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Synthesis, Crystal Structure and Conformation of N-Acetyl-$C^{\alpha,\alpha}$-diethylglycine-N′-methylamide

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Summary. Synthesis and X-ray structure analysis of N-acetyl-$C^{\alpha,\alpha}$-diethylglycine-N′-methylamide [$CH_3-CO-NH-C(C_2H_5)_2-CO-NHCH_3$] are described. The compound was obtained from the corresponding N-acetyl derivative [$CH_3-CO-NH-C(C_2H_5)_2-COOH$] through the mixed anhydride procedure. It crystallizes as monohydrate ($C_9H_{18}N_2O_2 \cdot H_2O$) in space group $P2_1/c$, $a = 7.139(1)$, $b = 11.823(2)$, $c = 15.778(3)$ Å, $\beta = 122.23(1)°$, $V = 1126.53$ Å^3, $D_m = 1.20$ Mgm^{-3} (room temperature), $R = 0.046$ for 1523 reflections. The crystal packing is dominated by two strong hydrogen bonds between the water molecule and two carbonyl oxygen atoms and two weak H-bonds to two amide-N-atoms of symmetry-equivalent molecules. The molecular conformation is closer to a 3_{10}-helix then an α-helix.

Keywords. N-Acetyl-$C^{\alpha,\alpha}$-diethylglycine-N′-methylamide, synthesis; Crystal structure; Conformation.

Synthese, Kristallstruktur und Konformation von N-Acetyl-$C^{\alpha,\alpha}$-diethylglycin-N′-methylamid

Zusammenfassung. Es wird über Synthese und die röntgenographische Strukturbestimmung von N-Acetyl-$C^{\alpha,\alpha}$-diethylglycin-N′-methyl-amid [$CH_3-CO-NH-C(C_2H_5)_2-CO-NH-CH_3$] berichtet. Die Verbindung wurde unter Anwendung der Methode der gemischten Anhydride aus dem entsprechenden N-Acetylderivat [$CH_3-CO-NH-C(C_2H_5)_2-COOH$] erhalten. Sie kristallisiert als Monohydrat ($C_9H_{18}N_2O_2 \cdot H_2O$) in der Raumgruppe $P2_1/c$ mit $a = 7.139(1)$, $b = 11.823(2)$, $c = 15.778(3)$ Å, $\beta = 122.23(1)°$, $V = 1126.53$ Å^3, $D_m = 1.20$ Mgm^{-3}, $D_x = 1.204$ Mgm^{-3} (Raumtemperatur). $R = 0.046$ für 1523 Reflexe. Die Kristallpackung ist dominiert durch zwei starke H-Brücken vom Wassermolekül zu zwei Carbonylsauerstoffatomen sowie zwei schwachen H-Brücken zu zwei Amid-N-atomen symmetrieequivalenter Moleküle. Die Konformation des Peptidgerüstes ist näher einer 3_{10} als einer α-Helix.

Introduction

$C^{\alpha,\alpha}$-Disubstituted α-aminoacids and their peptides are of interest because of the potential usefullness of residues of these amino acids as a new type of conformational constraint in the synthesis of enzyme-resistant analogues of bioactive peptides [1–3] and the widespread presence of α-aminoisobutyric acid (*Aib*), the prototype of this family of residues in the membrane-active peptide antibiotics (peptaibols) [4–6]. *R*-(−)-Isovaline (α-ethylalanine, *Iva*) is also constituent of naturally occurring peptide antibiotics [7], contrary to $C^{\alpha,\alpha}$-diethylglycine (*Deg*) and

$C^{\alpha,\alpha}$-dipropylglycine (*Dpg*) which are not found in the hydrolysates of natural products.

In recent years the structural preferences of selected derivatives and homooligopeptides from $C^{\alpha,\alpha}$-disubstituted α-aminoacid residues were determined by conformational energy computation, X-ray diffraction analysis and spectroscopic studies [8]. The results obtained indicate that 3_{10}-helix and the fully extended (C_5) conformation are preferentially adopted by long sequences of these residues, depending upon bulkiness and nature of their side chains.

Our interest in the stereochemistry of $C^{\alpha,\alpha}$-diethylglycine (*Deg*) was stimulated by the results of the study of conformation of $Tfa\text{-}Deg_n\text{-}O\text{-}t\text{-}Bu$ (n = 2–5) [9–11] and $\mathrm{ClCH_2-CO-}Deg\mathrm{-OH}$ [12]. In 1985 Barone et al. [13] have calculated the preferred conformations of N-acetyl-N′-methylamides of three α, α-dialkylglycines (*Aib, Deg, Dpg*). In order to explain the problem of conformation of $C^{\alpha,\alpha}$-diethylglycine residues in a linear peptides, crystal structure investigations of the title compound $\mathrm{CH_3-CO-NH-C(C_2H_5)_2-CO-NH-CH_3}$ have been undertaken [14]. $C^{\alpha,\alpha}$-Diethylglycine was prepared by Büchner synthesis from 3-pentanone via 5,5-diethylhydantoin according to the procedure of Abshire et al. [15]. The title compound was obtained from the corresponding N-acetyl derivative $\mathrm{CH_3-CO-NH-C(C_2H_5)_2-COOH}$ [16] through the mixed anhydride procedure. It crystallizes as monohydrate in two forms. We examined the structure of the more stable form.

In this paper we give details of X-ray diffraction analysis of N-acetyl-$C^{\alpha,\alpha}$-diethylglycine-N′-methylamide and compare these results with the free molecule structure calculated by molecular mechanics methods.

Experimental Part

Synthesis of N-Acetyl-$C^{\alpha,\alpha}$-diethylglycine-N′-methylamide ($\mathrm{CH_3-CO-NH-C(C_2H_5)_2-NHCH_3}$)

N-acetyl-α, α-diethylglycine [16] (0.81 g, 4.7 mmol) was dissolved in chloroform (20 ml) and treated with triethylamine (0.7 ml). After cooling (−20 °C) isobutyl chloroformate (0.69 ml, 5.2 mmol) was added to a stirred solution. The resulting mixture was stirred at −20 °C for further 20 min, then a cooled 33% solution of methylamine in ethanol (1.25 ml, 10 mmol) was added. This mixture was kept at −15 °C for the next 60 min, and stirred at room temperature overnight. The solvent was evaporated to leave an oil, which was dissolved in aqeous methanol. The resulting solution was successively treated with Dowex cation exchange resin (50 W × 4, H^+ form) and Dowex anion exchange resin (2 × 8, OH^- form). After purification the solution was evaporated to give the crude product as a waxy solid (0.86 g, 98%). The obtained solid was taken up in CH_2Cl_2 (20 ml), then ether (10 ml) and *n*-hexane (20 ml) was added. The resulting solution was refluxed for 10 min, and then left standing at room temperature for 24 h. The crystalline precipitate was filtered, dried (vacuum desiccator) and recrystallized from ethyl acetate-ether to give the product (0.49 g, 55%), m.p. 133.5°–137.0 °C, R_f = 0.57 ($CHCl_3$/*Me*OH), 7 : 3). A further recrystallization gave two specimens of the products: (i) as colourless needles, m.p. 137°–139 °C; (ii) as colourless granular solid, m.p. 133.5°–135.5 °C. Anal. calcd. for $C_9H_{18}N_2O_2$ (186.26): C 58.04, H 9.74, N 15.04; found: C 58.02, H 9.73, N 14.99. M^+ (E. I) 187. IR (KBr) υ_{max}: 3350, 3260, 2950, 1650, 1630, and 1525 cm^{-1}. NMR (80 MHz, CF_3COOH), δ (ppm): 0.88 (t, 6 H, $-CH_3$), 1.75–2.75 (m, 4 H, $-CH_2$), 2.45 (s, 3 H, CH_3-CO), 3.04 (s, 3 H, $-N-CH_3$), 7.3–7.7 (m, 1 H, $NH-CH_3$), 8.50 (s, 1 H, NH).

X-Ray Diffraction

Colourless needle-like crystals ca. 0.03 mm in diameter were grown from ethanol by slow evaporation at room temperature. Preliminary oscillation and Weissenberg photographs showed the crystal system to be monoclinic. Systematic reflection absences indicated the space group $P2_1/c$. The density D_m

Table 1. Fractional positional parameters and equivalent isotropic temperature factors $U_{ij} \cdot 10\,\text{Å}^2$ with the non hydrogen atoms with e.s.d's in parentheses

Atom	x/a	y/b	z/c	U_{eq}
O 3	0.53027 (8)	0.07918 (4)	0.38492 (4)	396 (3)
C 1	0.03795 (14)	0.03950 (7)	0.36664 (6)	451 (5)
C 2	0.08674 (12)	0.13371 (6)	0.44077 (5)	299 (3)
C 3	0.33765 (11)	0.29370 (5)	0.53431 (5)	261 (4)
C 4	0.38217 (11)	0.27127 (6)	0.63963 (5)	288 (4)
C 5	0.47705 (14)	0.14218 (6)	0.77587 (6)	423 (5)
C 6	0.55296 (12)	0.34003 (6)	0.54830 (5)	346 (4)
C 7	0.75632 (13)	0.26763 (7)	0.60699 (6)	459 (4)
C 8	0.15295 (12)	0.38392 (6)	0.48338 (5)	322 (4)
C 9	0.06751 (13)	0.40649 (7)	0.37393 (6)	426 (4)
N 1	0.27787 (9)	0.18918 (4)	0.47456 (4)	260 (3)
N 2	0.42746 (10)	0.16627 (5)	0.67480 (4)	303 (3)
O 1	−0.04051 (8)	0.15742 (4)	0.46788 (4)	403 (3)
O 2	0.38020 (10)	0.35179 (0)	0.68844 (4)	468 (3)

was measured by the flotation method in benzene and iobobenzene mixtures yielding $D_m = 1.20\,\text{Mg}\,\text{m}^{-3}$.

The data were collected on a Syntex P2_1 diffractometer in the $\omega/2\theta$ mode at room temperature. Graphite monochromatized CuK$_\alpha$ ($\lambda = 1.54178\,\text{Å}$) radiation was used. Unit cell parameters were refined by least squares procedure from the setting angles of 25 reflections in the θ range 26.5–34.1°. The 1523 unique reflections were collected in the h, k, l range: $0 \leqslant h \leqslant 7$, $0 \leqslant k \leqslant 12$, $-17 \leqslant l \leqslant 14$, 1408 of them with $F_0 > 2\sigma(F_0)$ were considered as observed. Lorentz and polarisation corrections were applied. Absorption effects were neglected (transmission factors 0.999 max and 0.918 min) [17]. Three standard reflections varied in intensity by < 3%.

Structure Determination and Refinement

The structure was solved by direct methods (MULTAN 78) [18] and refined by full-matrix least-squares with anisotropic temperature factors for non-hydrogen atoms. All hydrogen atoms were found from difference Fourier maps and refined isotropically. The reliability factors were: final $R = 0.046$, $R_w = 0.048$, $S(F^2) = 0.85$ for the observed reflections. The weighting scheme was $w = 1.0/\sigma^2$, $(\Delta/\sigma)_{\max}$ for non hydrogen atoms = 0.22 in final cycle, $(\Delta/\sigma)_{ave} = 0.03$. The largest $\Delta\rho$ peak in the final difference electron density map had a value of $0.31\,\text{eÅ}^{-3}$. Atomic scatterring factors were taken from the International Tables for X-ray Crystallography [19] for neutral atoms, and animalous-dispersion corrections for non-hydrogen atoms from Cramer and Liberman [20]. All calculations, except for MULTAN, were performed using XRAY 76 [21].

Positional and equivalent isotropic thermal parameters for non-hydrogen atoms are given in Table 1*.

Results and Discussion

A view of the molecule with the atom numbering is shown in Fig. 1. The X-ray study revealed one molecule of crystallyzing water, which forms two strong hy-

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* Additional material to the structure determination can be ordered from Fachinformationszentrum Energie, Physik, Mathematik, WD-7514, Eggenstein-Leopoldshafen 2, Federal Republic of Germany, referring to the deposition no. 56431, the names of the authors and the citation of the paper.

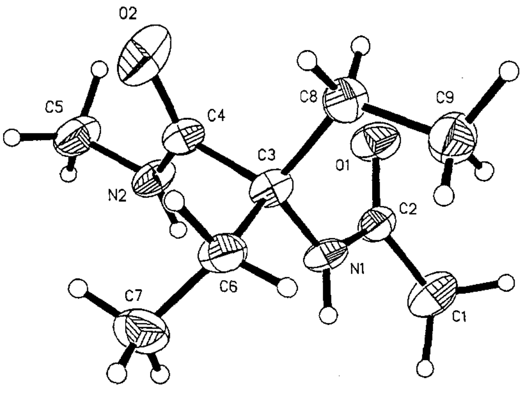

Fig. 1. View of the molecule of N-Acetyl-$C^{\alpha,\alpha}$-diethylglycine N′-methylamide

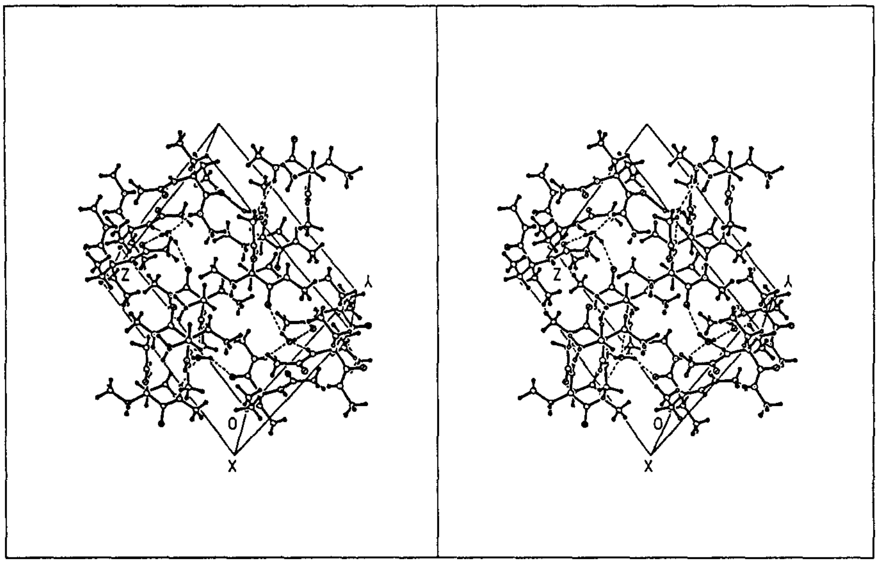

Fig. 2. The molecular packing and hydrogen bonding in the crystal

drogen bonds O $3^{I} \cdots$ O 1(2.750 (3) Å) and O $3^{II} \cdots$ O 2 (2.790 (6) Å) with the peptide molecule [symmetry code: (I) $x-1$, y, z; (II) x, $0.5-1$, -1, $0.5+z$]. The N 1-H and N 2-H groups are also weakly hydrogen bonded to the water molecule (N 1 $\cdots$ O 3 3.120 (1) Å; N 2 $\cdots$ O^{III} 3.116 (1) Å, (III): $1-x$, $-y$, $1-z$). A stereoscopic packing diagram is shown in Fig. 2. Table 2 gives torsion angles φ and ψ for $CH_3CO-NH-C(C_2H_5)_2]-NHCH_3$ in the crystal and in vacuum (as obtained from molecular mechanics calculations) using QCPE Program No. 395 [22]). The table also gives theoretical values for α-helical and 3_{10}-helical conformations and literature data for related structures. These data indicate, that the $C^{\alpha,\alpha}$-diethylglycine residue assumes a conformation closer to a 3_{10}- than to an α-helix, in contrast to other related compounds [23, 24]. These results have been confirmed by Barone et al. [13], who assumed a similarity in the geometry of $C^{\alpha,\alpha}$-diethylglycine with $C^{\alpha,\alpha}$-di-n-propylglycine.

Table 2. Torsion angles φ and ψ of *Ac-Deg*-$NHCH_3$ in comparison with literature data

	φ	ψ
1. *Ac-Deg*-$NHCH_3$ (this work)		
crystalline	68.1	19.4
free molecule	60.3	28.2
2. 3_{10}-helix [25]	60.0	30.0
3. α-helix	55.0	45.0
modified α-helix (α'-helix) [26]	55.0	60.0
4. *Ac-Aib*-NH*Me* [24]	−55.5	−39.3
5. *Boc-Aib* [23]	−54.2	−44.1
6. mean value of the *Aib* residue [27]	−56.5	−39.8

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References

[1] Spatola A. F. (1983) In: Weinstein B. (ed.) Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, Vol. 7., Marcel, Dekker, New York , p. 267

[2] Tourwé D. (1985) Janssen Chim. Acta **3**: 3

[3] Aubry A., Boussard G., Cung M. T., Marraud M., Vitoux B., (1988) J. Chim. Phys. Phys.-Chim. Biol **85**: 345

[4] Nagaray R., Balaram P. (1981) Acc. Chem. Res. **14**: 356

[5] Toniolo C., Benedetti E. (1988) ISI Atlas of Science Biochem. 1: 225

[6] Toniolo C. (1989) Biopolymers **28**: 247

[7] Brückner H., Nicholson G. J., Jung G., Kruse W., König W. A., (1980) Chromatographia **13**: 209

[8] Toniolo C., Benedetti E. (1991) Macromolecules **24**: 4004

[9] Bavoso A., Benedetti E., Di Blasio B., Pavone V., Pedone C., Toniolo C., Bonora G. M., Leplawy M. T., Redliński A. S., Kaczmarek K. (1985) In: Deber C. M., Hruby V. J., Kopple K. T. (eds) Peptides: Structure and Function. Proc. 9th Amer. Pept. Symp., Pierce Chemical Comp., Rockford, Ill. p. 193

[10] Toniolo C., Bonora G. M., Bavoso A., Benedetti E., Di Blasio B., Pavone C., Barone V., Lelj F., Leplawy M. T., Kaczmarek K., Redliński A. (1988) Biopolymers **27**: 373

[11] Benedetti E., Barone V., Bavoso A., Di Blasio B., Lelj F. Pavone V., Pedone C., Bonora G. M., Toniolo C., Leplawy M. T., Kaczmarek K., Redliński A., (1988) Biopolymers **27**: 353

[12] Valle G., Bonora G. M., Toniolo C., Hardy T. M., Leplawy M. T., Redliński A. S. (1986) J. Chem. Soc. Perkin Trans. II.: 885

[13] Barone V., Lelj F., Bavoso A., Di Blasio B., Grimaldi P., Pavone V., Pedone C. (1985) Biopolymers **24**: 1759

[14] Gałdecki Z., Luciak B. (1984) Acta Cryst. **A40**: C-72

[15] Abshire C. J., Berlinguet L. (1965) Can. J. Chem. **43**: 1232; Biochemistry **16**: 307

[16] Gałdecki Z., Luciak B., Leplawy M. T., Kaczmarek K., Redliński A. S. (1992) Z. Naturforsch. **47b**: 90

[17] North A. C. T., Phillips D. C., Matthews F. S. (1986) Acta Cryst. **A24**: 351

[18] Main P., Hull S. E., Lessinger L., Germain G., Declercq J. P., Woolfsoon M. M. (1978) MULTAN. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. Univs. of York. England and Louvain, Belgium

[19] International Tables for X-ray Crystallography (1974) Vol. IV. Kynoch Press; Birmingham, pp. 71–147

[20] Cramer D. T., Liberman D. (1970) J. Chem. Phys. **53**: 1891

[21] Stewart J. M. (1976) The X-Ray System. Techn. Rep. TR-465. Computer Science Center, Univ. of Maryland

[22] Allinger N. L., Yuh Y. H. (1980) Quantum Chemistry Programm Exchange QCPE Programm No. 395. Indiana University, Chemistry Department

[23] Mayr W., Jung G., Strähle J. (1980) Liebigs Ann. Chem. 715

[24] Aubry A., Protas J., Boussard G., Marraud M., Neel J. (1978) Biopolymers **17**: 1693

[25] Burgess A. W., Leach S. J. (1973) Biopolymers **12**: 2599

[26] Venkataram Prasad B. V., Sasisekharan V. (1979) Macromolecules **12**: 1107

[27] Van Roey P., Smith G. D., Balasubramanian T. M., Marshall G. R. (1981) Acta Cryst. (Suppl. C-64) **A37**: 03.2–07

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