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N-[*tert*-Butoxycarbonylglycyl-(*Z*)-α,β-dehydrophenylalanylglycyl-(*E*)-α,β-dehydrophenylalanylphenylalanyl]-4-nitroaniline ethanol solvate

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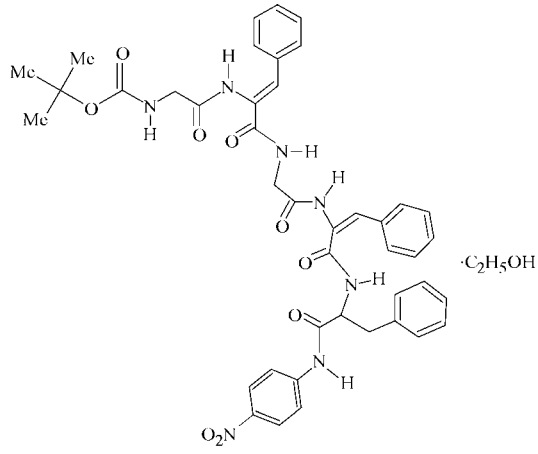
The α,β-dehydrophenylalanine residues influence the conformation of the title pentapeptide Boc^0–Gly^1–Δ^{Z}Phe^2–Gly^3–Δ^{E}Phe^4–L-Phe^5–*p*-NA ethanol solvate, $C_{42}H_{43}N_7O_9\cdot C_2H_5OH$. The first unsaturated phenylalanyl (Δ^{Z}Phe^2) and the third glycyl (Gly^3) residues form a type I β turn, while the second unsaturated phenylalanyl (Δ^{E}Phe^4) and the last phenylalanyl (L-Phe^5) residues are part of a type II β turn. All the amino acids in the peptide are linked *trans* to one another. The crystal structure is stabilized by intra- and intermolecular hydrogen bonds.

Comment

α,β-Dehydroamino acid residues (amino acids with a double bond between the C_α and C_β atoms) have been found in many biologically active peptides having antibiotic properties (Noda *et al.*, 1983). Incorporation of a dehydroamino acid into a peptide decreases conformational flexibility (Aubry *et al.*, 1984). The molecular structures of α,β-dehydrophenylalanine-containing (ΔPhe) peptides have shown that α,β-dehydrophenylalanine induces β turns (Venkatachalam, 1968) in short sequences with one ΔPhe residue (Główka *et al.*, 1987; Główka, 1988) and a 3_{10} helical conformation in longer sequences (Rajashankar *et al.*, 1992; Rajashankar, Ramakumar, Jain *et al.*, 1995; Rajashankar, Ramakumar, Mal *et al.*, 1995; Padmanabhan & Singh, 1993; Jain *et al.*, 1997). The number and position of ΔPhe residues and the type of neighbouring amino acids also play an important role in peptide chain conformation (Rajashankar *et al.*, 1996).

The present paper reports the crystal structure of the title pentapeptide Boc^0–Gly^1–Δ^{Z}Phe^2–Gly^3–Δ^{E}Phe^4–L-Phe^5–*p*-NA ethanol solvate (*p*-NA is *para*-nitroaniline), (I), containing one Δ^{Z}Phe (*Z* isomer of an α,β-dehydrophenylalanine residue, *i.e.* with the aromatic ring *cis* to the N atom) between two flexible glycine residues and one Δ^{E}Phe (*E* isomer of an α,β-dehydrophenylalanine residue, *i.e.* with the aromatic ring *trans* to the N atom) between glycine and phenylalanine residues. There is one molecule in the asymmetric part of the unit cell. The atom-numbering scheme and a general view of the molecule are shown in Fig. 1, while selected bond lengths and angles are given in Table 1.



(I)

The $C_\alpha{=}C_\beta$ (C8=C9 and C19=C20) distances for the ΔPhe residues of (I) are in agreement with those found in other structures containing ΔPhe (Główka, 1988). A shortening of about 0.045 (7) Å for the N2—C_α8 bond in Δ^{Z}Phe^2 and 0.041 (7) Å for the N4—C_α19 bond in Δ^{E}Phe^4 is observed with respect to the corresponding bonds in the saturated Phe^5 residue (N5—C_α28). The torsion angles χ^2 [6.3 (11)°], $\chi^{2,1}$ [22.3 (11)°] and $\chi^{2,2}$ [−160.4 (7)°] of the Δ^{Z}Phe^2 residue suggest that its side chain is almost planar. The torsion angles χ^4 [−172.3 (6)°], $\chi^{4,1}$ [38.3 (11)°] and $\chi^{4,2}$ [−144.2 (7)°] of the Δ^{E}Phe^4 residue suggest that, in this case, the side chain is antiperiplanar (Table 1). The steric contacts between the side-chain and main-chain atoms of Δ^{Z}Phe^2 and Δ^{E}Phe^4 are partially relaxed by rearrangement of the bond angles at the C_α and C_β atoms of these residues. As in other cases (Pieroni *et al.*, 1975, 1976–77; Aubry *et al.*, 1985), the cinnamic moieties of the ΔPhe residues in the title peptide are not planar. The torsion angles between the C=C and C=O bonds of Δ^{Z}Phe^2 and Δ^{E}Phe^4 are 29.1 (9) and −113.2 (8)°, respectively.

All the amino acids in the title pentapeptide are linked *trans* to one another. The deviations of all ω angles are not larger than 9°. The values of torsion angles φ and ψ of the Δ^{Z}Phe^2 and Gly^3 residues suggest a type I β turn conformation, while the torsion angles of Δ^{E}Phe^4 and Phe^5 indicate that these residues form a type II β turn. The torsion angles of the *tert*-butoxycarbonyl group (φ^0 and ω^0) correspond to a *trans–trans* conformation.

The conformation of (I) is stabilized by nine intramolecular and four intermolecular hydrogen bonds of different types, namely N—H···O, C—H···N, N—H···N and C—H···O (Table 2). The carbonyl O atoms of Gly^1 (O3) and Gly^3 (O5)

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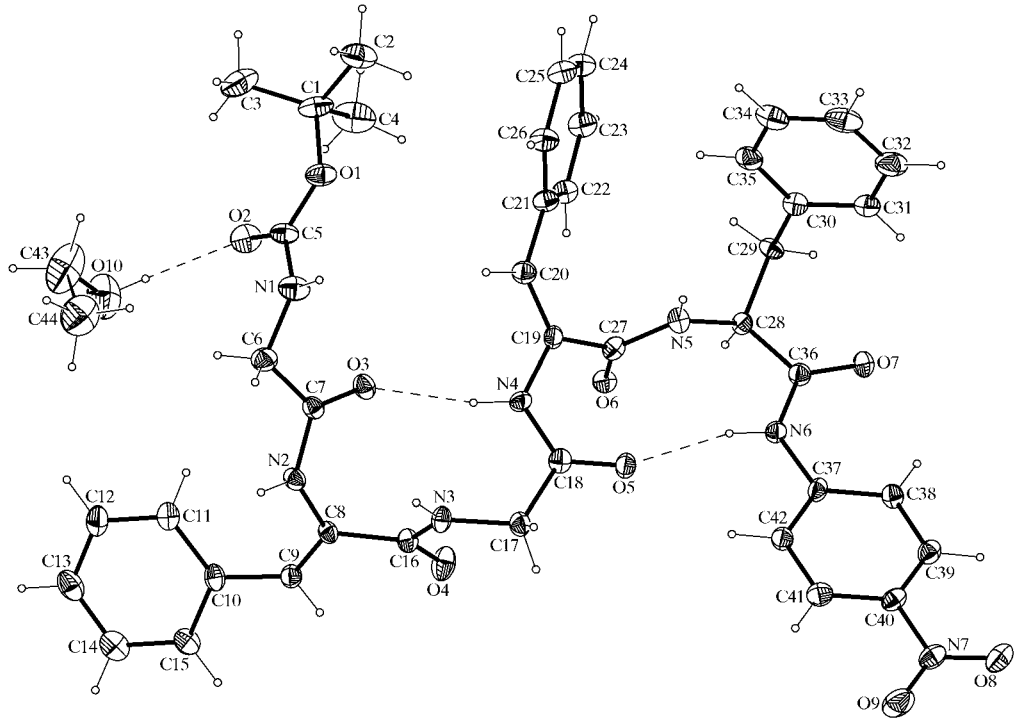

Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate intramolecular hydrogen bonds.

take part in N4—H4*D*···O3 and N6—H6*C*···O5 hydrogen bonds, respectively, as shown in Fig. 1. The π electrons of the aromatic ring of Δ^{E}Phe^{4} take part in C—H···π interactions with atom H4*B* of Boc and atom H35*A* of L-Phe^{5}. The distances and angles between C—H in the alkyl group and the centre of the Δ^{E}Phe^{4} ring (denoted *Cg*1) are 3.883 Å and 150°, respectively, for the C4—H4*B*···*Cg*1 contact and 3.557 Å and 172° for the C35—H35*A*···*Cg*1 contact (Table 2).

These results show that the presence of two α,β-dehydrophenylalanyl residues induces β turns in the pentapeptide Boc^{0}–Gly^{1}–Δ^{Z}Phe^{2}–Gly^{3}–Δ^{E}Phe^{4}–L-Phe^{5}–*p*-NA. This is consistent with the results for other short peptides, such as the tetrapeptide Boc^{0}–Gly^{1}–Δ^{Z}Phe^{2}–Gly^{3}–Phe^{4}–*p*-NA (Ejsmont *et al.*, 2001).

Experimental

The synthesis of Boc–Gly–Δ^{Z}Phe has been described by Makowski *et al.* (1985). Boc–Gly–Δ^{E}Phe–L-Phe–*p*-NA was obtained in the same manner as its *Z* isomer (Makowski *et al.*, 2001); instead of TBTU [2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate], isobutyl chloroformate (0.26 ml, 2 mmol) in tetrahydrofuran (3.5 ml) was used. Isomers *E* and *Z* of Boc–Gly–ΔPhe–L-Phe–*p*-NA were separated on a silica-gel H-60 column (Merck), eluting with EtOAc (1–40%) in benzene. Yields of isomers *E* and *Z* were 18 and 53%, respectively. Gly–Δ^{E}Phe–L-Phe–*p*-NA was obtained according to the method described by Makowski *et al.* (2001) and used for further synthesis without characterization. The only modification was that, instead of dissolution in ethyl ether and evaporation, the oily deblocked peptide was dissolved in propan-2-ol (20 ml) and precipitated with hexane. TFA (trifluoroacetic acid) (0.139 ml, 1 mmol) was added to a solution of Boc–Gly–Δ^{Z}Phe (0.16 g, 0.5 mmol) in tetrahydrofuran (2 ml) and the solution was cooled to 263 K. Isobutyl chloroformate (0.066 ml, 0.5 mmol) was then added and the mixture was left for 1.5 min at this temperature. Finally, Gly–Δ^{E}Phe–L-Phe–*p*-NA (0.3 g, 0.5 mmol) was added and the reaction was carried out for 22 h at room temperature. The precipitate which formed was filtered off and the solvent was removed under reduced pressure. The resulting oil was dissolved in EtOAc (50 ml) and washed successively with 2 *M* HCl (2 × 3 ml), saturated potassium bicarbonate (3 × 3 ml) and brine (3 ml). The organic layer was dried over $MgSO_4$, the drying agent was removed by filtration and the solvent was evaporated. The product was crystallized from EtOAc–benzene (1:1)/hexane. The purity of the peptide (100%) was checked by high-perfomance liquid chromatography using an Alltech Alltima column (C-18, 5 µm, 150 × 4.6 mm); solvent system: *A* 0.1% TFA, *B* MeCN, *A*:*B* 35:65, flow rate 1 ml min^{-1} [yield 0.305 g (77%), m.p. 476–478 K]. Elemental analysis calculated for $C_{42}H_{43}N_7O_9$: C 63.87, H 5.49%; found: C 64.04, H 5.28%. Long thin needle-shaped crystals of Boc^{0}–Gly^{1}–Δ^{Z}Phe^{2}–Gly^{3}–Δ^{E}Phe^{4}–L-Phe^{5}–*p*-NA·C_2H_5OH, (I), suitable for X-ray structure analysis, were grown at room temperature from a solution in ethanol. The crystals are sensitive and decompose in air.

Crystal data

$C_{42}H_{43}N_7O_9·C_2H_6O$
M_r = 835.90
Monoclinic, $P2_1$
a = 13.080 (4) Å
b = 8.998 (3) Å
c = 18.406 (5) Å
β = 99.37 (3)°
V = 2137.4 (11) Å^3
Z = 2
D_x = 1.299 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 7064 reflections
θ = 3–73°
μ = 0.77 mm^{-1}
T = 100 (2) K
Long thin needle, yellow
0.45 × 0.04 × 0.02 mm

Data collection

Oxford Xcalibur PX κ-geometry diffractometer with CCD area detector
ω and φ scans
Absorption correction: analytical (*CrysAlis RED*; Oxford Diffraction, 2003)
T_{min} = 0.828, T_{max} = 0.988
14 511 measured reflections
4423 independent reflections
2794 reflections with $I > 2\sigma(I)$
R_{int} = 0.085
θ_{max} = 73.5°
$h = -16 \rightarrow 13$
$k = -9 \rightarrow 11$
$l = -22 \rightarrow 19$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.072
$wR(F^2)$ = 0.192
S = 1.10
4423 reflections
552 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.085P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.57 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0051 (7)

Table 1
Selected geometric parameters (Å, °).

N2—C8	1.419 (7)	C8—C9	1.344 (9)
N4—C19	1.423 (8)	C19—C20	1.351 (8)
N5—C28	1.464 (7)	C28—C29	1.529 (8)
C9—C8—N2	123.2 (6)	N4—C19—C27	115.5 (5)
C9—C8—C16	118.8 (6)	N5—C28—C36	113.1 (5)
N2—C8—C16	117.9 (5)	N5—C28—C29	112.7 (5)
C20—C19—N4	119.4 (6)	C36—C28—C29	112.9 (5)
C20—C19—C27	124.8 (6)		
O1—C5—N1—C6	−176.9 (6)	N3—C17—C18—N4	13.6 (9)
C1—O1—C5—N1	−176.4 (6)	C17—C18—N4—C19	174.9 (6)
C5—N1—C6—C7	87.5 (8)	C18—N4—C19—C27	38.6 (8)
N1—C6—C7—N2	164.5 (6)	N4—C19—C20—C21	−172.3 (6)
C6—C7—N2—C8	171.5 (6)	C19—C20—C21—C22	38.3 (11)
C7—N2—C8—C16	59.1 (8)	C19—C20—C21—C26	−144.2 (7)
N2—C8—C9—C10	6.3 (11)	N4—C19—C27—N5	−120.8 (6)
C8—C9—C10—C15	−160.4 (7)	C19—C27—N5—C28	−176.3 (5)
C8—C9—C10—C11	22.3 (11)	C27—N5—C28—C36	−109.7 (7)
N2—C8—C16—N3	23.7 (9)	N5—C28—C36—N6	28.9 (8)
C8—C16—N3—C17	−177.1 (6)	C28—C36—N6—C37	176.1 (6)
C16—N3—C17—C18	82.2 (8)		

All H atoms were placed in calculated positions, with C—H distances in the range 0.95–1.00 Å and N—H distances of 0.88 Å, and were allowed to ride on their parent atoms, with U_{iso}(H) = 1.2U_{eq}(C,N). The absolute structure was chosen on the basis of the known absolute configuration of the L-phenylalanine residue. The Friedel pairs were merged. Owing to the large anisotropic displacement parameter, the ethanol molecule is certainly slightly disordered, but the type of disorder could not be resolved.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2003); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2003); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXD* (Sheldrick, 2002); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997); software used to prepare material for publication: *SHELXL97*.

Table 2
Hydrogen-bond geometry (Å, °).

The C—H···π interaction is a hydrogen bond occurring between C—H in an alkyl group and the π system of Δ^EPhe[4]. The centroid of the Δ^EPhe[4] ring is denoted *Cg*1.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*D*···O4^{i}	0.88	2.05	2.734 (8)	134
N2—H2*D*···O6^{i}	0.88	1.94	2.784 (7)	161
N3—H3*D*···O3^{i}	0.88	2.36	3.057 (7)	137
C6—H6*B*···O4^{i}	0.99	2.49	3.018 (10)	113
C13—H13*A*···O7^{ii}	0.95	2.42	3.222 (9)	142
C3—H3*B*···O2	0.98	2.33	2.924 (10)	118
C4—H4*A*···O2	0.98	2.55	3.085 (12)	114
C31—H31*A*···O7	0.95	2.51	3.101 (8)	120
C38—H38*A*···O7	0.95	2.21	2.820 (8)	121
C11—H11*A*···N2	0.95	2.52	3.080 (9)	118
N4—H4*D*···O3	0.88	2.09	2.925 (7)	158
N6—H6*C*···O5	0.88	2.12	2.974 (7)	163
N4—H4*D*···N3	0.88	2.36	2.766 (8)	108
N6—H6*C*···N5	0.88	2.35	2.764 (7)	109
O10—H10*A*···O2	0.84	2.00	2.843 (10)	178
C4—H4*B*···*Cg*1	0.98	3.00	3.883	150
C35—H35*A*···*Cg*1	0.95	2.61	3.557	172

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

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN1081). Services for accessing these data are described at the back of the journal.

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