Acta Crystallographica Section B
Structural Science
ISSN 0108-7681

Structural relationships in crystals accommodating different stereoisomers of 2-amino-3-methylpentanoic acid

Bjørn Dalhus* and Carl Henrik Görbitz

Department of Chemistry, University of Oslo, PO Box 1033, Blindern, N-0315 Oslo, Norway

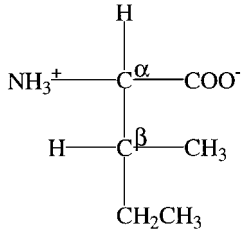
Correspondence e-mail: bjornda@kjemi.uio.no

Received 29 November 1999
Accepted 18 February 2000

A reinvestigation of the crystal structure of the 1:1 mixture of the two racemates DL-isoleucine and DL-*allo*-isoleucine, with a detailed analysis of interatomic distances between alternative side-chain positions, reveals a systematic distribution of the four stereoisomers in this crystal. Two different molecular chains exist in the crystal and each such chain accommodates a single diastereomeric pair only (L-isoleucine:D-*allo*-isoleucine or D-isoleucine:L-*allo*-isoleucine). The crystal is built up by a stacking of such chains in two dimensions and three different packing modes for the two types of chains are discussed. Crystallization experiments of the two individual racemates in the 1:1 mixture of DL-isoleucine:DL-*allo*-isoleucine have been undertaken. The structure of the racemate DL-isoleucine is presented. The molecular arrangements in this racemate and the 1:1 DL-isoleucine:DL-*allo*-isoleucine mixture are closely related. Furthermore, the spontaneous resolution of enantiomers upon crystallization of the other racemate, DL-*allo*-isoleucine, is rationalized on the basis of the aforementioned analysis of interatomic distances in the 1:1 DL-isoleucine:DL-*allo*-isoleucine complex. Structural data for a new L-isoleucine: D-*allo*-isoleucine complex are also given.

1. Introduction

The α-amino acid 2-amino-3-methylpentanoic acid (isoleucine) embodies two chiral C atoms, C^{α} and C^{β} (I), and consequently four stereoisomers exist. The isomer with absolute configuration *S* at both C^{α} and C^{β} (denoted [*S,S*]) is the naturally occurring α-amino acid L-isoleucine (L-Ile), while the [*R,R*]-isomer represents its enantiomer, D-isoleucine (D-Ile). The two stereoisomers [*S,R*] and [*R,S*] are L-*allo*-isoleucine (L-*allo*-Ile) and D-*allo*-isoleucine (D-*allo*-Ile), respectively. The four stereoisomers can form a total of four different 1:1 complexes; the racemates L-Ile:D-Ile [DL-Ile, (1)] and L-*allo*-Ile:D-*allo*-Ile [DL-*allo*-Ile, (2)] as well as the two diastereomeric complexes L-Ile:D-*allo*-Ile (3) and L-Ile:L-*allo*-Ile (4), Table 1. As part of our program dealing with hydrogen-bond geometries in the crystal structures of hydrophobic amino



acids (Dalhus & Görbitz, 1999, and references therein) crystallization experiments with these complexes have been

carried out and in this paper we describe the crystal structures of the racemate DL-Ile (1) and the 1:1 complex L-Ile:D-*allo*-Ile (3).

Additionally, we have redetermined the crystal structures of the 1:1:1:1 complex L-Ile:D-Ile:L-*allo*-Ile:D-*allo*-Ile (5), containing all four stereoisomers, and D-*allo*-Ile (6). These two structures have previously been reported by Benedetti *et al.* (1973) and Varughese & Srinivasan (1975), respectively, but the precision of the structural parameters is low by current standards, with no information on the hydrogen-bond geometries.

Crystal structures of seven 1:1 complexes of L-isoleucine with selected hydrophobic D-amino acids have been presented elsewhere (Dalhus & Görbitz, 1999).

2. Experimental

2.1. Crystallization

Aqueous solutions of the four 1:1 mixtures (1)–(4) (Table 1) as well as the equimolar mixture of all four stereoisomers (5) (Table 1) were prepared. Typically, 5–10 mg of each of the amino acids in question were mixed and dissolved in 1000–1500 µl of water. The various amino acid solutions were then mixed with tetramethoxysilane in the ratio 10:1 and 100–150 µl of the resulting mixtures were dispensed in each of 10–12 30 × 5 mm test-tubes, sealed with parafilm and left for some minutes to polymerize. Applying the vapor diffusion technique, ethanol or 2-propanol subsequently diffused into the gel at room temperature.

Table 1
Various complexes of different stereoisomers of 2-amino-3-methylpentanoic acid.

No.	Stereochemical configuration	Complex
(1)	[*S*,*S*]:[*R*,*R*]	L-Ile:D-Ile
(2)	[*S*,*R*]:[*R*,*S*]	L-*allo*-Ile:D-*allo*-Ile
(3)	[*S*,*S*]:[*R*,*S*]	L-Ile:D-*allo*-Ile
(4)	[*S*,*S*]:[*S*,*R*]	L-Ile:L-*allo*-Ile
(5)	[*S*,*S*]:[*R*,*R*]:[*S*,*R*]:[*R*,*S*]	L-Ile:D-Ile:L-*allo*-Ile:D-*allo*-Ile

Thin and soft plates of racemate (1) were formed with either alcohol as precipitating agents. Only a few crystals extinguished and brightened satisfactorily when rotated in plane-polarized light, and the specimen used for data collection (from the ethanol batch) was selected after testing a large number of crystals. The diffraction patterns for some of the other crystals are essentially two-dimensional with substantial streaking along c^*.

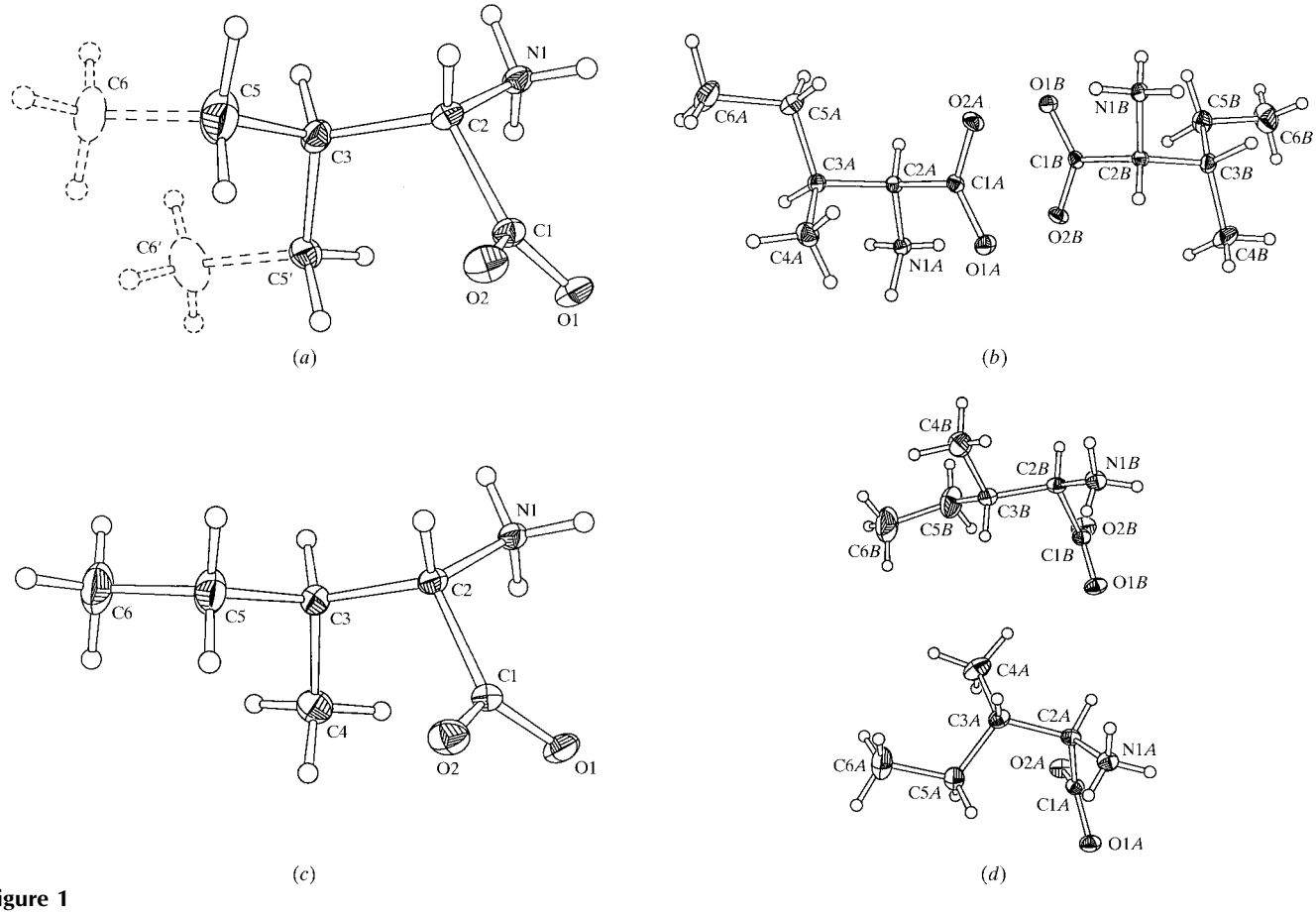


Figure 1
The asymmetric unit with atomic numbering for (*a*) DL-Ile:DL-*allo*-Ile (5), (*b*) L-Ile:D-*allo*-Ile (3) [molecule *A* is L-Ile and molecule *B* is D-*allo*-Ile], (*c*) DL-Ile [L-isomer only] (1) and (*d*) D-*allo*-Ile (6). Displacement ellipsoids are drawn at the 50% probability level. H atoms are arbitrarily scaled. In (*a*) the disordered C^{δ} methyl groups (C6 and C6′ with bonded H atoms) are dotted and the disordered $C^{\gamma 2}$ methyl groups (C4 and C4′ with bonded H atoms) have been omitted for clarity.

Table 2
Experimental details.

	(1)	(3)	(5)	(6)
Crystal data				
Chemical formula	$C_6H_{13}NO_2$	$C_6H_{13}NO_2$	$C_6H_{13}NO_2$	$C_6H_{13}NO_2$
Chemical formula weight	131.17	131.17	131.17	131.17
Cell setting	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	$P\overline{1}$	$P1$	$P\overline{1}$	$P2_1$
a (Å)	5.2289 (1)	5.2438 (2)	5.2493 (1)	9.6706 (1)
b (Å)	5.4102 (1)	5.3978 (2)	5.4006 (1)	5.2583 (1)
c (Å)	13.1095 (3)	13.2562 (6)	13.2778 (2)	14.1018 (2)
α (°)	96.332 (1)	93.042 (1)	92.9433 (6)	90
β (°)	90.622 (1)	92.811 (1)	92.8659 (5)	98.033 (1)
γ (°)	109.493 (1)	109.897 (1)	109.8571 (7)	90
V (Å^3)	347.02 (1)	351.42 (2)	352.66 (1)	710.05 (2)
Z	2	2	2	4
D_x (Mg m^{-3})	1.255	1.240	1.235	1.227
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
No. of reflections for cell parameters	4333	3483	6724	7959
μ (mm^{-1})	0.093	0.092	0.092	0.091
Temperature (K)	150 (2)	140 (2)	150 (2)	150 (2)
Crystal form	Plate	Plate	Plate	Plate
Crystal size (mm)	0.50 × 0.50 × 0.10	0.45 × 0.25 × 0.10	0.75 × 0.55 × 0.30	0.90 × 0.50 × 0.05
Crystal colour	Colourless	Colourless	Colourless	Colourless
Data collection				
Diffractometer	Siemens SMART CCD	Siemens SMART CCD	Siemens SMART CCD	Siemens SMART CCD
Data collection method	ω scans	ω scans	ω scans	ω scans
Absorption correction	Multi-scan (Sheldrick, 1996)	Multi-scan (Sheldrick, 996)	Multi-scan (Sheldrick, 1996)	Multi-scan (Sheldrick, 1996)
T_{min}	0.955	0.959	0.933	0.921
T_{max}	0.991	0.991	0.973	0.995
No. of measured reflections	8317	4788	9079	16 583
No. of independent reflections	5815	4029	6187	11 372
No. of observed reflections	4439	3746	5540	8967
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.0332	0.0096	0.0213	0.0286
θ_{max} (°)	40	32.5	40.0	40.0
Range of h, k, l	$-10 \rightarrow h \rightarrow 9$ $-9 \rightarrow k \rightarrow 11$ $-26 \rightarrow l \rightarrow 21$	$-8 \rightarrow h \rightarrow 5$ $-8 \rightarrow k \rightarrow 9$ $-22 \rightarrow l \rightarrow 22$	$-10 \rightarrow h \rightarrow 10$ $-10 \rightarrow k \rightarrow 10$ $-28 \rightarrow l \rightarrow 28$	$-16 \rightarrow h \rightarrow 20$ $-10 \rightarrow k \rightarrow 10$ $-30 \rightarrow l \rightarrow 25$
Refinement				
Refinement on	F^2	F^2	F^2	F^2
$R[F^2>2\sigma(F^2)]$	0.0576	0.0326	0.0605	0.0483
$wR(F^2)$	0.1562	0.0934	0.1915	0.1080
S	1.110	1.104	1.303	1.074
No. of reflections used in refinement	5815	4028	6187	11 371
No. of parameters used	101	201	116	196
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0888P)^2 + 0.0250P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0675P)^2 + 0.0025P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0561P)^2 + 0.1597P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0567P)^2 + 0.0061P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.001	0.001	0.032	−0.002
$\Delta\rho_{max}$ (e Å^{-3})	0.620	0.443	0.585	0.535
$\Delta\rho_{min}$ (e Å^{-3})	−0.463	−0.221	−0.344	−0.308
Extinction method	None	None	*SHELXTL* (Sheldrick, 1995)	None
Extinction coefficient	–	–	1.23 (7)	–
Source of atomic scattering factors	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)	*International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Computer programs				
Structure solution	*SHELXTL* (Sheldrick, 1995)	*SHELXTL* (Sheldrick, 1995)	*SHELXTL* (Sheldrick, 1995)	*SHELXTL* (Sheldrick, 1995)
Structure refinement	*SHELXTL* (Sheldrick, 1995)	*SHELXTL* (Sheldrick, 1995)	*SHELXTL* (Sheldrick, 1995)	*SHELXTL* (Sheldrick, 1995)

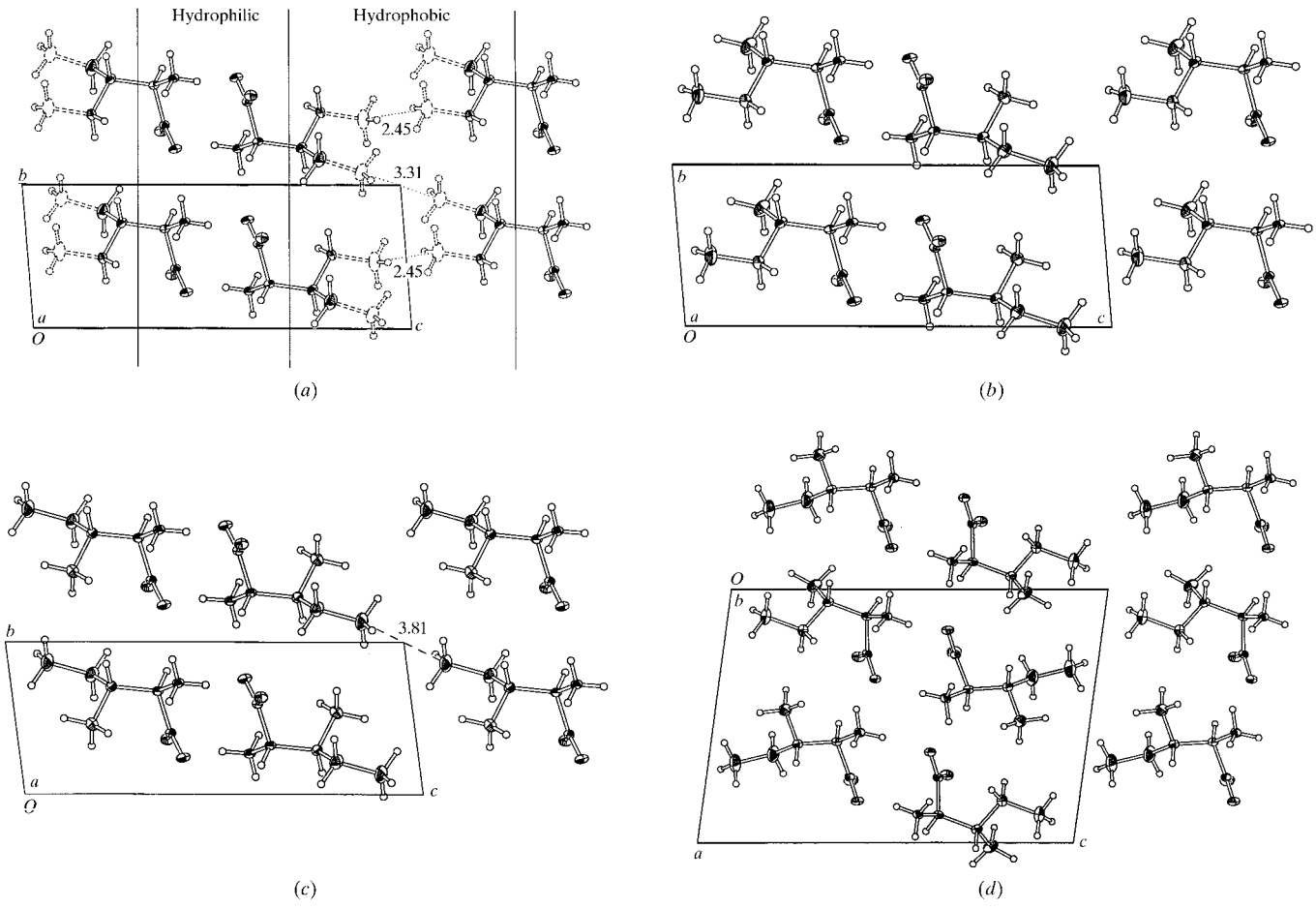


Figure 2
Molecular packing diagram for (*a*) DL-Ile:DL-*allo*-Ile (5), (*b*) L-Ile:D-*allo*-Ile (3), (*c*) DL-Ile (1) and (*d*) D-*allo*-Ile (6). In (*a*) the disordered C^{δ} methyl groups (C6 and C6′ with bonded H atoms) are drawn with broken lines and the disordered $C^{\gamma 2}$ methyl groups (C4 and C4′ with bonded H atoms) have been omitted for clarity. Furthermore, the three molecules in the upper row in (*a*) are translated one unit along the *a* axis relative to the molecules in the lower row. The short methyl···methyl contacts (in Å, see text) are indicated by dotted lines.

The two enantiomers of racemate (2) were always spontaneously resolved upon crystallization, rendering a structure determination of this racemate impossible.

Well diffracting plate-shaped crystals of complex (3) were obtained readily, with both ethanol and 2-propanol. However, ethanol seems to have a positive effect on the thickness of the crystals. Similarly, complex (5), with all four stereoisomers present, formed relatively large plates with both alcohols. The crystal used in the diffraction experiment was taken from the ethanol batch. Complex (4), on the other hand, gave only extremely thin needles (typically less than 0.01 mm) unsuitable for conventional X-ray diffraction experiments.

A thin plate of D-*allo*-Ile (6), crystallized using 2-propanol from a sample of known chirality, was used in the reinvestigation of this structure.

2.2. Data collection, structure determination and refinement

The data collections were performed with a Siemens SMART CCD diffractometer (Siemens, 1995) and nominally covered over a hemisphere of reciprocal space. The datasets are 99% complete to at least $\theta = 32.5^{\circ}$ [(1), (5) and (6)] and 40° (3). Friedel pairs have not been merged, since this introduces small systematic errors (*SHELXTL*; Sheldrick, 1995). Experimental conditions with information on the data reduction and refinement results are summarized in Table 2.[1] All structures were determined by direct methods using *SHELXTL* (Sheldrick, 1995).

All non-H atoms were refined anisotropically. Amino H atoms were refined isotropically. H atoms bonded to C were placed geometrically and refined with constraints to keep all C—H distances and all C—C—H angles on one C atom the same. Free rotation about C—C bonds was permitted for methyl groups. Isotropic displacement parameters for the H atoms were fixed at $1.5U_{eq}$ (for $-CH_3$) or $1.2U_{eq}$ (for $-CH_2-$ and $-CH-$) of the bonded C atom. In the model for (5) atoms C4, C5 and C6 correspond to D/L-Ile, while C4′, C5′ and C6′ correspond to D/L-*allo*-Ile. The occupancy of each stereoisomer was confined by symmetry to be 0.5. [A refinement of the occupancy factors gives 0.48 (1) and 0.52 (1) for C6 and C6′, respectively]. C6 and C6′ give rise to two independent peaks in the electron density map, while C4 and C5′

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: OS0046). Services for accessing these data are described at the back of the journal.

Table 3
Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$) for DL-Ile (1), L-Ile:D-*allo*-Ile (3), DL-Ile:DL-*allo*-Ile (5) and D-*allo*-Ile (6).

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	*y*	*z*	U_{eq}
DL-Ile (1)				
O1	0.80323 (9)	0.75963 (8)	0.58960 (4)	0.01627 (9)
O2	0.36212 (9)	0.63846 (9)	0.62394 (4)	0.01616 (9)
N1	0.81846 (10)	0.26922 (9)	0.57840 (4)	0.01351 (8)
C1	0.58380 (11)	0.59662 (10)	0.61346 (4)	0.01216 (8)
C2	0.58889 (10)	0.32193 (10)	0.63253 (4)	0.01191 (8)
C3	0.61101 (12)	0.29197 (11)	0.74779 (5)	0.01447 (9)
C4	0.81181 (15)	0.54061 (14)	0.80856 (6)	0.02060 (12)
C5	0.33004 (15)	0.2148 (2)	0.79270 (6)	0.02330 (13)
C6	0.3293 (2)	0.1342 (2)	0.90085 (7)	0.0371 (2)
D-Ile:D-*allo*-Ile (3)				
O1*A*	0.9524 (2)	0.6557 (2)	0.57652 (6)	0.0149 (2)
O2*A*	0.5127 (2)	0.5281 (2)	0.61114 (6)	0.01442 (15)
N1*A*	0.9645 (2)	0.1650 (2)	0.56582 (7)	0.0118 (2)
C1*A*	0.7340 (2)	0.4885 (2)	0.60067 (7)	0.0105 (2)
C2*A*	0.7406 (2)	0.2121 (2)	0.62044 (7)	0.0105 (2)
C3*A*	0.7765 (2)	0.1732 (2)	0.73401 (7)	0.0124 (2)
C4*A*	0.9848 (3)	0.4177 (3)	0.79132 (9)	0.0184 (2)
C5*A*	0.5015 (3)	0.0912 (3)	0.78135 (9)	0.0203 (2)
C6*A*	0.5155 (3)	−0.0009 (3)	0.88809 (9)	0.0303 (2)
O1*B*	0.3355 (2)	0.15514 (15)	0.40100 (6)	0.01413 (15)
O2*B*	0.7748 (2)	0.2815 (2)	0.36717 (6)	0.0144 (2)
N1*B*	0.3217 (2)	0.6441 (2)	0.41060 (7)	0.0117 (2)
C1*B*	0.5541 (2)	0.3217 (2)	0.37729 (7)	0.0108 (2)
C2*B*	0.5494 (2)	0.5993 (2)	0.35807 (7)	0.0109 (2)
C3*B*	0.5233 (2)	0.6409 (2)	0.24385 (8)	0.0141 (2)
C4*B*	0.8033 (3)	0.7279 (3)	0.20184 (11)	0.0264 (3)
C5*B*	0.3228 (3)	0.3951 (3)	0.18385 (8)	0.0187 (2)
C6*B*	0.2612 (3)	0.4403 (3)	0.07347 (8)	0.0318 (3)
DL-Ile:DL-*allo*-Ile (5)				
O1	0.30806 (12)	0.75015 (11)	0.58772 (5)	0.01528 (10)
O2	−0.13094 (12)	0.62306 (12)	0.62196 (5)	0.01533 (10)
N1	0.32122 (13)	0.26020 (12)	0.57762 (5)	0.01253 (10)
C1	0.08990 (14)	0.58294 (13)	0.61158 (5)	0.01132 (10)
C2	0.09599 (13)	0.30626 (13)	0.63118 (5)	0.01136 (10)
C3	0.1269 (2)	0.26586 (15)	0.74491 (6)	0.01437 (11)
C4†	0.3310 (2)	0.5107 (2)	0.80368 (7)	0.02080 (15)
C5†	−0.1495 (2)	0.1817 (2)	0.78999 (9)	0.0256 (2)
C6†	−0.1310 (6)	0.0921 (6)	0.8984 (2)	0.0337 (5)
C4′†	−0.1495 (2)	0.1817 (2)	0.78999 (9)	0.0256 (2)
C5′†	0.3310 (2)	0.5107 (2)	0.80368 (7)	0.02080 (15)
C6′†	0.3840 (7)	0.4649 (7)	0.9153 (2)	0.0344 (5)
D-*allo*-Ile (6)				
O1*A*	0.64390 (5)	0.61873 (11)	0.58600 (4)	0.01513 (8)
O2*A*	0.73315 (5)	0.99335 (10)	0.63843 (4)	0.01703 (9)
N1*A*	0.89125 (6)	0.40288 (11)	0.57706 (4)	0.01317 (8)
C1*A*	0.74430 (6)	0.76242 (12)	0.61626 (4)	0.01199 (9)
C2*A*	0.89164 (6)	0.64770 (12)	0.63091 (5)	0.01219 (9)
C3*A*	0.94808 (6)	0.60705 (13)	0.73830 (5)	0.01464 (10)
C4*A*	1.01413 (9)	0.8529 (2)	0.78089 (7)	0.0249 (2)
C5*A*	0.83562 (8)	0.5049 (2)	0.79516 (5)	0.01878 (11)
C6*A*	0.89085 (12)	0.4393 (2)	0.89933 (6)	0.0304 (2)
O1*B*	1.16317 (5)	1.22830 (11)	0.58923 (4)	0.01637 (9)
O2*B*	1.24741 (6)	1.62364 (11)	0.61395 (4)	0.02034 (10)
N1*B*	1.43383 (6)	1.04848 (12)	0.60816 (4)	0.01535 (9)
C1*B*	1.25852 (6)	1.38685 (12)	0.61819 (5)	0.01262 (9)
C2*B*	1.39799 (6)	1.27240 (13)	0.66580 (5)	0.01338 (9)
C3*B*	1.38807 (7)	1.18566 (14)	0.76921 (5)	0.01600 (11)
C4*B*	1.52314 (9)	1.0579 (2)	0.81456 (7)	0.0289 (2)
C5*B*	1.34993 (10)	1.4083 (2)	0.83059 (6)	0.0320 (2)
C6*B*	1.31314 (10)	1.3257 (2)	0.92814 (7)	0.0469 (3)

† C4, C5 and C6 apply to D/L-Ile, while C4′, C5′ and C6′ apply to D/L-*allo*-Ile. The occupancy factors for all six atoms are fixed at 0.5.

share the same set of parameters (constrained by the *EXYZ* and *EADP* cards in *SHELXTL*; Sheldrick, 1995), as do also C5 and C4′.

3. Results and discussion

Atomic coordinates for all four structures are listed in Table 3. Selected geometric parameters are given in Table 4 and hydrogen-bond geometries are listed in Table 5. Figs. 1(*a*)–(*d*) show the molecular conformations, including atomic numbering for the four structures.

3.1. Molecular geometry

There are no unusual features in the overall geometry for the molecules in these four structures, Table 4. In both DL-

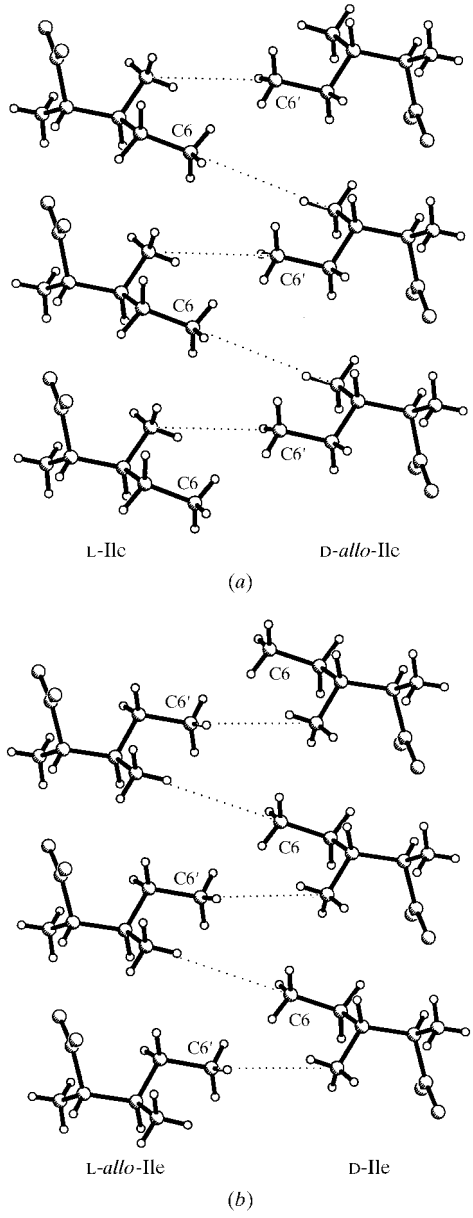


Figure 3
(*a*) Chain of L-Ile:D-*allo*-Ile molecules in (5). (*b*) Chain of D-Ile:L-*allo*-Ile molecules in (5).

Table 4
Selected distances and torsions (Å, °) for DL-Ile (1), L-Ile:D-*allo*-Ile (3), DL-Ile:DL-*allo*-Ile (5) and D-*allo*-Ile (6).

DL-Ile (1)			
O1—C1	1.2592 (7)	C2—C3	1.5445 (8)
O2—C1	1.2591 (7)	C3—C5	1.5307 (9)
N1—C2	1.4927 (7)	C3—C4	1.5328 (9)
C1—C2	1.5427 (7)	C5—C6	1.5282 (12)
O1—C1—C2—N1	−22.95 (7)	N1—C2—C3—C5	−153.14 (5)
N1—C2—C3—C4	81.48 (6)	C2—C3—C5—C6	169.79 (7)
L-Ile:D-*allo*-Ile (3)			
O1*A*—C1*A*	1.2619 (12)	O1*B*—C1*B*	1.2589 (13)
O2*A*—C1*A*	1.2622 (13)	O2*B*—C1*B*	1.2602 (13)
N1*A*—C2*A*	1.4950 (15)	N1*B*—C2*B*	1.4932 (15)
C1*A*—C2*A*	1.5397 (15)	C1*B*—C2*B*	1.542 (2)
C2*A*—C3*A*	1.5425 (13)	C2*B*—C3*B*	1.5486 (14)
C3*A*—C4*A*	1.531 (2)	C3*B*—C4*B*	1.525 (2)
C3*A*—C5*A*	1.534 (2)	C3*B*—C5*B*	1.535 (2)
C5*A*—C6*A*	1.531 (2)	C5*B*—C6*B*	1.533 (2)
O1*A*—C1*A*—C2*A*—N1*A*	−23.81 (12)	O1*B*—C1*B*—C2*B*—N1*B*	22.43 (12)
N1*A*—C2*A*—C3*A*—C4*A*	81.08 (11)	N1*B*—C2*B*—C3*B*—C4*B*	152.52 (11)
N1*A*—C2*A*—C3*A*—C5*A*	−153.38 (10)	N1*B*—C2*B*—C3*B*—C5*B*	−82.05 (12)
C2*A*—C3*A*—C5*A*—C6*A*	169.10 (10)	C2*B*—C3*B*—C5*B*—C6*B*	172.06 (10)
DL-Ile:DL-*allo*-Ile (5)†			
O1—C1	1.2611 (9)	C3—C4	1.5338 (12)
O2—C1	1.2623 (9)	C3—C5	1.5289 (13)
N1—C2	1.4937 (9)	C5—C6	1.551 (3)
C1—C2	1.5404 (9)	C3—C4′	1.5289 (13)
C2—C3	1.5453 (10)	C3—C5′	1.5338 (12)
C5′—C6′	1.542 (2)		
O1—C1—C2—N1	−23.30 (9)	N1—C2—C3—C4′	−152.95 (7)
N1—C2—C3—C4	81.64 (8)	N1—C2—C3—C5′	81.64 (8)
N1—C2—C3—C5	−152.95 (7)	C2—C3—C5′—C6′	−174.73 (14)
C2—C3—C5—C6	169.89 (15)		
D-*allo*-Ile (6)			
O1*A*—C1*A*	1.2569 (8)	O1*B*—C1*B*	1.2676 (8)
O2*A*—C1*A*	1.2623 (8)	O2*B*—C1*B*	1.2504 (9)
N1*A*—C2*A*	1.4944 (8)	N1*B*—C2*B*	1.4986 (9)
C1*A*—C2*A*	1.5344 (8)	C1*B*—C2*B*	1.5424 (8)
C2*A*—C3*A*	1.5512 (9)	C2*B*—C3*B*	1.5437 (9)
C3*A*—C4*A*	1.5271 (11)	C3*B*—C4*B*	1.5275 (11)
C3*A*—C5*A*	1.5356 (10)	C3*B*—C5*B*	1.5316 (11)
C5*A*—C6*A*	1.5306 (11)	C5*B*—C6*B*	1.5312 (14)
O1*A*—C1*A*—C2*A*—N1*A*	17.68 (8)	O1*B*—C1*B*—C2*B*—N1*B*	43.22 (7)
N1*A*—C2*A*—C3*A*—C4*A*	152.47 (6)	N1*B*—C2*B*—C3*B*—C4*B*	56.35 (8)
N1*A*—C2*A*—C3*A*—C5*A*	−81.92 (7)	N1*B*—C2*B*—C3*B*—C5*B*	−179.37 (6)
C2*A*—C3*A*—C5*A*—C6*A*	174.68 (7)	C2*B*—C3*B*—C5*B*—C6*B*	169.71 (3)

† C4, C5 and C6 apply to D/L-Ile, whilst C4′, C5′ and C6′ apply to D/L-*allo*-Ile.

Ile:DL-*allo*-Ile (5) and L-Ile:D-*allo*-Ile (3) the conformation of D-*allo*-Ile corresponds to that of molecule *A* in the D-*allo*-Ile (6) structure. The molecular conformation of L-Ile is similar in the three structures where this molecule is present, (1), (3) and (5).

3.2. Crystal packing

The molecular packing arrangement in the four structures is illustrated in Figs. 2(*a*)–(*d*). The layer-like build-up of crystals is a consequence of the dual character of these molecules; the charged α-amino and α-carboxylate groups form hydrogen bonds with each other, while the hydrophobic side chains are involved in van der Waals' interactions only. The hydrophilic and hydrophobic layers are emphasized in Fig. 2(*a*).

3.2.1. DL-Ile:DL-*allo*-Ile (5).

This structure is a mixture of all four stereoisomers of the title compound. In the original structure description (Benedetti *et al.*, 1973)[2] the crystal is described as a solid solution of the two racemic pairs DL-Ile and DL-*allo*-Ile in a ratio not significantly different from 1:1.

A close inspection of the interatomic distances between the alternative positions for the disordered side-chain atoms in the hydrophobic layer reveals two relatively short C···C contacts; C6′···C6′^{i} [symmetry code: (i) $-x+1, -y+1, -z+2$] 2.452 (5) Å and C6···C6^{ii} [symmetry code: (ii) $-x, -y, -z+2$] 3.315 (6) Å, Fig. 2(*a*). The corresponding shortest H···H contacts are 1.84 and 2.45 Å, respectively. The molecules involved in these contacts form chains parallel to the *ab* diagonal. To avoid these short methyl···methyl contacts, one of the two conflicting positions in each such contact has to be vacant. This restriction gives rise to two different molecular chains, one with the diastereomeric pair L-Ile:D-*allo*-Ile (Fig. 3*a*) and one with D-Ile:L-*allo*-Ile (Fig. 3*b*). Allthough the structure is locally non-centrosymmetric, the overall structure is centrosymmetric. The 1:1:1:1 ratio between the four stereoisomers is a direct consequence of the 1:1 ratio between the diastereomers in each molecular chain combined with the centrosymmetric space group.

A complete hydrophobic layer is generated by a stacking of the molecular arrangements depicted in Figs. 3(*a*) and (*b*). Three alternative models exist for the build-up of this hydrophobic layer:

(i) a stacking of one of the depicted arrangements only,
(ii) a systematic alternating stacking and
(iii) a random stacking of the two arrangements.

In the first model only a single diastereomeric pair (L-Ile:D-*allo*-Ile or D-Ile:L-*allo*-Ile) is present within a specific hydrophobic layer. The molecular distribution in this model is illu-

[2] Erroneously registered as DL-isoleucine (Refcode DLILEU) in the Cambridge Structural Database (Allen & Kennard, 1993).

strated in Fig. 4(*a*). Since only two of the four stereoisomers in the crystal are included in each hydrophobic layer, the crystal must be built up by a stacking of two types of layer, one with the pair L-Ile:D-*allo*-Ile and one with D-Ile:L-*allo*-Ile. This model puts no restriction on the ratio between the two aforementioned diastereomeric pairs.

If, on the other hand, an alternating stacking of the arrangements in Figs. 3(*a*) and (*b*) is assumed, all four stereoisomers coexist in a single hydrophobic layer and, automatically, in equimolar numbers. The Ile and *allo*-Ile molecules within a single molecular layer alternate along both the *a* and *b* axes, Fig. 4(*b*).

The last model, with a random stacking of the aforementioned alternative arrangements, also represents a model in which all four stereoisomers are present within each hydrophobic layer. However, as with the first model, the ratio between the two diastereomeric pairs can, in principle, take any value.

From the above analysis of the short methyl···methyl contacts – unveiling two different molecular arrangements encompassing a single diastereomeric pair – it may be concluded that the distribution of the four stereoisomers is not random throughout the crystal. However, it is not possible, from the structural data for (5), to establish which of the three proposed arrangements most likely occurs in the crystals. There are only small differences in the short non-bonding methyl···methyl distances in the three models; all such contacts across the hydrophobic layer in the three models have C···C distances in the range 3.91–3.93 Å, with corresponding H···H distances between 2.63 and 2.79 Å.

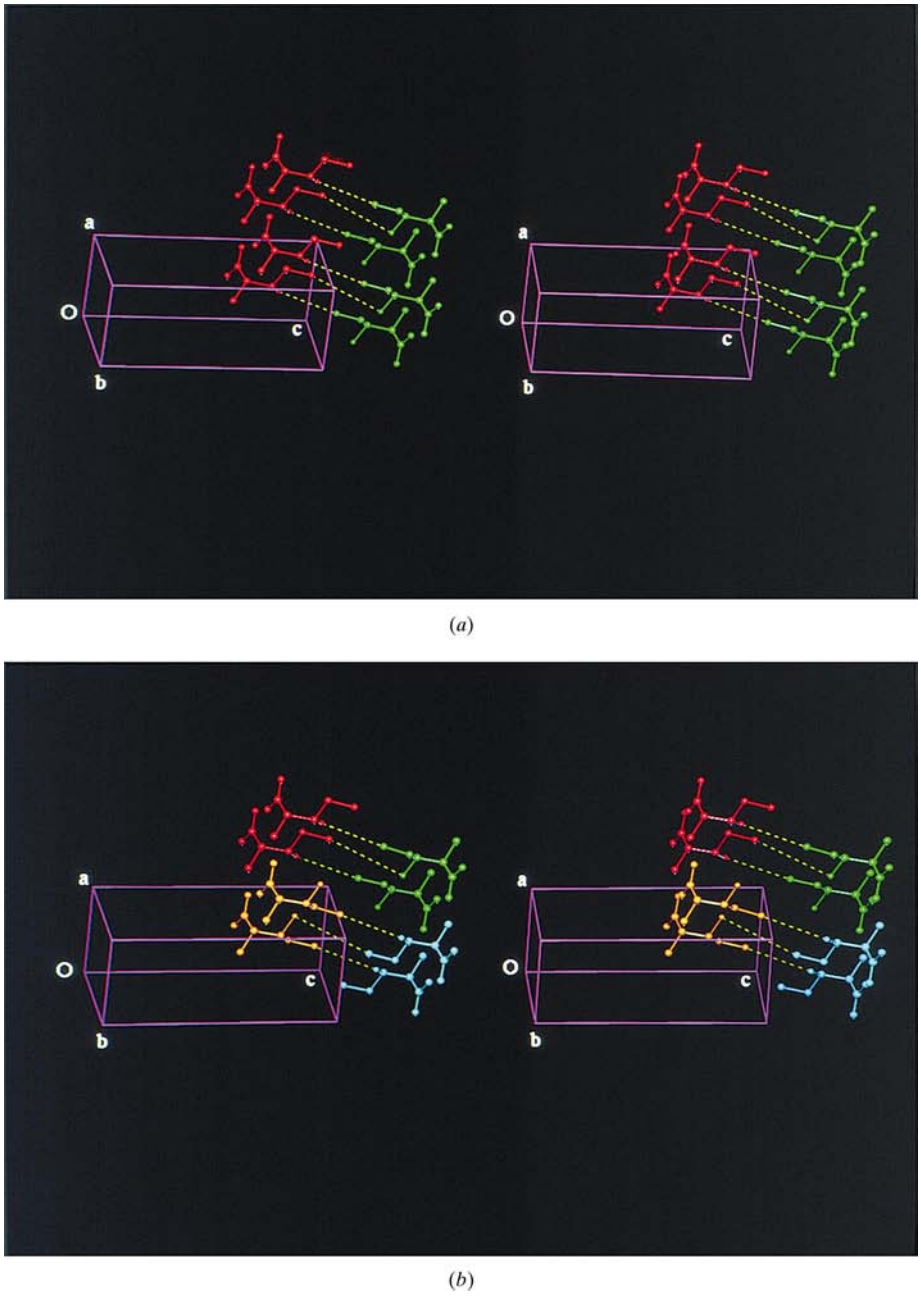


Figure 4
Stereoplot illustrating two of the three proposed molecular packing arrangements in a single hydrophobic layer of DL-Ile:DL-*allo*-Ile (5). (*a*) Layer accommodating a single diastereomeric pair (red = L-Ile, green = D-*allo*-Ile). (*b*) Layer with all four stereoisomers present (red = L-Ile, orange = L-*allo*-Ile, green = D-*allo*-Ile, blue = D-Ile). The contacts illustrated in Figs. 3(*a*) and (*b*) are displayed with yellow dots.

3.2.2. L-Ile:D-*allo*-Ile (3). The two stereoisomers in this complex aggregate in double layers, one with L-Ile and one with D-*allo*-Ile, Fig. 2(*b*). The molecular packing in the hydrophobic layer in this structure (Fig. 2*b*) and the L-Ile:D-*allo*-Ile double layer (Fig. 3*a*) in the first model for (5) is identical. The C6···C6′^{iii} [symmetry code: (iii) $-x, -y+1, -z+2$] 3.935 (5) Å contact in (5) is only slightly altered in this complex; in (3) the corresponding distance is 3.918 (2) Å. The other C6′···C6^{ii} 3.913 (5) Å contact in (5) is practically unchanged in (3), 3.910 (2) Å. It is noteworthy that the molecular conformations in (3) and in the L-Ile:D-*allo*-Ile pair in (5) are almost identical; the largest difference for corresponding torsion angles is 2.7° [C2*B*—C3*B*—C5*B*—C6*B* for D-*allo*-Ile in (3) and C2—C3—C5′—C6′ for D-*allo*-Ile in (5)], Table 4.

3.2.3. DL-Ile (1). Analogous to (3), the two enantiomers in this racemate crystallize in double layers, with the D-*allo*-Ile molecules in (3) replaced by D-Ile (Fig. 2*c*). The structure of (1) can be generated from the structure of (5) by occupying all the C6 positions and leaving all the C6′ positions vacant.

Table 5
Hydrogen-bond geometry (Å, °).

D—H, H···A[a] and D—H···A based on experimental H-atom positions; H···A[b] for N—H bonds normalized to 1.030 Å (Taylor & Kennard, 1983).

D—H···A	D—H	H···A[a]	H···A[b]	D—H···A	D···A
DL-Ile (1)					
N1—H1···O2^{i}	0.95 (1)	1.97 (1)	1.886	164 (1)	2.888 (1)
N1—H2···O1^{ii}	0.85 (1)	1.91 (1)	1.725	175 (1)	2.752 (1)
N1—H3···O2^{iii}	0.91 (1)	2.10 (1)	1.988	157 (1)	2.955 (1)
L-Ile:D-*allo*-Ile (3)					
N1*A*—H1*A*···O2*A*^{i}	1.06 (4)	1.86 (3)	1.889	162 (2)	2.887 (1)
N1*A*—H2*A*···O1*A*^{ii}	0.92 (3)	1.83 (3)	1.712	175 (2)	2.740 (1)
N1*A*—H3*A*···O2*B*	0.79 (2)	2.19 (2)	1.972	159 (2)	2.943 (1)
N1*B*—H1*B*···O2*B*^{iv}	0.84 (2)	2.06 (2)	1.879	164 (1)	2.878 (1)
N1*B*—H2*B*···O1*B*^{v}	0.89 (2)	1.85 (2)	1.715	177 (2)	2.744 (1)
N1*B*—H3*B*···O2*A*	0.93 (2)	2.09 (2)	2.001	156 (2)	2.967 (1)
DL-Ile:DL-*allo*-Ile (5)					
N1—H1···O2^{i}	0.91 (2)	2.00 (2)	1.889	164 (2)	2.888 (1)
N1—H2···O1^{ii}	0.89 (2)	1.85 (2)	1.715	175 (2)	2.742 (1)
N1—H3···O2^{vi}	0.82 (2)	2.16 (2)	1.956	165 (2)	2.958 (1)
D-*allo*-Ile (6)					
N1*A*—H1*A*···O2*A*^{ii}	0.88 (2)	1.98 (2)	1.828	169 (1)	2.845 (1)
N1*A*—H2*A*···O1*B*^{ii}	0.89 (1)	1.88 (1)	1.740	175 (1)	2.768 (1)
N1*A*—H3*A*···O1*B*^{vii}	0.88 (2)	2.13 (2)	2.009	145 (1)	2.891 (1)
N1*B*—H1*B*···O2*B*^{ii}	0.85 (2)	2.05 (2)	1.874	165 (1)	2.879 (1)
N1*B*—H2*B*···O2*A*^{i}	0.90 (1)	2.00 (1)	1.871	167 (1)	2.881 (1)
N1*B*—H3*B*···O1*A*^{viii}	0.89 (1)	1.88 (1)	1.739	172 (2)	2.761 (1)

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

The short C6···C6^{ii} distance of 3.315 (6) Å in (5) (Fig. 2*a*) must then be increased to permit the presence of methyl groups in all the C6 positions. Indeed, this is precisely what happens in the crystal of DL-Ile; the C6···C6^{iv} [symmetry code: (iv) $-x+1, -y, -z+2$] distance is increased by 0.5 Å to 3.810 (3) Å (Fig. 2*c*).

This repositioning of the terminal C6 methyl groups is feasible without gross alterations in the molecular arrangement (Figs. 2*a* and *c*) and the hydrogen-bond arrangement in the hydrophilic layer is left intact, Table 5.

3.2.4. Spontaneous resolution of DL-*allo*-Ile (2). If the structure of (5) is used as a model template for the generation of the structure of DL-*allo*-Ile – by occupying all C6′ positions and leaving all the C6 positions vacant – a molecular packing with a short C6′···C6′^{ii} contact of only 2.45 Å is obtained (Fig. 2*a*). In DL-Ile a shift of 0.5 Å in the C6···C6^{iv} interaction was achieved by minor modifications in the molecular packing, while in DL-*allo*-Ile the required shift is approximately 1.5 Å. The observed separation of the enantiomers upon crystallization suggests that it is not possible to rearrange the molecules in this hypothetical DL-*allo*-Ile structure and eliminate the unfavorable C6′···C6′^{ii} interaction without disrupting the hydrogen-bond pattern. It is thus possible to account for the spontaneous resolution of the enantiomers in DL-*allo*-Ile at the molecular level. The molecular arrangement in the enantiomeric structure (6), with an alternative hydrogen-bond arrangement, is energetically favored (Fig. 2*d*).

3.2.5. D-*allo*-Ile (6). Each enantiomer in the racemate DL-*allo*-Ile forms crystals with two crystallographically independent molecules. Further, the hydrogen-bond arrangement is different from that found in (1), (3) and (5), Table 5. The two independent molecules in D-*allo*-Ile (6) (Figs. 1*d* and 2*d*), differ in the side-chain conformation; in molecule *A* $\chi^{1,1}$ (N1—C2—C3—C5) is *gauche*$^{-}$, while in molecule *B* the corresponding torsion is *trans*. Furthermore, the carboxylate group is approximately symmetric in molecule *A*, but clearly asymmetric in molecule *B*, Table 4.

3.2.6. L-Ile:L-*allo*-Ile (4). Only extremely thin needles were obtained upon crystallization of (4) and the crystal shape for this complex is different from those of the individual amino acids L-Ile (Görbitz & Dalhus, 1996) and L-*allo*-Ile, which both form plate-shaped crystals. This could very well indicate that the molecular arrangement, and hence the hydrogen-bond pattern, in the 1:1 complex (4) is different from that of the individual amino acid structures. Unfortunately, the needles were much too thin for diffraction experiments with a conventional in-house diffractometer.

3.2.7. Hydrogen bonding. Experimental and normalized (Taylor & Kennard, 1983) hydrogen-bond geometries are listed in Table 5. The hydrogen-bond patterns in (1), (3) and (5) are isostructural, apart from the increased number of hydrogen bonds due to the lower symmetry in (3). This hydrogen-bond arrangement recurs in other racemates of hydrophobic amino acids with branched side chains; DL-leucine (Di Blasio *et al.*, 1975) and DL-valine (triclinic polymorph: Dalhus & Görbitz, 1996; monoclinic polymorph: Mallikarjunan & Thyagaraja Rao, 1969). The amino H1 (C′—C$^{\alpha}$—N—H = *gauche*$^{+}$) and H2 (C′—C$^{\alpha}$—N—H *trans*) atoms in (1), (3) and (5) have normalized hydrogen-bond distances within ranges of 0.010 Å (1.879–1.889 Å) and 0.013 Å (1.712–1.725 Å), respectively.

The purchase of a Siemens SMART diffractometer was made possible through financial support from The Research Council of Norway (NFR).

References

Allen, F. H. & Kennard, O. (1993). *Chem. Des. Autom. News*, **8**, 1, 31–37.
Benedetti, E., Pedone, C. & Sirigu, A. (1973). *Acta Cryst.* B**29**, 730–733.
Dalhus, B. & Görbitz, C. H. (1996). *Acta Cryst.* C**52**, 1759–1761.
Dalhus, B. & Görbitz, C. H. (1999). *Acta Cryst.* C**55**, 1547–1555.
Di Blasio, B., Pedone, C. & Sirigu, A. (1975). *Acta Cryst.* B**31**, 601–602.
Görbitz, C. H. & Dalhus, B. (1996). *Acta Cryst.* C**52**, 1464–1466.
Mallikarjunan, M. & Thyagaraja Rao, S. (1969). *Acta Cryst.* B**25**, 296–303.
Sheldrick, G. M. (1995). *SHELXTL.* Version 5.03. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1996). *Sadabs.* University of Göttingen, Germany.
Siemens (1995). *SMART/SAINT.* Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Taylor, R. & Kennard, O. (1983). *Acta Cryst.* B**39**, 133–138.
Varughese, K. I. & Srinivasan, R. (1975). *J. Cryst. Mol. Struct.* **5**, 317–328.