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N-Benzyloxycarbonyl-L-aminosuccinyl-L-phenylalaninamide (Z-L-Asu-L-Phe-NH$_2$)

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Abstract. $C_{21}H_{21}N_3O_5$, $M_r = 395{\cdot}42$, orthorhombic, $P2_12_12_1$, $a = 5{\cdot}935\,(2)$, $b = 13{\cdot}037\,(1)$, $c = 25{\cdot}992\,(2)$ Å, $V = 2011\,(1)$ Å^3, $Z = 4$, $D_x = 1{\cdot}31$ Mg m^{-3}, $\lambda(\mathrm{Cu}\,K\alpha) = 1{\cdot}5418$ Å, $\mu = 0{\cdot}74$ mm^{-1}, $F(000) = 832$, room temperature, final $R = 0{\cdot}046$ for 1343 observed reflections. The title compound adopts a type II′ β-turn conformation in the solid state, stabilized by a 4→1 intramolecular hydrogen bond between the CO of the protecting benzyloxycarbonyl group and the NH$_2$ of the terminal amide group. These results indicate that the β-turn conformation, already found in the solid state for peptides embodying the sequence Asu-Gly or Asu-Ala, is highly preferred, even when the residue next to the aminosuccinyl moiety has a bulkier side chain. In the crystal, rows of hydrogen-bonded molecules are held together by van der Waals forces between hydrophobic phenyl groups.

Introduction. In protein chemistry the succinimide ring is an intermediate in the non-enzymatic deamidation of the asparaginyl side chain (Johnson & Aswad, 1985; Clarke, 1985) and it may play, as recently suggested (O'Connor, Aswad & Clarke, 1984), an important role in the repair or degradation of proteins.

We are currently investigating structural and conformational parameters of model peptides embodying this cyclic imide structure, hereafter indicated as Asu peptides (Capasso, Mattia, Mazzarella & Zagari, 1984*a*,*b*; Capasso, Mazzarella, Sica & Zagari, 1984, 1987). Our studies have indicated that these peptides strongly prefer a type II′ β-turn conformation (Venkatachalam, 1968).

In order to investigate the role of the side chain of the residue *X* on the conformational stability of peptides containing the sequence Asu-*X*, we have synthesized and studied, by X-ray analysis, the blocked dipeptide Z-L-Asu-L-Phe-NH$_2$.

Experimental. Title compound synthesized according to procedure previously described (Schön & Rill, 1987). Crystals from methanol, $0{\cdot}50 \times 0{\cdot}05 \times 0{\cdot}03$ mm, Enraf–Nonius CAD-4F diffractometer, Ni-filtered Cu $K\alpha$ radiation; lattice parameters from 25 reflections ($17 \leq \theta \leq 21°$); data collection: $\omega/2\theta$ scan, as suggested by peak-shape analysis; two intensity monitoring reflections (2% variation); 2226 independent reflections with $\theta \leq 70°$, $0 \leq h \leq 7$, $0 \leq k \leq 15$, $0 \leq l \leq 31$, 1343 with $I > 2{\cdot}5\sigma(I)$; Lp correction, absorption ignored. Structure solved by *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980); anisotropic full-matrix (on *F*), H atoms from geometrical considerations, isotropic with

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Table 1. *Fractional coordinates and equivalent isotropic thermal parameters* (Å^2) *for non*-H *atoms with e.s.d.'s in parentheses*

$$B_{\rm eq} = \tfrac{1}{3}\textstyle\sum_i B_{ii}.$$

	x	y	z	$B_{\rm eq}$
O(1)	0·0537 (6)	0·2166 (2)	0·7243 (1)	3·65 (7)
O(2)	0·6663 (6)	0·0079 (3)	0·7400 (1)	4·85 (9)
O(3)	0·0036 (6)	0·1427 (3)	0·8902 (1)	3·46 (7)
O(4)	0·2058 (7)	0·0471 (2)	0·8341 (1)	3·86 (8)
O(5)	0·1169 (8)	−0·1224 (3)	0·6600 (1)	5·8 (1)
N(1)	0·2208 (7)	0·2223 (3)	0·8334 (1)	3·06 (8)
N(2)	0·3485 (6)	0·1020 (3)	0·7215 (1)	2·49 (8)
N(3)	0·1565 (7)	−0·0862 (3)	0·7437 (1)	3·19 (8)
C(1)	−0·5750 (9)	0·1677 (4)	0·9820 (2)	4·0 (1)
C(2)	−0·4184 (9)	0·1443 (4)	0·9449 (2)	3·6 (1)
C(3)	−0·2399 (9)	0·0785 (3)	0·9552 (2)	3·0 (1)
C(4)	−0·0751 (10)	0·0496 (4)	0·9144 (2)	4·0 (1)
C(5)	0·1476 (9)	0·1301 (4)	0·8508 (2)	3·2 (1)
C(6)	−0·5557 (10)	0·1263 (4)	1·0310 (2)	4·3 (1)
C(7)	0·3610 (8)	0·2268 (4)	0·7876 (2)	3·0 (1)
C(8)	0·2321 (8)	0·1838 (3)	0·7410 (2)	2·68 (9)
C(9)	0·5778 (8)	0·1617 (4)	0·7891 (2)	3·6 (1)
C(10)	0·5455 (8)	0·0803 (4)	0·7489 (2)	3·3 (1)
C(11)	0·2605 (9)	0·0420 (3)	0·6783 (2)	2·7 (1)
C(12)	0·1742 (9)	−0·0635 (4)	0·6942 (2)	3·3 (1)
C(13)	−0·2188 (10)	0·0373 (4)	1·0043 (2)	3·9 (1)
C(14)	−0·3784 (11)	0·0619 (4)	1·0418 (2)	4·5 (1)
C(15)	0·4298 (9)	0·0360 (4)	0·6329 (2)	3·2 (1)
C(16)	0·4747 (8)	0·1401 (4)	0·6102 (2)	3·1 (1)
C(17)	0·6518 (10)	0·2000 (4)	0·6266 (2)	4·5 (1)
C(18)	0·6890 (11)	0·2964 (4)	0·6066 (2)	6·3 (2)
C(19)	0·5455 (12)	0·3350 (5)	0·5699 (2)	6·4 (2)
C(20)	0·3696 (12)	0·2760 (5)	0·5526 (2)	6·0 (2)
C(21)	0·3328 (10)	0·1804 (5)	0·5732 (2)	4·8 (1)

the same $B_{\rm eq}$ as the atoms to which they are bonded, not refined. Final $R = 0{\cdot}046$, $wR = 0{\cdot}051$, $w = 1/\sigma^2(F_o)$, $S = 1{\cdot}97$; final $(\Delta/\sigma)_{\rm max} = 0{\cdot}01$, max. and min. heights in final $\Delta\rho$ map 0·21 and −0·20 e Å^{-3}; scattering factors from *International Tables for X-ray Crystallography* (1974); Enraf–Nonius (1979) *SDP* software and PDP11/34 computer of the Centro di Metodologie Chimico-Fisiche dell'Università di Napoli. Final atomic parameters of the non-H atoms are listed in Table 1.*

Discussion. A view of the molecule together with the numbering scheme is shown in Fig. 1. The geometrical parameters (Table 2) of the peptide main chain compare well with those found for the related compounds Boc-L-Asu-Gly-OMe (Capasso *et al.*, 1984*a*), Boc-L-Asu-Gly-Gly-OMe (Capasso *et al.*, 1984*b*), Boc-L-Asu-L-Ala-Gly-OMe (Capasso *et al.*, 1984) and Boc-L-Asu-Gly-L-Ala-OMe (Capasso, Mazzarella, Sica & Zagari, 1987). It is worth noting that, in the present case also, the distances C(8)—N(2) and C(10)—N(2) are significantly longer than the C′—N bond in linear peptides (Capasso, Mazzarella, Sica & Zagari, 1987). The geometrical parameters of the Phe side chain and the protecting benzyloxycarbonyl group are also in the expected range (Sinha, Pattabhi, Raghunathan & Gabe, 1984; Bando, Tanaka, Ashida & Kakudo, 1978).

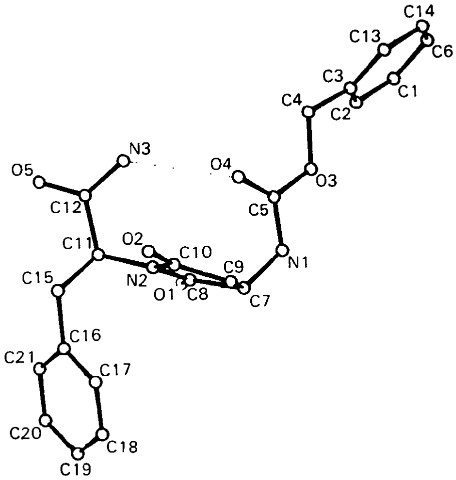

Fig. 1. The observed conformation of Z-L-Asu-L-Phe-NH$_2$ with the numbering scheme.

Table 2. *Bond lengths* (Å) *and angles* (°) *with their e.s.d.'s in parentheses*

O(1)—C(8)	1·221 (6)	O(2)—C(10)	1·207 (6)
O(3)—C(4)	1·444 (6)	O(3)—C(5)	1·344 (6)
O(4)—C(5)	1·216 (6)	N(1)—C(5)	1·356 (6)
N(1)—C(7)	1·454 (6)	N(2)—C(8)	1·368 (6)
N(2)—C(10)	1·398 (6)	N(2)—C(11)	1·463 (5)
C(1)—C(2)	1·374 (7)	C(1)—C(6)	1·390 (7)
C(2)—C(3)	1·389 (7)	C(3)—C(4)	1·492 (7)
C(3)—C(13)	1·391 (6)	C(6)—C(14)	1·374 (8)
C(7)—C(8)	1·539 (6)	C(7)—C(9)	1·542 (7)
C(9)—C(10)	1·502 (7)	N(3)—C(12)	1·324 (6)
O(5)—C(12)	1·223 (6)	C(11)—C(12)	1·525 (7)
C(11)—C(15)	1·552 (6)	C(13)—C(14)	1·395 (8)
C(15)—C(16)	1·504 (7)	C(16)—C(17)	1·378 (7)
C(16)—C(21)	1·382 (7)	C(17)—C(18)	1·378 (8)
C(18)—C(19)	1·373 (9)	C(19)—C(20)	1·372 (9)
C(20)—C(21)	1·374 (8)		

C(4)—O(3)—C(5)	115·7 (6)	C(5)—N(1)—C(7)	119·5 (7)
C(8)—N(2)—C(10)	113·1 (6)	C(8)—N(2)—C(11)	121·3 (6)
C(10)—N(2)—C(11)	125·5 (6)	C(2)—C(1)—C(6)	120·1 (8)
C(1)—C(2)—C(3)	121·2 (8)	C(2)—C(3)—C(4)	121·3 (8)
C(2)—C(3)—C(13)	118·9 (8)	C(4)—C(3)—C(13)	119·7 (8)
O(3)—C(4)—C(3)	107·9 (7)	O(3)—C(5)—O(4)	124·2 (8)
O(3)—C(5)—N(1)	110·5 (7)	O(4)—C(5)—N(1)	125·3 (8)
C(1)—C(6)—C(14)	119·1 (9)	N(1)—C(7)—C(8)	110·2 (6)
N(1)—C(7)—C(9)	115·8 (7)	C(8)—C(7)—C(9)	103·5 (6)
O(1)—C(8)—N(2)	125·4 (7)	O(1)—C(8)—C(7)	125·7 (7)
N(2)—C(8)—C(7)	108·9 (6)	C(7)—C(9)—C(10)	105·4 (7)
O(2)—C(10)—N(2)	123·9 (8)	O(2)—C(10)—C(9)	127·5 (8)
N(2)—C(10)—C(9)	108·6 (7)	N(2)—C(11)—C(12)	113·2 (6)
N(2)—C(11)—C(15)	112·3 (6)	C(12)—C(11)—C(15)	112·2 (7)
N(3)—C(12)—O(5)	122·9 (8)	N(3)—C(12)—C(11)	119·4 (7)
O(5)—C(12)—C(11)	117·6 (7)	C(3)—C(13)—C(14)	119·4 (8)
C(11)—C(15)—C(16)	111·6 (7)	C(15)—C(16)—C(17)	121·6 (8)
C(15)—C(16)—C(21)	120·6 (8)	C(17)—C(16)—C(21)	117·7 (8)
C(16)—C(17)—C(18)	121·5 (9)	C(17)—C(18)—C(19)	119·8 (10)
C(18)—C(19)—C(20)	119·6 (10)	C(19)—C(20)—C(21)	120·0 (10)
C(16)—C(21)—C(20)	121·3 (9)	C(6)—C(14)—C(13)	121·2 (9)

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* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44573 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The conformation of the molecule is of the type II′ β bend with Asu and Phe residues in the second and third position respectively. The two blocking groups, the Z group at the amino end and the NH_2 group at the carboxyl end, occupy the first and fourth position of the bend respectively and are linked by a 4→1 intramolecular hydrogen bond, typical of a reverse turn [N(3)···O(4), 2·937 (4) Å and C(5)–O(4)···N(3) and O(4)···H–N(3) angles, 141·7 (7) and 162·0 (2)° respectively]. The most relevant torsion angles are presented in Table 3 along with the values for an ideal type II′ β turn. It must be emphasized that the torsion angles ψ_1 and ω_1 are restrained to a value close to −120 and 180° respectively by the closure condition of the succinimide ring.

As found in the other Asu peptides studied by us, the deviation from planarity of the five-membered ring is generally small but meaningful. The puckering amplitude (Cremer & Pople, 1975) of the ring in the present structure is only 0·072 (4) Å and the phase of 358 (3)°, calculated for the sequence C(9)C(7)C(8)N(2)C(10), indicates that the small deformation is consistent with a 'pure envelope' conformation, with C(9) out of the mean plane through the remaining four atoms of the ring. This small displacement slightly relaxes the interactions between the substituents on C(7) and C(9), which in a fully planar structure would be eclipsed. On the other hand, the puckering of the ring lowers the intramolecular hydrogen-bonding energy by increasing the distance between N(3) and O(4). Thus in Asu peptides, folded in a β-turn conformation, the puckering of the ring is generally small, whereas it is significantly larger when the internal hydrogen bond is not formed, as in the blocked dipeptide Boc-L-Asu-Gly-OMe (Capasso *et al.*, 1984*a*).

The conformation of the Phe side chain is characterized by the values of $\chi_1 = -63{\cdot}6\,(7)°$ and $\chi_2 = 92{\cdot}6\,(9)°$, as expected for an aromatic side chain. The Z group assumes a fully extended *trans–trans* conformation about the N(1)–C(5) and C(5)–O(3) bonds respectively [$\omega_0 = -174{\cdot}1\,(8)°$; $\theta_1 = -176{\cdot}2\,(7)°$], as is most frequently found for structures containing a secondary N atom (Bando *et al.*, 1978). The two phenyl rings are strictly planar, with no atom deviating more than 0·010 Å from the least-squares plane.

The packing is determined by the hydrogen-bonding network. The terminal amide N(3) donates toward the carbonyl O(1) atom of the succinimide ring and the urethane N(1) donates toward the carbonyl O(5) atom {N(1)···O(5^i), 2·854 (4); O(1)···N(3^i), 2·977 (4) Å [symmetry code: (i) $-x, \frac{1}{2}+y, \frac{3}{2}-z$]}. The hydrogen-bonding network gives rise to rows of molecules which run parallel to **b** (Fig. 2). The polar cores of adjacent molecules are linked together by hydrogen bonds, whereas the apolar phenyl groups of the Phe residue and the Z group protrude alternately from the surface of the rows. These rows are held together in the crystals solely by van der Waals forces between hydrophobic groups.

Table 3. *Torsion angles* (°)

		Observed	Predicted for type II′ β turn
φ_1	C(5)–N(1)–C(7)–C(8)	61·5 (7)	60
ψ_1	N(1)–C(7)–C(8)–N(2)	−120·4 (7)	−120
ω_1	C(7)–C(8)–N(2)–C(11)	176·9 (8)	180
φ_2	C(8)–N(2)–C(11)–C(12)	−106·9 (7)	−80
ψ_2	N(2)–C(11)–C(12)–N(3)	9·1 (7)	0

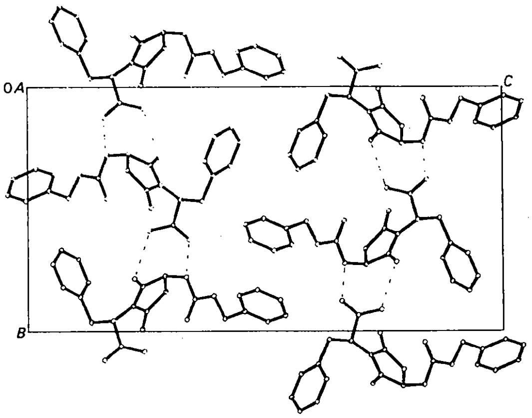

Fig. 2. Packing diagram projected on the *bc* plane showing the intermolecular hydrogen bonds (broken lines).

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