Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

An oxazol-5(4*H*)-one[1] from benzyloxycarbonyl-(Aib)$_4$-OH

Marco Crisma,* Fernando Formaggio and Claudio Toniolo

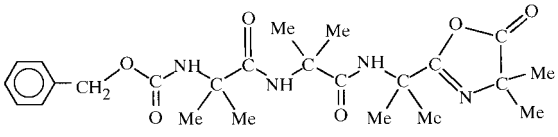
Biopolymer Research Centre, CNR, Department of Organic Chemistry, University of Padova, Via Marzolo 1, 35131 Padova, Italy
Correspondence e-mail: biop02@chor.unipd.it

Received 27 January 2000
Accepted 3 March 2000

Benzyl *N*-[8-(4,4-dimethyl-5-oxo-4,5-dihydrooxazol-2-yl)-2,5,-5,8-tetramethyl-3,6-dioxo-4,7-diazanon-2-yl]carbamate, $C_{24}H_{34}N_4O_6$, an oxazol-5(4*H*)-one from *N*-α-benzyloxycarbonyl-(Aib)$_4$-OH (Aib = α-aminoisobutyryl) represents the longest peptide oxazolone so far characterized by X-ray diffraction. The overall geometry of the oxazolone ring compares well with literature data. The Aib(1) and Aib(2) residues are folded into a type III β-bend, while the conformation adopted by Aib(3), preceding the oxazolone moiety, is semi-extended. The disposition of the oxazolone ring relative to the preceding residue is stabilized by C—H···N and C—H···O intramolecular interactions.

Comment

Intramolecular dehydration of peptides or *N*-acylamino acid derivatives carrying a free carboxy terminus leads to 2-substituted oxazol-5(4*H*)-ones. Such activated compounds are of use for peptide synthesis involving C$^\alpha$-tetrasubstituted α-amino acids. All peptide oxazolones so far characterized by X-ray diffraction derive from di- or tripeptides (Toniolo *et al.*, 1996; Crisma *et al.*, 1997, 1998). Therefore, their peptide chain is not long enough to allow the onset of a regular secondary structure. We herewith report the X-ray structure of the title peptide oxazolone, (I), derived from the tetrapeptide *Z*-(Aib)$_4$-OH (*Z* is benzyloxycarbonyl and Aib is α-amino-isobutyric acid).



(I)

The bond distances and angles of the oxazolone ring in (I) compare well with those averaged from the published X-ray structures of 2-alkyl-oxazol-5(4*H*)-ones (Toniolo *et al.*, 1996; Crisma *et al.*, 1997). In particular, the double bond character of the C3═N4 bond and the widening of both the C3*A*—C3—N4 and the C4*A*—C4—O4 exocyclic bond angles compared with the C3*A*—C3—O3 and O3—C4—O4 bond angles, respectively, are confirmed.

The oxazolone ring is nearly planar. The largest displacements from the mean plane are observed for atoms C4*A* and N4 [−0.023 (2) and 0.017 (2) Å, respectively]. For the ring substituents, atoms C3*A* and O4 are displaced out of the plane by −0.017 (3) and 0.055 (2) Å, respectively.

The urethane and peptide bonds are *trans*. However, a significant deviation from the *trans* planarity is observed for the C2*A*—C2—N3—C3*A* torsion angle [−164.78 (16)°]. The disposition of the benzyloxycarbonylamino moiety is described by the values of the torsion angles C07—O*U*—C0—N1 [−175.88 (16)°], C01—C07—O*U*—C0 [99.2 (2)°] and C02—C01—C07—O*U* [99.8 (2)°].

An intramolecular hydrogen bond is observed between the N3-H group and the O0 carbonyl O atom of the *Z*-protecting group, giving rise to an intramolecularly hydrogen-bonded ten-membered ring structure (β-bend). The sets of the φ,ψ backbone torsion angles in the peptide chain are −60.5 (2) and −25.5 (2)°, and −59.4 (2) and −28.7 (2)°, for the Aib(1) and Aib(2) residues, respectively. These values are close to those of an ideal type III β-bend (Venkatachalam, 1968).

The values of the φ (C2—N3—C3*A*—C3) and ψ (N3—C3*A*—C3—N4) torsion angles for the Aib(3) residue are 48.4 (2) and −140.36 (18)°, respectively. The sign of this φ angle is opposite to those of the preceding residues, thus reversing the screw sense of the peptide chain. The conformation of this residue, although unusual for an Aib, falling in the semi-extended *F* region of the conformational map (Zimmerman *et al.*, 1977), has been found previously in the structures of other oxazolones containing Aib as the penultimate residue (Toniolo *et al.*, 1996). It must be noted that such a conformation leads to a *cisoid* arrangement of the atoms C3*B*1 and N4, the value of the C3*B*1—C3*A*—C3—N4 torsion angle

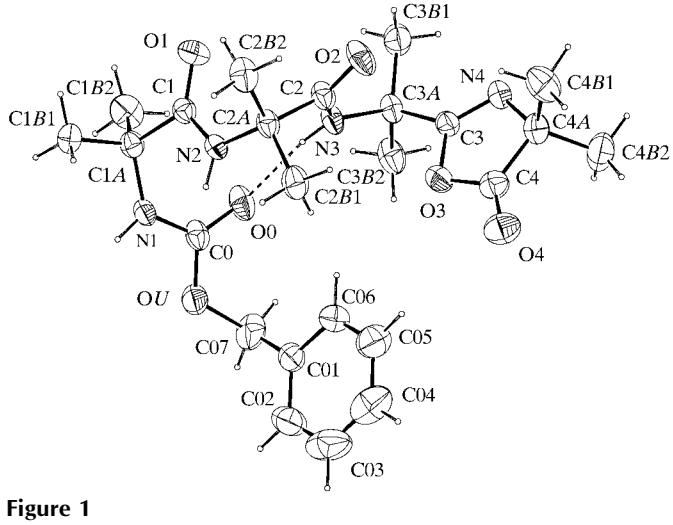


Figure 1
A view of (I) with the atom-numbering scheme. The intramolecular hydrogen bond is represented as a dashed line. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

[1] Alternative name: 4,4-dimethyl-2-[1-(phenylmethoxycarbonyl-2-methyl-alanyl-2-methylalanylamino)-1-methylethyl]oxazol-5(4*H*)-one.

being −17.4 (3)°. As a consequence, the intramolecular distance between C3*B*1 and N4 is 2.871 (3) Å. Among the geometrically calculated H atoms linked to C3*B*1, the H3*B*2 atom is located 2.66 Å from N4, and the value of the C3*B*1—H3*B*2···N4 angle is 93°. On the other hand, the C3*B*2 atom is in a *gauche*$^-$ disposition relative to the O3 atom [the torsion angle C3*B*2—C3*A*—C3—O3 is −73.31 (18)°], leading to a C3*B*2···O3 distance of 3.041 (3) Å, an H3*B*4···O3 distance of 2.70 Å and a C3*B*2—H3*B*4···O3 angle of 102°. The C—H···N and C—H···O angles reported above are quite acute. However, they are consistent with the observation that both interactions give rise to a five-membered ring. Both C—H···N and C—H···O interactions described above, although weak, might contribute to the stabilization of the disposition of the oxazolone ring relative to the preceding residue.

The angle between the normals to the average planes of the oxazolone ring and the benzyloxycarbonyl phenyl ring is 26.7 (1)°. The folded conformation of the peptide chain forces the oxazolone and phenyl rings to approach each other, the shortest separation being observed between atoms C05 and O3 [3.668 (3) Å].

In the packing mode of (I) an intermolecular hydrogen bond is observed between the N1—H group and O1($x, \frac{1}{2}-y, z-\frac{1}{2}$). As a result, chains of molecules are formed running parallel to the *c* direction. The N2-H group does not participate in any hydrogen bonding.

Experimental

Compound (I) was prepared from *Z*-(Aib)$_4$-OH and acetic anhydride according to the procedure described by Jones *et al.* (1965). Crystallization was carried out from a solution in ethyl acetate–petroleum ether by vapour diffusion (m.p. 430 K).

Crystal data

$C_{24}H_{34}N_4O_6$
M_r = 474.55
Monoclinic, $P2_1/c$
a = 9.324 (2) Å
b = 25.149 (3) Å
c = 11.753 (2) Å
β = 108.00 (5)°
V = 2621.1 (8) Å^3
Z = 4
D_x = 1.203 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 48 reflections
θ = 7–12°
μ = 0.087 mm^{-1}
T = 293 (2) K
Prism, colourless
0.6 × 0.4 × 0.4 mm

Table 1
Selected geometric parameters (Å, °).

C3*A*—C3	1.510 (3)	C4*A*—C4*B*2	1.518 (3)
C3—N4	1.259 (2)	C4*A*—C4*B*1	1.539 (3)
C3—O3	1.397 (2)	C4—O4	1.196 (2)
N4—C4*A*	1.468 (2)	C4—O3	1.374 (2)
C4*A*—C4	1.516 (3)		
N4—C3—O3	117.23 (15)	O4—C4—O3	121.66 (19)
N4—C3—C3*A*	128.92 (16)	O4—C4—C4*A*	131.2 (2)
O3—C3—C3*A*	113.79 (14)	O3—C4—C4*A*	107.14 (17)
C3—N4—C4*A*	106.66 (15)	C4—O3—C3	105.28 (14)
N4—C4*A*—C4	103.53 (16)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···O0	0.86	2.21	3.052 (2)	167
N1—H1···O1^{i}	0.86	2.11	2.9627 (18)	169

Symmetry code: (i) $x, \frac{1}{2}-y, z-\frac{1}{2}$.

Data collection

Philips *PW*1100 diffractometer
θ–2θ scans
4649 measured reflections
4427 independent reflections
3058 reflections with $I > 2\sigma(I)$
R_{int} = 0.020
θ_{max} = 24.71°
$h = -10 \rightarrow 10$
$k = 0 \rightarrow 29$
$l = 0 \rightarrow 13$
3 standard reflections
every 50 reflections
intensity decay: negligible

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.132
S = 1.003
4427 reflections
315 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0835P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.021
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

Data collection was performed up to $\sin\theta/\lambda$ = 0.5882 Å^{-1}; the crystal did not significantly diffract at higher resolution. A planarity restraint was applied to the phenyl ring. The H atoms were included in calculated positions and refined as riding, with U_{iso} values 1.2 (or 1.5 for the methyl groups) times the U_{eq} of the parent atoms. Geometrical calculations were performed with the program *PARST* (Nardelli, 1995).

Data collection: *FEBO* (Belletti, 1993); cell refinement: *FEBO*; data reduction: *FEBO*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1998); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1097). Services for accessing these data are described at the back of the journal.

References

Belletti, D. (1993). *FEBO*. Internal Report 1/93. Centro di Studio per la Strutturistica Diffractometrica del CNR, Parma, Italy.
Crisma, M., Valle, G., Formaggio, F. & Toniolo, C. (1998). *Z. Kristallogr. New Cryst. Struct.* **213**, 315–316.
Crisma, M., Valle, G., Formaggio, F., Toniolo, C. & Bagno, A. (1997). *J. Am. Chem. Soc.* **119**, 4136–4142.
Jones, D. S., Kenner, G. W., Preston, J. & Sheppard, R. C. (1965). *J. Chem. Soc.* pp. 6227–6239.
Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.
Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.
Spek, A. L. (1998). *PLATON*. University of Utrecht, The Netherlands.
Toniolo, C., Crisma, M. & Formaggio, F. (1996). *Biopolymers*, **40**, 627–651.
Venkatachalam, C. M. (1968). *Biopolymers*, **6**, 1425–1436.
Zimmerman, S. S., Pottle, M. S., Némethy, G. & Scheraga, H. A. (1977). *Macromolecules*, **10**, 1–9.