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Design of peptides with α,β-dehydro residues: a dipeptide with a branched β-carbon dehydro residue at the (*i*+1) position, methyl *N*-(benzyloxycarbonyl)-α,β-didehydrovalyl-L-tryptophanate

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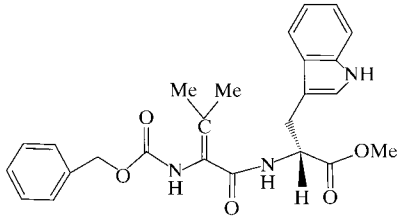
The structure of the title peptide, $C_{25}H_{27}N_3O_5$, has been determined and its conformation analysed. Values of the standard peptide torsion angles are $\varphi_1 = -44.2\,(3)^\circ$, $\psi_1 = 135.9\,(2)^\circ$, $\varphi_2 = -141.6\,(2)^\circ$ and $\psi_2^T = 168.0\,(2)^\circ$. The crystal structure is stabilized by an intermolecular hydrogen bond, with an N···O distance of 2.919 (3) Å, which is formed between screw-axis-related NH and CO groups of dehydrovaline residues.

Comment

α,β-Dehydroamino acids are strong inducers of folded conformations in peptides. A set of design rules have been developed with dehydrophenylalanine (ΔPhe), dehydroleucine (ΔLeu), dehydro-α-aminobutyric acid (ΔAbu) and dehydroalanine (ΔAla) (Singh & Kaur, 1996). However, the branched β-carbon residues, such as valine and isoleucine,



(II)

have not been used so far as dehydro residues, although the conformational preferences of valine and isoleucine are known to be different from those of other residues. In order to develop new design rules with dehydrovaline (ΔVal) and dehydroisoleucine (ΔIle), the structure of a dipeptide with ΔVal, (II), has been determined.

The structure (Fig. 1) shows that the C1*A*—C1*B* distance of 1.339 (3) Å in ΔVal corresponds to a standard C=C double-bond distance of 1.32 Å (Rose *et al.*, 1985). Due to unfavourable interactions between the atoms of the backbone and those of the side chain, the N1—C1*A*—C1*P* angle closes to

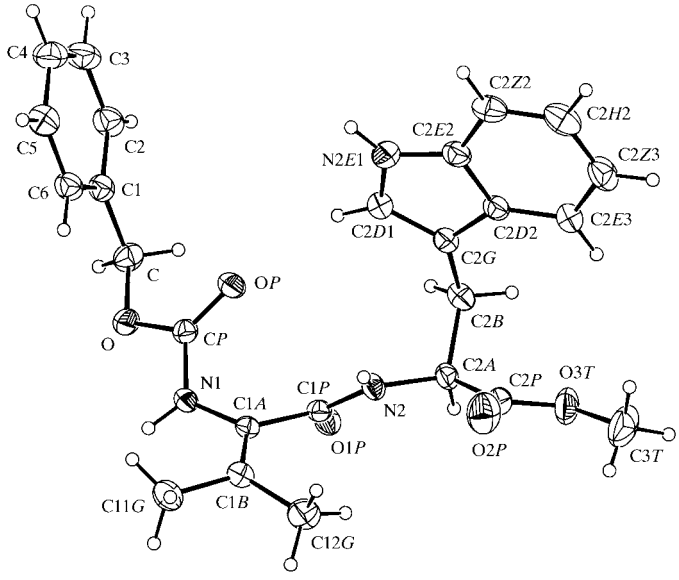


Figure 1
The molecular structure of the title peptide shown with the atom-numbering scheme and 30% probability displacement ellipsoids.

114.2 (2)°. The other two angles, N1—C1*A*—C1*B* and C1*P*—C1*A*—C1*B*, are 121.3 (2) and 123.5 (2)°, respectively.

The peptide adopts a conformation characterized by the torsion angles φ_1 (C*P*—N1—C1*A*—C1*P*) = −44.2 (3)°, ψ_1 (N1—C1*A*—C1*P*—N2) = 135.9 (2)°, φ_2 (C1*P*—N2—C2*A*—C2*P*) = −141.6 (2)° and ψ_2^T (N2—C2*A*—C2*P*—O3*T*) = 168.0 (2)°. It may be noted that the values of the torsion angles of ΔVal correspond to the φ,ψ values of an (*i*+1)th residue in a β-turn II conformation. This indicates that the ΔVal residue at the (*i*+1) position may promote a β-turn II conformation. The values of the torsion angles $\chi_1^{1,1}$ (N1—C1*A*—C1*B*—C1*G*1) and $\chi_1^{1,2}$ (N1—C1*A*—C1*B*—C1*G*2) of dehydrovaline are −6.6 (4) and 170.1 (3)°, respectively, and indicate that the ΔVal side chain is essentially planar.

The crystal packing is stabilized by a hydrophobic region formed by the aromatic rings of tryptophans and the benzene rings of benzyloxycarbonyl (Cbz) groups. The packing is further stabilized by an intermolecular hydrogen bond formed between the screw-axis-related NH and CO groups of the ΔVal residue [N1—H1···O1*P*^{i}: N1···O*P*^{i} = 2.919 (3) Å, H1···O1*P*^{i} = 2.16 Å and N1—H1···O1*P*^{i} = 147°; symmetry code: (i) $-x, y-\frac{1}{2}, -z+\frac{1}{2}$].

Experimental

The synthesis of Cbz–ΔVal–OH, (I), was carried out by condensation of 3-methyl-2-oxo-butanoic acid (1 g, 7.2 mmol) with benzyl carbamate (1.98 g, 10.8 mmol) and *p*-toluenesulfonic acid (0.47 g, 2.1 mmol) in dry benzene. The reaction mixture was refluxed at 373 K for 8 h using a Dean–Stark water remover. The solution was then extracted with saturated sodium bicarbonate. The extracts were neutralized by adding concentrated HCl dropwise to yield a white solid, which was filtered off and recrystallized from benzene. The solid product of Cbz–ΔVal–OH was obtained in 67% yield. For the synthesis of Cbz–ΔVal–L-Trp–OCH_3 (Trp is L-tryptophan), (II), *N*-methylmorpholine (0.29 ml, 2.69 mmol) was added to a chilled (263 K) solution of (I) (0.67 g, 2.69 mmol) in tetrahydrofuran. This was followed by the addition of isobutyl chloroformate (0.36 ml, 2.69 mmol) and the resulting solution was stirred for 20 min. A precooled solution of L-Trp–OCH_3·HCl (0.82 g, 3.2 mmol) was added to the reaction mixture. The resulting solution was stirred for 2 h at 273 K and then overnight at room temperature. After completion of the reaction (monitored by thin-layer chromatography), the solvent was removed under vacuum; the resulting residual material was dissolved in ethyl acetate and washed successively with water, 10% sodium bicarbonate, 5% citric acid and water. The organic layer was dried over anhydrous sodium sulfate and then evaporated to yield 72% of (II) (m.p. 438 K). The peptide was recrystallized from a solution in acetone–water (4:1) by slow evaporation.

Crystal data

$C_{25}H_{27}N_3O_5$
M_r = 449.50
Monoclinic, *A*2
a = 17.1524 (9) Å
b = 6.1439 (9) Å
c = 22.6183 (11) Å
β = 107.791 (12)°
V = 2269.6 (4) Å^3
Z = 4
D_x = 1.315 Mg m^{-3}
Cu *K*α radiation
Cell parameters from 25 reflections
θ = 0–25°
μ = 0.76 mm^{-1}
T = 293 (2) K
Prism, colourless
0.3 × 0.2 × 0.1 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: empirical (*SDP*; Enraf–Nonius, 1979)
T_{min} = 0.835, T_{max} = 0.928
2576 measured reflections
2576 independent reflections
2434 reflections with $I > 2\sigma(I)$
θ_{max} = 75.6°
$h = 0 \rightarrow 21$
$k = 0 \rightarrow 7$
$l = -28 \rightarrow 26$
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.146
S = 1.04
2576 reflections
302 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1137P)^2 + 0.5403P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0018 (4)

All H atoms were visible in difference maps and were allowed for as riding atoms (with C—H distances of 0.93–0.98 Å and an N—H distance of 0.86 Å). In this light-atom structure, it was not possible to establish the absolute configuration from the Flack (1983) parameter [0.1 (3)]; the configuration chosen and shown in both the Scheme and Fig. 1 was determined by the configuration of the starting material in the synthesis (L-tryptophan).

Data collection: *SDP* (Enraf–Nonius, 1979); cell refinement: *SDP*; data reduction: SDP; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2001); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: VJ1138). Services for accessing these data are described at the back of the journal.

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