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X-ray studies on crystalline complexes involving amino acids and peptides. XL. Conformational variability, recurring and new features of aggregation, and effect of chirality in the malonic acid complexes of DL- and L-arginine

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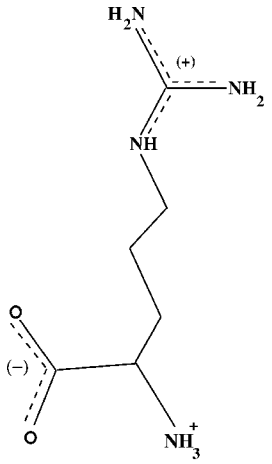
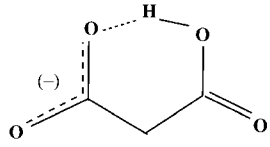
The crystal structures of the complexes of malonic acid with DL- and L-arginine, which contain positively charged argininium ions and negatively charged semimalonate ions, further demonstrate the conformational flexibility of amino acids. A larger proportion of folded conformations than would be expected on the basis of steric consideration appears to occur in arginine, presumably because of the requirements of hydrogen bonding. The aggregation pattern in the DL-arginine complex bears varying degrees of resemblance to patterns observed in other similar structures. An antiparallel hydrogen-bonded dimeric arrangement of arginine, and to a lesser extent lysine, is a recurring motif. Similarities also exist among the structures in the interactions with this motif and its assembly into larger features of aggregation. However, the aggregation pattern observed in the L-arginine complex differs from any observed so far, which demonstrates that all the general patterns of amino-acid aggregation have not yet been elucidated. The two complexes represent cases where the reversal of the chirality of half the amino-acid molecules leads to a fundamentally different aggregation pattern.

1. Introduction

This laboratory is pursuing a long-range programme that aims to elucidate the geometrical features of possible biomolecular interactions at atomic resolution. We primarily employ an approach that involves the preparation and X-ray analysis of crystalline complexes of amino acids and peptides. The results of the programme have provided valuable information on interaction and aggregation patterns of amino acids and peptides and the effect of chirality on these patterns (Suresh & Vijayan, 1983*a*,*b*, 1985; Vijayan, 1980, 1988; Saraswathi & Vijayan, 2002). Our results also have interesting implications for the role of molecular interactions and aggregation in abiotic polymerization, for chiral discrimination and self-assembly during chemical evolution and the origin of life (Vijayan, 1980, 1988; Saraswathi & Vijayan, 2001). The current focus of the programme is on complexes of basic amino acids with carboxylic acids that are believed to have existed in the prebiotic milieu. In this context, the complexes that involve formic, acetic, succinic, glycolic, oxalic, maleic and glutaric acids have already been analysed (Prasad & Vijayan, 1993*a*; Suresh *et al.*, 1994; Suresh & Vijayan, 1995, 1996; Chandra *et al.*, 1998; Pratap *et al.*, 2000; Saraswathi & Vijayan, 2001). Also determined are the structures of malonic-acid complexes of DL- and L-histidine (Saraswathi & Vijayan, 2002). Here we report the complexes of malonic acid with DL- and L-arginine.



(I)



(II)

2. Materials and methods

Crystals of the L-arginine complex were obtained by the diffusion of butanol into an aqueous solution of L-arginine (Sigma) and malonic acid (AR, E-Merck) that were mixed in a 1:1.5 molar ratio. DL-Arginine (Sigma) and malonic acid mixed in a 1:2 molar ratio were used to grow the crystals of the DL-arginine complex with isopropyl alcohol as the precipitant. 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 refined by the full-matrix least-squares method using *SHELXL*97 (Sheldrick, 1997*b*). The water H atoms and the H atoms that belong to the carboxyl group of the semimalonate ions 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 1
Experimental details.

	DL-Arginine	L-Arginine
Crystal data		
Chemical formula	$C_6H_{15}N_4O_2\cdot C_3H_3O_4\cdot H_2O$	$C_6H_{15}N_4O_2\cdot C_3H_3O_4$
Chemical formula weight	296.29	278.27
Cell setting, space group	Monoclinic, $C2/c$	Triclinic, $P1$
a, b, c (Å)	19.559 (2), 5.0296 (6), 28.407 (4)	5.353 (6), 6.931 (8), 9.922 (11)
α, β, γ (°)	90, 90.553 (2), 90	69.530 (16), 89.035 (17), 71.128 (16)
V (Å^3)	2794.3 (6)	324.4 (6)
Z	8	1
D_x (Mg m^{-3})	1.409	1.425
Radiation type	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.121	0.120
Temperature (K)	293 (2)	293 (2)
Crystal form, colour	Platy, colourless	Platy, colourless
Crystal size (mm)	0.47 × 0.07 × 0.05	0.42 × 0.27 × 0.15
Data collection		
Diffractometer	CCD	CCD
Data collection method	ω–2θ scans	ω–2θ scans
No. of measured, independent and observed reflections	11194, 2077, 1471	3424, 2525, 2415
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0856	0.0304
θ_{max} (°)	23.52	27.27
Range of h, k, l	$-21 \rightarrow h \rightarrow 21$ $-5 \rightarrow k \rightarrow 5$ $-31 \rightarrow l \rightarrow 31$	$-6 \rightarrow h \rightarrow 6$ $-8 \rightarrow k \rightarrow 8$ $-12 \rightarrow l \rightarrow 12$
Refinement		
Refinement on	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0685, 0.1408, 1.115	0.0384, 0.1068, 0.978
No. of reflections and parameters used in refinement	2077, 193	2525, 176
H-atom treatment	Mixed	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0582P)^2 + (0.2137P)]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0838P)^2 + (0.0032P)]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.000	0.000
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.214, −0.215	0.296, −0.173

Computer programs used: *SMART*, *SAINT* (Bruker, 2001), *SHELXS*97 (Sheldrick, 1997*a*), *SHELXL*97 (Sheldrick, 1997*b*), MS Word 2000.

3. Results and discussion

3.1. Molecular structure

Perspective views of the molecules in the two structures are given in Fig. 1. The arginine molecules (I) are positively charged with protonated α-amino and guanidyl groups and deprotonated α-carboxylate groups in both structures. Malonic-acid molecules (II) exist as negatively charged semimalonate ions in both structures. The torsion angles that define the conformation of the molecules are listed in Table 2.

Our work with crystalline complexes has provided a measure of the conformational variability of amino-acid side chains, as we have been examining a few amino acids in different environments. This is particularly relevant to long side chains like that of arginine. The side-chain conformation of arginine is defined by torsion angles χ^1, χ^2, χ^3, χ^4 and χ^5 (IUPAC-IUB Commission on Biochemical Nomenclature, 1970). Because of the planarity of the guanidyl group, χ^5[1] is always close to zero. χ^4 represents a rotation about an sp^3–sp^2 bond and has preferred values in the neighbourhood of $\pm 90^\circ$ and 180°. χ^1, χ^2 and χ^3 represent rotations about C—C single bonds and each has preferred values of around $\pm 60^\circ$ and 180°. Thus, the argininyl side chain can assume 81 unique conformations. Of these, 18 have been observed in 57 crystal structures that contain arginine but do not contain metal ions (Prasad & Vijayan, 1990; Cambridge Structural Database, 2002). The side chain of the argininium ion in L-arginine

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE0019). Services for accessing these data are described at the back of the journal.

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

The IUPAC-IUB nomenclatures for the torsion angles are indicated in parentheses.

DL-Arginine complex		L-Arginine complex	
N1—C2—C1—O1 (ψ^1)	−28.9 (4)	N1—C2—C1—O1 (ψ^1)	−30.3 (2)
N1—C2—C3—C4 (χ^1)	−177.0 (3)	N1—C2—C3—C4 (χ^1)	−63.2 (2)
C2—C3—C4—C5 (χ^2)	174.4 (3)	C2—C3—C4—C5 (χ^2)	177.3 (2)
C3—C4—C5—N6 (χ^3)	−177.4 (3)	C3—C4—C5—N6 (χ^3)	70.1 (2)
C4—C5—N6—C7 (χ^4)	92.1 (4)	C4—C5—N6—C7 (χ^4)	−120.1 (2)
C5—N6—C7—N8 (χ^{51})	−1.1 (6)	C5—N6—C7—N8 (χ^{51})	8.3 (3)
O11—C13—C14—C15	3.4 (6)	O11—C13—C14—C15	−1.2 (3)
C13—C14—C15—O16	−4.9 (6)	C13—C14—C15—O16	4.4 (3)

malonate is the 19th unique conformation to be observed in crystal structures. The conformation that is found for the ion in the DL-arginine complex has already been observed in six other complexes (Prasad & Vijayan, 1990; Chandra *et al.*, 1998; Srinivasan & Rajaram, 1997; Wang *et al.*, 1994; Venkatraman *et al.*, 1997; Nagata *et al.*, 1995).

An extended side chain *trans* to the α-carboxylate group is considered to be the preferred conformation of amino acids, especially those with long side chains. This statement is certainly true of lysine (Prasad & Vijayan, 1991), which is structurally very similar to arginine except for the replacement of the guanidyl group by an amino group. However, as can be seen from Fig. 2, which gives the distributions of χ^1, χ^2, χ^3 and χ^4 that are observed in crystal structures that contain arginine, this statement is not true of arginine. The values of χ^1, which define the orientation of the side chain with respect to the rest of the molecule, are nearly evenly distributed in regions around 60°, 180° and −60°, whereas, in general, values of around −60° (side chain *trans* to the α-carboxylate group) are favoured in amino acids. χ^2 is the only torsion angle that shows an overwhelming preference for one of the three possibilities; almost all the values are around 180°, which corresponds to a *trans* conformation. Most of the values of χ^3 are around 180°, but a number of them also occur around 60° and −60°. The scatter is higher in χ^4, presumably because the guanidyl group is invariably involved in hydrogen bonding. Hydrogen bonds appear to be responsible for the occurrence of a larger proportion of folded conformations than would be expected based on simple steric considerations. Among the functional groups present in amino acids, the guanidyl group has the highest hydrogen-bonding potential. The group also has a high potential to take part in specific interactions (Salunke & Vijayan, 1981; Vijayan, 1988) that involve stringent geometrical requirements. These requirements seem to outweigh preferences based on steric considerations.

The semimalonate ion has the same planar conformation as it has in its complexes with histidine (Saraswathi & Vijayan, 2002) and in many other structures (Briggman & Oskarsson, 1978; Djinovic *et al.*, 1990; Kalsbeek, 1992; Barnes & Weakley, 2000). The conformation is stabilized by an internal hydrogen bond, which is short but asymmetric (Tables 3 and 4).

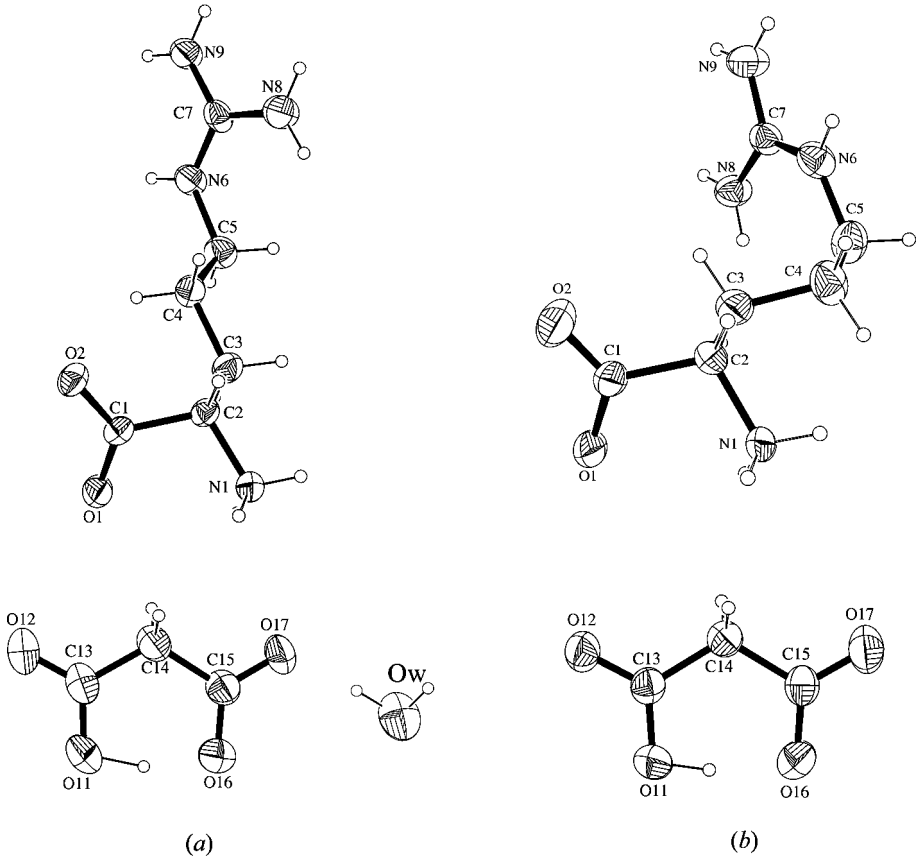


Figure 1
ORTEP diagrams of argininium and semimalonate ions in (*a*) the DL-arginine complex and (*b*) the L-arginine complex. The displacement ellipsoids are at the 50% probability level. The numbering scheme is indicated. All figures except Fig. 2 were generated using *ORTEP*3 (Farrugia, 1998).

3.2. Hydrogen bonding and crystal structure

The crystal structures of the two complexes are given in Figs. 3 and 4. The parameters of the hydrogen bonds that are present in the structures are listed in Tables 3 and 4.

As in many other binary complexes that involve amino acids, the unlike molecules in the DL-arginine complex aggregate into alternating layers (Vijayan, 1988; Venkatraman *et al.*, 1997; Pratap *et al.*, 2000) that are stacked perpendicular to the longest crystallographic axis. In each amino-acid layer, argininium ions form dimers around inversion centres. In each dimer, the ions are in an anti-parallel arrangement and are held together by two type *B* specific interactions (Salunke & Vijayan, 1981; Vijayan, 1988), which are related to

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

D—H···A	d(H···A) (Å)	d(D···A) (Å)	<DHA (°)
N1—H1A···O2^{i}	1.95	2.828 (4)	171
N1—H1B···O21^{ii}	1.878	2.746 (4)	165
N1—H1C···O2^{iii}	2.18	3.006 (3)	154
N6—H6···O2^{iv}	2.08	2.926 (4)	170
N8—H8A···O11^{v}	2.29	3.118 (5)	161
N8—H8B···O16	2.07	2.918 (4)	171
N9—H9A···O1^{iv}	2.14	2.905 (4)	149
N9—H9B··· O17	1.96	2.823 (3)	176
O11—H11···O16	1.36 (6)	2.443 (5)	158 (5)
OW—HWA···O17^{vi}	1.94 (5)	2.788 (5)	170 (4)
OW—HWB···O12^{vii}	1.76 (6)	2.710 (5)	165 (5)

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

each other by an inversion centre. Each specific interaction involves two parallel hydrogen bonds between the guanidyl group of one ion and the α-carboxylate group of the other. These dimers form a ribbon along **a**. Adjacent dimers in the ribbon are connected by an N—H···O hydrogen bond between an α-carboxylate and an amino group and this bond's centrosymmtric equivalent. They are then stacked along **b**. Adjacent ribbons are connected by an N—H···O hydrogen bond. This hydrogen bond, and its equivalents produced by **b** translation, form a head-to-tail sequence in which the α-amino and the α-carboxylate groups of adjacent molecules are brought into periodic hydrogen-bonded proximity (Vijayan, 1980, 1988; Suresh & Vijayan, 1983*a*,*b*).

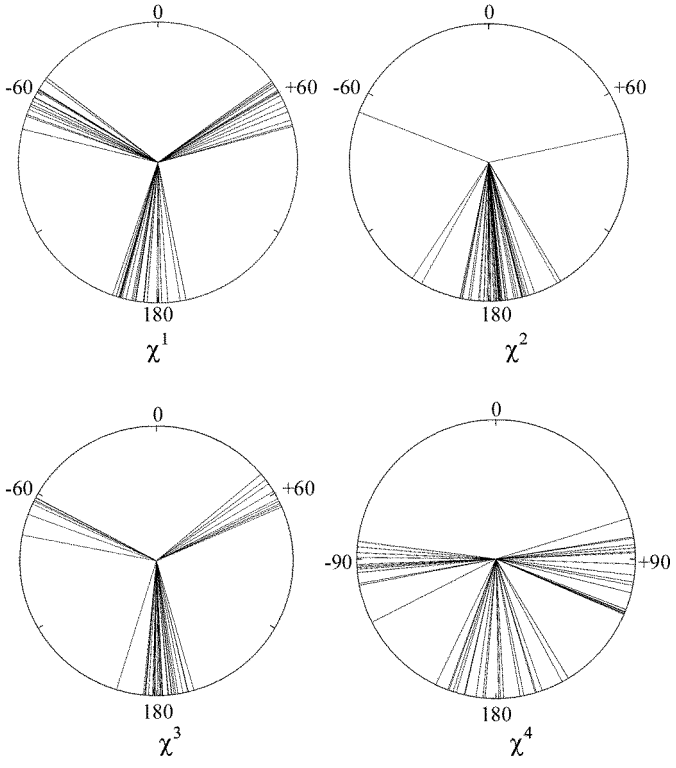


Figure 2
Distribution of the torsion angles that define the conformation of the arginyl side chain in crystal structures. See the text for details. Generated using the program *ORIGIN*, version 5.0.

Table 4
Parameters of hydrogen bonds in the L-arginine complex.

D—H···A	d(H···A) (Å)	d(D···A) (Å)	<DHA(°)
N1—H1A···O17	2.03	2.778 (4)	141
N1—H1B···O1^{i}	1.90	2.724 (4)	152
N1—H1C···O12^{ii}	2.03	2.811 (3)	146
N6—H6···O12^{iii}	2.21	3.033 (4)	159
N8—H8A···O2^{iv}	2.07	2.853 (4)	152
N8—H8B···O16^{v}	2.2	3.056 (3)	175
N9—H9A···O1^{iv}	2.26	2.865 (4)	127
N9—H9B···O17^{v}	2.04	2.900 (3)	178
O11—H11···O16	1.49 (7)	2.423 (3)	165 (7)

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

Adjacent layers of amino acids are connected through a layer of semimalonate ions and water molecules. Semimalonate ions, which are interconnected by water molecules, form twofold helices around 2_1 screw axes. The helices are

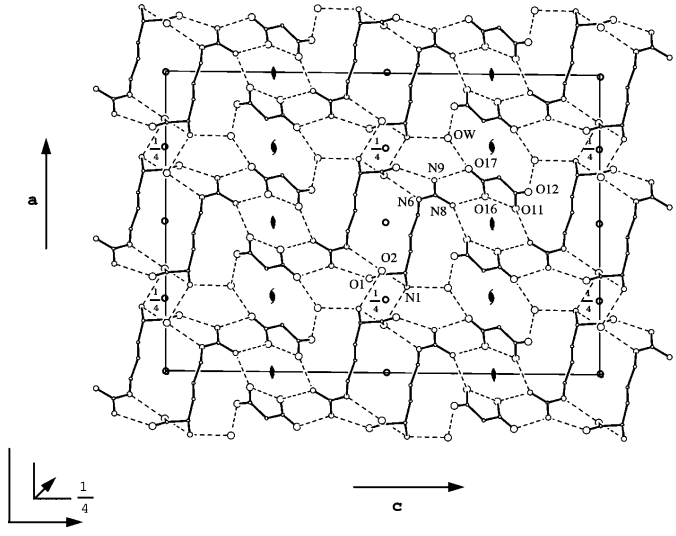


Figure 3
Crystal structure of the DL-arginine complex.

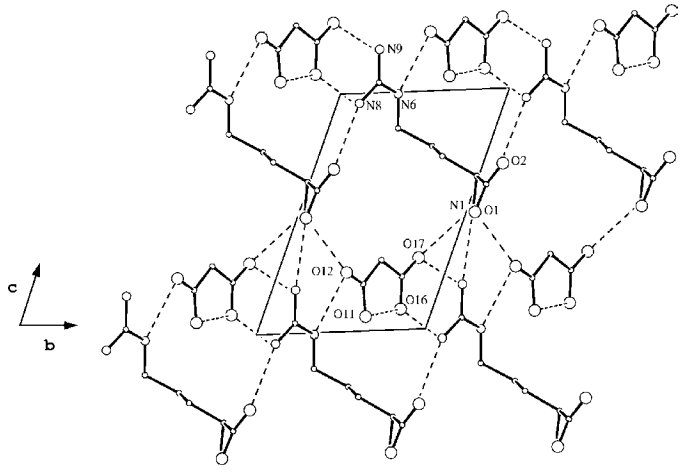


Figure 4
Crystal structure of the L-arginine complex.

stacked along **a** to form a layer. The helices do not interact among themselves. They are interconnected by the amino-acid molecules. Only the side chain of the argininium ion interacts with the semimalonate ion. This interaction includes a type *A* guanidyl–carboxylate specific interaction (Salunke & Vijayan, 1981; Vijayan, 1988).

The aggregation pattern in the L-arginine complex is entirely different from that in the DL-arginine complex. It is also different from any observed so far in crystals that contain amino acids. The unlike molecules do not aggregate into alternating layers. The amino-acid molecules form columns that are stabilized by head-to-tail sequences and are parallel to the shortest cell dimension. The columns are interconnected primarily by interactions between the guanidyl group and the α-carboxylate group. The voids that are left behind by the resulting arrangement of amino-acid molecules are filled by semimalonate ions. Most of the interactions of the semimalonate ions with the amino-acid molecules involve the guanidyl group; a specific interaction of type *A* also involves this group (Salunke & Vijayan, 1981; Vijayan, 1988). Semimalonate ions interact with α-amino groups as well.

3.3. Comparison with similar structures and conclusions

Our work on crystalline complexes has shown that amino acid and peptide aggregation follow a few, often predictable, general patterns and their variants. The structure of L-arginine semimalonate demonstrates that all the general patterns have not yet been elucidated. As mentioned earlier, the aggregation pattern in the structure appears to differ from those observed so far.

The aggregation pattern in the DL-arginine complex, on the other hand, bears varying degrees of resemblance to those observed in other similar complexes. To begin with, aggregation into alternating layers of unlike molecules is observed in most of these complexes. Furthermore, as illustrated in Fig. 5, dimerization involving an antiparallel arrangement of arginine molecules/argininium ions occurs widely (Suresh *et al.*, 1994; Chandra *et al.*, 1998; Prasad & Vijayan, 1990; Soman *et al.*, 1990). Most often the two molecules are related by an inversion centre. In many instances, the similarity among structures also extends to interactions with the carboxylic acids that flank the dimer. Interestingly, there are structures in which lysine molecules also dimerize in an antiparallel fashion (Venkatraman *et al.*, 1997; Suresh & Vijayan, 1995). The way in which the dimers are interconnected to form ribbons and then layers in DL-arginine semimalonate has also been observed in other complexes that involve arginine (Suresh & Vijayan, 1983*a*,*b*; Soman *et al.*, 1989; Chandra *et al.*, 1998; Suresh *et al.*, 1994) and lysine (Venkatraman *et al.*, 1997; Suresh & Vijayan, 1995). Thus, although new patterns of amino-acid aggregation are still being identified, the aggregation of these molecules appears to follow a few well defined patterns or their variants.

Our work on complexes has also consistently addressed the question of the effect of chirality on molecular aggregation. In the crystal structures of amino acids, the effect of the reversal of chirality of half the molecules (as in the comparison between DL- and L-amino-acid structures) is mostly accommodated through minor rearrangements while the essentials of the aggregation pattern are retained (Soman *et al.*, 1989; Nandhini *et al.*, 2001). This happens only in a few instances in the carboxylic-acid complexes of amino acids (Soman *et al.*, 1988, 1989; Soman & Vijayan, 1989, and references therein; Prasad & Vijayan, 1993*b*; Ravishankar *et al.*, 1998; Saraswathi & Vijayan, 2002). Most often, reversal of chirality in half the amino-acid molecules leads to a different aggregation pattern (Suresh *et al.*, 1986, 1994; Soman *et al.*, 1990; Venkatraman *et al.*, 1997; Chandra *et al.*, 1998; Saraswathi *et al.*, 2001). There are cases where the patterns in the DL- and L-amino-acid complexes retain some elements of similarity (Hu *et al.*, 1989; Nandhini *et al.*, 2001; Saraswathi & Vijayan, 2002). The structures of the malonic-acid complexes of arginine represent cases where the two patterns are altogether different.

The diffraction data were collected using a CCD facility and the computations were performed at the Supercomputer Education and Research Centre at the Indian Institute of

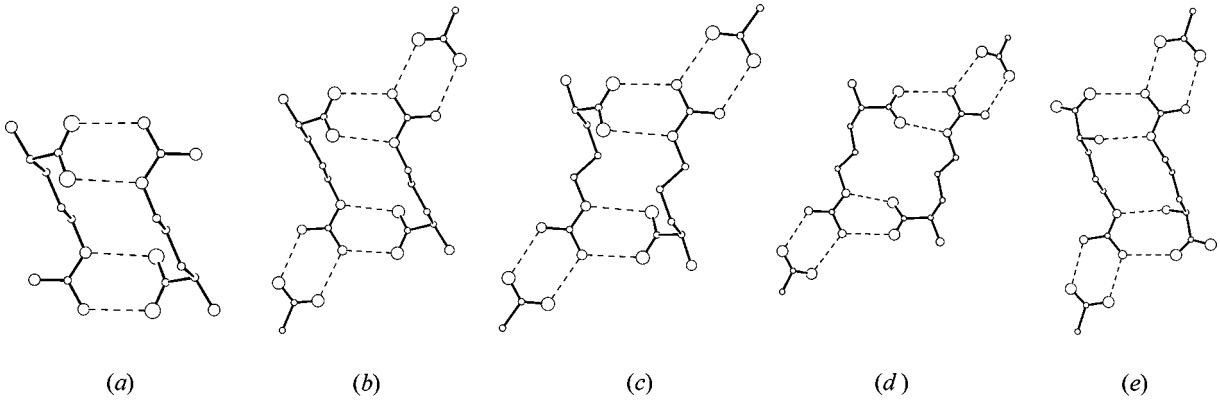


Figure 5
Dimers that involve an antiparallel arrangement in the structures in the complexes of DL-arginine with (*a*) oxalic, (*b*) malonic and (*c*) succinic acids and (*d*) DL-glutamate, and in the structures of (*e*) DL-arginine dihydrate. Type *A* specific interactions of the guanidyl groups with carboxylate groups also exist in most of the complexes.

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