

tert-Butyl N-{2-[N-(N,N'-dicyclohexyl-ureidocarbonyl)ethyl]carbamoyl]-prop-2-yl}carbamate

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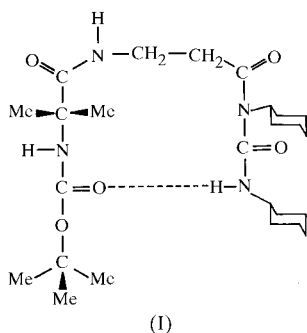
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The title compound, C₂₅H₄₄N₄O₅, exhibits a turn with the main chain reversing direction, held together by an intramolecular N—H···O hydrogen bond. In the urea fragment, a notable amide C—N bond between the carboxyl C and the tertiary N atom shows marked single-bond character [1.437 (2) Å]. The dihedral angle of the β-alanyl residue, centrally located in the turn, is *gauche* [69.2 (2)°]. The packing is mediated by two intermolecular hydrogen bonds and van der Waals contacts involving the methyl moieties and the cyclohexyl rings.

Comment

Naturally occurring proteins and synthetic peptides frequently exhibit β-bend or turn conformations. The reverse turn, wherein the directionality of the polypeptide suffers a change,



has been known to play an important role in protein folding (Ptitsyn, 1981). It is well documented that the α-amino isobutyryl (Aib) residue has a high propensity for regular secondary structures such as α-helices or β-bends in designed synthetic oligopeptides (Prasad & Balaram, 1984; Karle *et al.*, 1986). The target compound, (I), was synthesized to investigate the conformation of the turn on the incorporation of an extra C atom (β-alanyl) into the main chain.

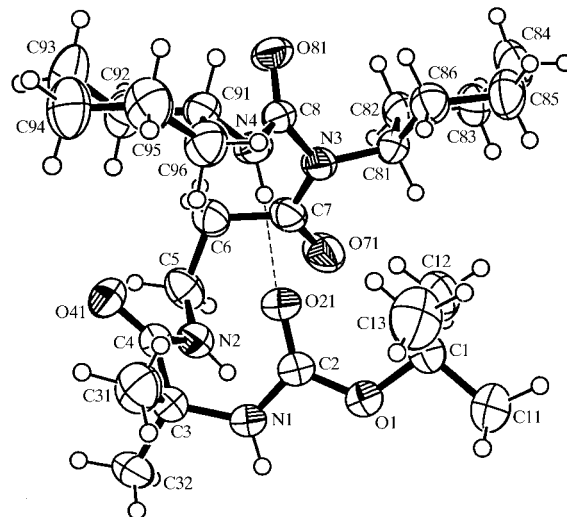


Figure 1
The molecular structure of (I) showing 50% probability displacement ellipsoids (Burnett & Johnson, 1996). H atoms are shown as spheres of arbitrary radii.

The C—O and C—N bonds adjacent to the carbonyl O atoms (O21, O41, O71, O81) show partial double-bond character due to resonance with the bond lengths ranging from 1.334 (2)–1.368 (2) Å. It is important to note that the C8—N3 amide bond [1.437 (2) Å] exhibits marked single-bond character. The overall conformation of the molecule is that of a turn held together by a strong N—H···O=C hydrogen bond between N4 and O21 located at the extremities. The molecule thus forms a 13-membered ring motif (Venkatachalam, 1968; Nataraj *et al.*, 1995). The O21 atom also forms van der Waals contacts with N2 [3.147 (2) Å], coming in close proximity to C96 [3.615 (3) Å], an atom on the cyclohexyl ring. There is an additional contact between O41 and C92 of 3.588 (3) Å.

The conformation of the molecule is thus decided by free torsional rotations about N1—C3, C3—C4, N2—C5, C5—C6, C6—C7 and N3—C8. Of these, the torsion angles N1—C3—C4—N2 [39.0 (2)°] and C5—C6—C7—N3 [−155.6 (2)°] exhibit significant deviations from either the *gauche* or *trans* conformations, the rest being (−)*gauche*. In particular, the torsion angle N2—C5—C6—C7, the C-α—C-β bond of the β-alanyl residue, is 69.2 (2). This is important as the two atoms are centrally located in the turn, the reversal of direction in the chain being effected between atoms C3 and C8. Out of the four carbonyl bonds C2—N1, C4—N2, C7—N3 and C8—N4, it is only in the case of C6—C7—N3—C8 [6.9 (2)°] that the flanking C atoms, C6 and C8, are in the *cis* configuration, the rest being *trans*. There is close correspondence in the torsion angles up to C4—N2—C5—C6 from the Boc terminal end between this molecule and *t*-Boc-Aib-Aib-β-Ala-NHMe (Pavone *et al.*, 1992).

The crystal packing is mediated by the two intermolecular hydrogen bonds N1—HN1···O81 and N2—HN2···O71. In addition, there are packing interactions involving the apolar atoms of the cyclohexyl ring, the methyl groups bonded to C1 (C11, C12, C13) and C3 (C31, C32), and atoms C5 and C6.

Experimental

t-Boc-Aib-OH was coupled to β -Ala-OMe in dichloromethane using dicyclohexylcarbodiimide (DCC)/1-hydroxybenzotriazole at 273–277 K for an hour. The resulting dipeptide, Boc-Aib- β -Ala-OMe, was hydrolysed using methanol/sodium hydroxide (1 N) at room temperature to obtain the dipeptide acid Boc-Aib- β -Ala-OH, which was then treated with DCC in *N,N*-dimethylformamide to give the final compound. Crystals were obtained by slow evaporation from a water/methanol mixture.

Crystal data

$C_{25}H_{44}N_4O_5$	$D_m = 1.14 \text{ Mg m}^{-3}$
$M_r = 480.64$	D_m measured by flotation in xylene/bromoform
Triclinic, $P\bar{1}$	Cu $K\alpha$ radiation
$a = 9.9960 (10) \text{ \AA}$	Cell parameters from 25 reflections
$b = 10.933 (2) \text{ \AA}$	$\theta = 10\text{--}30^\circ$
$c = 14.385 (3) \text{ \AA}$	$\mu = 0.641 \text{ mm}^{-1}$
$\alpha = 78.13 (2)^\circ$	$T = 293 (2) \text{ K}$
$\beta = 83.740 (10)^\circ$	Plate, colourless
$\gamma = 65.590 (10)^\circ$	$0.88 \times 0.63 \times 0.50 \text{ mm}$
$V = 1400.4 (4) \text{ \AA}^3$	
$Z = 2$	
$D_x = 1.140 \text{ Mg m}^{-3}$	

Data collection

Enraf-Nonius CAD-4 four-circle automatic diffractometer	$h = 0 \rightarrow 12$
2 ω scans	$k = -12 \rightarrow 13$
5941 measured reflections	$l = -15 \rightarrow 17$
5622 independent reflections	3 standard reflections every 60 reflections
4579 reflections with $F_o > 4\sigma(F_o)$	frequency: 60 min
$R_{int} = 0.042$	intensity decay: none
$\theta_{max} = 74.68^\circ$	

Table 1

Selected geometric parameters (\AA , $^\circ$).

O21–C2	1.217 (2)	O41–C4	1.222 (2)
N3–C7	1.368 (2)	N4–C8	1.334 (2)
N3–C8	1.437 (2)	N4–C91	1.461 (2)
N3–C81	1.480 (2)	N2–C4	1.339 (2)
O81–C8	1.212 (2)	N2–C5	1.441 (2)
O1–C2	1.343 (2)	O71–C7	1.222 (2)
O1–C1	1.461 (2)	C4–C3	1.540 (2)
N1–C2	1.345 (2)	C7–C6	1.502 (2)
N1–C3	1.461 (2)	C5–C6	1.513 (2)
C7–N3–C8	122.6 (1)	N4–C8–N3	113.6 (1)
C7–N3–C81	117.9 (1)	N2–C4–C3	116.3 (1)
C2–O1–C1	120.9 (1)	N1–C3–C4	110.7 (1)
C2–N1–C3	120.8 (1)	N3–C7–C6	118.3 (1)
C8–N4–C91	122.6 (1)	N2–C5–C6	112.6 (1)
C4–N2–C5	121.6 (2)	C7–C6–C5	113.3 (2)
O1–C2–N1	110.9 (1)		
C81–N3–C7–C6	–161.9 (1)	C91–N4–C8–N3	–172.7 (2)
C8–N3–C7–C6	6.9 (2)	C4–N2–C5–C6	72.9 (2)
C7–N3–C8–N4	71.2 (2)	C5–N2–C4–C3	177.2 (2)
C81–N3–C8–N4	–120.1 (2)	N2–C4–C3–N1	39.0 (2)
C1–O1–C2–N1	–179.3 (0.13)	N3–C7–C6–C5	–155.6 (2)
C3–N1–C2–O1	169.1 (1)	N2–C5–C6–C7	69.2 (2)
C2–N1–C3–C4	58.7 (2)		

Table 2

Hydrogen-bonding geometry (\AA , $^\circ$).

$D\text{---}H\cdots A$	$D\text{---}H$	$H\cdots A$	$D\cdots A$	$D\text{---}H\cdots A$
N4–HN4 \cdots O21	0.90 (2)	2.07 (2)	2.964 (2)	173 (2)
N1–HN1 \cdots O81 ⁱ	0.87 (2)	2.20 (2)	3.036 (2)	161 (2)
N2–HN2 \cdots O71 ⁱⁱ	0.88 (2)	2.17 (2)	2.906 (2)	142 (2)

Symmetry codes: (i) $1 + x, y, z$; (ii) $2 - x, -y, -z$.

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0780P)^2 + 0.1745P]$
$R[F^2 > 2\sigma(F^2)] = 0.046$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.139$	$(\Delta/\sigma)_{max} = 0.013$
$S = 1.060$	$\Delta\rho_{max} = 0.17 \text{ e \AA}^{-3}$
5622 reflections	$\Delta\rho_{min} = -0.21 \text{ e \AA}^{-3}$
475 parameters	Extinction correction: <i>SHELXL97</i> (Sheldrick, 1997)
H atoms treated by a mixture of independent and constrained refinement	Extinction coefficient: 0.0110 (8)

All the H atoms in the structure were located from difference Fourier maps [N–H 0.874 (19)–0.904 (18) \AA and C–H 0.91 (3)–1.05 (3) \AA], except for those bonded to C12 which were geometrically fixed (C–H 0.96 \AA). Absorption corrections were not applied as the T_{max}/T_{min} ratio was 1.11, marginally greater than 1.10.

Data collection: *CAD-4 Software* (Enraf-Nonius, 1994); cell refinement: *CAD-4 Software*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE1142). Services for accessing these data are described at the back of the journal.

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