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Pseudopolymorphism of *N*-acetyl-L-phenylalanine methyl ester

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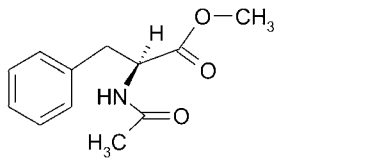
The structures of two pseudopolymorphs of *N*-acetyl-L-phenylalanine methyl ester, L-AcFOMe, were determined at both 293 (2) and 150 (2) K. At room temperature, the orthorhombic phase $C_{12}H_{15}NO_3$ (I), with space group $P2_12_12_1$, converts into the tetragonal phase $C_{12}H_{15}NO_3\cdot 0.5H_2O$ (II), with space group $P4_12_12$, in the presence of water. In the structures of both pseudopolymorphs, alternating layers of hydrophilic and hydrophobic intermolecular interaction can be distinguished. In the hydrophilic layers the structures are stabilized by moderate hydrogen bonds of the type N—H···O for the anhydrous L-AcFOMe and of types N—H···O and O—H···O for the hemihydrate. Weak C—H···π interactions are observed within the hydrophobic layers: for (I) they are of type III [Malone *et al.* (1997). *J. Chem. Soc. Faraday Trans.* **93**, 3429–3436], whereas typical type I edge-to-face interactions are present for (II). The differences between the hydrogen-bonding networks of (I) and (II) are discussed in terms of graph-set analysis.

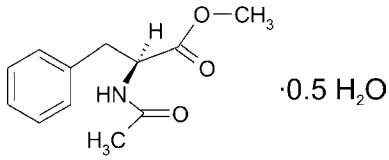
1. Introduction

In the course of systematic investigations into the possible interaction between selected antiarrhythmic agents of class I and class III (Weirich & Wenzel, 2000), and amino acid residues present in the ion-channel selectivity filters (K^+: Tseng, 2001; Na^+: Balser, 1999), we have carried out a series of co-crystallization experiments. Protected L-phenylalanine was used because the chemical blocking of the amino and carboxyl groups made it similar to the residues in the peptide-forming selectivity filters. During these investigations two pseudopolymorphs of *N*-acetyl-L-phenylalanine methyl ester, L-AcFOMe, were found. Knowledge of the crystal structures of protected amino acids and the evaluation of steric and electronic complementarity of the potential components are important in the design and control of co-crystallization processes (Desiraju, 1997).

In crystal engineering of such co-crystals one should consider the significance of polymorphism and pseudopolymorphism (Nangia & Desiraju, 1999; Kumar *et al.*, 1999). *N*-Acetyl-L-phenylalanine methyl ester seems to present a good example of pseudopolymorphism. For this compound two pseudopolymorphs were found: the orthorhombic phase ($P2_12_12_1$) of the anhydrous *N*-acetyl-L-phenylalanine methyl ester, $C_{12}H_{15}NO_3$ (I), and the tetragonal phase ($P4_12_12$) of the hemihydrate $C_{12}H_{15}NO_3\cdot 0.5H_2O$ (II).



(I)



(II)

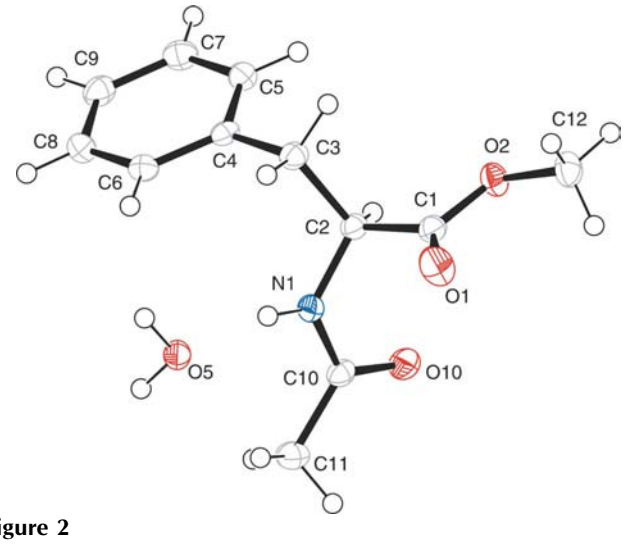


Figure 2
The contents of the asymmetric unit for (II) at 150 (2) K, showing the atom-numbering scheme. The water molecule lies on a crystallographic twofold axis at $(x, -x, \frac{1}{4})$. Displacement ellipsoids are drawn at the 50% probability level.

2. Experimental

2.1. Crystal growth

Protected L-phenylalanine, L-AcFOMe, was purchased from Bachem Chemical Company. Crystals of (I) suitable for X-ray structure determination were obtained by slow evaporation at room temperature from a mixture of 2-propanol and water (molar ratio 1:1) containing L-AcFOMe with an equimolar amount of procainamide hydrochloride [*p*-amino-*N*-(2-(diethylamino)ethyl)benzamide hydrochloride; Sigma Chemical Company], which provided the proper ionic strength for successful crystallization of orthorhombic phase (I).

After some time, a spontaneous re-crystallization process occurred to produce crystals of (II) containing one water molecule per two molecules of L-AcFOMe. Crystallization of L-AcFOMe from solvents such as toluene, from a mixture of *n*-heptane and chloroform, or at the chloroform–toluene interface produces only orthorhombic crystals (I) which were stable under these conditions, *i.e.* in an anhydrous environment (Roman, 2007).

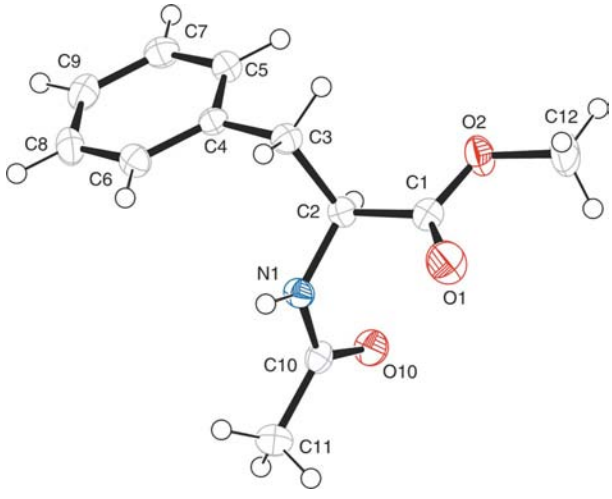


Figure 1
The contents of the asymmetric unit for (I) at 150 (2) K, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

2.2. Diffraction experiments and refinement

Table 1 provides a summary of the experimental details.[1] Single-crystal diffraction measurements were performed on a Nonius KappaCCD diffractometer (Nonius, 1997) at 293 (2) and 150 (2) K using an Oxford Cryosystems Cryostream Series 700 cooler (Cosier & Glazer, 1986). The standard strategies were used for data collection, cell refinement and data processing (Otwinowski & Minor, 1997). *SIR*92 (Altomare *et al.*, 1994) was used to solve the structures and *SHELXL*97 (Sheldrick, 2008) was employed for structure refinement by full-matrix least-squares against F^2 using all data. Owing to the absence of significant anomalous scattering and the fact that the absolute configuration of purchased materials was known, Friedel pairs were merged. Space groups were assigned from the systematic absences observed in the diffraction patterns. The H atoms attached to C atoms of the methyl (C12), methylene (C3) and methine (C2) groups and those of the benzene ring (C5–C9) were included in geometrically calculated positions and refined using a riding model with $U_{iso}(H) = 1.2U_{eq}$ (parent atom). For the sp^2-bound methyl group (C11) the H atoms were located in a circular difference-Fourier synthesis (Sheldrick, 2008) and refined as part of a rigid rotating group with $U_{iso}(H) = 1.2U_{eq}(C11)$. The H atom bound to N in (I) was located in a difference-Fourier map and refined freely, while the H atoms bound to N and O atoms in (II) were located in difference-Fourier maps and refined using a riding model with $U_{iso}(H) = 1.2U_{eq}$ (parent atom). The following

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM5052). Services for accessing these data are described at the back of the journal.

Table 1
Crystal data, physical properties and experimental details for two pseudopolymorphs of *N*-acetyl-L-phenylalanine methyl ester at 293 (2) and 150 (2) K.

	Orthorhombic form		Tetragonal form	
	(I*a*)	(I*b*)	(II*a*)	(II*b*)
Crystal data				
Chemical formula	$C_{12}H_{15}NO_3$	$C_{12}H_{15}NO_3$	$2C_{12}H_{15}NO_3{\cdot}H_2O$	$2C_{12}H_{15}NO_3{\cdot}H_2O$
M_r	221.25	221.25	460.52	460.52
Cell setting, space group	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$	Tetragonal, $P4_12_12$	Tetragonal, $P4_12_12$
Temperature (K)	293 (2)	150 (2)	293 (2)	150 (2)
a, b, c (Å)	4.9910 (1), 8.7145 (2), 28.0411 (7)	4.9488 (2), 8.6359 (6), 27.6622 (10)	7.1582 (1), 7.1582 (1), 47.5286 (6)	7.0900 (1), 7.0900 (1), 47.1426 (5)
V (Å^3)	1219.62 (5)	1182.21 (10)	2435.36 (6)	2369.77 (5)
Z	4	4	4	4
D_x (Mg m^{-3})	1.205	1.243	1.256	1.291
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.09	0.09	0.09	0.10
Crystal form, colour	Prism, colourless	Prism, colourless	Prism, colourless	Prism, colourless
Crystal size (mm)	0.32 × 0.20 × 0.16	0.32 × 0.20 × 0.16	0.32 × 0.12 × 0.12	0.36 × 0.35 × 0.20
Data collection				
Diffractometer	Nonius KappaCCD	Nonius KappaCCD	Nonius KappaCCD	Nonius KappaCCD
Data collection method	φ scans and ω scans to cover asymmetric fraction	ω scans at χ = 55°	ω scans at χ = 55°	ω scans at χ = 55°
Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan
T_{min}	0.973	0.972	0.971	0.967
T_{max}	0.986	0.986	0.989	0.981
No. of measured, independent and observed reflections	8443, 1656, 1126	8592, 2019, 1736	11 430, 1738, 1270	6431, 1674, 1570
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.025	0.028	0.026	0.013
θ_{max} (°)	27.5	30.1	27.5	27.4
Refinement				
Refinement on	F^2	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.042, 0.116, 0.98	0.039, 0.096, 1.04	0.045, 0.119, 1.06	0.035, 0.093, 1.08
No. of reflections	1656	2019	1738	1674
No. of parameters	151	150	152	151
H-atom treatment	Mixture of independent and constrained refinement	Mixture of independent and constrained refinement	Constrained to parent site	Constrained to parent site
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0634P)^2 + 0.0884P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0476P)^2 + 0.1338P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0566P)^2 + 0.2801P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0431P)^2 + 0.7149P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.007	< 0.0001	< 0.0001	< 0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.14, −0.17	0.20, −0.20	0.17, −0.17	0.20, −0.24
Extinction method	*SHELXL*	None	*SHELXL*	None
Extinction coefficient	0.047 (8)	–	0.019 (3)	–

Computer programs used: *KappaCCD Server Software* (Nonius, 1997), *DENZO-SMN*, *HKL DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997), *SIR*92 (Altomare *et al.*, 1994), *SHELXL*97 (Sheldrick, 2008), *PLATON* (Spek, 2003), *ORTEP*3 (Farrugia, 1997).

programs were used for visual interpretation and structural drawings: *ORTEP*3 for Windows (Farrugia, 1997), *PLATON* (Spek, 2003) and *MERCURY* (Macrae *et al.*, 2006). In order to facilitate a comparison, all atomic labelling was kept the same. Selected geometric data generated by *SHELXL*97 (Sheldrick, 2008) are collected in Table 2.

3. Discussion

In this work we report two pseudopolymorphs of *N*-acetyl-L-phenylalanine methyl ester. While the crystal structure of *N*-acetyl-L-phenylalanine is known (Stout *et al.*, 2000), for the crystalline unprotected L-phenylalanine only unit-cell dimensions were previously published (Khawas & Murthy, 1968; Khawas, 1970, 1985). Although according to Khawas (1985) L-phenylalanine forms two polymorphs (α and β), both of space group $P222_1$, the crystal structure of L-phenylalanine itself is yet to be found.

The asymmetric units of L-AcFOMe (I) and L-AcFOMe·$0.5H_2O$ (II) at 150 (2) K are shown in Figs. 1 and 2. The orthorhombic phase of *N*-acetyl-L-phenylalanine methyl ester (I) is unstable in the presence of water and its crystals convert to the tetragonal hemihydrate. Selected geometrical parameters for (I) and (II) at both 293 (2) and 150 (2) K are given in Table 2. The bond distances and valence angles observed for the crystalline forms of L-AcFOMe are typical and similar to each other with the biggest differences observed for the ester group. The most significant change concerns the value of the

Table 2
Selected geometrical parameters (Å, °) for two pseudopolymorphs of *N*-acetyl-L-phenylalanine methyl ester at (*a*) 293 (2) and (*b*) 150 (2) K.

Parameter	(I*a*)	(I*b*)	(II*a*)	(II*b*)
N1—C2	1.443 (3)	1.448 (2)	1.452 (3)	1.450 (2)
N1—H1	0.92 (3)	0.95 (3)	0.81 (3)	0.91 (2)
C1—O1	1.194 (3)	1.198 (2)	1.182 (3)	1.198 (2)
C1—O2	1.326 (3)	1.332 (2)	1.332 (3)	1.340 (2)
C10—O10	1.225 (3)	1.232 (2)	1.234 (3)	1.241 (2)
C10—C11	1.490 (3)	1.501 (2)	1.507 (3)	1.500 (2)
N1—C2—C1	111.2 (2)	111.2 (1)	110.9 (2)	111.2 (1)
N1—C2—C3	111.7 (2)	111.5 (1)	110.5 (2)	110.7 (1)
C1—C2—C3	111.9 (2)	111.6 (1)	108.5 (2)	108.2 (1)
C1—O2—C12	116.5 (2)	115.8 (2)	115.6 (2)	115.0 (1)
C10—N1—C2—C3	151.8 (2)	153.6 (1)	160.9 (2)	161.0 (2)
O1—C1—C2—C3	100.5 (3)	101.2 (2)	83.5 (3)	84.0 (2)
O2—C1—C2—C3	−78.6 (2)	−79.0 (2)	−93.6 (2)	−93.0 (2)

O1—C1—C2—C3 torsion angle in (I) and (II). The presence of water molecules in the crystal structure caused a reversal of the L-AcFOMe molecular conformation from (+) anticlinal in (I) to (+) synclinal in (II), and there is a corresponding effect on the O2—C1—C2—C3 torsion angle, *i.e.* the change from (−) synclinal in (I) to (−) anticlinal in (II). There is no obvious difference in molecular geometry between the crystal structures at 293 (2) and 150 (2) K (see Table 2).

Considering the importance of the conformation of amino acid residues in peptides, the torsion angles, which characterize the backbone conformation of several known L-phenylalanine derivatives, are compared in Table 3. Besides two pseudopolymorphs of *N*-acetyl-L-phenylalanine methyl ester, the following compounds were taken into account: *N*-acetyl-L-phenylalanine (AcF; Stout *et al.*, 2000), the small peptide GFG (glycyl-L-phenylalanyl-glycine monohydrate; Marsh & Glusker, 1961) and L-phenylalanine hydrochloride

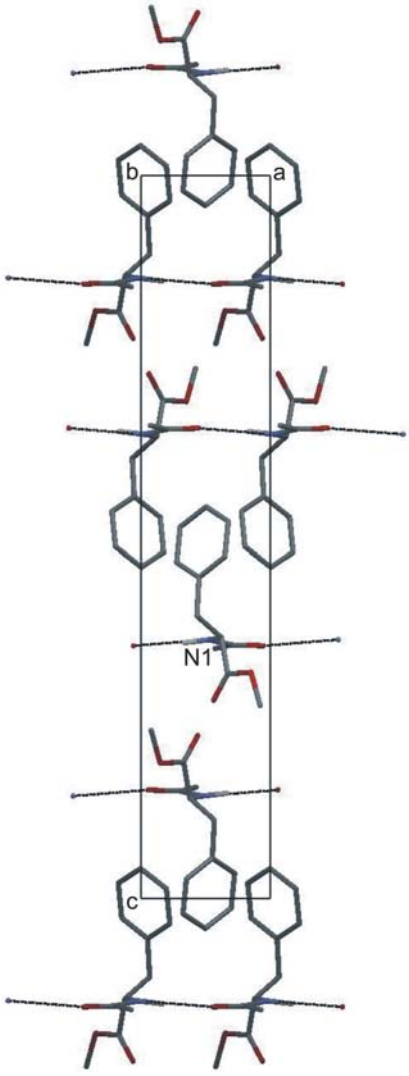


Figure 3
Projection of the crystal structure of (I) at 150 (2) K along [010] showing alternating hydrophilic and hydrophobic layers parallel to (001). In the hydrophilic region N1—H1···O10 ($x+1, y, z$) hydrogen bonds dominate, whereas in the hydrophobic part weak interactions C8—H8···*Cg*1 ($x+\frac{1}{2}, -y+\frac{1}{2}, -z$), not marked here, are observed.

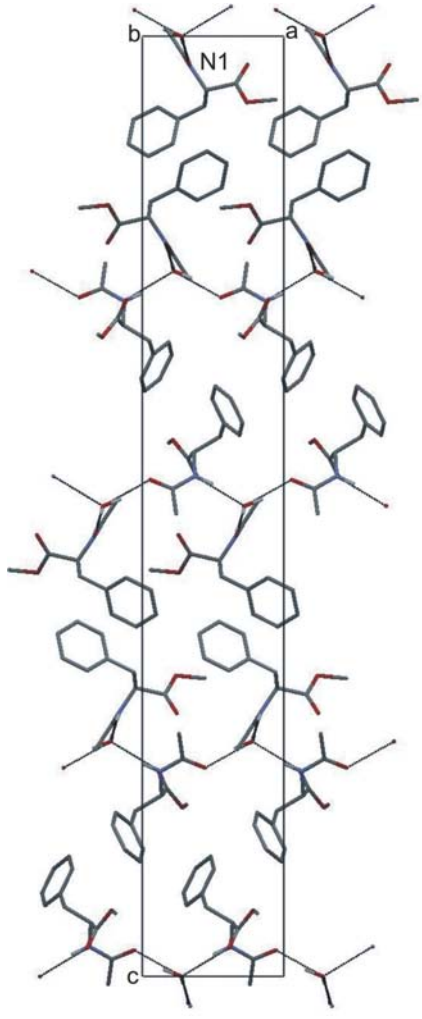


Figure 4
Projection of the crystal structure of (II) at 150 (2) K along [010] showing alternating hydrophilic and hydrophobic layers parallel to (001). In the hydrophilic region N1—H1···O5 (x, y, z) hydrogen bonds dominate, whereas in the hydrophobic part weak edge-to-face interactions between aromatic rings [C5—H5···*Cg*1 ($-x+\frac{1}{2}, y+\frac{1}{2}, -z+\frac{1}{4}$) and C12—H12···*Cg*1 ($x-1, y, z$), not marked in this drawing] are observed.

Table 3
A comparison of torsion angles (°) describing the conformation of backbones in L-phenylalanine derivatives; φ, ψ, χ and ω are defined in agreement with the IUPAC–IUB Commission on Biochemical Nomenclature (1970).

Torsion angle	Symbol	AcFOMe, 293 K	AcFOMe, 150 K	AcFOMe·0.5H_2O, 293 K	AcFOMe·0.5H_2O, 150 K	AcF†	GFG‡	F·HCl§
C2—N1—C10—C11	ω	176.9 (2)	176.7 (1)	177.7 (2)	179.0 (2)	174.21	−175	–
C10—N1—C2—C1	φ	−82.6 (3)	−81.2 (2)	−78.8 (3)	−78.6 (2)	−83.81	−126	–
O1—C1—C2—N1	$\psi1$	−25.1 (4)	−23.9 (2)	−38.1 (4)	−37.8 (2)	150.02	−46	−2.93
O2—C1—C2—N1¶	$\psi2$	155.9 (2)	155.9 (1)	144.9 (2)	145.3 (1)	−32.40	132	175.99
N1—C2—C3—C4	$\chi1$	−71.4 (3)	−71.0 (2)	−72.0 (3)	−71.7 (2)	−72.44	−175	60.72
C1—C2—C3—C4	$\chi2$	163.3 (2)	164.0 (1)	166.3 (2)	166.2 (1)	162.56	70	−62.54
C2—C3—C4—C6	–	92.1 (3)	91.4 (2)	96.8 (3)	96.8 (2)	125.26	102	−96.69

† *N*-Acetyl-L-phenylalanine (Stout *et al.*, 2000). ‡ Glycyl-L-phenylalanyl-glycine monohydrate (Marsh & Glusker, 1961). § L-Phenylalanine hydrochloride (Al-Karaghouli & Koetzle, 1975; Gurskaya & Vainshtein, 1964). The data for evaluation of torsion angles in the case of AcF, GFG and F·HCl were taken from the Cambridge Structural Database (Allen, 2002, Version 5.28), refcodes COQHAR, GPAGLM, PHALNC01 and PHALNC10, respectively. ¶ Equivalent to N2—C1—C2—N1 in tripeptides.

Table 4
Hydrogen-bonding contact distances (Å) and angles (°) involving the respective centroids *Cg*1 in the orthorhombic and tetragonal pseudo-polymorphic crystals of *N*-acetyl-L-phenylalanine methyl ester at 293 (2) and 150 (2) K, where *Cg*1 is the centre of gravity of the C4–C9 benzene ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
(I*a*)				
N1—H1···O10^{i}	0.92 (3)	2.14 (3)	3.046 (3)	168 (2)
C12—H12*C*···O1^{ii}	0.96	2.68	3.560 (4)	153
C11—H11*C*···O1^{iii}	0.96	2.59	3.548 (3)	174
C9—H9···O10^{iv}	0.93	2.66	3.533 (3)	156
C8—H8···*Cg*1^{iv}	0.93	3.10	3.84 (4)	141
(I*b*)				
N1—H1···O10^{i}	0.95 (2)	2.06 (2)	3.003 (2)	168 (2)
C12—H12*C*···O1^{ii}	0.98	2.63	3.545 (3)	155
C11—H11*C*···O1^{iii}	0.98	2.46	3.423 (2)	166
C9—H9···O10^{iv}	0.95	2.55	3.445 (2)	156
C8—H8···*Cg*1^{iv}	0.95	3.04	3.81 (4)	139
(II*a*)				
N1—H1···O5	0.88	2.11	2.983 (3)	171
O5—H51···O10^{i}	0.85	1.91	2.753 (2)	168
C5—H5···*Cg*1^{ii}	0.93	2.82	3.66 (4)	151
C12—H12*C*···*Cg*1^{iii}	0.96	2.62	3.44 (5)	143
(II*b*)				
N1—H1···O5	0.91	2.03	2.932 (2)	170
O5—H51···O10^{i}	0.90	1.84	2.727 (2)	168
C5—H5···*Cg*1^{ii}	0.95	2.80	3.66 (4)	152
C12—H12*C*···*Cg*1^{iii}	0.98	2.53	3.35 (4)	142

Symmetry codes: for (I*a*): (i) $x+1, y, z$; (ii) $-x+2, y-\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x+2, y+\frac{1}{2}, -z+\frac{1}{2}$; (iv) $x+\frac{1}{2}, -y+\frac{1}{2}, -z$; for (I*b*): (i) $x+1, y, z$; (ii) $-x+2, y-\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x+2, y+\frac{1}{2}, -z+\frac{1}{2}$; (iv) $x+\frac{1}{2}, -y+\frac{1}{2}, -z$; for (II*a*): (i) $-y+1, -x, -z+\frac{1}{2}$; (ii) $-x+\frac{1}{2}, y+\frac{1}{2}, -z+\frac{1}{4}$; (iii) $x-1, y, z$; for (II*b*): (i) $-y+1, -x, -z+\frac{1}{2}$; (ii) $-x+\frac{1}{2}, y+\frac{1}{2}, -z+\frac{1}{4}$; (iii) $x-1, y, z$.

(F·HCl; Al-Karaghouli & Koetzle, 1975; Gurskaya & Vainshtein, 1964).

In particular, the GFG peptide seems to be important in this comparison because G residues are similar to the protecting groups in L-AcFOMe and moreover such a sequence of amino acid is characteristic for the selectivity filter in the potassium channel of hERG type (Tseng, 2001).

As can be seen in Table 3, the presence of water molecules in the crystal structure of (II) did not significantly influence the backbone conformation. The rotation of the AcF carboxyl group around the C—C bond caused the exchange of the $\psi1$ and $\psi2$ torsion angles, whereas in GFG the φ, $\chi1$ and $\chi2$ torsion angles were subjected to significant changes, when compared with the appropriate torsion angles of L-AcFOMe. The torsion angles that characterize the backbone conformation of F·HCl are completely different from those in L-AcFOMe and GFG. This observation could be important during the selection of appropriate compounds for co-crystallization with antiarrhythmic agents. The use of F·HCl for such an experiment seems to be inappropriate owing to the different molecular geometry of L-phenylalanine in this compound.

The packing of protected amino acid molecules in the crystal structures (I) and (II) is governed by hydrogen-bond networks. In (II) the number of hydrogen bonds increases owing to the presence of the water molecules. Figs. 3 and 4 show the molecular packing of (I) and (II) at 150 (2) K. Molecules of the protected L-phenylalanine in the space group $P2_12_12_1$ (I) form hydrophilic and hydrophobic layers alternating along [001]. In the hydrophilic layers the molecules are connected by moderate hydrogen bonds of the N—H···O type parallel to the *a* direction and two types of C—H···O interactions (Table 4). The hydrophobic layers are stabilized by C—H···π interactions of type III in the classification of Malone *et al.* (1997).

In the tetragonal phase (II) alternating hydrophilic and hydrophobic layers along [001] are also observed. The pattern of hydrogen bonding in the hydrophilic layers is different from that in (I) owing to the mediating role of the water molecules which lie on a crystallographic twofold axis ($x, -x, \frac{1}{4}$). Donor–acceptor functions of water molecules, which each donate two and accept two hydrogen bonds, stabilize the crystalline structure of (II) and increase the symmetry of the space group from $P2_12_12_1$ to that of its minimal non-isomorphic supergroup (type I) $P4_12_12$ (*International Tables for Crystallography*, Vol. A, 1983). The hydrophilic layers of (II) are stabilized by two types of moderate hydrogen bonds (N—H···O and O—H···O), the geometry of which is given in Table 4. In the hydrophobic layers two types of weak C—H···π interactions dominate: C12—H12···*Cg*1 (where *Cg*1 is the centre of gravity of the C4–C9 benzene ring) and the edge-to-face interactions C5—H5···*Cg*1 ($-x+\frac{1}{2}, y+\frac{1}{2}, -z+\frac{1}{4}$), which play a crucial role in the packing architecture of (II).

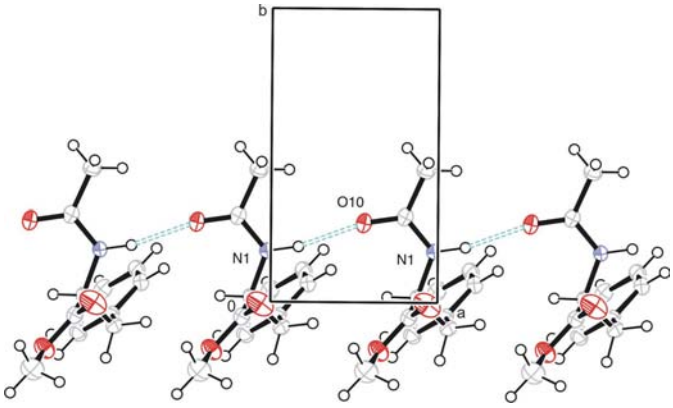


Figure 5
A $C_1^1(4)$ chain in the structure of (I) at 150 (2) K in projection along [001] showing the hydrogen-bond system, at the first-level graph set, expanding along [100].

Figs. 5 and 6 show the patterns of hydrogen bonds in the structures of (I) and (II), respectively, at 150 (2) K. Using graph-set analysis (Etter *et al.*, 1990; Bernstein *et al.*, 1995; Grell *et al.*, 1999), it can be pointed out that in the hydrogen-bond pattern of (I) only first-level $C_1^1(4)$ chains along the *a* direction are present (Fig. 5). In the structure of (II) two types of moderate hydrogen bonds form second-level symmetrically related chains $C_2^2(6)$ running along the *a* and *b* directions. Fig. 6(*a*) shows a single $C_2^2(6)$ chain. The chains parallel to the *a* and *b* directions interpenetrate at the water O5 atom (Fig. 6*b*). Thus, the hydrogen-bond pattern could be described as the second-level $R_8^8(24)$ ring (Fig. 6*c*) responsible for the tetragonal symmetry of phase (II). It is worthwhile noting that the rings are fused and define periodicity in the layer perpendicular to the fourfold screw axis (Fig. 6*d*). The graph-set analysis performed for (I) and (II) shows that this

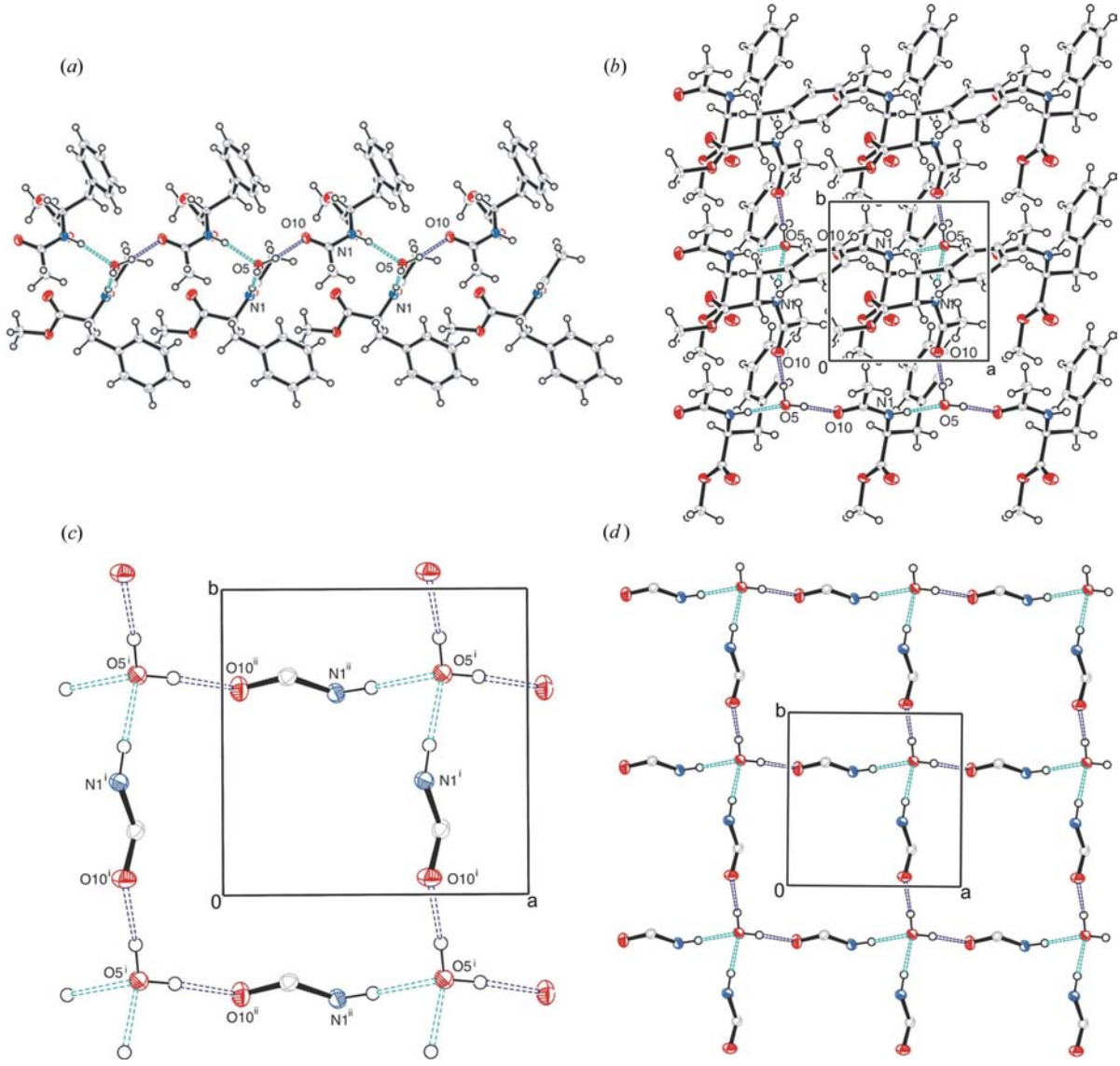


Figure 6
Second-level hydrogen-bond system of (II) at 150 (2) K: (*a*) $C_2^2(6)$ chain expanding along [010]; (*b*) projection of the layer at $\frac{1}{2}c$ onto (001); (*c*) $R_8^8(24)$ ring formed by two interpenetrating $C_2^2(6)$ chains running along [100] and [010], and viewed along *c* [(i) $x+\frac{1}{2}, -y+\frac{1}{2}, -z+\frac{3}{4}$, (ii) $-y+\frac{1}{2}, x+\frac{1}{2}, z+\frac{1}{4}$]; (*d*) condensed $R_8^8(24)$ rings in the $xy\frac{1}{2}$ layer in projection onto (001).

approach provides crucial information about the hydrogen-bond pattern which defines the packing of L-AcFOMe molecules in (I) and (II), and the symmetry of the crystal structures.

4. Concluding remarks

(i) Two pseudopolymorphs were found for L-AcFOMe: the orthorhombic phase, which is stable only in anhydrous conditions, and the tetragonal one, which could be obtained by re-crystallization of the orthorhombic phase in the presence of water.

(ii) The main differences in the structures of two pseudopolymorphs result from hydrogen-bond patterns of the first level for (I) and of the second level for (II), as was revealed by graph-set analysis. The hydrogen-bond pattern of (II) described by condensed rings $R_8^8(24)$ is compatible with the tetragonal space-group symmetry.

(iii) The structural investigation of two pseudopolymorphs shows similar backbone conformation of the molecules and in general similar packing arrangements of the alternating hydrophilic and hydrophobic layers.

(iv) Owing to the similarity of its backbone torsion angles to those in GFG, L-AcFOMe could be considered as an analogue of the selectivity filters in ionic channels, the potassium channels in particular, and may be used for co-crystallization with antiarrhythmic agents in the study of their intermolecular interactions.

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