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The Crystal and Molecular Structure of *N*-Acetyl-DL-phenylalanine-*N*-methylamide

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Crystals of the title compound grown from an aqueous solution are monoclinic, space group $P2_1/n$, with $a=19{\cdot}45$ (4), $b=4{\cdot}98$ (1), $c=12{\cdot}29$ (2) Å, $\beta=91{\cdot}92$ (7)° and $Z=4$. The structure was solved by the symbolic addition method and refined by the method of least-squares to an R value of 0·06 for 645 reflexions. The molecule adopts an extended conformation and the φ_{CN} and ψ_{CC} angles are close to those given for the pleated-sheet structure. The C^γ atom is situated at the *trans* position to the carbonyl carbon atom and the benzene ring is nearly perpendicular to the $C^\alpha C^\beta C^\gamma$ plane. Successive molecules translated in the **b** direction are bound together through hydrogen bonds to form a sheet which closely resembles the parallel-chain pleated-sheet structure.

Introduction

N-Acetyl-amino acid-*N*-methylamides, $CH_3CONHCHRCONHCH_3$ (R = amino acid side chain), which contain only one amino acid side chain along with two peptide groups, are the simple model compounds of the polypeptides. Following the structural study by infrared spectroscopy carried out by Mizushima *et al.* (1953, 1954), Tsuboi, Shimanouchi & Mizushima (1959) and Koyama, Shimanouchi, Sato & Tatsuno (1971), an X-ray study of the crystal structures has been undertaken. This paper describes the result of the structure determination of the phenylalanine derivative.

Experimental

Crystals grown from an aqueous solution were thick plates with well developed {100} faces. The density was measured by the flotation method using a mixed solution of dichloroethane and benzene. The lattice constants and intensity data were derived from measurements made on a Rigaku four-circle X-ray diffractometer using Ni-filtered Cu $K\alpha$ radiation.

Crystal data

N-Acetyl-DL-phenylalanine-*N*-methylamide
(DL-APh*N*MA)
$C_{12}H_{16}N_2O_2$, M.W. 220·2
Monoclinic, $P2_1/n$
$a=19{\cdot}45\pm0{\cdot}04$, $b=4{\cdot}98\pm0{\cdot}01$, $c=12{\cdot}29\pm0{\cdot}02$ Å
$\beta=91{\cdot}92\pm0{\cdot}07°$
$U=1190{\cdot}3$ Å^3
$D_m=1{\cdot}22_9$, $D_x=1{\cdot}22_5$ g cm^{-3}, $Z=4$.

Intensities were measured by the 2θ–ω scanning method with a scan speed of 4° min^{-1} in 2θ. Background was measured by stationary counting at both sides of the diffraction peak for 10 s. 645 independent reflexions within $2\theta=134°$ were measured which had net intensities greater than three times their standard deviation. The number of reflexions corresponds to about 30% of the theoretically possible number in the same range of angles. Since the size of the crystal was only about $0{\cdot}05\times0{\cdot}7\times0{\cdot}2$ mm, no absorption correction was applied. After correction for Lorentz and polarization factors, the normalized structure factors, E were calculated using the scale and temperature factors ($B=4{\cdot}2$ Å^2) determined by a Wilson plot.

Determination and refinement of the structure

The structure was solved by the symbolic addition method (Karle & Karle, 1966). The specification of the origin and the assignment of unknown symbols were made as shown in Table 1. From the $\sum_2$ relationship, it became apparent that $a=c$ and $d=0$. Four sets of possible phase assignment for a and b were examined and the phases were extended by the tangent formula. One of the sets, $a=0$ and $b=0$, gave the lowest R value of 0·18 for 153 reflexions having E's greater than 1·4. The resulting E map revealed the locations of all the 16 atoms comprising the molecule.

Table 1. *Starting set*

h	k	l	$\lvert E\rvert$	Phase angle
2	5	$\bar{4}$	3·293	0
3	3	$\overline{10}$	2·945	π
1	1	$\bar{1}$	2·387	π
5	4	$\bar{3}$	2·985	a
2	5	0	2·779	b
6	4	$\bar{9}$	2·509	c
6	1	9	2·424	d

Refinement of the atomic parameters was carried out first by the block-matrix least-squares method. The positions of all 16 hydrogen atoms were determined on the difference electron-density map calculated at the stage when R was 0·12. Further refinement by the block-matrix least-squares method gave an R value of 0·06. The final stage of the refinement was carried out by two cycles of full-matrix least-squares calculation using the program *ORFLS* (Busing, Martin & Levy, 1962). In this calculation, the temperature factors were chosen to be isotropic for hydrogen atoms and anisotropic for other atoms. The weighting scheme was:

$$\sqrt{w}=1\cdot0\,,\quad \text{when}\quad F_o\le 15;$$

$$\sqrt{w}=\exp\left(-0\cdot0014\,F_o^2+0\cdot11\,F_o-1\cdot34\right),\quad \text{when}\quad 15<F_o<62;$$

$$\sqrt{w}=1\cdot0\,,\quad \text{when}\quad F_o\ge 62\,.$$

The R value stood at 0·06. The final atomic parameters and their estimated standard deviations are listed in Table 2.*

Discussion of the structure

Molecular structure

A stereoscopic view of the molecule drawn by the *ORTEP* program (Johnson, 1965) is shown in Fig. 1.

Table 3. *Bond lengths and their estimated standard deviations* (Å)

	DL-APh*N*MA[1]	GlyPhe-Gly[2]	DL-AL*N*MA[3]	Peptide model[4]
C(2)—C(1)	1·488 (15) 1·513* (19)	1·53	1·56	1·53
C(2)—N(1)	1·348 (10)	1·39	1·30	1·32
C(2)—O(1)	1·225 (9) 1·244* (15)	1·21	1·25	1·24
C(3)—C(4)	1·509 (12)	1·55	1·54	1·53
C(3)--C(6)	1·554 (14)	1·52	1·52	
C(3)—N(1)	1·436 (11)	1·46	1·44	1·47
C(4)—N(2)	1·310 (11)	1·34	1·32	1·32
C(4)—O(2)	1·263 (10) 1·285* (16)	1·23	1·24	1·24
N(2)—C(5)	1·456 (15) 1·472* (13)	1·46	1·44	1·47
C(6)—C(7)	1·472 (13)	1·50		
C(7)—C(8)	1·376 (15)	1·35		
C(7)—C(12)	1·378 (13)	1·37		
C(8)—C(9)	1·368 (18)	1·42		
C(9)—C(10)	1·388 (16)	1·36		
C(10)–C(11)	1·380 (17)	1·35		
C(11)–C(12)	1·376 (16)	1·44		

* Corrected for 'riding motion' by the method of Busing & Levy (1964). References: (1) Present study. (2) Marsh & Glusker (1961). (3) Ichikawa & Iitaka (1969). (4) Pauling & Corey (1953).

Table 2. *Atomic parameters and their standard deviations*

Temperature factors are of the form $T=\exp\left[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\right]$.
Positional parameters of the hydrogen atoms are $\times 10^3$. Positional and thermal parameters of the other atoms are $\times 10^4$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	5456 (7)	2381 (23)	6313 (10)	48 (5)	327 (46)	90 (9)	29 (12)	24 (5)	13 (16)
C(2)	5894 (4)	3397 (15)	5431 (6)	26 (3)	197 (33)	59 (6)	−10 (9)	2 (4)	6 (12)
C(3)	6597 (5)	2179 (17)	3891 (7)	37 (4)	267 (40)	72 (8)	−31 (10)	16 (4)	17 (13)
C(4)	6193 (5)	1695 (16)	2838 (7)	36 (4)	268 (39)	69 (8)	7 (10)	20 (4)	−33 (14)
C(5)	5535 (8)	3443 (29)	1279 (9)	39 (4)	609 (68)	76 (10)	9 (15)	−20 (7)	9 (20)
C(6)	7292 (5)	638 (22)	3946 (8)	33 (3)	294 (43)	94 (9)	20 (12)	16 (5)	−12 (16)
C(7)	7702 (4)	1123 (16)	4956 (7)	27 (3)	298 (37)	63 (8)	9 (9)	4 (5)	−19 (14)
C(8)	7627 (7)	−354 (22)	5891 (11)	37 (4)	482 (52)	95 (11)	2 (13)	2 (6)	11 (20)
C(9)	8018 (6)	91 (20)	6820 (11)	40 (4)	421 (57)	98 (11)	9 (12)	17 (6)	46 (19)
C(10)	8495 (6)	2164 (23)	6833 (11)	33 (4)	508 (60)	111 (11)	34 (15)	7 (6)	−7 (22)
C(11)	8601 (6)	3652 (20)	5907 (10)	34 (4)	370 (48)	115 (11)	−17 (13)	3 (6)	15 (19)
C(12)	8194 (5)	3115 (20)	4995 (9)	26 (3)	456 (52)	93 (9)	−26 (12)	10 (5)	27 (19)
N(1)	6179 (3)	1526 (12)	4796 (5)	33 (2)	230 (30)	58 (5)	−10 (7)	19 (3)	6 (10)
N(2)	5974 (4)	3740 (13)	2256 (7)	52 (3)	183 (30)	92 (7)	30 (8)	13 (4)	19 (11)
O(1)	6000 (4)	5801 (11)	5312 (5)	52 (3)	236 (29)	100 (5)	−2 (8)	24 (3)	−20 (10)
O(2)	6093 (4)	−703 (11)	2539 (5)	63 (3)	308 (28)	90 (5)	−25 (8)	−0 (3)	23 (10)

Table 2 (*cont.*)

	x	y	z	B
H(C1)	500 (5)	349 (20)	631 (7)	6·67 (2·47)
H′(C1)	566 (4)	297 (21)	715 (8)	6·74 (2·56)
H″(C1)	543 (3)	79 (17)	639 (4)	3·00 (1·26)
H(N1)	609 (3)	−49 (16)	505 (4)	3·05 (1·09)
H(C3)	672 (3)	364 (15)	392 (4)	3·00 (1·32)
H(N2)	599 (3)	559 (40)	254 (5)	3·00 (1·30)
H(C5)	510 (9)	301 (37)	125 (15)	13·93 (6·61)
H′(C5)	570 (9)	429 (62)	62 (14)	14·67 (6·57)
H″(C5)	555 (8)	181 (21)	103 (23)	19·05 (4·92)
H(C6)	713 (5)	−89 (22)	395 (7)	4·33 (2·71)
H′(C6)	754 (6)	84 (30)	321 (9)	6·98 (3·49)
H(C8)	720 (7)	−126 (20)	591 (9)	9·19 (4·53)
H(C9)	786 (5)	−79 (23)	749 (8)	4·48 (2·35)
H(C10)	883 (5)	223 (19)	743 (8)	8·32 (3·07)
H(C11)	893 (4)	510 (21)	585 (7)	7·93 (2·41)
H(C12)	831 (5)	414 (20)	442 (7)	5·48 (2·47)

Bond lengths and angles are listed in Tables 3 and 4 along with those found in other related compounds. The values are in general agreement with the reported values, but some of them, such as the bond lengths C(1)–C(2) and C(3)–N(1), are shorter than the normal values by about 0·04 Å. This shortening, especially that of C(1)–C(2), seems to be caused by the librational thermal motions of the atoms. A correction for the effect was made with the *ORFFE* program (Busing, Martin & Levy, 1964) based on the variance–covariance matrix obtained by the *ORFLS* program. In Table 3 the bond lengths corrected by assuming simply that the second atom librates around the first atom are also shown.

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* The table of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30294 (5 pp.). Copies can be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Bond angles and their estimated standard deviations* (°)

	DL-APh*N*MA[1]	GlyPhe-Gly[2]	DL-AL*N*MA[3]	Peptide model[4]
N(1)—C(2)—C(1)	116·3 (7)	110	115·8	114
N(1)—C(2)—O(1)	122·2 (7)	126	122·7	125
C(1)—C(2)—O(1)	121·5 (8)	123	121·4	121
C(4)—C(3)—C(6)	112·6 (8)	109	106·8	
C(4)—C(3)—N(1)	109·6 (7)	107	112·0	111
C(6)—C(3)—N(1)	111·6 (7)	107	112·0	
N(2)—C(4)—C(3)	119·7 (8)	114	116·7	114
N(2)—C(4)—O(2)	122·2 (8)	124	122·8	125
C(3)—C(4)—O(2)	118·1 (8)	122	120·5	121
C(7)—C(6)—C(3)	113·7 (8)	115	114·5	
C(8)—C(7)—C(6)	123·1 (9)	122		
C(8)—C(7)—C(12)	116·7 (9)	119		
C(6)—C(7)—C(12)	120·2 (8)	119		
C(9)—C(8)—C(7)	122·6 (1·1)	119		
C(10)-C(9)—C(8)	118·9 (1·1)	121		
C(11)-C(10)-C(9)	120·6 (1·1)	120		
C(12)-C(11)-C(10)	118·0 (1·1)	119		
C(7)—C(12)-C(11)	123·2 (1·0)	122		
C(2)—N(1)—C(3)	123·1 (7)	118		123
C(4)—N(2)—C(5)	122·9 (9)	120		123

References: (1) Present study. (2) Marsh & Glusker (1961). (3) Ichikawa & Iitaka (1969). (4) Pauling & Corey (1953).

As is clearly seen in Fig. 1, the conformation of the molecule is essentially the same as that of the β-structure in proteins. The torsion angles around the N-C$^\alpha$ and C$^\alpha$-C′ bonds, φ and ψ, which define the conformation of the polypeptide chains, are plotted on the φ-ψ chart (Ramachandran, Ramakrishnan & Sasisekharan, 1963) shown in Fig. 2. The values are also listed in Table 5 along with other torsion angles and are compared with the corresponding angles in other related compounds. As seen in Fig. 2, the φ and ψ values are close to those given for the parallel-chain pleated-sheet* structure. The conformation of the molecule can also be described by defining the relations between the following four planar groups: two peptide groups, the side-chain aliphatic group and the side-chain benzene ring. The deviations of atoms from the least-

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* Abbreviated to PCP.

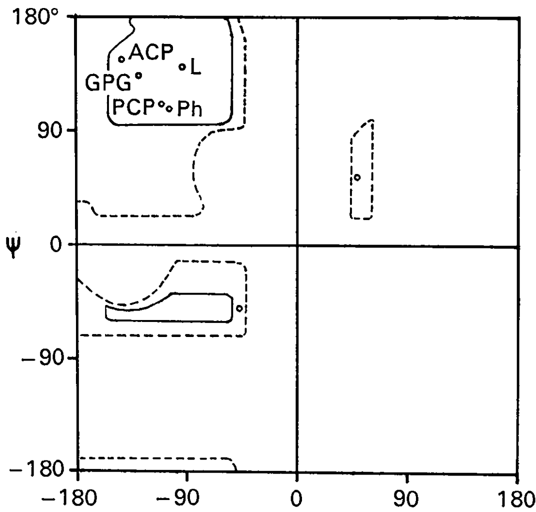
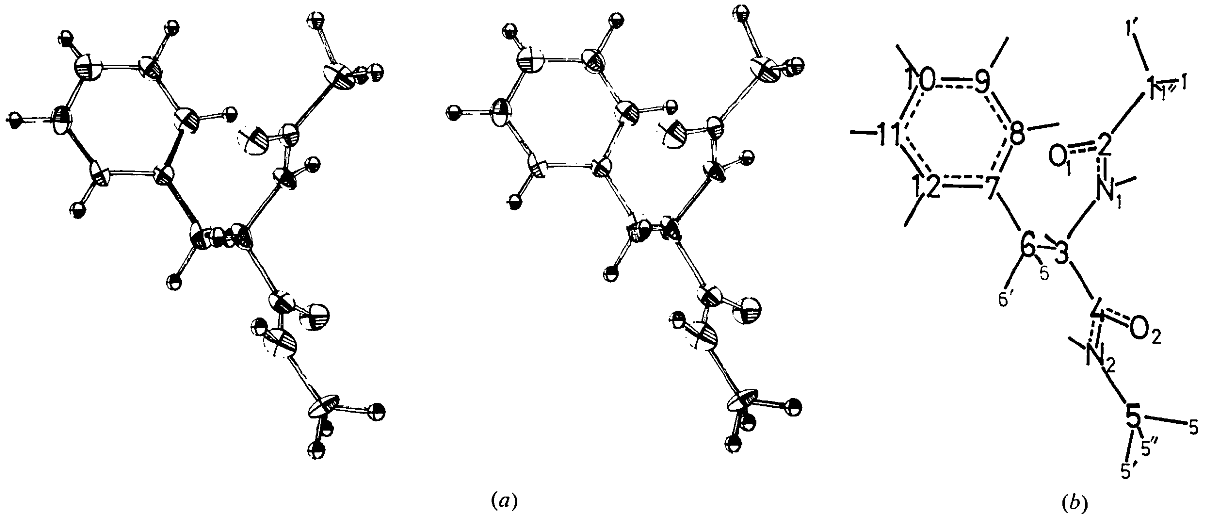


Fig. 2. φ-ψ chart showing the allowed conformations for polypeptide chains. Solid lines enclose the fully allowed regions and broken lines the outer-limit regions (after Ramachandran *et al.*, 1963). The angles for the following structures are plotted. ACP: antiparallel-chain pleated sheet (φ, ψ values are from Schellman & Schellman, 1964). PCP: parallel-chain pleated sheet (Schellman & Schellman, 1964). Ph: APh*N*MA (present work). GPG: GlyPheGly (Marsh & Glusker, 1961). L: AL*N*MA (Ichikawa & Iitaka, 1969).



(*a*) (*b*)

Fig. 1. (*a*) A stereoscopic view of the molecule. The non-hydrogen atoms are represented by 20% probability ellipsoids and the hydrogen atoms are arbitrarily scaled spheres. (*b*) Numbering of the molecule.

squares planes and the dihedral angles between the planes are given in Table 6. The dihedral angle at the α-carbon atom between the two peptide planes, 69·2°, is close to those found in *N*-acetyl-DL-leucine-*N*-methylamide† (71·6°, Ichikawa & Iitaka, 1969) and glycylphenylalanylglycine‡ (53·8°, Marsh & Glusker, 1961) and comparable with that proposed for the PCP structure (62·2°, Pauling & Corey, 1953).

It should be noted that the χ angle shown in Table 5 differs greatly from that found for the phenylalanyl residue in GlyPheGly, indicating that in the present structure C^{γ} is nearly at the *trans* position to the carbonyl carbon atom while in GlyPheGly it is *trans* to the imino nitrogen atom. Such a rotation of the C^{γ} atom about the C^{α}–C^{β} bond has often been found in the derivatives of phenylalanine, as already mentioned by Lakshminarayanan, Sasisekharan & Ramachandran (1967). The disposition of the benzene ring with respect to the $C^{\alpha}C^{\beta}C^{\gamma}$ plane is, as shown in Table 6, nearly perpendicular, which is also commonly observed in phenylalanyl residues.

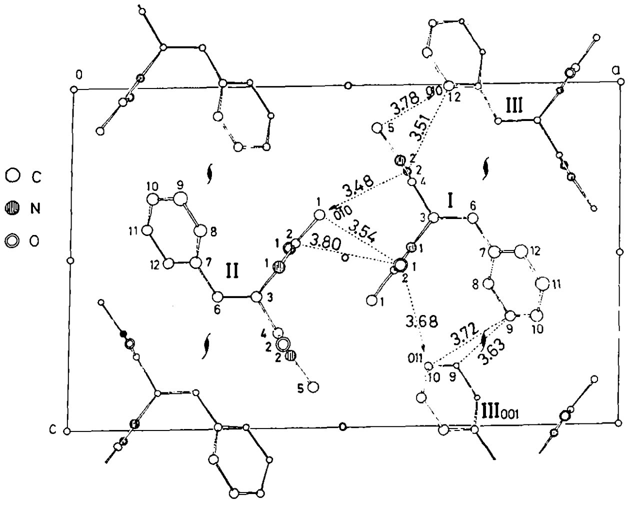


Fig. 3. Projection of the crystal structure along the *b* axis. Short intermolecular distances less than 3·8 Å are shown by dotted lines. The molecules are, I at x,y,z; II at $1-x, 1-y, 1-z$; III at $1\frac{1}{2}-x, -\frac{1}{2}+y, \frac{1}{2}-z$.

Table 6. *Least-squares planes through various groups of atoms*

The equations of the planes are of the form $AX+BY+CZ=D$, where X, Y and Z are coordinates (in Å) referred to the orthogonal axes, $X \parallel a^*, Y \parallel b$ and $Z \parallel c$ respectively, and D is the origin-to-plane distance.

Plane	Plane-forming atoms	Deviation (Å)	Coefficients	
Peptide group I (Plane 1)	C(1)	−0·008	*A*	0·806
	C(2)	−0·005	*B*	−0·054
	C(3)	−0·014	*C*	0·590
	N(1)	0·021	*D*	12·855
	O(1)	0·006		
	H(N1)*	0·113		
Peptide group II (Plane 2)	C(3)	−0·024	*A*	0·839
	C(4)	0·002	*B*	0·021
	C(5)	−0·035	*C*	−0·544
	N(2)	0·047	*D*	8·436
	O(2)	0·010		
	H(N2)*	−0·091		
Aliphatic group (Plane 3)	C(3)		*A*	0·448
	C(6)		*B*	0·774
	C(7)		*C*	−0·448
			D	4·627
Benzene ring (Plane 4)	C(6)	0·000	*A*	−0·686
	C(7)	0·005	*B*	0·651
	C(8)	0·001	*C*	0·325
	C(9)	−0·013	*D*	−8·095
	C(10)	0·019		
	C(11)	−0·012		
	C(12)	0·000		
	H(C8)*	0·299		
	H(C9)*	0·186		
	H(C10)*	−0·175		
	H(C11)*	−0·017		
	H(C12)*	−0·050		

Dihedral angle between:

Plane 1 and Plane 2	69·2°
Plane 2 and Plane 3	86·9
Plane 3 and Plane 1	49·8
Plane 3 and Plane 4	87·1

* Not included in the least-squares calculation.

Crystal structure

The projection of the crystal structure along the *b* axis is shown in Fig. 3. Of particular interest is the presence of a sheet structure which closely resembles that found in the PCP structure. As shown in Fig. 4, successive molecules translated by **b** are hydrogen-bonded through their amide nitrogen and oxygen atoms

Table 5. *Torsion angles* (°)

		DL-APh*N*MA[1]	GlyPheGly[2] Phe residue	DL-AL*N*MA[3]
φ	τ[C(2)–N(1)–C(3)–C(4)]	−105·5	−126·3	−93·8
ψ	τ[N(1)–C(3)–C(4)–N(2)]	107·9	131·9	140·4
ω_1	τ[C(1)–C(2)–N(1)–C(3)]	178·1	−175·4	177·2
ω_2	τ[C(3)–C(4)–N(2)–C(5)]	−175·0	179·7	174·1
χ^1	τ[N(1)–C(3)–C(6)–C(7)]	−57 (0·4)	−174 (0·7)	−56·6
$\chi^{2,1}$	τ[C(3)–C(6)–C(7)–C(8)]	87·4	102·5	−174·3
$\chi^{2,2}$	τ[C(3)–C(6)–C(7)–C(12)]	−93·2	−81·5	−48·9

References: (1) Present study. (2) Marsh & Glusker (1961). (3) Ichikawa & Iitaka (1969).

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† Abbreviated to AL*N*MA.
‡ Abbreviated to GlyPheGly.

to form a sheet extending along the *b* axis. This sheet, although in the present structure each constituent peptide chain involves only one amino acid residue with two amide groups, represents just the fundamental unit of the PCP structure. A similar sheet structure has already been found in GlyPheGly.

The distance between C(1) and C(5) which corresponds to the repeat distance of the peptide backbone (the chain repeat) is 6·20 Å. This value is comparable with 6·74 Å in GlyPheGly and 6·50 Å in the proposed structure of PCP. The *b*-axis length of the present crystal, 4·98 Å, may represent approximately the distance between the adjacent chains within the sheet (the backbone spacing). This distance is 4·90 Å (*c* axis length) in GlyPheGly and 4·85 Å in the proposed structure of PCP.

The packing of the molecules is clearly seen in Fig. 3. The terminal methyl groups interact with those of the neighbouring molecules through van der Waals forces. The three methyl hydrogen atoms at C(5) have the largest temperature factors of about 16 Å^2 and it seems that they undergo a hindered rotation about the N(2)–C(5) bond. The hydrogen atoms at C(1), on the other hand, are fixed at the position where one of them is *trans* to O(1). There are also some close contacts between the benzene rings, the shortest being 3·60 Å found between C(9) and its equivalents related by a screw diad axis.

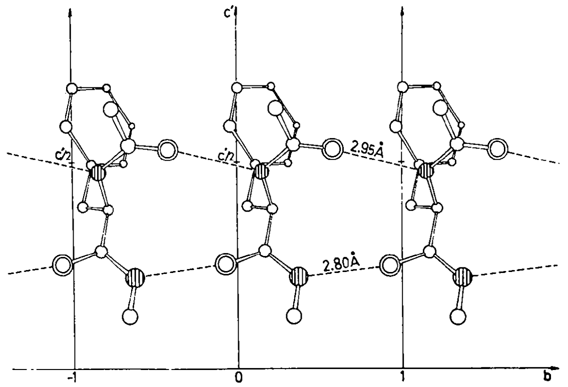

Fig. 4. Projection of the crystal structure along the *a* axis showing that the hydrogen-bonded molecules form a sheet similar to the parallel-chain pleated sheet.

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References

Busing, W. R., Martin, K. O. & Levy, H. A. (1962). *ORFLS*. ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge. Tennessee.

Busing, W. R., Martin, K. O. & Levy, H. A. (1964). *ORFFE*. ORNL-TM-306, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Ichikawa, T. & Iitaka, Y. (1969). *Acta Cryst.* **B25**, 1824–1833.

Johnson, C. K. (1965). *ORTEP*. ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Karle, J. & Karle, I. L. (1966). *Acta Cryst.* **21**, 849–859.

Koyama, Y., Shimanouchi, T., Sato, M. & Tatsuno, T. (1971). *Biopolymers*, **10**, 1059–1074.

Lakshminarayanan, A. V., Sasisekharan, V. & Ramachandran, G. N. (1967). *Conformation of Biopolymers*, Vol. 1, p. 61. London, New York: Academic Press.

Marsh, R. E. & Glusker, J. P. (1961). *Acta Cryst.* **14**, 1110–1116.

Mizushima, S., Shimanouchi, T., Tsuboi, M., Kuratani, K., Sugita, T., Mataga, N. & Souda, R. (1953). *J. Amer. Chem. Soc.* **75**, 1863–1865.

Mizushima, S., Tsuboi, M., Shimanouchi, T., Sugita, T. & Yoshimoto, T. (1954). *J. Amer. Chem. Soc.* **76**, 2479–2481.

Pauling, L. & Corey, R. B. (1953). *Proc. Natl. Acad. Sci. U.S.* **39**, 253–256.

Ramachandran, G. N., Ramakrishnan, C. & Sasisekharan, V. (1963). *J. Mol. Biol.* **7**, 95–99.

Schellman, J. A. & Schellman, C. (1964). *The Proteins, Composition, Structure, and Function*, Vol. II, edited by H. Neurath, p. 19. London & New York: Academic Press.

Tsuboi, M., Shimanouchi, T. & Mizushima, S. (1959). *J. Amer. Chem. Soc.* **81**, 1406–1411.