**References**

Enraf–Nonius (1985). *Structure Determination Package*. Enraf–Nonius, Delft, The Netherlands.

JOHNSON, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

LETCHER, R. & YUE, T.-Y. (1992). *J. Chem. Soc. Chem. Commun.* Submitted.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1982). *MULTAN*11/82. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.

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# Structure of 1-[(Benzyloxycarbonyl)amino]cyclopropane-1-carbohydroxamic Acid*

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**Abstract.** $C_{12}H_{14}N_2O_4$ (Z-Ac$_3$c-NHOH, Z = benzyloxycarbonyl, Ac$_3$c = 1-amino-1-cyclopropanecarboxylic acid, NHOH = hydroxamic acid), $M_r = 250.25$, monoclinic, $P2_1/n$, $a = 25.010$ (2), $b = 6.144$ (1), $c = 8.169$ (1) Å, $\beta = 93.30$ (2)°, $V = 1253.2$ (3) Å$^3$, $Z = 4$, $D_m = 1.32$, $D_x = 1.326$ g cm$^{-3}$, $\lambda$(Mo $K\alpha$) = 0.71069 Å, $\mu = 0.943$ cm$^{-1}$, $F(000) = 528.0$, $T = 298$ K, final $R$ value for 1807 [$I \geq 2.5\sigma(I)$] reflections is 0.053. The conformation of the urethane —CONH— bond is unusual (*cis*). The Ac$_3$c amino-acid residue is folded and the set of backbone torsion angles falls in the uncommon *B* ('bridge') region of the energy map. The conformation of the *R*—C(=O)—NHOH moiety is synperiplanar.

**Introduction.** During the past few years it has become increasingly apparent that $C^{\alpha,\alpha}$-disubstituted glycines may be exploited to design analogs of bioactive peptides with restricted conformational flexibility (Toniolo & Benedetti, 1988). In this connection, a distinct conformational preference of the 1-amino-1-cyclopropanecarboxylic acid (Ac$_3$c) residue for the *B* ('bridge') region of the energy map (Zimmerman, Pottle, Némethy & Scheraga, 1977) was observed (Benedetti, Di Blasio, Pavone, Pedone, Santini, Crisma, Valle & Toniolo, 1989).

Electrophilic cyclopropane-containing compounds, including Ac$_3$c peptides, have been found to be latent irreversible inhibitors of chemotherapeutically significant metallopeptidases (Breckenridge & Suckling, 1986; Suckling 1986, 1988). The potential utility of Z-Ac$_3$c-OH as an enzyme inhibitor has been enhanced by synthesizing its hydroxamic acid derivative. It has been shown that amino-acid and peptide hydroxamates are potent inhibitors (Nishino & Powers, 1978) and bind to metallopeptidases with the —NHOH group complexed to the metal (Holmes & Matthews, 1981).

**Experimental.** Colourless crystals of Z-Ac$_3$c-NHOH were obtained from an acetone/petroleum ether solution by slow evaporation. X-ray diffraction data were collected on a Philips PW 1100 four-circle diffractometer with the $\theta/2\theta$ scan mode (scan width 1.0°, scan speed 0.02° s$^{-1}$) and Mo $K\alpha$ radiation (graphite monochromated). The crystal had approximate dimensions 0.2 × 0.2 × 0.3 mm. Unit-cell parameters were determined from least-squares refinement of 25 reflections with $15 \leq \theta \leq 28°$. Data were collected to a maximum $2\theta = 56°$ and for $-33 \leq h \leq 32$, $0 \leq k \leq 8$, $0 \leq l \leq 10$. Three standard reflections were measured every 180 min. 3021 independent reflections were obtained, 1807 with $I \geq 2.5\sigma(I)$. $R_{int}$ for 188 equivalent reflections was 0.015. Intensities were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods using *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Anisotropic refinement based on *F* was carried out by conventional least-squares procedures with unit weights. The scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). The H atoms were localized in the difference Fourier maps and isotropically refined in the last least-squares cycle. For all calculations the *SHELX*76 (Sheldrick, 1976) program was used. The final $R$ value was 0.053. $S = 1.14$. $(\Delta/\sigma)_{max}$ in the final refinement cycle for non-H atoms was 0.025.

* Linear Oligopeptides. 258. Part 257: Valle, Formaggio, Crisma, Toniolo, Boesten, Polinelli, Schoemaker & Kamphuis (1992).

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Table 1. *Fractional coordinates and equivalent isotropic thermal parameters* (Å$^2$)

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

| | $x$ | $y$ | $z$ | $B_{eq}$ |
|---|---|---|---|---|
| C(1) | 0.16056 (9) | 0.9397 (4) | 0.4343 (3) | 3.92 (6) |
| C(2) | 0.1729 (1) | 0.0674 (5) | 0.3020 (3) | 4.97 (7) |
| C(3) | 0.2073 (1) | 0.2411 (6) | 0.3213 (4) | 6.05 (9) |
| C(4) | 0.2298 (1) | 0.2923 (5) | 0.4730 (5) | 6.13 (10) |
| C(5) | 0.2175 (1) | 0.1687 (6) | 0.6074 (4) | 6.06 (9) |
| C(6) | 0.1835 (1) | 0.9927 (5) | 0.5874 (3) | 5.21 (9) |
| C(7) | 0.1242 (1) | 0.7486 (5) | 0.4042 (3) | 4.69 (7) |
| O(1) | 0.10980 (6) | 0.6625 (3) | 0.5583 (2) | 4.05 (5) |
| C(8) | 0.07587 (9) | 0.4933 (4) | 0.5508 (3) | 3.51 (6) |
| O(2) | 0.05965 (7) | 0.4073 (3) | 0.4243 (2) | 4.79 (5) |
| N(1) | 0.06170 (8) | 0.4357 (3) | 0.7008 (2) | 3.65 (5) |
| C(9) | 0.07880 (9) | 0.5462 (4) | 0.8489 (3) | 3.32 (5) |
| C(10) | 0.0906 (1) | 0.4093 (4) | 0.9995 (3) | 4.89 (7) |
| C(11) | 0.1353 (1) | 0.5144 (4) | 0.9174 (3) | 4.62 (7) |
| C(12) | 0.05523 (9) | 0.7651 (4) | 0.8769 (3) | 3.36 (5) |
| O(3) | 0.07282 (7) | 0.8792 (3) | 0.9933 (2) | 4.56 (5) |
| N(2) | 0.01539 (8) | 0.8260 (3) | 0.7749 (2) | 3.91 (5) |
| O(4) | −0.00496 (7) | 1.0365 (3) | 0.7823 (2) | 4.68 (5) |

$0.26 > \Delta\rho > -0.24$ e Å$^{-3}$. 219 parameters were refined.

Table 1 gives the final atomic coordinates and equivalent isotropic thermal parameters.*

**Discussion.** The molecular structure of Z-Ac$_3$c-NHOH with the numbering of atoms is illustrated in Fig. 1. Selected bond lengths, bond angles and torsion angles are given in Table 2.

The values of bond lengths and bond angles are in agreement with literature data on the geometry of Z-urethane derivatives, Ac$_3$c residues, and the hydroxamic acid unit. In particular:

(i) The decrease of the bond angle at the C(8) atom of the benzyloxycarbonyl moiety, O(1)—C(8)—N(1), by about 6.5 (2)°, as compared with the corresponding bond angle at C′ in the peptide group, C$^\alpha$—C′—N (Benedetti, 1982), is probably related to the reduced repulsion between the O(1) atom and the nearest substituent on the N atom in the urethane group (Benedetti, Pedone, Toniolo, Dudek, Némethy & Scheraga, 1983), as compared with the corresponding repulsion involving the C$^\alpha$ atom of the peptide group.

(ii) In the cyclopropyl ring the *distal* bond [1.484 (4) Å] is significantly shorter than the *vicinal* sides [1.505 (3) and 1.503 (3) Å]. The exocyclic N(1)—C(9)—C(12) bond angle is significantly higher than the tetrahedral value. The N(1)—C(9) and C(9)—C(12) bond lengths are significantly shortened compared to C$^\alpha$-*mono*substituted $\alpha$-amino acids (Benedetti, 1982), a clear indication of the conjugative ability of the cyclopropyl moiety (Allen, 1981).

* 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 55064 (13 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: GE0293]

Table 2. *Selected bond lengths* (Å), *bond angles* (°) *and torsion angles* (°)

| | | | |
|---|---|---|---|
| C(7)—O(1) | 1.430 (3) | O(1)—C(8)—N(1) | 111.2 (2) |
| O(1)—C(8) | 1.341 (3) | O(1)—C(8)—O(2) | 123.9 (2) |
| C(8)—O(2) | 1.209 (3) | O(2)—C(8)—N(1) | 124.9 (2) |
| C(8)—N(1) | 1.343 (3) | C(8)—N(1)—C(9) | 124.4 (2) |
| N(1)—C(9) | 1.431 (3) | N(1)—C(9)—C(12) | 117.1 (2) |
| C(9)—C(10) | 1.505 (3) | N(1)—C(9)—C(10) | 117.5 (2) |
| C(10)—C(11) | 1.503 (3) | N(1)—C(9)—C(11) | 118.8 (2) |
| C(9)—C(12) | 1.491 (3) | C(10)—C(9)—C(12) | 116.0 (2) |
| C(10)—C(11) | 1.484 (4) | C(11)—C(9)—C(12) | 115.6 (2) |
| C(12)—O(3) | 1.242 (3) | C(9)—C(12)—N(2) | 116.8 (2) |
| C(12)—N(2) | 1.316 (3) | C(9)—C(12)—O(3) | 120.1 (2) |
| N(2)—O(4) | 1.393 (3) | O(3)—C(12)—N(2) | 123.1 (2) |

| | | | |
|---|---|---|---|
| C(7)—O(1)—C(8)—N(1) | −175.2 (2)* | N(1)—C(9)—C(12)—N(2) | 9.0 (3) |
| O(1)—C(8)—N(1)—C(9) | 2.4 (3) | N(1)—C(9)—C(10)—C(11) | 108.8 (2) |
| C(8)—N(1)—C(9)—C(12) | 71.9 (3) | N(1)—C(9)—C(11)—C(10) | −106.5 (2) |

* Only values for the left-handed molecules are given.

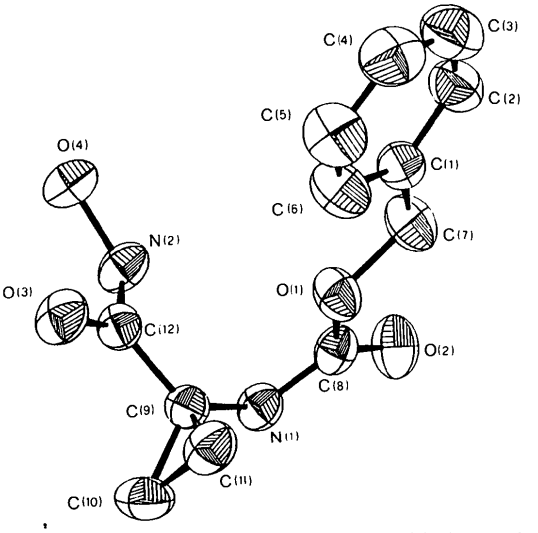


Fig. 1. Molecular structure of Z-Ac$_3$c-NHOH with the numbering of atoms (ellipsoids at 50% probability).

(iii) The hydroxamic acid unit is found in its normal —C(=O)—NHOH tautomeric form (Chimiak & Milewska, 1988; Kjøller Larsen, 1988).

The opening of the O(3)—C(12)—N(2) bond angle should be related to repulsion between the two *cis*-situated O atoms.

The secondary urethane linkage adopts the unusual *cis* conformation. This structural property, accompanied by the *trans* C(7)—O(1)—C(8)—N(1) torsion angle, allows us to classify this urethane moiety as the uncommon type *b* (Benedetti, Pedone, Toniolo, Némethy, Pottle & Scheraga, 1980).

The Ac$_3$c residue is folded and the set of C(8)—N(1)—C(9)—C(12) and N(1)—C(9)—C(12)—N(2) backbone torsion angles falls in the unusual *B* ('bridge') region of the conformational map (Zimmerman, Pottle, Némethy & Scheraga, 1977). As for the torsion angles relating the cyclopropane ring to the peptide chain, N(1)—C(9)—C(10)—C(11) and N(1)—C(9)—C(11)—C(10), the values observed

are reasonably close to the ideal *skew* ($s^+$, $s^-$ or $\pm 120°$) conformations.

The conformation of the *R*C(=O)—NHOH moiety is synperiplanar (Kjøller Larsen, 1988). The O(3)···O(4) *intra*molecular distance [2.703 (3) Å] is in the range suitable for O—H···O bonding, but this is not observed. Rather, the O—H bond is part of the *inter*molecular hydrogen-bonding scheme (see below).

The crystal packing of the Z-Ac$_3$c-NHOH molecules is characterized by three intermolecular hydrogen bonds between: (i) the hydroxamic acid O(4)—H and O(3)=C(12) groups of symmetry-related ($-x$, $2-y$, $2-z$) molecules; (ii) the hydroxamic acid N(2)—H and urethane O(2)=C(8) groups of symmetry-related ($-x$, $1-y$, $1-z$) molecules; and (iii) the urethane N(1)—H group and the hydroxamic acid O(4) atom of symmetry-related ($x$, $y-1$, $z$) molecules. The O(4)···O(3) separation is 2.620 (3) Å, whereas the N(2)···O(2) and N(1)···O(4) distances are 2.806 (3) and 3.060 (3) Å, respectively.

### References


ALLEN, F. H. (1981). *Acta Cryst.* B**37**, 890–900.

BENEDETTI, E. (1982). *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Vol. 6, edited by B. WEINSTEIN, pp. 105–184. New York: Dekker.

BENEDETTI, E., DI BLASIO, B., PAVONE, V., PEDONE, C., SANTINI, A., CRISMA, M., VALLE, G. & TONIOLO, C. (1989). *Biopolymers*, **28**, 175–184.

BENEDETTI, E., PEDONE, C., TONIOLO, C., DUDEK, M., NÉMETHY, G. & SCHERAGA, H. A. (1983). *Int. J. Pept. Protein Res.* **21**, 163–181.

BENEDETTI, E., PEDONE, C., TONIOLO, C., NÉMETHY, G., POTTLE, M. S. & SCHERAGA, H. A. (1980). *Int. J. Pept. Protein Res.* **16**, 156–172.

BRECKENRIDGE, R. J. & SUCKLING, C. J. (1986). *Tetrahedron*, **42**, 5665–5677.

CHIMIAK, A. & MILEWSKA, M. J. (1988). *Progress in the Chemistry of Organic Natural Compounds*, Vol. 53, edited by W. HERZ, H. GRISEBACH, G. W. KIRBY & C. TAMM, pp. 203–277. Wien: Springer.

HOLMES, M. A. & MATTHEWS, B. W. (1981). *Biochemistry*, **20**, 6912–6920.

KJØLLER LARSEN, I. (1988). *Acta Cryst.* B**44**, 527–533.

MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1978). *MULTAN*78. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.

NISHINO, N. & POWERS, J. C. (1978). *Biochemistry*, **17**, 2846–2850.

SHELDRICK, G. M. (1976). *SHELX*76. Program for crystal structure determination. Univ. of Cambridge, England.

SUCKLING, C. J. (1986). *Biochem. Soc. Trans.* pp. 402–404.

SUCKLING, C. J. (1988). *Angew. Chem. Int. Ed. Engl.* **27**, 537–552.

TONIOLO, C. & BENEDETTI, E. (1988). *ISI Atlas of Science: Biochemistry*, Vol. 1, pp. 225–230.

VALLE, G., FORMAGGIO, F., CRISMA, M., TONIOLO, C., BOESTEN, W. H. J., POLINELLI, S., SCHOEMAKER, H. E. & KAMPHUIS, J. (1992). *Z. Kristallogr.* In the press.

ZIMMERMAN, S. S., POTTLE, M. S., NÉMETHY, G. & SCHERAGA, H. A. (1977). *Macromolecules*, **10**, 1–9.


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# Structure of the (1:1:1) Complex 2*a*,2*b*,2*c*,2*d*,2*e*,2*f*,3*a*,3*g*,6*a*,6*b*,6*c*,6*d*,6*e*,6*f*,6*g*-Pentadeca-*O*-methyl-β-cyclodextrin–1,7-Dioxaspiro[5.5]undecane–Methanol


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**Abstract.** $C_{67}H_{120}O_{38}$, $M_r = 1533.66$, triclinic, $P1$, $a = 10.673$ (3), $b = 15.776$ (3), $c = 16.103$ (4) Å, $\alpha = 122.77$ (2), $\beta = 110.09$ (2), $\gamma = 68.13$ (2)°, $V = 2080$ Å$^3$, $Z = 1$, $D_x = 1.20$ g cm$^{-3}$, $\lambda$(Cu $K\alpha$) = 1.54056 Å, $\mu = 8.10$ cm$^{-1}$, $F(000) = 826$, $T = 293$ K, final $R = 0.078$ for 6294 reflections. The study of the title methylated cyclodextrin molecule reveals an over-methylation on one residue coupled with an O(2)–O(3) permutated methylation on the neighbouring residue. The important dissymmetry of the host molecule leads to chiral discrimination of the dioxaspiro[5.5]undecane 'guest' molecule, yielding a complex of only the *S* enantiomer which is completely enclosed in the cyclodextrin cavity.


**Introduction.** Cyclodextrins (CD's), cyclic oligosaccharides having α(1–4) linked glucose units, are formed by the enzymatic degradation of amylose and are well documented for their ability to form inclusion complexes with a wide variety of 'guest' molecules (Szetjli, 1989). Many studies of crystal structures of CD complexes have been reported (Saenger, 1980; Le Bas & Rysanek, 1987). Methylated CD (MCD) complexes have already been stu-

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