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N-Acetylglycyl-L-alaninamide and *N*-Acetyl-L-alanyl-L-alaninamide †

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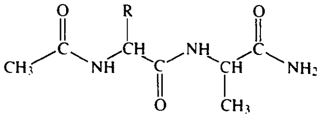
Abstract

The main conformations of *N*-acetylglycyl-L-alaninamide (NAGAA), $C_7H_{13}N_3O_3$, and *N*-acetyl-L-alanyl-L-alaninamide (NAA_2A), $C_8H_{15}N_3O_3$, occur in the *F* and *E* regions, respectively, of the φ, ψ map, according to the classification of Zimmerman, Pottle, Némethy & Scheraga [*Macromolecules* (1977), **10**, 1–9]. In both structures, the packing is governed by intermolecular hydrogen bonds which involve all the donor groups. In the NAGAA crystal, each molecule shares eight hydrogen bonds with eight nearest molecules, thus forming a three-dimensional network of hydrogen bonds. The methyl groups lie at van der Waals distances in channels which grow parallel to *b* and around the screw axis. In NAA_2A, screw-related molecules are joined by three hydrogen bonds and form ribbons which extend parallel to the *bc* plane, alternately at $x = 0$ and 0.5. A fourth hydrogen bond connects the ribbons along the direction of the *a* axis.

Comment

N-Acetyl peptidoamides are useful model compounds for the investigation of peptide interactions and the preferred conformations in polypeptide chains. As part of our continuing studies concerning crystallographic determinations (Puliti, Mattia & Lilley, 1993, and references therein), as well as some thermodynamic parameters connected with phase transitions, whose trends have been discussed on the basis of crystallographic results (Barone, Giancola, Lilley, Mattia & Puliti, 1992), we present here the crystal structures of *N*-acetylglycyl-L-alaninamide (NAGAA) and *N*-acetyl-L-alanyl-L-alaninamide (NAA_2A).



NAGAA R = H
NAA_2A R = CH_3

Perspective views of the NAGAA and NAA_2A molecules are shown in Figs. 1(*a*) and 1(*b*), respectively. For each molecule, the peptide linkage between the residues displays close to the ideal *trans* form.

In NAGAA, the φ_1 and ψ_1 torsion angles are rather similar to those of φ_2 and ψ_2 (see Table 2) and fall in the *F* region of the Zimmerman map (Zimmerman, Pottle, Némethy & Scheraga, 1977). Although this region does

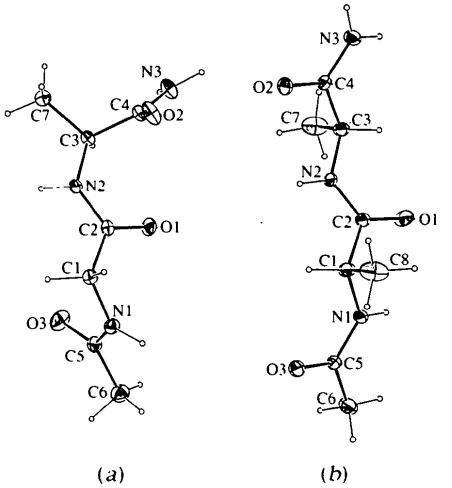


Fig. 1. Perspective views of the molecules with the atomic labelling schemes for non-H atoms: (*a*) NAGAA and (*b*) NAA_2A. Displacement ellipsoids are shown at the 30% probability level.

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† The authors dedicate this paper to the memory of Professor George Némethy, who spent some periods of his activities in Naples during recent years.

not include an energy minimum for the glycine, many Gly residues in peptide structures occur in the *F* (*F**) region. In particular, Gly conformations such as that in the NAGAA molecule have been observed recently in both independent molecules in the structure of *N*-acetyl-L-prolylglycinamide (Puliti, Mattia & Lilley, 1993).

The NAA$_2$A molecule is in an almost extended conformation and the alanine methyls protrude in opposite directions with respect to the best plane of the peptide skeleton. Both Ala residues fall in the *E* region and φ and ψ torsion angles are close to the values found for antiparallel pleated sheets: β-poly-L-alanine (Arnott, Dover & Elliott, 1967), di-L-alanine hydrochloride (Tokuma, Ashida & Kakudo, 1969) and tri-L-alanine (Fawcett, Camerman & Camerman, 1975). The conformations of several small peptide crystals are revealed in the *E* or *F* regions (Puliti, Mattia, Barone & Giancola, 1989, 1991; Puliti, Mattia, Barone, Della Gatta & Ferro, 1990; Puliti, Mattia & Lilley, 1992, 1993). In these regions, the potential-energy surfaces are largely isoenergetic (Vasquez, Némethy & Scheraga, 1983, and references therein) and very shallow energy barriers separate the local minima.

For the NAA$_2$A molecule we have evaluated the conformational energy map, using the molecular geometry derived from the crystallographic study and a procedure (interaction-energy contributions and minimizing method) analogous to that employed in <u>*ECEPP*</u> (empirical conformational energy program for peptides) and updated versions (Némethy, Pottle & Scheraga, 1983). It appears that the conformation observed in the NAA$_2$A crystal [$\varphi_1 = -151.4(2)$, $\psi_1 = 142.0(2)$; $\varphi_2 = -141.5(2)$, $\psi_2 = 148.1(2)°$] corresponds to a relative minimum, which is only 4.6 kJ mol^{-1} higher in energy than the absolute minimum that occurs within the *C* region at $\varphi = -80$, $\psi = 76°$. The small difference in energies is a consequence of the flatness of the energy surfaces in these regions, and thus, small changes (energetically the most favourable) in intermolecular interactions in the crystals are sufficient to cause new local minima.

The packing of NAA$_2$A (Fig. 2) is ruled by four intermolecular hydrogen bonds. Screw-related molecules are linked together by three hydrogen bonds, giving rise to ribbons which extend parallel to the *bc* plane, alternately at $x = 0$ and 0.5. The fourth hydrogen bond, N3—H3···O3, connects the ribbons along a direction that forms a stair framework. The alanine methyl groups settle in apolar regions at distances greater than 4 Å. The acetyl methyl groups of molecules belonging to different ribbons face each other at van der Waals distance.

In the crystal of NAGAA, efficient molecular packing (Fig. 3) is stabilized by a three-dimensional network of hydrogen bonds. Each molecule shares eight hydrogen bonds with eight different molecules (Table 3). The methyl groups lie, at distances greater than 3.8 Å, in the apolar channel around the screw axis at $x = 0$, $z = 0.5$.

In both structures there are some C$_\alpha$—H···O short intermolecular interactions (3.27–3.51 Å), but the H-atom geometry is well beyond accepted values for an attractive interaction involving activated C—H groups (Taylor & Kennard, 1982).

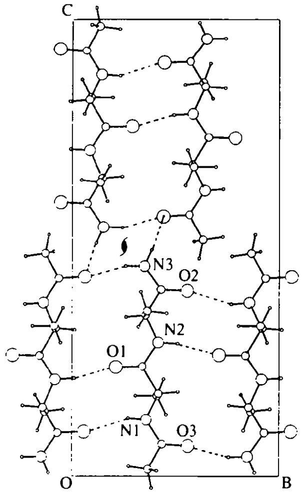

Fig. 2. Crystal packing of NAA$_2$A projected along the *a*-axis direction. For clarity, only O and N atoms are labelled. Dashed lines indicate hydrogen bonds; the symmetry relations of the acceptors are reported in Table 6.

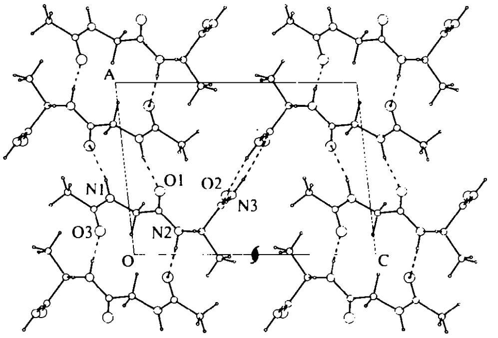

Fig. 3. Crystal packing of NAGAA projected on the *ac* plane. For clarity, only O and N atoms are labelled. Dashed lines indicate hydrogen bonds: the symmetry relations of the acceptors are reported in Table 3.

Experimental

The syntheses of NAGAA and NAA$_2$A were described previously by Milburn (1984) and Lilley (1988). Crystals of NAGAA were obtained by slow evaporation from ethyl ether; those of NAA$_2$A by slow evaporation from ethanol–ethyl ether solution.

NAGAA

Crystal data

$C_7H_{13}N_3O_3$
$M_r = 187.20$
Monoclinic
$P2_1$
$a = 8.189$ (3) Å
$b = 5.047$ (1) Å
$c = 11.305$ (5) Å
$\beta = 96.12$ (2)°
$V = 464.6$ (5) Å^3
$Z = 2$
$D_x = 1.338$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 24 reflections
$\theta = 22$–25°
$\mu = 0.850$ mm^{-1}
$T = 293$ K
Flattened prism
0.45 × 0.18 × 0.06 mm
Colourless

Data collection

Enraf–Nonius CAD-4F diffractometer
ω–2θ scans
Absorption correction: none
1090 measured reflections
1090 independent reflections
1065 observed reflections $[I \geq 2.5\sigma(I)]$

$\theta_{\max} = 76$°
$h = 0 \rightarrow 10$
$k = 0 \rightarrow 6$
$l = -14 \rightarrow 14$
4 standard reflections
frequency: 240 min
intensity decay: 2%

Refinement

Refinement on F
$R = 0.030$
$wR = 0.033$
$S = 0.91$
1065 reflections
157 parameters
Only coordinates of H atoms refined
$w = 1/[\sigma^2(F_o) + (0.01F_o)^2 + 1]$ (Killean & Lawrence, 1969)

$(\Delta/\sigma)_{\max} = 0.03$
$\Delta\rho_{\max} = 0.18$ e Å^{-3}
$\Delta\rho_{\min} = -0.16$ e Å^{-3}
Extinction correction: Stout & Jensen (1968)
Extinction coefficient: 8.4 (6) × 10^{-6}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* NAGAA

$$B_{eq} = (1/3)\Sigma_i\Sigma_j B_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
O1	0.3673 (2)	0.5000	0.1356 (1)	3.14 (3)
O2	0.3386 (2)	0.2696 (3)	0.4089 (1)	3.87 (3)
O3	0.1341 (2)	0.5044 (5)	−0.1293 (1)	4.36 (3)
N1	0.3253 (2)	0.2026 (4)	−0.0737 (1)	2.67 (3)
N2	0.1345 (2)	0.3366 (4)	0.1948 (1)	2.38 (3)
N3	0.3450 (2)	0.7113 (4)	0.4322 (2)	3.10 (3)
C1	0.2417 (2)	0.1273 (4)	0.0274 (2)	2.60 (4)
C2	0.2535 (2)	0.3410 (4)	0.1225 (2)	2.26 (3)
C3	0.1328 (2)	0.5251 (4)	0.2911 (2)	2.33 (3)
C4	0.2842 (2)	0.4910 (5)	0.3814 (2)	2.42 (3)
C5	0.2633 (2)	0.3959 (5)	−0.1458 (2)	2.80 (4)
C6	0.3601 (3)	0.4697 (6)	−0.2465 (2)	3.92 (5)
C7	−0.0208 (3)	0.4800 (7)	0.3529 (2)	3.83 (5)

Table 2. *Geometric parameters* (Å, °) *for* NAGAA

O1—C2	1.226 (2)	N2—C3	1.448 (3)
O2—C4	1.230 (3)	N3—C4	1.324 (3)
O3—C5	1.223 (3)	C1—C2	1.518 (3)
N1—C1	1.444 (2)	C3—C4	1.529 (2)
N1—C5	1.336 (3)	C3—C7	1.520 (3)
N2—C2	1.337 (2)	C5—C6	1.502 (3)
C1—N1—C5	119.6 (2)	C4—C3—C7	109.2 (2)
C2—N2—C3	121.0 (2)	O2—C4—N3	122.9 (2)
N1—C1—C2	111.9 (2)	O2—C4—C3	121.1 (2)
O1—C2—N2	122.0 (2)	N3—C4—C3	115.8 (2)
O1—C2—C1	122.7 (2)	O3—C5—N1	120.8 (2)
N2—C2—C1	115.2 (2)	O3—C5—C6	122.7 (2)
N2—C3—C4	110.9 (2)	N1—C5—C6	116.5 (2)
N2—C3—C7	108.8 (2)		
C5—N1—C1—C2 φ_1	−69.8 (2)	C2—N2—C3—C7	177.1 (2)
C1—N1—C5—C6 ω'	177.9 (2)	N1—C1—C2—N2 ψ_1	156.0 (2)
C3—N2—C2—C1 ω	178.5 (2)	N2—C3—C4—N3 ψ_2	145.1 (2)
C2—N2—C3—C4 φ_2	−62.8 (2)		

Table 3. *Hydrogen-bonding geometry* (Å, °) *for* NAGAA

D—H···A	H···A	D···A	D—H···A
N1—H1···O1^{i}	1.92 (3)	2.872 (2)	167 (2)
N2—H2···O3^{ii}	1.89 (3)	2.802 (2)	169 (3)
N3—H3···O2^{iii}	2.04 (3)	2.830 (2)	145 (2)
N3—H4···O2^{iv}	2.09 (2)	3.006 (2)	170 (3)

Symmetry codes: (i) $1-x, y-\frac{1}{2}, -z$; (ii) $-x, y-\frac{1}{2}, -z$; (iii) $x, 1+y, z$; (iv) $1-x, \frac{1}{2}+y, 1-z$.

NAA$_2$A

Crystal data

$C_8H_{15}N_3O_3$
$M_r = 201.23$
Orthorhombic
$P2_12_12_1$
$a = 5.5005$ (4) Å
$b = 9.429$ (1) Å
$c = 20.712$ (2) Å
$V = 1074.2$ (3) Å^3
$Z = 4$
$D_x = 1.244$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 24 reflections
$\theta = 21$–26°
$\mu = 0.767$ mm^{-1}
$T = 293$ K
Flattened prism
0.66 × 0.20 × 0.04 mm
Colourless

Data collection

Enraf–Nonius CAD-4F diffractometer
ω–2θ scans
Absorption correction: none
1314 measured reflections
1314 independent reflections
1237 observed reflections $[I \geq 2.5\sigma(I)]$

$\theta_{\max} = 75$°
$h = 0 \rightarrow 6$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 25$
3 standard reflections
frequency: 240 min
intensity decay: 1%

Refinement

Refinement on F
$R = 0.036$
$wR = 0.040$
$S = 0.97$
1237 reflections
173 parameters
Only coordinates of H atoms refined
$w = 1/[\sigma^2(F_o) + (0.01F_o)^2 + 1]$ (Killean & Lawrence, 1969)

$(\Delta/\sigma)_{\max} = 0.10$
$\Delta\rho_{\max} = 0.15$ e Å^{-3}
$\Delta\rho_{\min} = -0.15$ e Å^{-3}
Extinction correction: Stout & Jensen (1968)
Extinction coefficient: 2.1 (1) × 10^{-6}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 4. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* NAA$_2$A

$$B_{eq} = (1/3)\Sigma_i\Sigma_j B_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	*y*	*z*	B_{eq}
O1	0.4686 (6)	0.2114 (2)	0.23695 (7)	6.33 (6)
O2	0.3700 (4)	0.5564 (1)	0.40379 (7)	3.92 (4)
O3	0.4403 (4)	0.5603 (2)	0.06558 (7)	4.07 (4)
N1	0.4670 (4)	0.3581 (2)	0.12206 (8)	2.92 (4)
N2	0.4746 (4)	0.4166 (2)	0.29028 (8)	3.06 (4)
N3	0.3755 (5)	0.3494 (2)	0.45757 (8)	3.67 (4)
C1	0.3495 (5)	0.4183 (2)	0.17867 (9)	3.31 (5)
C2	0.4387 (5)	0.3402 (2)	0.23807 (9)	3.23 (5)
C3	0.5508 (5)	0.3555 (2)	0.35116 (9)	3.01 (4)
C4	0.4222 (4)	0.4292 (2)	0.40623 (9)	2.83 (4)
C5	0.5083 (5)	0.4343 (2)	0.06933 (9)	3.01 (4)
C6	0.6416 (6)	0.3672 (3)	0.0148 (1)	4.36 (6)
C7	0.8238 (6)	0.3645 (4)	0.3601 (1)	5.60 (7)
C8	0.0751 (6)	0.4110 (4)	0.1739 (1)	6.39 (8)

Table 5. *Geometric parameters* (Å, °) *for* NAA$_2$A

O1—C2	1.226 (3)	N3—C4	1.327 (3)
O2—C4	1.235 (3)	C1—C2	1.515 (3)
O3—C5	1.248 (3)	C1—C8	1.514 (4)
N1—C1	1.454 (3)	C3—C4	1.511 (3)
N1—C5	1.327 (3)	C3—C7	1.516 (4)
N2—C2	1.315 (3)	C5—C6	1.488 (3)
N2—C3	1.448 (3)		
C1—N1—C5	121.9 (2)	N2—C3—C7	111.8 (2)
C2—N2—C3	122.8 (2)	C4—C3—C7	110.2 (2)
N1—C1—C2	108.7 (2)	O2—C4—N3	122.6 (2)
N1—C1—C8	111.9 (2)	O2—C4—C3	121.6 (2)
C2—C1—C8	110.7 (2)	N3—C4—C3	115.8 (2)
O1—C2—N2	122.6 (2)	O3—C5—N1	121.0 (2)
O1—C2—C1	120.6 (2)	O3—C5—C6	120.3 (2)
N2—C2—C1	116.8 (2)	N1—C5—C6	118.6 (2)
N2—C3—C4	109.8 (2)		
C5—N1—C1—C2 φ_1	−151.4 (2)	C2—N2—C3—C7	95.8 (3)
C1—N1—C5—C6 ω'	176.7 (2)	N1—C1—C2—N2 ψ_1	142.0 (2)
C3—N2—C2—C1 ω	177.6 (2)	N2—C3—C4—N3 ψ_2	148.1 (2)
C2—N2—C3—C4 φ_2	−141.5 (2)	C5—N1—C1—C8	85.9 (3)

Table 6. *Hydrogen-bonding geometry* (Å, °) *for* NAA$_2$A

D—H···*A*	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O2^{i}	2.19 (3)	3.030 (2)	160 (2)
N2—H2···O1^{ii}	2.00 (3)	2.853 (2)	161 (3)
N3—H3···O3^{iii}	2.02 (3)	2.957 (3)	174 (3)
N3—H4···O3^{i}	2.07 (3)	2.948 (2)	165 (2)

Symmetry codes: (i) $1 - x, y - \frac{1}{2}, \frac{1}{2} - z$; (ii) $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$; (iii) $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$.

The structures were solved by means of the *MULTAN*11/82 package (Main *et al.*, 1982). All calculations were performed using *SDP* software (Enraf–Nonius, 1985) on a MicroVAX 3100 computer.

The authors wish to thank Professor T. H. Lilley for the NAGAA and NAA$_2$A samples.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: AS1117). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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