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N-[*tert*-Butoxycarbonylglycyl-(*Z*)-α,β-dehydrophenylalanylglycyl-(*E*)-α,β-dehydrophenylalanyl]glycine methyl ester dihydrate

Maciej Makowski,[a] Marek Lisowski,[b]* Anna Maciąg[b] and Tadeusz Lis[b]

[a]Institute of Chemistry, University of Opole, 48 Oleska Street, 45-052 Opole, Poland, and [b]Faculty of Chemistry, University of Wrocław, 14 Joliot-Curie Street, 50-383 Wrocław, Poland

Correspondence e-mail: mbl@wchuwr.chem.uni.wroc.pl

Key indicators

Single-crystal X-ray study
T = 100 K
Mean σ(C–C) = 0.012 Å
Disorder in main residue
R factor = 0.072
wR factor = 0.114
Data-to-parameter ratio = 9.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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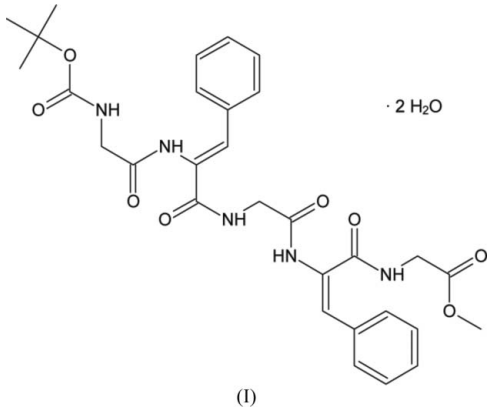
The title pentapeptide, Boc^0—Gly^1–Δ^ZPhe^2—Gly^3–Δ^EPhe^4—Gly^5—OMe, $C_{30}H_{35}N_5O_8\cdot 2H_2O$, adopts the type I β-turn conformation for the Δ^ZPhe^2—Gly^3 residues. It is stabilized by a $4 \rightarrow 1$ intramolecular hydrogen bond between the Δ^EPhe^4 NH and Gly^1 CO groups. All the amino acid residues in the pentapeptide sequence are linked *trans* to each other. The crystal structure is stabilized by intra- and intermolecular hydrogen bonds.

Comment

α,β-Dehydroamino acid residues contain a double bond between the Cα and Cβ atoms. They have been found in several microbial peptides and antibiotics (Noda *et al.*, 1983; Spatola, 1983). Dehydropeptides [peptides containing dehydroamino acid residue(s) in their sequences] show enhanced resistance to enzymatic degradation (Shimohigashi *et al.*, 1987). The insertion of dehydroamino acid residues into the peptide sequence also results in a distinct increase of the binding ability of dehydropeptides to metal ions (Brasuń *et al.*, 2004). The dehydroamino acid residues restrict the conformation of the peptide backbone in dehydropeptides and they are strong inducers of folded conformations (Singh & Kaur, 1996). The most studied dehydroamino acid residue so far has been dehydrophenylalanine, Δ^ZPhe (Vijayaraghavan *et al.*, 1998, and references therein; Siddiqui, 1999; Kubica *et al.*, 2000). Crystal structures of different Δ^ZPhe-containing peptides have shown that Δ^ZPhe induces β-turns in short sequences with one Δ^ZPhe (Główka *et al.*, 1987; Główka, 1988; Aubry *et al.*, 1991) and a right-handed 3_{10}-helical conformation in longer peptides (Rajashankar *et al.*, 1992; Padmanabhan & Singh, 1993; Rajashankar, Ramakumar, Jain & Chauhan, 1995; Rajashankar, Ramakumar, Mal, Jain & Chauhan, 1995; Jain *et al.*, 1997). It has been found (Vijayaraghavan *et al.*, 1998, and references therein) that a ΔPhe residue adopts one of the three conformations with average φ and ψ torsion angles of 80 and 0°, −60 and 140°, or −60 and −30°, or their enantiomeric values. It has also been observed that ΔPhe residues at the (*i*+2) position in a three-peptide unit sequence induce a type II β-turn conformation with φ and ψ torsion angles values falling close to 80° and 0°, respectively (Singh *et al.*, 1987; Główka, 1988; Patel *et al.*, 1990; Busseti *et al.*, 1992). Studies of sequences containing more than one ΔPhe residue, or one ΔPhe and another dehydroamino acid residue, separated by one or more saturated residue(s), have shown that these peptides adopt a 3_{10}-helical conformation with φ and ψ torsion angles of about −60 and −30°, respectively (Singh & Kaur, 1996; Padyana *et al.*, 2003; Goel *et al.*, 2005). The present paper describes the crystal structure of the title hydrated penta-

peptide, (I), containing two dehydrophenylalanyl residues, surrounded by flexible glycyl ones.



(I)

The first and second dehydrophenylalanine residues are of the *Z* and *E* configuration, respectively. There is one molecule in the asymmetric unit. A perspective view with the numbering scheme is shown in Fig. 1. Table 1 lists selected geometric parameters. The bond lengths of Cα═Cβ (C8═C9 and C19═C20) are consistent with those obtained from other studies of pentapeptides containing ΔPhe residues, and correspond well to the classical C═C double-bond distance of 1.337 Å (Dickerson & Geis, 1969). The lengths of the N2—C8, C8—C16, N4—C19 and C19—C27 bonds indicate that in both ΔPhe residues the carbonyl group and N atom are conjugated with the styrene substituent.

Owing to the shortening of the distance between the Cα and Cβ atoms, the side-chain atoms of the ΔPhe residues are closer to the main chain than in their saturated counterpart. This results in some rearrangement of the bond angles at Cα and Cβ. The values of the N—Cα—C′ bond angle in the dehydro residues are found to be smaller than the standard trigonal bond angle of 120°, whereas the bond angles Cα—Cβ—Cγ are considerably larger in both ΔPhe residues. The bond angle N—Cα═Cβ is noticeably larger in the case of the Δ^{Z}Phe^{2} residue, whereas in the case of Δ^{E}Phe^{4} the value of this angle falls below 120°. Constraints imposed on the pentapeptide backbone are partially relaxed through the distortions in the geometry. All the amino acid residues are linked *trans* to each other. The deviations from the ideal value of ±180° are not larger than 6°. The values of torsion angles χ^{2} = −4.2 (14)°, $\chi^{2,1}$ = −44.9 (13)° and $\chi^{2,2}$ = 138.0 (9)° indicate that the side chain of the Δ^{Z}Phe^{2} residue is synperiplanar, and the χ^{4} = 171.5 (8)°, $\chi^{4,1}$ = 167.9 (9)° and $\chi^{4,2}$ = −10.1 (16)° torsion angles suggest that the side chain of Δ^{E}Phe^{4} is almost planar. The dihedral angles between the C═C and C═O bonds of Δ^{Z}Phe^{2} and Δ^{E}Phe^{4} are −47.0 (10) and −41.1 (15)°, respectively.

There is one intramolecular 4 → 1 hydrogen bond (N4—H4···O3) which indicates the presence of a β-turn conformation for the Δ^{Z}Phe^{2}—Gly^{3} residues. The torsion angles φ and ψ in the two residues correspond to the type I β-turn. The standard values of φ and ψ angles for that β-turn are −60 and −30°, and −90 and 0°. The angles present in the Δ^{Z}Phe^{2} and Gly^{3} residues are −40 and −42°, and −80 and 0°, respectively. The peptide studied is very similar to Boc^{0}–Gly^{1}–Δ^{Z}Phe^{2}–Gly^{3}–Δ^{E}Phe^{4}–L–Phe^{5}–*p*-NA (*p*-NA is *p*-nitroaniline), whose crystal structure was established a short time ago (Makowski *et al.*, 2005), the only difference being the amino acid residue at position 5 and the C-terminal blocking group. In that peptide, there is a type I′ β-turn on the Δ^{Z}Phe^{2} and Gly^{3} residues and a type II′ β-turn on the Δ^{E}Phe^{4} and Phe^{5} residues. Both these turns are stabilized by 4 → 1 hydrogen bonds, one between Δ^{E}Phe^{4} NH and Gly^{1} CO and another between *p*-NA NH and Gly^{3} CO. The latter turn is not possible in the case of the title peptide because there is no proton donor at the corresponding position in the peptide chain. As can be seen, the lack of the Phe^{5} residue and the *p*-NA group results in a β-turn on the N-terminal tetrapeptide which is a mirror image of that in the chiral peptide (Makowski *et al.*, 2005). The conformation of the peptide is stabilized by inter- and intramolecular hydrogen bonds of different types, namely N—H···O, O—H···O, C—H···O and N—H···N. Geometric parameters of hydrogen bonds are presented in Table 2. The results clearly show that introduction of two α,β-dehydrophenylalanyl residues into the peptide sequence induces the β-turn conformation.

Experimental

The synthesis of the title compound was described by Brasuń *et al.* (2004). The crystals were grown by slow diffusion of hexane into an ethyl acetate–methanol (20:1 *v*/*v*) solution of the compound at room temperature.

Crystal data

$C_{30}H_{35}N_5O_8{\cdot}2H_2O$
M_r = 629.66
Orthorhombic, $P2_12_12$
a = 15.371 (4) Å
b = 23.889 (6) Å
c = 8.940 (3) Å
V = 3282.7 (16) Å^3
Z = 4
D_x = 1.274 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 5475 reflections
θ = 3–73°
μ = 0.81 mm^{-1}
T = 100 (2) K
Needle, colourless
0.04 × 0.03 × 0.14 mm

Data collection

Xcalibur PX κ-geometry CCD diffractometer
ω and φ scans
Absorption correction: analytical (*CrysAlis RED*; Oxford Diffraction, 2003)
T_{min} = 0.910, T_{max} = 0.983
22419 measured reflections
3775 independent reflections
1835 reflections with $I > 2\sigma(I)$
R_{int} = 0.146
θ_{max} = 76.7°
$h = -19 \rightarrow 15$
$k = -30 \rightarrow 22$
$l = -9 \rightarrow 10$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.072
$wR(F^2)$ = 0.114
S = 1.18
3775 reflections
417 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/\sigma^2(F_o^2)$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.40 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}

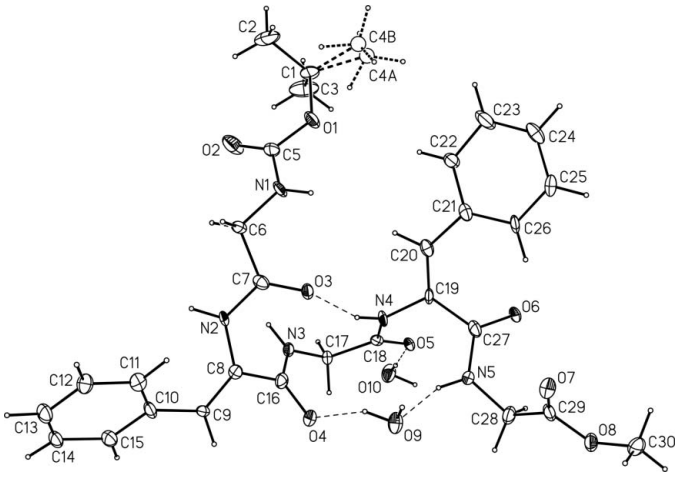


Figure 1
The molecular structure of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate intramolecular hydrogen bonds. The disordered methyl group in Boc^0 is drawn with dashed lines.

Table 1
Selected geometric parameters (Å, °).

N2—C8	1.437 (8)	N4—C19	1.430 (9)
C8—C9	1.321 (9)	C19—C20	1.332 (10)
C9—C8—N2	123.8 (7)	C20—C19—N4	116.1 (7)
C9—C8—C16	119.4 (7)	C20—C19—C27	127.5 (8)
N2—C8—C16	115.9 (7)	N4—C19—C27	116.4 (7)
C8—C9—C10	128.0 (7)	C19—C20—C21	132.4 (8)
C1—O1—C5—N1	−177.4 (8)	C16—N3—C17—C18	−80.2 (9)
O1—C5—N1—C6	176.3 (8)	N3—C17—C18—N4	0.2 (10)
C5—N1—C6—C7	135.2 (9)	C17—C18—N4—C19	−176.0 (6)
N1—C6—C7—N2	−161.0 (7)	C18—N4—C19—C27	−52.9 (11)
C6—C7—N2—C8	177.4 (7)	C20—C19—C27—O6	−41.1 (15)
C7—N2—C8—C16	−39.2 (11)	N4—C19—C27—N5	−39.9 (11)
C9—C8—C16—O4	−47.0 (12)	N4—C19—C20—C21	171.5 (8)
N2—C8—C16—N3	−42.1 (10)	C19—C20—C21—C26	−10.1 (16)
N2—C8—C9—C10	−4.2 (14)	C19—C20—C21—C22	167.9 (9)
C8—C9—C10—C15	138.0 (9)	C19—C27—N5—C28	176.8 (7)
C8—C9—C10—C11	−44.9 (13)		
C8—C16—N3—C17	−174.9 (7)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N4—H4···O3	0.88	2.03	2.869 (8)	160
N3—H3···O6^{i}	0.88	2.08	2.944 (8)	166
N2—H2···O5^{i}	0.88	2.01	2.885 (7)	174
N5—H5···O9	0.88	2.06	2.853 (9)	149
O9—H9*A*···O4	0.86	2.09	2.831 (9)	143
O9—H9*B*···O10^{ii}	0.86	2.07	2.794 (9)	141
O10—H10*A*···O7^{iii}	0.86	2.16	2.967 (9)	156
O10—H10*B*···O5	0.86	2.09	2.947 (9)	177
C2—H2*B*···O2	0.98	2.35	2.970 (10)	121
C3—H3*C*···O2	0.98	2.42	3.031 (12)	120
C6—H6*A*···O2	0.99	2.36	2.761 (9)	103
N4—H4···N3	0.88	2.31	2.741 (8)	110
N5—H5···N4	0.88	2.53	2.825 (8)	100
C26—H26*A*···O6	0.95	2.48	3.101 (10)	122
C28—H28*A*···O2^{iv}	0.99	2.22	3.145 (11)	155
C28—H28*B*···O8^{v}	0.99	2.60	3.337 (10)	131
C28—H28*A*···O2^{iv}	0.99	2.22	3.145 (11)	155
C26—H26*A*···O6	0.95	2.48	3.101 (10)	122

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

All H atoms, except those belonging to water molecules, were positioned geometrically, with C—H distances in the range 0.95–0.99 Å and N—H distances of 0.88 Å, and refined using a riding model, with $U_{iso}(H) = 1.5U_{eq}$(methyl C) or $1.2U_{eq}$(other C). Water H atoms were located in a difference Fourier map and refined with the constraint O—H = 0.86 Å. In the absence of significant anomalous dispersion effects, Friedel pairs were merged. During refinement, it was found that the position of the C4 atom in the Boc^0 group was disordered, as a result of the large anisotropic displacement parameter between two alternative sites, and both seemed to have equal occupancies of 0.5 for C4*A* and C4*B*. The refinement was carried out using anisotropic displacement parameters for all non-H atoms, except that C4*A* and C4*B* were refined isotropically. Due to the small dimensions of the crystal, a large number of reflections have the intensity $< 2\sigma(I)$; this results in the high value of R_{int}.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2003); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2003); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997); software used to prepare material for publication: *SHELXL97*.

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