small adjustments in essentially the same pattern.

1. Introduction

We have been pursuing a program of X-ray studies on crystalline complexes involving amino acids and peptides in order to explore, at atomic resolution, the geometrical features of biologically significant interactions (Bhat & Vijayan, 1976; Suresh & Vijayan, 1983; Vijayan, 1988). The aggregation and interaction patterns elucidated during the course of these investigations have been found to be relevant to chemical evolution with particular reference to prebiotic polymerization and chiral effects (Vijayan, 1980, 1988). The current focus of the program has been on complexes involving small carboxylic acids, particularly those believed to have existed in the prebiotic milieu. In this context, the complexes containing formic, acetic, succinic, glycolic, oxalic and maleic acids have already been analysed (Prasad & Vijayan, 1993; Suresh, Prasad & Vijayan, 1994; Suresh & Vijayan, 1995, 1996; Chandra *et al.*, 1998; Pratap *et al.*, 2000). Also determined are the structures of glutaric acid complexes of DL- and L-lysine (Saraswathi *et al.*, 2001). Here we report the complexes of glutaric acid with L-arginine and L-histidine and present a comparative study of the glutaric acid complexes of lysine, arginine and histidine.

2. Materials and methods

Crystals of the L-arginine complex were obtained by diffusion of isobutyl alcohol (AR, Emerck) into an aqueous solution of

Table 1
Experimental details.

	L-Arginine complex	L-Histidine complex (form *A*)	L-Histidine complex (form *B*)
Crystal data			
Chemical formula	$C_5H_6O_4^{2-}\cdot 2C_6H_{15}N_4O_2^{+}\cdot 2H_2O$	$C_5H_7O_4^{-}\cdot C_6H_{10}N_3O_2^{+}\cdot H_2O$	$C_5H_7O_4^{-}\cdot C_{10}H_{10}N_3O_2^{+}\cdot C_6H_9N_3O_2$
Chemical formula weight	516.57	1221.17	884.88
Cell setting, space group	Monoclinic, *C*2	Orthorhombic, $P2_12_12_1$	Triclinic, *P*1
a, *b*, *c* (Å)	19.008 (3), 5.073 (2), 13.6723 (19)	8.335 (1), 8.856 (1), 19.522 (2)	5.791 (1), 13.110 (3), 14.360 (3)
α, β, γ (°)	90, 101.109 (13), 90	90, 90, 90	110.46 (2), 89.78 (1), 95.62 (2)
V (Å^3)	1293.5 (6)	1441.0 (3)	1016.0 (4)
Z	2	4	2
D_x (Mg m^{-3})	1.326	1.407	1.446
Radiation type	Cu $K\alpha$	Cu $K\alpha$	Cu $K\alpha$
No. of reflections for cell parameters	25	25	25
θ range (°)	18–30	10–30	10–30
μ (mm^{-1})	0.924	1.013	0.987
Temperature (K)	293 (2)	293 (2)	293 (2)
Crystal form, colour	Needle, colourless	Needle, colourless	Platy, colourless
Crystal size (mm)	0.4 × 0.05 × 0.05	0.5625 × 0.375 × 0.0625	0.8 × 0.6 × 0.5
Data collection			
Diffractometer	CAD-4	CAD-4	CAD-4
Data collection method	ω–2/θ scans	ω–2/θ scans	ω–2/θ scans
Absorption correction	Empirical (North *et al.*, 1968)	Cylinder (Dwiggins, 1975)	Numerical (Dwiggins, 1975)
T_{min}	0.9553	0.8444	0.6044
T_{max}	0.9997	0.8482	0.6287
No. of measured, independent and observed parameters	1545, 1494, 1161	1609, 1609, 1295	6281, 4174, 4023
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0327	0.0000	0.0310
θ_{max} (°)	74.83	74.85	75.09
Range of *h*, *k*, *l*	$-5 \rightarrow h \rightarrow 23$ $-6 \rightarrow k \rightarrow 6$ $-17 \rightarrow l \rightarrow 16$	$0 \rightarrow h \rightarrow 9$ $0 \rightarrow k \rightarrow 11$ $0 \rightarrow l \rightarrow 24$	$0 \rightarrow h \rightarrow 7$ $-16 \rightarrow k \rightarrow 16$ $-17 \rightarrow l \rightarrow 17$
No. and frequency of standard reflections	2 every 60 min	3 every 60 min	3 every 60 min
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2>2\sigma(F^2)]$, $wR(F^2)$, *S*	0.0534, 0.1581, 1.11	0.0549, 0.1444, 1.159	0.0419, 0.124, 1.129
No. of reflections and parameters used in refinement	1494, 170	1609, 199	4174, 566
H-atom treatment	Mixed	Mixed	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0833P)^2 + 0.7082P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0698P)^2 + 0.3704P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0853P)^2 + 0.1628P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.005	0.004	0.000
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.227, −0.231	0.242, −0.292	0.332, −0.372
Extinction method	*SHELXL*	*SHELXL*	*SHELXL*
Extinction coefficient	0.0053 (9)	0.028 (2)	0.0187 (17)

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

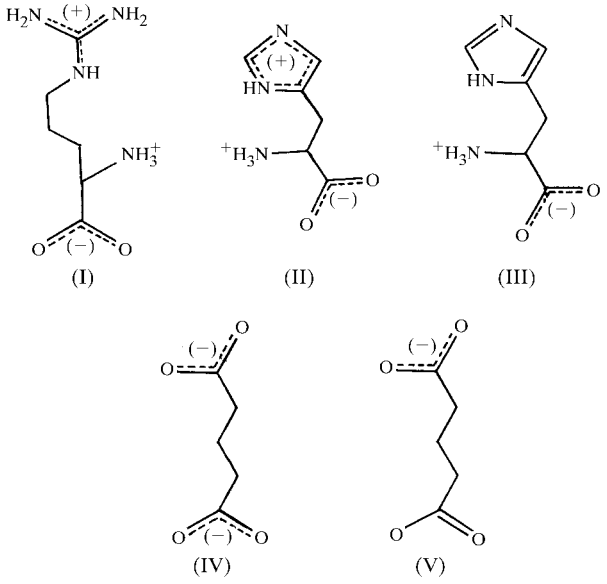
L-arginine (Sigma) and glutaric acid (AR, Emerck) mixed in an equimolar ratio. Form *A* of the L-histidine complex was obtained by the diffusion of acetonitrile (AR, Emerck) into an aqueous solution of L-histidine (Sigma) and glutaric acid mixed in a 1:6 molar ratio. Form *B* of the L-histidine complex was obtained when isobutyl alcohol was used rather than acetonitrile. Extensive attempts to crystallize the corresponding DL-amino acid complexes were not fruitful. Crystal data, details of data collection and refinement statistics are given in Table 1. The structures were solved by direct methods using *SHELXS*97 (Sheldrick, 1997*a*) and *SHELXL*97 (Sheldrick, 1997*b*). All the non-H atoms were refined anisotropically. All H atoms were located from difference Fourier maps. The H atoms except those belonging to water molecules were treated as riding on the heavier atoms to which they are attached. The torsion angles defining the positions of amino H atoms and the carboxyl H atoms were allowed to vary. The positions of water H atoms were refined isotropically with a restraint on the H—O—H angle. The positional and equivalent isotropic thermal parameters of the non-H atoms in the three structures are given as supplementary material.[1]

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE0013). Services for accessing these data are described at the back of the journal.

3. Results and discussion

3.1. Ionization state and stoichiometry

The amino acid molecules in the arginine complex (I) and form *A* of the histidine complex (II) are zwitterionic with protonated and positively charged amino groups, side chains and negatively charged carboxylate groups. Both contain one water molecule for each amino acid molecule. The arginine complex, however, contains a doubly negatively charged glutarate ion (IV) situated on a twofold special position, while a singly negatively charged semiglutarate ion (V) compensates the positive charge on the histidinium ion in form *A* of the histidine complex. Thus, the two complexes may be simply described as L-arginine hemiglutarate (half a glutarate) monohydrate and L-histidine semiglutarate monohydrate. The situation in form *B* of the histidine complex is more complex. The α-amino and the α-carboxylate groups in all the four crystallographically independent histidine molecules are respectively positively and negatively charged. The imidazole group is protonated in two, while the remaining two are neutral (III). The two positive charges are compensated by two semiglutarate ions, each carrying a negative charge. Thus, the stoichiometry of the amino acid molecules and the semiglutarate ions are different in the two forms.



3.2. Molecular conformation

Perspective views of the molecules in the three structures are given in Fig. 1. The torsion angles that define the molecular conformation of arginine (IUPAC-IUB Commission on Biochemical Nomenclature, 1970), in its complex are $\psi^1 = -31.3\ (5)$, $\chi^1 = -174.3\ (3)$, $\chi^2 = 177.9\ (3)$, $\chi^3 = 64.9\ (5)$, $\chi^4 = -160.2\ (5)$ and $\chi^{51} = 5.9\ (7)^\circ$. The somewhat folded side chain is *trans* to the α-amino group. The conformation of the arginine molecule in the present complex is similar to that observed in one of the molecules in L-arginine D-aspartate (Suresh *et al.*, 1986), in DL-arginine acetate monohydrate (Soman *et al.*, 1989) and L-arginine formate dihydrate (Suresh,

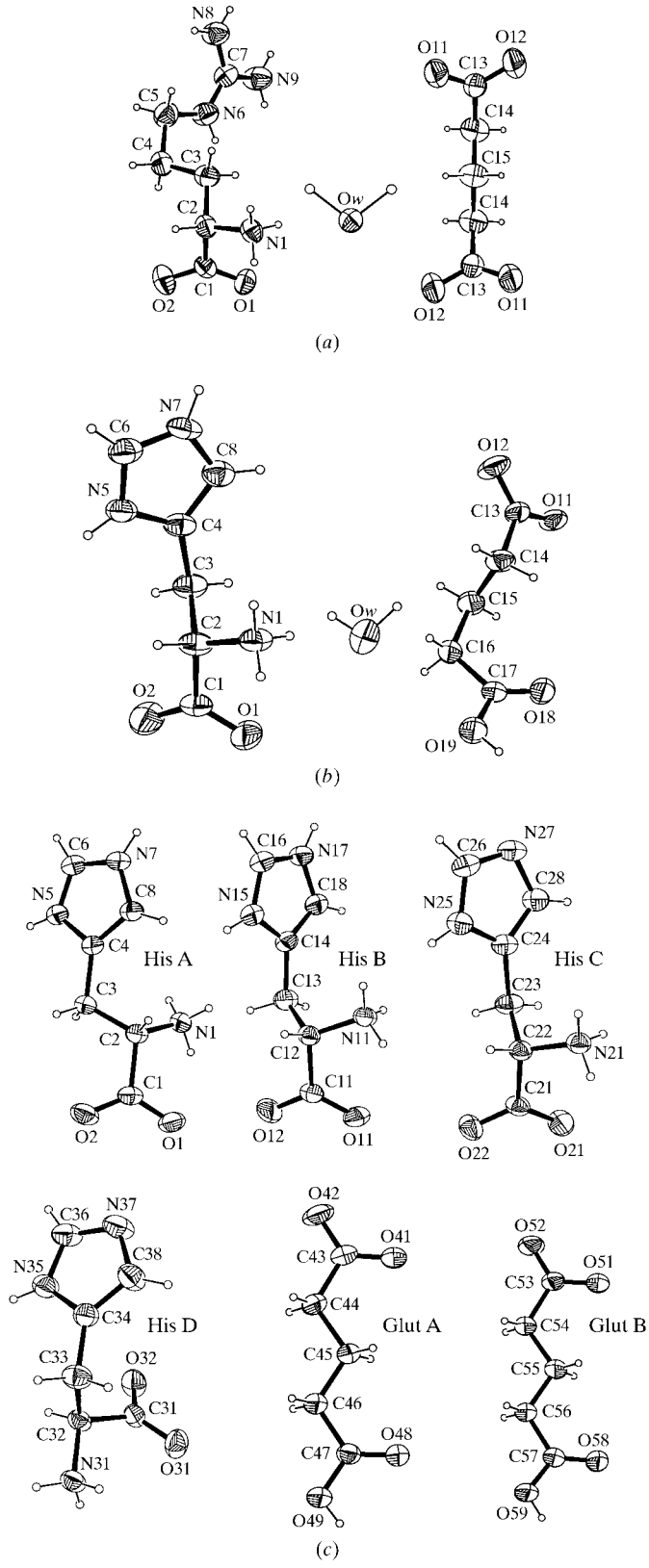


Figure 1
*ORTEP*3 (Farrugia, 1998) diagrams of amino and carboxylic acid molecules in (*a*) the L-arginine complex, (*b*) form *A* of the L-histidine complex and (*c*) form *B* of the L-histidine complex. The displacement ellipsoids are at 50% probability level. The numbering scheme is indicated.

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

L-Histidine complex (form *A*)	N1—C2—C1—O1 (ψ^1)	−10.8 (5)
	N1—C2—C3—C4 (χ^1)	−66.0 (5)
	C2—C3—C4—N5 (χ^{21})	−70.0 (5)
	O11—C13—C14—C15	–68.2 (6)
	C13—C14—C15—C16	−176.7 (3)
	C14—C15—C16—C17	−72.8 (6)
	C15—C16—C17—O18	−9.8 (8)
L-Histidine complex (form *B*)		
His A	N1—C2—C1—O1 (ψ^1)	25.4 (3)
	N1—C2—C3—C4 (χ^1)	−61.0 (3)
	C2—C3—C4—N5 (χ^{21})	163.5 (3)
His B	N11—C12—C11—O11 (ψ^1)	2.9 (4)
	N11—C12—C13—C14 (χ^1)	−51.9 (4)
	C12—C13—C14—N15 (χ^{21})	−73.0 (4)
His C	N21—C22—C21—O21 (ψ^1)	−30.7 (4)
	N21—C22—C23—C24 (χ^1)	−64.3 (4)
	C22—C23—C24—N25 (χ^{21})	−68.1 (4)
His D	N31—C32—C31—O31 (ψ^1)	−34.1 (4)
	N31—C32—C33—C34 (χ^1)	177.3 (3)
	C32—C33—C34—N35 (χ^{21})	71.3 (4)
Glut A	O41—C43—C44—C45	−0.6 (5)
	C43—C44—C45—C46	−175.7 (3)
	C44—C45—C46—C47	−178.2 (3)
	C45—C46—C47—O48	−2.1 (5)
Glut B	O51—C53—C54—C55	−5.3 (6)
	C53—C54—C55—C56	175.0 (4)
	C54—C55—C56—C57	−179.7 (4)
	C55—C56—C57—O58	−6.3 (6)

Padmanabhan & Vijayan, 1994). The glutarate ion in the structure is located on a twofold axis. The torsion angles that define the conformation of glutarate ion in this complex are O11—C13—C14—C15 = −73.6 (6), C13—C14—C15—C14′ = 179.8 (4)°. The two crystal forms of the histidine complex illustrate the conformational variability of the amino acid molecule and the semiglutarate ion. The relevant torsion angles are listed in Table 2. Four of the five histidine molecules assume an open conformation 1(*g*−) (Bhat & Vijayan, 1978) with the imidazole groups *trans* to the α-carboxylate group. The remaining one has an open conformation 2(*t*) with the imidazole group *trans* to the α-amino group. The preferred values of χ^{21} (IUPAC-IUB Commission on Biochemical Nomenclature, 1970) are in the neighbourhood of 90 or −90° as appropriate for a torsion angle about an sp^3–sp^2 bond. Requirements of hydrogen bonding involving the two ring N atoms often lead to substantial departures from the ideal values of the torsion angle. However, the departure observed in molecule *A* in form *B* is unusual.

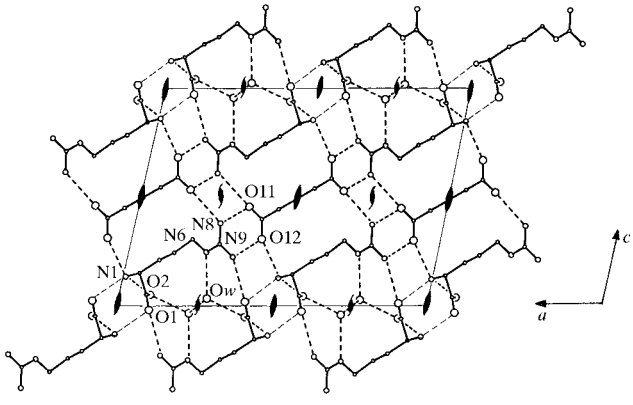


Figure 2
Crystal structure of the L-arginine complex.

Table 3
Parameters of hydrogen bonds in the L- arginine complex.

D—H···*A*	*d*(*D*···*A*) (Å)	∠*D*—H···*A* (°)
N1—H1*A*···O2^{i}	2.733 (5)	177
N1—H1*B*···O12^{ii}	2.687 (4)	165
N1—H1*C*···O1^{iii}	2.753 (5)	165
N6—H6···*OW*^{iv}	2.948 (5)	170
N8—H8*A*···O11^{i}	2.797 (6)	178
N8—H8*B*···O11^{v}	2.881 (4)	156
N9—H9*A*···O12^{i}	2.857 (7)	177
N9—H9*B*···O1^{vi}	2.955 (4)	145
OW—H1*W*···O2^{vi}	2.738 (4)	168 (5)
OW—H2*W*···*OW*^{vii}	2.940 (6)	157 (6)

Symmetry codes: (i) $x, y+1, z$; (ii) $x+\frac{1}{2}, y+\frac{1}{2}, z$; (iii) $-x+2, y, -z$; (iv) x, y, z; (v) $-x+\frac{3}{2}, y+\frac{1}{2}, -z+1$; (vi) $-x+\frac{3}{2}, y+\frac{1}{2}, -z$; (vii) $-x+\frac{3}{2}, y-\frac{1}{2}, -z$.

3.3. Hydrogen bonding and molecular aggregation

The crystal structures of the three complexes are shown in Figs. 2–4. The parameters of the hydrogen bonds that stabilize them are listed in Tables 3–5.

The aggregation of amino acids in the structure of the arginine complex can be described as consisting of pairs of arginine molecules stacked around twofold axes along the shortest cell dimension. The two molecules in each pair are twofold related and are interconnected by two N—H···O hydrogen bonds involving α-amino and α-carboxylate groups. The pairs in the column are stabilized by two twofold related N—H···O2 hydrogen bonds and their translational equiva-

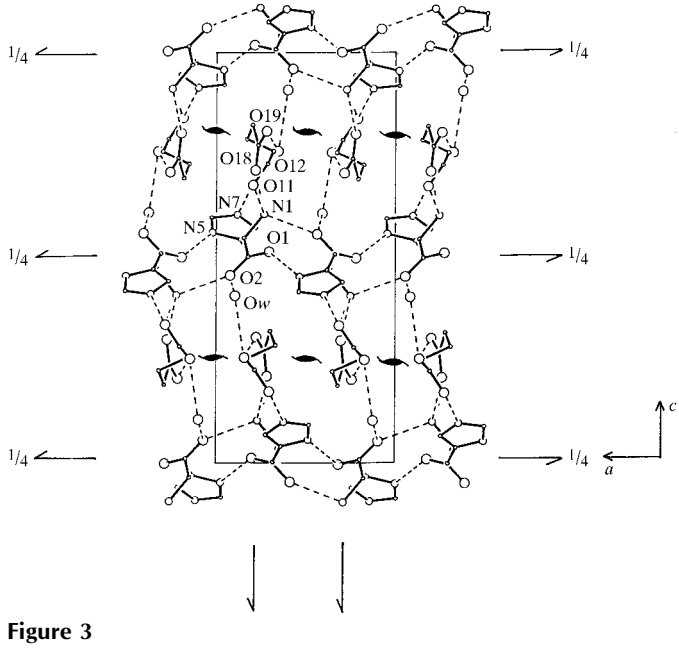


Figure 3
Crystal structure of the L-histidine complex (form *A*).

Table 4
Parameters of hydrogen bonds in form *A* of the L-histidine complex.

D—H···*A*	*d*(*D*···*A*) (Å)	∠*D*—H···*A* (°)
N1—H1*A*···O2^{i}	2.765 (5)	175
N1—H1*B*···O18^{ii}	2.963 (4)	170
N1—H1*C*···O11^{iii}	2.726 (4)	171
N5—H5···O1^{iv}	2.694 (5)	151
N7—H7···O11^{ii}	2.699 (4)	175
O19—H19···O12^{iii}	2.574 (5)	153
O*W*—H1*W*···O12^{v}	2.924 (5)	163 (5)
O*W*—H2*W*···O2^{vi}	2.804 (5)	173 (7)

Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (ii) x, y, z; (iii) $x, y+1, z$; (iv) $x+\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (v) $-x+\frac{3}{2}, -y, z-\frac{1}{2}$; (vi) $x, y-1, z$.

Table 5
Parameters of hydrogen bonds in form *B* of the L-histidine complex.

D—H···*A*	*d*(*D*···*A*) (Å)	∠*D*—H···*A* (°)
N1—H1*A*···O1^{i}	2.617 (3)	112
N1—H1*B*···O2^{ii}	2.866 (3)	165
N1—H1*C*···O32^{i}	2.662 (4)	162
N5—H5···O48^{iii}	2.710 (4)	159
N7—H7···O51^{iv}	2.557 (5)	176
N11—H11*A*···O22^{v}	2.770 (4)	173
N11—H11*B*···O12^{vi}	2.718 (3)	167
N11—H11*C*···O2^{ii}	3.152 (5)	153
N15—H15···O58^{i}	2.840 (4)	166
N17—H17···O41^{vii}	2.573 (4)	174
N21—H21*A*···O31^{i}	2.784 (3)	172
N21—H21*B*···O22^{ii}	2.813 (3)	176
N21—H21*C*···O42^{vi}	2.812 (4)	176
N25—H25···O11^{viii}	2.883 (3)	160
N31—H31*A*···O21^{ii}	2.805 (3)	159
N31—H31*B*···O32^{ii}	2.792 (4)	168
N31—H31*C*···O52^{iv}	2.680 (4)	152
N35—H35···O1^{ii}	2.777 (3)	162
O49—H49···N27^{ix}	2.707 (4)	172
O59—H59···N37^{ii}	2.576 (5)	162

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

lent. The linear arrangements thus formed are head-to-tail sequences of type S2 (Suresh & Vijayan, 1983). Adjacent columns are interconnected by N—H···O hydrogen bonds between the guanidyl and the α-carboxylate groups of adjacent screw-related molecules and water bridges, to form a layer in the *ab* plane. In fact, the water molecules between adjacent columns in the layer form an infinite hydrogen-bonded chain parallel to **b**. The layers of amino acid molecules are interconnected by the glutarate ions situated on another set of twofold axes. There are altogether four N—H···O hydrogen bonds between the two sets of molecules, three of which involve the guanidyl group. Two of them constitute a specific interaction (Salunke & Vijayan, 1981; Vijayan, 1988) between guanidyl and carboxylate groups and involve two parallel N—H···O hydrogen bonds.

Interestingly, and indeed surprisingly, the structure of L-arginine hemiglutarate monohydrate (space group, *C*2) is nearly identical to that of DL-arginine acetate monohydrate (space group $P2_1/c$; Soman *et al.*, 1989). The cell parameters of the two crystals differ by less than 1% each. The symmetry that relates the two molecules in the amino acid pair is an inversion centre, instead of a twofold axis, in the latter. The transition from the doubly charged glutarate ion to the singly charged acetate ion essentially involves the removal of the central C atom in the former situated on a symmetry element. The near isomorphism of the two structures provides a good example of situations in which the effects of a change in chirality is accommodated by small alterations in essentially the same aggregation pattern. It turns out that the structure of DL-arginine formate dihydrate also has a structure similar to those involving the glutarate and the acetate ions. That involving the succinate ions shares some important features with the structures of the other three complexes. Indeed, as noted in relation to the then known three structures (Suresh, Padmanabhan & Vijayan, 1994), the basic pattern of amino acid–carboxylic acid interactions are similar in the four complexes (Fig. 5).

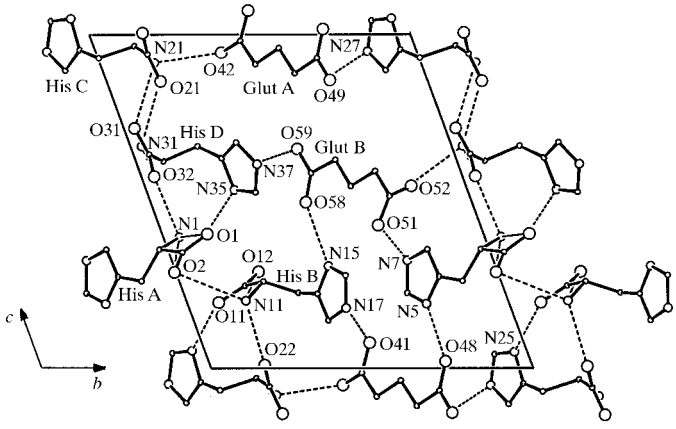


Figure 4
Crystal structure of the L-histidine complex (form *B*).

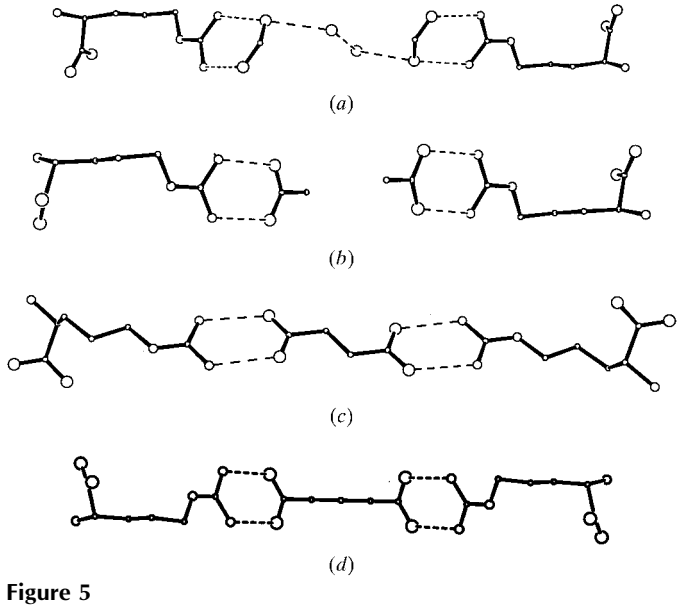


Figure 5
A basic element of amino acid aggregation in DL-arginine complexed with (*a*) formic acid, (*b*) acetic acid, (*c*) succinic acid and (*d*) in L-arginine complexed with glutaric acid.

Table 6
Composition of complexes involving glutaric acid.

A = neutral amino acid; *A*+ = positively charged amino acid; (I) = semiglutarate; (II) = glutarate; *W* = water.

Complex with	*A*	*A*+	(I)	(II)	*W*
DL-Lysine		1	1		
L-Lysine		1	1		
L-Arginine		1		1/2	1
L-Histidine (form *A*)		1	1		1
L-Histidine (form *B*)	1	1	1		

The crystal structure of L-histidine semiglutarate monohydrate (form *A* of the histidine complex) follows the familiar pattern of unlike molecules aggregating into separate alternating layers stacked along the longest crystallographic axis (Vijayan, 1988). The basic element of aggregation in the amino acid layer is a ribbon of histidine molecules centred around the 2_1 screw axis parallel to **a**. The ribbon is stabilized by two sets of hydrogen bonds. The first set involves an N1—H···O2 hydrogen bond and its symmetry equivalents and leads to a Z2 head-to-tail sequence (Suresh & Vijayan, 1983) with a periodicity corresponding to the *a* cell dimension (8.335 Å), which falls within the range generally observed for such sequences (Vijayan, 1988). The second set involves a hydrogen bond between the side chain N5 and the carboxylate oxygen O1, and its symmetry equivalents. Interestingly, such ribbons also occur in L-histidine semisuccinate (Prasad & Vijayan, 1993; Fig. 6), again emphasizing the relative invariance of some elementary patterns of amino acid aggregation. In L-histidine semiglutarate the ribbons then stack along **b** to form the amino acid layer. As often happens in the case of other dicarboxylic acids (Prasad & Vijayan, 1991; Chandra *et al.*, 1998; Saraswathi *et al.*, 2001), semiglutarate ions form long hydrogen-bonded chains, parallel to **b** in the present case. These ions interconnect the histidine layers through direct hydrogen bonds and a water bridge. The semiglutarate chains do not interact among themselves. The same is true about the histidine ribbons. They are interconnected by histidine molecules and semiglutarate ions, respectively.

While the structures of L-arginine hemiglutarate monohydrate and L-histidine semiglutarate monohydrate emphasize the relatively invariant features of amino acid aggregation, form *B* of the histidine complex illustrates the possible variability. Neutral and positively charged histidine molecules co-exist in the structure. However, both of them form part of an amino acid layer in the *ab* plane. In the layer, each molecule is connected with the adjacent molecule related by a translation, through an N1—H···O2 (or equivalent such as N11—H···O12) hydrogen bond. Thus, there are four S2 head-to-tail sequences, corresponding to four crystallographically independent amino acid molecules, in the structure. These sequences are interconnected by several N—H···O hydrogen bonds, but none of them gives rise to periodic features. Nδ1 of the two neutral molecules are also hydrogen bonded to the carboxylate groups of adjacent molecules in the layer. The side chains of amino acid molecules project out of the layer, with adjacent side chains pointing in opposite directions. The voids left behind when the layers stack along **c** are occupied by the semiglutarate ions. The OH (O49, O59) of the neutral carboxyl groups hydrogen bond to the non-protonated Nε2 of the neutral amino acid molecules, a rare instance where O—H···N hydrogen bonds occur. The other O atoms in the semiglutarate ion hydrogen bond, as acceptors, to the N atoms in the protonated amino and imidazole groups.

4. Comparative study of amino acid–carboxylic acid complexes

4.1. Ionization and stoichiometry

Earlier studies in this laboratory on complexes of dicarboxylic acids with basic amino acids have been characterized by the presence of variability in ionization states and the stoichiometry in them (Prasad & Vijayan, 1993; Chandra *et al.*, 1998). The same is true about the glutaric acid complexes reported here and in an earlier communication (Saraswathi *et al.*, 2001). A comparision of the five complexes, in terms of the ionic species and stoichiometry, is given in Table 6. In all the crystals except one, the amino acid molecules carry a net positive charge with a negatively charged α-carboxylate group, a positively charged α-amino group and a positively charged side chain. Neutral and positively charged amino acid molecules co-exist in form *B* of the L-histidine complex. Singly negatively charged semiglutarate ions exist in all crystals except in that of the L-arginine complex where the counter ion is doubly negatively charged. A simple 1:1 stoichiometry between the two types of molecules is found in three of the complexes. The stoichiometry is 2:1 in the remaining two. The asymmetric unit of the L-arginine complex consists of one

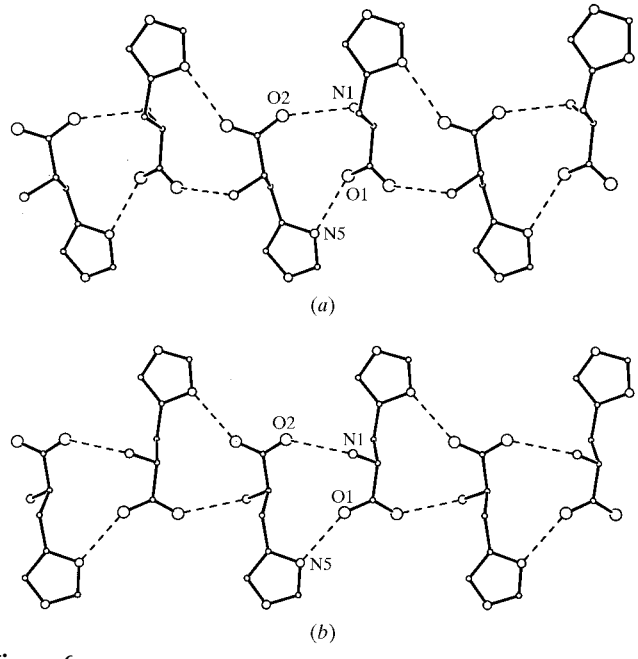


Figure 6
Ribbon-like arrangement of histidine molecules in the complexes of L-histidine with (*a*) glutaric acid (form *A*) and (*b*) succinic acid.

positively charged zwitterionic argininium ion and half a glutarate ion situated on a twofold axis, in addition to a water molecule. That in form *B* of the histidine complex is made up of two neutral histidine molecules and two positively charged histidinium ions and two semiglutarate ions.

Among the amino acid complexes of dicarboxylic acids studied in this laboratory, those involving maleic acid (Pratap *et al.*, 2000) do not exhibit variability in ionization and stoichiometry presumably on account of the strong internal hydrogen bond between the carboxyl/carboxylate groups in the semimaleate ion. On the contrary, those involving succinic acid, oxalic acid and glutaric acid do. The most frequently occurring species are strongly positively charged zwitterionic amino acid molecules and singly negatively charged semidicarboxylate ions. Neutral and even doubly positively charged basic amino acids occur, but only infrequently. Neutral dicarboxylic acid molecules have been observed so far only in the succinic acid complexes. Also, doubly negatively charged dicarboxylate ions occur more frequently in succinic acid complexes than in those involving the other dicarboxylic acids. Thus, the variability in ionization state appears to be more pronounced in succinic acid than in other dicarboxylic acids. There is no correlation between the ionization state of the dicarboxylic acid and the chemical nature of the amino acid or its chirality. Also, two states co-exist in the same crystal. Thus, the situation observed in the complexes appears to represent the variability in the response of a molecule to the presence in its neighbourhood of another type of molecule.

4.2. Molecular conformation

The conformations of the amino acid molecules in the complexes do not merit special mention. They follow a familiar pattern and have been examined earlier in considerable detail (Prasad & Vijayan, 1990, 1991, 1993). The five amino acid complexes, among them, contain one glutarate ion

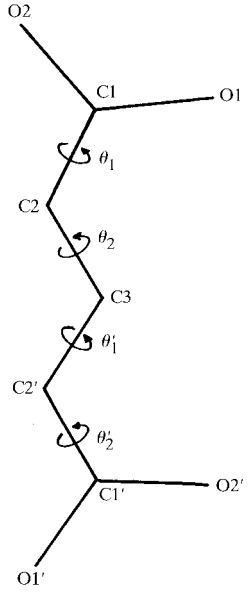


Figure 7
Torsion angles that define glutaric acid conformation.

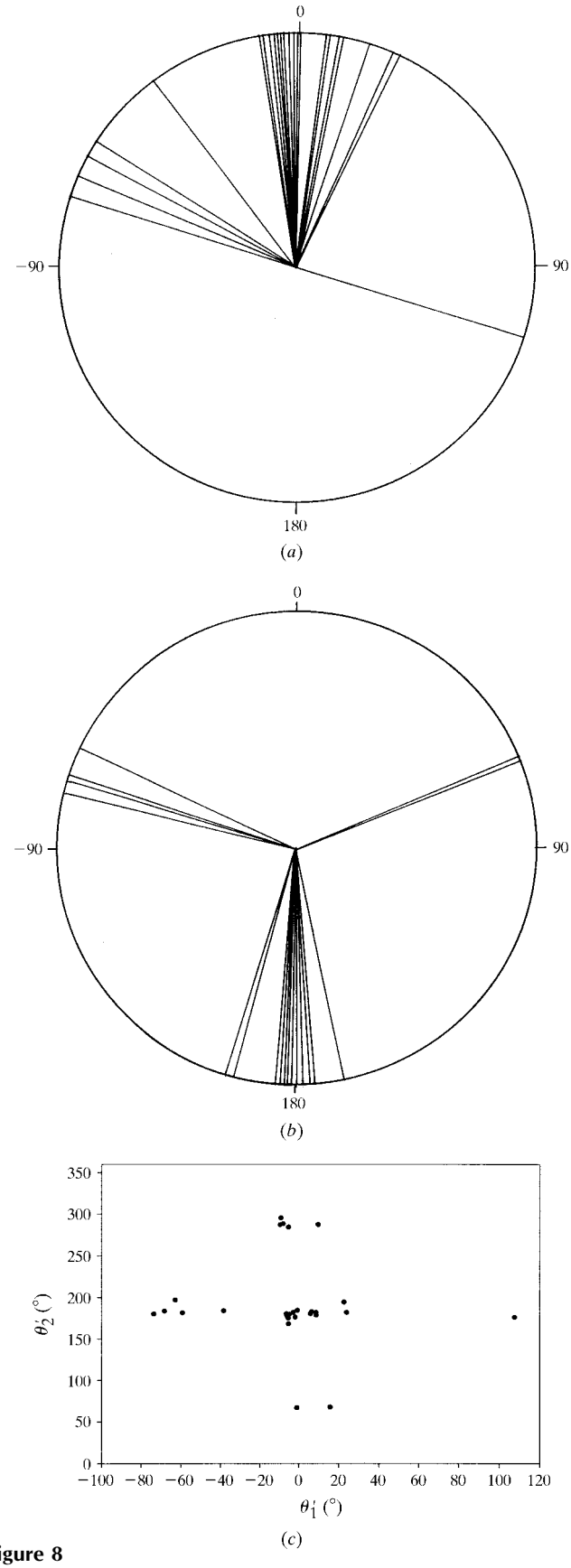


Figure 8
Distribution of (*a*) θ_1 and (*b*) θ_2 observed in crystal structures containing glutaric acid molecules, and semiglutarate and glutarate ions. (*c*) Combined distribution of θ_1 and θ_2.

and six crystallographically independent semiglutarate ions. Seven glutaric acid molecules, one glutarate ion and one semiglutarate ion are observed in other crystal structures (Morrison & Robertson, 1949; Karle *et al.*, 1997; Liao *et al.*, 1996; Vanier & Brisse, 1982). The torsion angles that define their conformation are illustrated in Fig. 7. In the glutaric acid molecule and the glutarate ion, the two halves of the molecule are chemically equivalent. They are not in the semiglutarate ion, but the distribution of θ_1 and θ_1', and θ_2 and θ_2' do not show any stricking differences. Therefore, θ_1 and θ_1', and θ_2 and θ_2' are clubbed together in the illustrations given in Figs. 8(*a*)–(*c*). Clearly θ_1 has preferred values around 0°, although departures from this value frequently occur. Understandably, θ_2 has values corresponding to the three staggered conformations, with the *trans* conformation occurring much more frequently than the other two. Thus, the three species of glutaric acid prefer a fully extended conformation with low barrier against departures from it.

4.3. Molecular aggregation

The glutaric acid complexes of lysine, arginine and histidine exhibit considerable variation in amino acid aggregation, among themselves. In fact, the patterns in DL- and L-lysine complexes and form *B* of the histidine complex are different from those observed so far in structures containing amino acids. In contrast, the amino acid molecules in the L-arginine complex and form *A* of the L-histidine complex follow the familiar patterns observed in other complexes. The patterns in DL-lysine and L-lysine complexes (Saraswathi *et al.*, 2001) are entirely different. However, the pattern in L-arginine hemiglutarate is almost exactly the same as that in DL-arginine acetate. Such contrasting effects caused by a change in chirality have been observed several times in amino acid complexes. In several cases, the reversal in the chirality of half the amino acid molecules leads to drastic changes in amino acid aggregation. In other cases, the effect of the reversal is accommodated through small changes in essentially the same aggregation pattern.

The glutarate ion in L-arginine hemiglutarate monohydrate, with two deprotonated carboxylate groups, cannot interact among themselves through hydrogen bonds. The remaining four glutaric acid complexes contain semiglutarate ions. Infinite chains stabilized by O—H···O hydrogen bonds between the carboxyl and carboxylate groups of neighbouring ions are formed in two of them. In the other two, each semiglutarate ion or pairs of them are surrounded by amino acid molecules. Such variations in aggregation are exhibited by other dicarboxylic acids also in their amino acid complexes.

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