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Cyclo(L-leucyl-α,β-dehydrophenylalanine): the first diketopiperazine containing an α,β-dehydrophenylalanine residue

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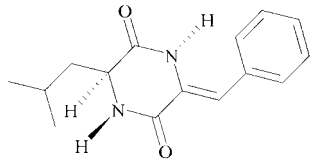
The title compound (systematic name: 3-benzylidene-6-isobutylpiperazine-2,5-dione), $C_{15}H_{18}N_2O_2$, an α,β-dehydrophenylalanine containing diketopiperazine, crystallizes in the space group *P*1 with two molecules in the asymmetric unit arranged antiparallel to one another. The α,β-dehydrophenylalanine (ΔPhe) residue in this cyclic peptide retains its planarity but deviates from the standard conformations observed in its linear analogues. Each type of molecule forms a linear chain with molecules of the same type *via* pairwise N—H···O hydrogen bonds, while weaker C—H···O interactions link the chains together to form a three-dimensional network.

Comment

Diketopiperazines (piperazine-2,5-diones) are the simplest models for the study of *cis*-peptide geometries and for studying the influence of side chains on ring conformations. The present structure analysis of the title molecule, cyclo(L-Leu–ΔPhe), (I), was undertaken as a continuation of our investigations of the diketopiperazine (DKP) structure (Suguna *et al.*, 1982, 1984, 1985) and of the peptides containing ΔPhe residues. While the structures of several DKPs containing protein amino acids and α-aminoisobutyric acid (AIB) are known, this is perhaps the first report of a DKP incorporating a dehydro amino acid residue. In our laboratory, this constrained amino acid has been successfully incorporated in the *de novo* design of secondary structure elements, 3_{10} helices and supersecondary structural elements (Rajashankar *et al.*, 1996; Ramagopal *et al.*, 2001; Rudresh *et al.*, 2004; Mathur *et al.*, 2004). The α,β-dehydrophenyalanine residues induce β-bend structures in short peptides and a 3_{10} helical conformation in longer peptides. The most favourable conformations of ΔPhe are (φ, ψ) ∼ (−60, −30°), (−60, 150°) and (80, 0°), or their enantiomers. In the case of linear peptides, (φ, ψ) usually assume the conformation (60, 30°) or (−60, −30°). The leucyl side chain is of particular interest, since many diketopiperazines containing this residue have been found to be the factors causing a bitter taste (Minamiura *et al.*, 1972; Shiba *et al.*, 1974, 1981).



(I)

In the structure of (I), two diketopiperazine molecules, *A* and *B*, are present in the asymmetric unit. The displacement ellipsoid representation of the molecules shown in Fig. 1 illustrates an overall view of the structure. The two molecules are chemically equivalent but crystallographically independent. They are antiparallel to each other and are arranged such that the ΔPhe side chain of one shields the DKP ring of the other. The arrangement is different from that seen in other DKPs, such as cyclo(L-Leu–L-Tyr) (Suguna *et al.*, 1984), cyclo(Phe–Phe) (Benedetti *et al.*, 1976) or cyclo(Pro–D-Phe) (Ramani *et al.*, 1976), where the aromatic ring of one molecule shields the DKP ring of the same molecule. This behaviour may be attributed to the fact that the ΔPhe residue as a whole is rigid and rotation about the $C^{\alpha}{=}C^{\beta}$ bond is restricted. Due to this, the entire molecule adopts an extended rather than a folded conformation.

The φ and ψ angles of the ΔPhe residue are very different from what is observed in ΔPhe-containing linear peptides, *i.e.* (60, 30°) and (−60, −30°). They are close to zero, with φ (C1′*A*—N2*A*—C2*A*—C2′*A*) = 1.3 (4)° and ψ (N1*A*—C2′*A*—C2*A*—N2*A*) = −4.3 (4)° for molecule *A*, and φ (C1′*B*—N2*B*—C2*B*—C2′*B*) = −8.8 (4)° and ψ (N1*B*—C2′*B*—C2*B*—N2*B*) = 6.6 (3)° for molecule *B*. These values for ΔPhe may be a consequence of the cyclization of the peptide. The angles at the C^{β} atoms of the leucyl side chains are 112.2 (2) and

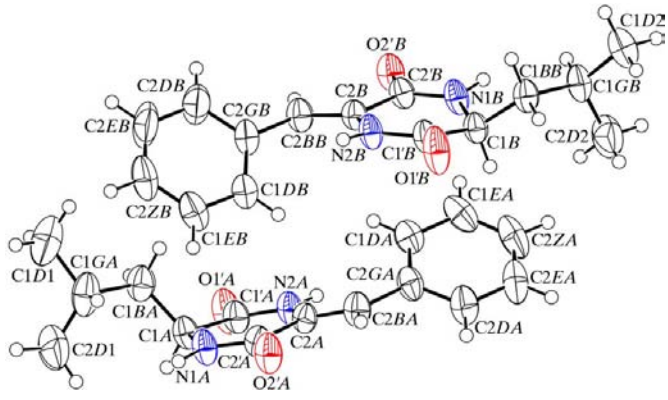


Figure 1
Plot of the two independent molecules of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

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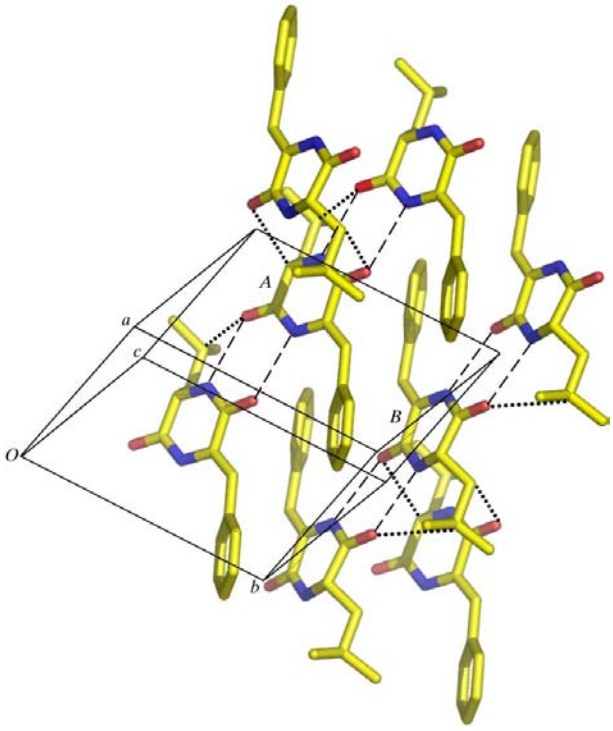

Figure 2
A view of the packing down the *a* axis. The strong N—H···O hydrogen bonds between similar molecules related by the *a* translation are shown as dashed lines, and the weaker C—H···O interactions between the translated molecules and crystallographically independent molecules are shown as dotted lines.

111.6 (2)° in molecules *A* and *B*, respectively, indicating that these atoms are axial to the DKP rings. The molecule acquires an extended conformation, with the χ^2 dihedral angles being 177.5 (3) and 176.0 (3)°, respectively, for molecules *A* and *B*.

The torsion angles φ, ψ and ω (Table 1) of the peptide backbone indicate that the DKP ring adopts a boat conformation, as in the case of other phenylalanine-containing DKPs (Suguna *et al.*, 1985; Ramani *et al.*, 1976; Benedetti *et al.*, 1976). The deviations of the leucyl and ΔPhe C^{α} atoms from the mean plane passing through the remaining atoms of the DKP ring are −0.067 and −0.04 Å for molecule *A*, and 0.13 and 0.09 Å for molecule *B*, respectively. The DKP ring thus assumes a boat conformation in both molecules.

The crystal packing of (I) is illustrated in Fig. 2. Molecules *A* and *B* form hydrogen-bonded ribbons with molecules of the same type *via* N—H···O interactions between adjacent molecules related by translation along the *a* axis (Table 2). Weaker C—H···O interactions observed between molecules *A* and *B* link the ribbons into an overall three-dimensional network.

Experimental

The title compound was synthesized by solution-phase peptide synthesis (Gupta *et al.*, 1990). It was crystallized by controlled slow evaporation from a solution of the peptide in a 1:1 methanol–dioxane mixture at room temperature. Colourless rod-shaped crystals of (I) suitable for X-ray diffraction appeared within 4–5 d.

Crystal data

$C_{15}H_{18}N_2O_2$
M_r = 258.31
Triclinic, *P*1
a = 6.2384 (5) Å
b = 9.8255 (7) Å
c = 12.5432 (9) Å
α = 69.344 (1)°
β = 78.054 (1)°
γ = 79.396 (1)°
V = 698.64 (9) Å^3
Z = 2
D_x = 1.228 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 5071 reflections
θ = 4–54°
μ = 0.08 mm^{-1}
T = 293 (2) K
Rod, colourless
0.46 × 0.26 × 0.15 mm

Data collection

Bruker SMART CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.865, T_{max} = 0.988
7333 measured reflections
2872 independent reflections
2649 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 27.3°
h = −8 → 7
k = −12 → 12
l = −15 → 16

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.113
S = 1.11
2872 reflections
348 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.058P)^2 + 0.0935]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.013
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.17 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.018 (5)

Table 1
Backbone torsion angles (°).

C2′*A*—N1*A*—C1*A*—C1′*A*	8.9 (4)	C2′*B*—N1*B*—C1*B*—C1′*B*	−21.8 (4)
N1*A*—C1*A*—C1′*A*—N2*A*	−11.2 (4)	N2*B*—C1′*B*—C1*B*—N1*B*	18.1 (4)
C1*A*—C1′*A*—N2*A*—C2*A*	6.8 (4)	C1*B*—C1′*B*—N2*B*—C2*B*	−4.3 (4)
C1*A*—N1*A*—C2′*A*—C2*A*	−1.4 (4)	C2′*B*—C2*B*—N2*B*—C1′*B*	−8.8 (4)
C1′*A*—N2*A*—C2*A*—C2′*A*	1.3 (4)	C1*B*—N1*B*—C2′*B*—C2*B*	9.7 (4)
N1*A*—C2′*A*—C2*A*—N2*A*	−4.3 (4)	N2*B*—C2*B*—C2′*B*—N1*B*	6.6 (3)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1*A*—H1*A*···O1′*A*^{i}	0.86	2.04	2.874 (3)	164
N2*A*—H2*A*···O2′*A*^{ii}	0.86	2.04	2.870 (3)	161
N1*B*—H1*B*···O1′*B*^{ii}	0.86	2.17	2.915 (3)	146
N2*B*—H2*B*···O2′*B*^{i}	0.86	2.10	2.926 (3)	162
C1*A*—H1*A*1···O2′*B*^{iii}	0.98	2.54	3.314 (4)	136
C1*GA*—H1*GA*···O1′*A*^{i}	0.98	2.65	3.484 (4)	144
C1*GB*—H1*GB*···O1′*B*^{ii}	0.98	2.67	3.432 (4)	135
C1*BB*—H1*B*3···O2′*A*^{iv}	0.97	2.68	3.432 (4)	135

Symmetry codes: (i) *x* + 1, *y*, *z*; (ii) *x* − 1, *y*, *z*; (iii) *x* + 1, *y* − 1, *z*; (iv) *x* − 1, *y* + 1, *z*.

As the anomalous dispersion effects were not significant, Friedel opposites were merged prior to the final round of refinement. The absolute structure was assigned by reference to the starting materials. All H atoms were generated geometrically and were allowed to ride on their parent atoms, with C—H distances in the range 0.93–0.98 Å and N—H distances of 0.86 Å, and with $U_{iso}(H) = 1.2U_{eq}(C,N)$.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SAINT-Plus* (Bruker, 2001); data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *WinGX* (Farrugia, 1999) and *PARST* (Nardelli, 1995).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1602). Services for accessing these data are described at the back of the journal.

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