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Dipeptide (Z)-Pro-ψ[CO-N(NH$_2$)]-Ala-NH^{i}Pr

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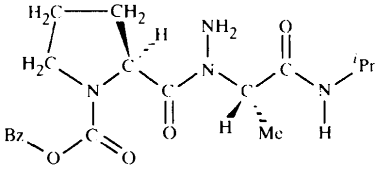
Abstract

The dipeptide, *N*-benzyloxycarbonylprolyl-*N*-aminoalanine isopropylamide, $C_{19}H_{28}N_4O_4$, assumes an extended conformation at variance with the β-folded conformation of its *N*-amino glycine-containing analogue. The *N*-amino amide is *trans* planar and has similar dimensions to the standard peptide group. One of the *N*-amino H atoms is intramolecularly hydrogen bonded to the C-terminal amide carbonyl group.

Comment

In contrast to *N*-methylation, *N*-amination of the peptide group has received little attention, mainly because of difficulties in obtaining optically pure α-hydrazino acids ($N^{\beta}H_2$-$N^{\alpha}H$-CH*R*-CO_2H) and regioselective acylation of their α-nitrogen (Vidal *et al.*, 1993, 1997). The conformational analysis of the ^{t}BuCO-Pro-ψ[CO-N(NH$_2$)]-Gly-NH^{i}Pr *N*-amino dipeptide in solution and in the solid state has revealed a βII-folded structure with a *trans* *N*-amino amide group (Marraud *et al.*, 1993; Dupont *et al.*, 1993).

The absolute (*S*,*S*) configuration of the dipeptide, (I), is known from that of the starting proline and alanine materials. The three-dimensional structure shows that the *N*-amino amide group is *trans* planar with dimensions similar to those of the standard peptide group (Benedetti, 1977), and the *N*-amino group is practically bisected by the amide plane. The molecule assumes an extended conformation (Fig. 1) and engages in intermolecular hydrogen bonds of the N—H···O=C type (Table 2). One of the *N*-amino H atoms is at a hydrogen-bond distance from the C-terminal oxygen of the same molecule, so closing a six-membered pseudocycle.



(I)

This open conformation is also present in solution, as revealed by the large solvent sensitivity of the ^{i}PrNH resonance in NMR spectroscopy [1.91 p.p.m. shift from

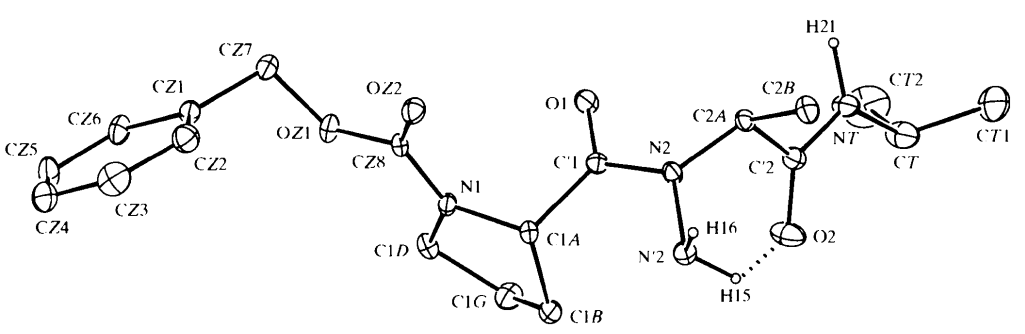


Fig. 1. Conformation of the title molecule showing the intramolecular hydrogen bond (broken line) between the *N*-amino group and the O2 atom. The displacement ellipsoids are drawn at the 25% probability level and H atoms linked to N atoms are included as small circles of an arbitrary radius.

$CDCl_3$ to $(CD_3)_2SO$], but there is no indication for the existence in solution of the intramolecular interaction observed in the crystal. It differs significantly from the βII-folded structure of the ^{t}BuCO-Pro-ψ[CO-N(NH_2)]-Gly-NH^{i}Pr *N*-amino dipeptide (Dupont *et al.*, 1993). A folded structure would create steric hindrances in the dipeptide between the alanine methyl group and the middle carbonyl in a βII-turn, or with the *N*-amino group in a βI-turn. It should be noted that the *N*-amino amide function does not assume the *cis* conformation in solution or in the crystal, in contrast to the *N*-methyl peptide analogues (Aubry *et al.*, 1985; Marraud *et al.*, 1993).

Experimental

To a cold (273 K) solution of (*Z*)-L-Pro-OH (1.99 g, 8 mmol) in tetrahydrofuran (THF) (10 ml), dicyclohexylcarbodiimide (0.82 g, 4 mmol) was added in one portion. Dicyclohexylurea was filtered off 1 h later. The filtrate containing the symmetric anhydride (Z-L-Pro)$_2$O was added dropwise with stirring to Boc-ψ(CO-NH-NH)-L-Ala-NH^{i}Pr (0.98 g, 4 mmol) in a cold (273 K) mixture of THF (10 ml) and *N*-methylmorpholine (0.44 ml, 4 mmol) [Boc-ψ(CO-NH-NH)-L-Ala-NH^{i}Pr was obtained from Boc-ψ(CO-NH-NH)-L-Ala-OH (Vidal *et al.*, 1993) by classical aminolysis of the *O*-succinimide ester (Bodanszky, 1988)], and the solution was allowed to reach room temperature for 1 h. After addition of dichloromethane (50 ml), the organic phase was successively washed three times with a 10% aqueous solution of citric acid (10 ml), and a 5% aqueous solution of sodium hydrogen carbonate. The organic phase was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give (*Z*)-L-Pro-ψ[CO-N(NHBoc)]-L-Ala-NH^{i}Pr as a white powder. The dipeptide (*Z*)-L-Pro-ψ[CO-N(NH_2)]-L-Ala-NH^{i}Pr was obtained by acidolysis of the Boc group with 3 *N* HCl in ethyl acetate (Bodanszky, 1988) and purified by silica gel chromatography with dichloromethane containing 5% 2-propanol (R_f = 0.45; m.p. = 409 K; yield = 55%). By slow evaporation of an ethyl acetate solution we have obtained single crystals of poor quality of the title compound.

Crystal data

$C_{19}H_{28}N_4O_4$
$M_r = 376.45$
Monoclinic
*C*2
$a = 30.968\ (2)$ Å
$b = 6.003\ (2)$ Å
$c = 11.394\ (2)$ Å
$\beta = 107.26\ (1)°$
$V = 2022.7\ (8)$ Å^3
$Z = 4$
$D_x = 1.236$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.54180$ Å
Cell parameters from 25 reflections
$\theta = 20–30°$
$\mu = 0.719$ mm^{-1}
$T = 293\ (2)$ K
Prism
0.3 × 0.2 × 0.1 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none

$\theta_{max} = 69.79°$
$h = 0 \rightarrow 36$
$k = 0 \rightarrow 6$
$l = -13 \rightarrow 13$

1704 measured reflections
1704 independent reflections
1155 reflections with $I > 2\sigma(I)$

2 standard reflections
frequency: 90 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.054$
$wR(F^2) = 0.159$
$S = 0.971$
1657 reflections
253 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0546P)^2 + 2.1592P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.018$

$\Delta\rho_{max} = 0.171$ e Å^{-3}
$\Delta\rho_{min} = -0.209$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0019 (3)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 0.6 (7)

Table 1. *Selected torsion angles (°)*

OZ1—CZ8—N1—C1*A*	177.5 (4)	N1—C1*A*—C′1—N2	169.1 (5)
CZ8—N1—C1*A*—C′1	−73.4 (6)	C1*A*—C′1—N2—C2*A*	167.5 (5)
N1—C1*A*—C1*B*—C1*G*	28.5 (6)	C′1—N2—C2*A*—C′2	−83.5 (7)
C1*A*—C1*B*—C1*G*—C1*D*	−33.5 (7)	N2—C2*A*—C′2—N*T*	160.1 (6)
C1*A*—N1—C1*D*—C1*G*	−6.6 (6)	C2*A*—C′2—N*T*—C*T*	175.5 (8)
C1*B*—C1*G*—C1*D*—N1	24.8 (7)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N′2—H15···O2	0.874 (11)	2.27 (6)	2.920 (7)	131 (6)
N′2—H16···O1^i	0.868 (11)	2.16 (4)	2.918 (7)	146 (7)
N*T*—H21···OZ2^{ii}	1.024 (11)	2.01 (2)	3.016 (6)	165 (6)

Symmetry codes: (i) $x, y - 1, z$; (ii) $1 - x, y, 1 - z$.

The H atoms attached to N′2 and to N*T* were placed at 0.87 and 1.03 Å, respectively, in the direction obtained from the refinement (Taylor & Kennard, 1983). Other H atoms were included in a riding model at geometrically calculated positions. Each H atom displacement parameter was fixed at $1.3U_{eq}$ of the carrier atom.

Data collection: *CAD*-4 *Software* (Enraf-Nonius, 1989). Cell refinement: *CAD*-4 *Software*. Data reduction: *PROCESS* in *MolEN* (Fair, 1990). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP* (Johnson, 1970).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1278). Services for accessing these data are described at the back of the journal.

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Absolute configuration of 2-(1,4-benzodioxan-2-yl)imidazolinium bromide

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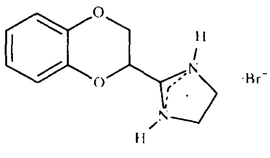
Abstract

The title compound, $C_{11}H_{13}N_2O_2^+\cdot Br^-$, crystallizes in the $P2_12_12_1$ space group. The absolute configuration of the therapeutically active molecule idazoxan [2-(1,4-benzodioxan-2-yl)imidazoline] could be resolved in this hydrobromide salt. The asymmetric C atom of the benzodioxanyl group is bonded to an H atom and to a C atom of the imidazolinium ring. (+)-Idazoxan has the *S* configuration. Packing of molecules in the crystal is stabilized by weak N—H···Br [N···Br = 3.226 (5) and 3.217 (5) Å] hydrogen bonding.

Comment

Idazoxan [(±)-2-(1,4-benzodioxan-2-yl)imidazoline (CAS registry number 79944-58-4)] is a potent and highly selective α-2-adrenoreceptor antagonist. The potential of this new chemical entity is currently under clinical evaluation. Idazoxan has one asymmetric C atom on the benzodioxanyl ring (C10) and therefore exhibits two enantiomers. However, idazoxan undergoes facile exchange of hydrogen (H10) at 308 K in phosphate buffer maintained at pH 7.4. It is therefore possible that some racemization of the enantiomers of idazoxan occurs during pharmacological testing. To confirm this hypothesis, we have prepared and determined the configuration of the title compound, (I), a highly crystalline enantiomer salt.



(I)

The *S* configuration of the molecule of (I) is shown in Fig. 1. Benzodioxan is attached, through the asymmetric C10 atom, to the imidazole cycle, which is protonated at one N atom. The sums of the angles around the N atoms are nearly 360° and atoms H12 and H15 refined close [0.16 (7) and 0.01 (6) Å, respectively] to the imidazole mean plane. The bonding scheme (scheme 2) has been determined by extended Hückel molecular orbital calculations. Analysis at the N12—C11—N15 edges shows that σ bonding results from sp^2 hybridized orbitals. Combination of the p_z (out of the imidazole plane) orbitals, represented in the second scheme, leads to a delocalized π bond involving atoms N12, C11 and N15 and a non-bonding pair delocalized over N12 and N15. Bonding overlap populations of 1.04, 1.02, 0.67 and 0.65 for C11—N12, C11—N15, C13—N12 and C14—N15, respectively (1.290, 1.294, 1.442 and 1.478 Å, respectively) are consistent with bond orders of 1.5 and 1.0. Noteworthy is the discrepancy with corresponding bond orders of 1.9 and 1.0, obtained from the empirical Pauling formula, $d_1 - d_n = 0.6\log(n)$ (Pauling, 1947, 1949). Atoms H12 and H15, attached to N12 and N15, are involved in weak hydrogen

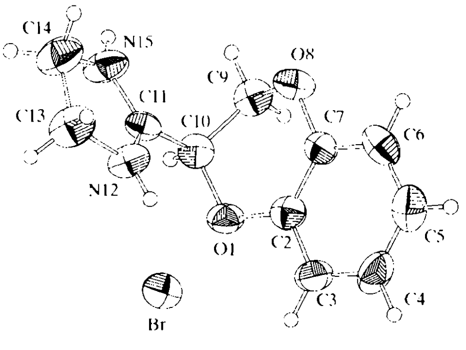


Fig. 1. Molecular structure of the title compound, showing 50% probability displacement ellipsoids for non-H atoms. H atoms are shown as spheres of an arbitrary radius.

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