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X-ray studies on crystalline complexes involving amino acids and peptides. XXXVII. Novel aggregation patterns and effect of chirality in the complexes of DL- and L-lysine with glutaric acid

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The complexes of glutaric acid with DL-lysine contain singly positively charged zwitterionic lysinium ions and singly negatively charged semi-glutarate ions. Both the ions exhibit different conformations in the two complexes. The structures contain head-to-tail sequences of amino acids. However, the aggregation patterns in the two complexes are entirely different, demonstrating the effect of chirality on molecular aggregation. These patterns also turn out to be different from those so far observed, in structures containing amino acids. The structures contain characteristic interaction patterns involving linear arrays of alternating amino and carboxylate groups.

1. Introduction

In addition to its original objective of elucidating at the atomic resolution the geometrical features of possible non-covalent interactions involving proteins (Bhat & Vijayan, 1976; Suresh & Vijayan, 1983; Vijayan, 1988), our program on crystalline complexes of amino acids and peptides appears to have implications on the role of molecular interactions and aggregation in prebiotic polymerization, chiral discrimination and self-assembly during chemical evolution and the origin of life (Vijayan, 1980; Suresh & Vijayan, 1983; Vijayan & Suresh, 1985; Vijayan, 1988; Ravishankar *et al.*, 1998). The current focus of the program is on complexes with simple carboxylic acids including those believed to have existed in the prebiotic milieu. The results of the programme have been particularly interesting in relation to aggregation and interaction patterns, and the variabilities in stoichiometries and ionization states. Indeed the complexes illustrate how the behaviour of one type of molecule is modified in the presence of another. In most instances, the L and DL forms of the same amino acid were complexed with the same carboxylic acid and the comparison of the two structures in each case gave evidence for the effect of chirality on aggregation and molecular characteristics. In one instance, the study led to the first demonstration of chiral separation of amino acids using an achiral molecule (Suresh & Vijayan, 1996).

For obvious reasons, the complexes studied have primarily involved the basic amino acids lysine, arginine and histidine. The carboxylic acids complexed with them have been formic, acetic, succinic, glycolic, oxalic and maleic acid (Prasad &

Vijayan, 1993*a*; Suresh, Prasad & Vijayan, 1994; Suresh & Vijayan, 1995*b*, 1996; Chandra *et al.*, 1998; Pratap *et al.*, 2000). Here we report the crystal structures of the complexes of glutaric acid, the largest dicarboxylic acid used so far in the program, with DL- and L-lysine.

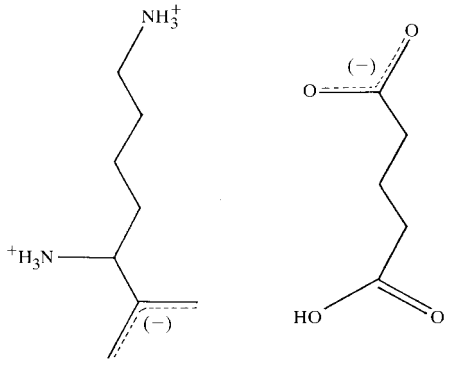
2. Experimental

Crystals of the L-lysine complex were obtained by the diffusion of isobutyl alcohol into an aqueous solution of L-lysine (Sigma) and glutaric acid (AR, E-Merck) mixed in a 1:3 molar ratio. DL-Lysine (Sigma) and glutaric acid mixed in a 1:2 molar ratio were used for growing the crystals of the DL-lysine complex with 2-propanol 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 full-matrix least-squares using *SHELXL*97 (Sheldrick, 1997*b*). The H atoms were treated as riding on the heavier atoms to which they are attached. The positional and equivalent isotropic thermal parameters of the non-H atoms in the two structures are given as supplementary material.[1]

3. Results and discussion

3.1. Molecular dimensions

Perspective views of the molecules in the two structures are given in Fig. 1. The lysine molecules in both the structures are zwitterionic (I) and carry a net positive charge each. The glutaric acid molecules exist as semi-glutarate ions (II) with a neutral carboxyl group and a negatively charged carboxylate



(I) (II)

in each ion. The torsion angles that define the conformation of the molecules are listed in Table 2. The lysine side chains in both the structures have a fully extended conformation. However, the side chain is *trans* to the α-carboxylate group in the DL complex but *trans* to the α-amino group in the L complex, corresponding to sterically the most favourable and the second most favourable arrangements (Prasad & Vijayan, 1991). The semi-glutarate ions have distinctly different conformations in the two structures. The central carbon

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE0009). Services for accessing these data are described at the back of the journal.

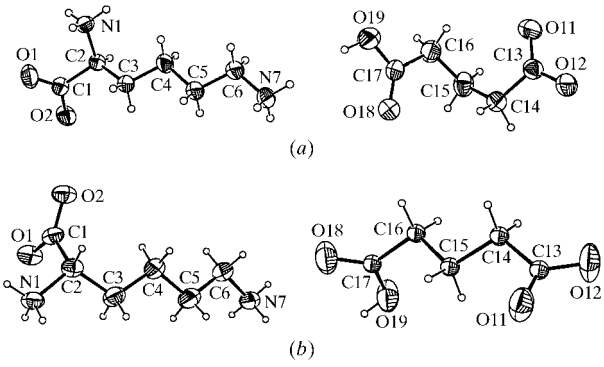


Figure 1
*ORTEP*3 (Farrugia, 1998) diagrams of the lysinium and the semi-glutarate ions in (*a*) the DL-lysine complex and (*b*) the L-lysine complex. The displacement ellipsoids are at the 50% probability level. The numbering scheme is indicated. H atoms are shown as small circles.

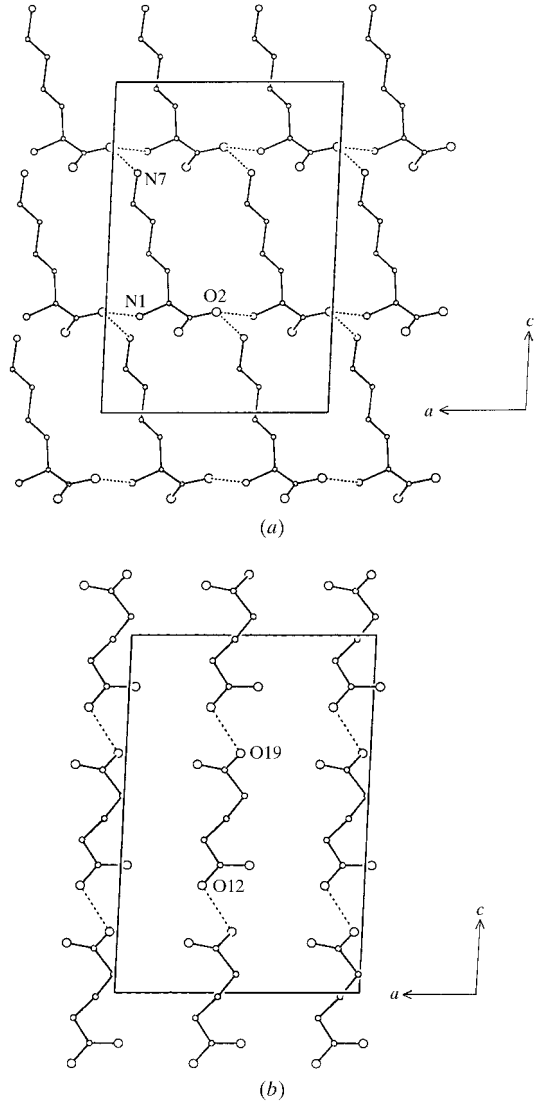


Figure 2
(*a*) Corrugated interconnected sheets of amino acids in the DL-lysine complex. O, N and C atoms are indicated by circles of decreasing size. Only atoms which make hydrogen bonds are labelled. Hydrogen bonds are indicated by broken lines. The same convention is also used in the subsequent figures. (*b*) Arrangement of hydrogen-bonded ribbons of semi-glutarate ions in the DL-lysine complex.

Table 1
Experimental details.

	(I)	(II)
Crystal data		
Chemical formula	$C_6H_{15}N_2O_2\cdot C_5H_7O_4$	$C_6H_{15}N_2O_2\cdot C_5H_7O_4$
Chemical formula weight	278.31	278.31
Cell setting, space group	Monoclinic, I_a	Trigonal, $P3_1$
a, b, c (Å)	10.398 (6), 8.662 (2), 15.393 (6)	9.044 (1), 9.044 (1), 14.943 (3)
α, β, γ (°)	90, 93.06 (2), 90	90, 90, 120
V (Å^3)	1384.4 (10)	1058.5 (3)
Z	4	3
D_x (Mg m^{-3})	1.335	1.310
Radiation type	Cu $K\alpha$	Cu $K\alpha$
No. of reflections for cell parameters	25	25
θ range (°)	10–30	10–30
μ (mm^{-1})	0.917	0.899
Temperature (K)	293 (2)	293 (2)
Crystal form, colour	Rectangular, colourless	Needle, colourless
Crystal size (mm)	0.8 × 0.5 × 0.2	1.0 × 0.44 × 0.31
Data collection		
Diffractometer	CAD-4	CAD-4
Data collection method	ω–2/θ scans	ω–2/θ scans
Absorption correction	Numerical (Dwiggins, 1975)	Empirical (North *et al.*, 1968)
T_{min}	0.7139	0.9454
T_{max}	0.7277	0.9996
No. of measured, independent and observed parameters	2138, 1426, 1382	1745, 1452, 1387
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0198	0.0499
θ_{max} (°)	75.18	75.61
Range of h, k, l	$0 \rightarrow h \rightarrow 13$ $0 \rightarrow k \rightarrow 10$ $-19 \rightarrow l \rightarrow 19$	$0 \rightarrow h \rightarrow 9$ $0 \rightarrow k \rightarrow 9$ $-17 \rightarrow l \rightarrow 18$
No. and frequency of standard reflections	3 every 60 min	3 every 60 min
Refinement		
Refinement on	F^2	F^2
$R[F^2>2\sigma(F^2)]$, $wR(F^2)$, S	0.0398, 0.1517, 1.301	0.063, 0.1418, 1.185
No. of reflections and parameters used in refinement	1426, 174	1452, 174
H-atom treatment	Mixed	Mixed
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0986P)^2 + 0.2437P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0208P)^2 + 1.5074P]$, 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})	0.277, −0.249	0.31, −0.309
Extinction method	*SHELXL*97	*SHELXL*97 (Sheldrick, 1997*b*)
Extinction coefficient	0.0038 (10)	0.035 (2)

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

backbone has a folded conformation in the DL complex, while it has a fully extended conformation in the L complex. The orientations of the terminal carboxyl and carboxylate groups with respect to the rest of the ion are also different in the two structures.

3.2. Molecular aggregation

Both the structures are stabilized by extensive networks of hydrogen bonds. The parameters of these bonds are given in Tables 3 and 4.

In the structure of the DL-lysine complex, the zwitterionic amino acid molecules are arranged in corrugated inter-connected sheets, illustrated in Fig. 2(*a*), while the semi-glutarate ions form hydrogen-bonded ribbons (Fig. 2*b*). They come together in the crystal structure (Fig. 3) in such a way that the ribbons are effectively surrounded by amino acid molecules. Similar arrangements have been observed in other amino acid–carboxylic acid complexes as well (Prasad & Vijayan, 1993*a*; Ravishankar *et al.*, 1998). Linear hydrogen-bonded arrangements of dicarboxylic acids have also been observed previously (Prasad & Vijayan, 1991; Chandra *et al.*, 1998). However, as explained below, the specific aggregation pattern of amino acid molecules observed in the structure is new.

The basic elements of amino acid aggregation in the structure (Fig. 2*a*) are head-to-tail sequences, in which α-amino and α-carboxylate groups are brought into periodic hydrogen-bonded proximity. In each sequence the adjacent molecules are related by an **a** glide and are connected by a N1$\cdots$O2 hydrogen bond. Such a sequence is referred to as a DL2 head-to-tail sequence (Suresh & Vijayan, 1983). DL sequences, often with periodicities close to that in the present structure (10.398 Å), frequently occur in crystals containing D and L amino acids (Suresh *et al.*, 1986; Soman & Vijayan, 1989; Prasad & Vijayan, 1993*a*; Suresh & Vijayan, 1995*a*,*b*). The formation of hydrogen-bonded centrosymmetric dimers is the other frequently occurring mode of aggregation found in crystals containing amino acids of mixed chirality (Soman & Vijayan, 1989; Soman *et al.*, 1989; Prasad & Vijayan, 1990, 1991, 1993*b*; Suresh, Padmanabhan & Vijayan, 1994; Suresh & Vijayan, 1995*a*; Venkatraman *et al.*, 1997). Where the DL2 sequences occur, they often align in such a way as to produce double layers of amino acids (Soman & Vijayan, 1989; Prasad & Vijayan, 1991, 1993*b*; Suresh & Vijayan, 1995*a*). That does not happen in the present structure. The arrays of amino acids involved in DL2 sequences are interconnected by N7$\cdots$O2 hydrogen bonds. The adjacent amino acid arrays in the structure are related by body centring. When one molecule in one array forms a N7$\cdots$O2 hydrogen bond with a molecule related by $a/2 + b/2 + c/2$ in another array, the neighbouring molecule in the first array forms a N7$\cdots$O2 hydrogen bond with a

Table 2
Torsion angles (°) that define the conformation of the molecules.

A—*B*—*C*—*D*	Torsion angle (°)
DL-Lysine complex	
N1—C2—C1—O1 (ψ^1)	−14.0 (4)
N1—C2—C3—C4 (χ^1)	−62.2 (3)
C2—C3—C4—C5 (χ^2)	−170.7 (3)
C3—C4—C5—C6 (χ^3)	−176.4 (3)
C4—C5—C6—N7 (χ^4)	−178.6 (3)
O11—C13—C14—C15	9.8 (5)
C13—C14—C15—C16	−72.9 (4)
C14—C15—C16—C17	−71.8 (4)
C15—C16—C17—O18	−7.9 (5)
L-Lysine complex	
N1—C2—C1—O1 (ψ^1)	−43.6 (6)
N1—C2—C3—C4 (χ^1)	176.6 (5)
C2—C3—C4—C5 (χ^2)	−172.9 (5)
C3—C4—C5—C6 (χ^3)	170.0 (6)
C4—C5—C6—N7 (χ^4)	−171.2 (5)
O11—C13—C14—C15	−38.4 (8)
C13—C14—C15—C16	−176.5 (5)
C14—C15—C16—C17	176.1 (5)
C15—C16—C17—O18	107.5 (7)

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

D—H···*A*	*d*(*D*···*A*) (Å)	∠ *DHA* (°)
N1—H1*A*···O11^{i}	2.849 (4)	161
N1—H1*B*···O2^{ii}	2.780 (4)	151
N1—H1*C*···O18^{iii}	3.054 (4)	137
N7—H7*A*···O2^{iv}	2.779 (4)	160
N7—H7*B*···O12^{v}	2.807 (4)	161
N7—H7*C*···O11^{iv}	2.934 (4)	138
O19—H19···O12^{vi}	2.506 (4)	162

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

molecule related to it by $a/2 - b/2 + c/2$ in yet another array. Thus, as shown in Fig. 3, each array is connected to two other arrays, which are related by $a/2 + b/2 + c/2$ and $a/2 - b/2 + c/2$, leading to a three-dimensional network of amino acid molecules. The hydrogen-bonded semi-glutarate chains are located in the channels formed by the network of amino acid molecules. The interactions between the amino acid molecules and the semi-glutarate ions involve α- and ε-amino groups.

The relation between DL-lysine semi-glutarate and L-lysine semi-glutarate involves the reversal of the chirality of half the molecules of one component in the binary complex. There are instances in which the effects of such a reversal are accommodated through small adjustments, leaving the aggregation pattern essentially unchanged (Soman *et al.*, 1988, 1989). In many other instances, the reversal leads to profound changes in the aggregation pattern (Suresh *et al.*, 1986; Suresh, Padmanabhan & Vijayan, 1994; Soman *et al.*, 1990; Venkatraman *et al.*, 1997; Chandra *et al.*, 1998). The latter is true in lysine semi-glutarate. The aggregation patterns in the DL- and L-lysine complexes are altogether dissimilar.

The arrangement of amino acid molecules in the crystals of L-lysine semi-glutarate is illustrated in Fig. 4. The amino acid molecules related by the 3_1 screw axes at ($2a/3$, $b/3$) form a head-to-tail sequence (Fig. 4) stabilized by a N1···O2 hydrogen bond and its symmetry equivalents. All head-to-tail sequences of amino acids observed so far, except one, are generated by cell translations, 2_1 screw axes or glide planes. The exception is the sequence generated by the threefold screw axis in one crystal form of glycine (Iitaka, 1961). However, the geometrical features of that sequence is entirely different from those of the sequence in L-lysine semi-glutarate. In the complex, the threefold helical sequences are interconnected by interactions involving the side chain amino group in one sequence and the carboxylate group in a neighbouring sequence in such a way that the carbon backbones of lysyl side chains are stacked around the 3_1 screw at ($a/3$, $2b/3$). The interstices around **c** cell edges are occupied by semi-glutarate ions. Unlike in the DL-lysine complex, the semi-glutarate ions do not interact among themselves. The protonated oxygen in the ion hydrogen bonds as a donor with O1 of the amino acid molecule. The other carboxyl/carboxylate O atoms are hydrogen bonded to N1 or N7 as acceptors.

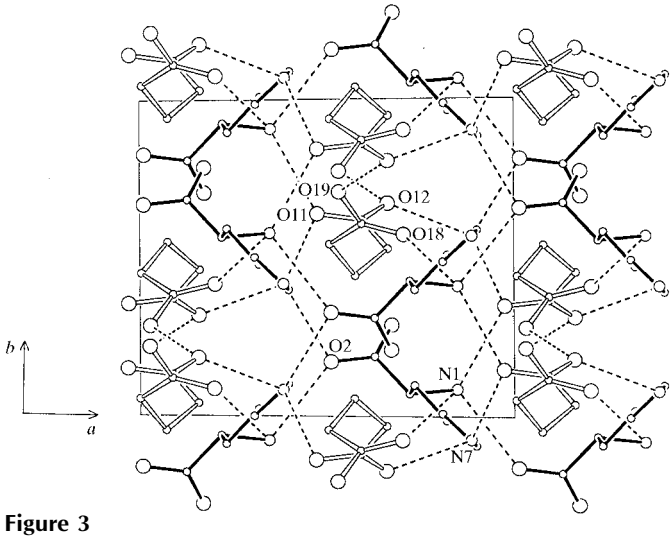


Figure 3
Crystal structure of the DL-lysine complex. Filled and open bonds represent the amino and the glutaric acids, respectively, in this figure and in Fig. 4. Symmetry elements have not been indicated in the figures to minimize overcrowding.

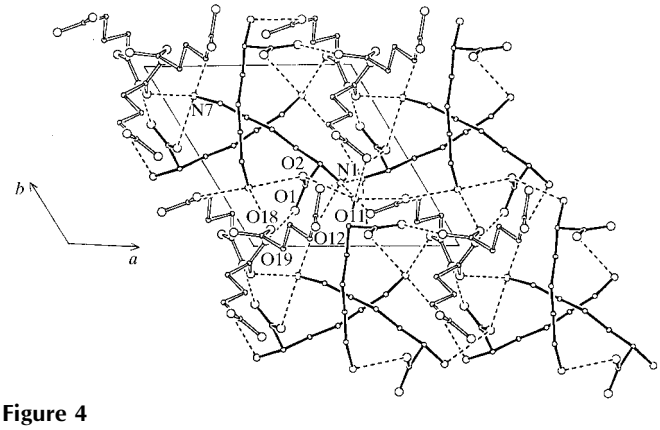


Figure 4
Crystal structure of the L-lysine complex.

3.3. Characteristic interaction patterns

Unlike the guanidyl group of arginine, the amino group cannot take part in specific interactions, but they are often involved in characteristic interaction patterns (Vijayan, 1988; Soman *et al.*, 1988; Suresh, Prasad & Vijayan, 1994; Venkatraman *et al.*, 1997). The most frequently occurring pattern consists of a linear array of alternating amino and carboxylate groups. Both the structures contain such patterns. Each involve the L-lysine α- and ε-amino groups and carboxylate O atoms from both the components in the complex. Those occurring in the two structures are essentially of the same type (Fig. 5), in spite of the fundamentally different aggregation patterns.

4. Concluding remarks

The crystal structures of binary complexes, analysed primarily in this laboratory, have demonstrated the propensity of amino acids to adopt one or other of a few reasonably well defined aggregation patterns. The same has been true about specific interactions and characteristic interaction patterns. The elucidation of such aggregation and interaction patterns are of considerable importance in understanding multi-molecular self-assembly systems, including those involved in the later stages of chemical evolution. The structures reported here reveal two new aggregation patterns. They do, however, contain central elements found in the patterns identified earlier, for example, head-to-tail sequences. The DL2 sequence of the type observed in the DL-lysine complex is a common feature observed in many structures containing amino acids of both chiralities. However, the arrangement of sequences and the interactions among them seen in the present structure have not been observed so far. The linear hydrogen-bonded arrangement of the semi-glutarate ion found in one of the structures has also been observed in a few other amino acid–dicarboxylic acid complexes. A characteristic linear pattern involving alternating amino and carboxylate groups observed often in complexes containing lysine also occur in the present complexes, despite their novel aggregation patterns. Furthermore, the structures once again demonstrate the profound effect a change in chirality can have on molecular aggregation.

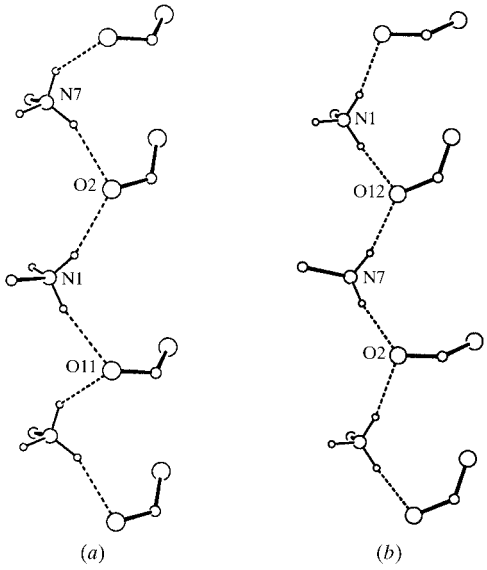


Figure 5
Characteristic interaction pattern in (*a*) the DL-lysine complex and (*b*) the L-lysine complex.

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

D—H$\cdots A$	$d(D\cdots A)$ (Å)	$\angle DHA$ (°)
N1—H1*A*$\cdots$O12^{i}	2.729 (6)	164
N1—H1*B*$\cdots$O2^{ii}	3.096 (6)	162
N1—H1*C*$\cdots$O11^{iii}	2.683 (7)	158
N7—H7*A*$\cdots$O18^{iv}	2.781 (8)	148
N7—H7*B*$\cdots$O2^{v}	2.923 (6)	167
N7—H7*C*$\cdots$O12^{vi}	2.685 (6)	161
O19—H19$\cdots$O1^{vii}	2.502 (7)	147

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

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