

## The Crystal Structure of L-Alanyl-L-serine

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The dipeptide L-alanyl-L-serine crystallizes in the orthorhombic space group  $P2_12_12_1$  with  $a = 18.053$  (6),  $b = 9.389$  (4),  $c = 4.858$  (3) Å. The structure has been solved by direct methods using diffractometer data, and refined to  $R = 0.055$  for 1308 unique reflexions. The molecule is a zwitterion. The presence of a disordered water molecule cannot be ruled out. The peptide backbone is in an extended conformation.

### Introduction

Detailed structural studies of small peptides are important since a knowledge of their conformation and hydrogen-bonding geometry provides insight into the structures of proteins and the mechanism of protein–nucleic acid interaction. The crystal structure of L-alanyl-L-serine has been determined as part of a series of peptide structures being studied in this laboratory.

### Experimental

Crystals in the form of elongated prisms and flat plates were obtained from water/acetone mixtures. Crystal data are summarized in Table 1. Intensities were measured with an automated Stoe two-circle diffractometer, using monochromated Mo  $K\alpha$  radiation and two prismatic crystals mounted respectively about  $c$  ( $0.6 \times 0.1 \times 0.1$  mm, layers 0–4, 2424 reflexions) and  $a$  ( $0.5 \times 0.1 \times 0.1$  mm, layers 0–8, 883 reflexions).  $L_p$  corrections were applied but no correction for absorption was made; inter-layer scale factors were derived by least-squares analysis of equivalent reflexions from different layers. Averaging equivalent reflexions gave 1312 unique reflexions with  $F > 4\sigma(F)$ . Cell dimensions were obtained by least-squares analysis of 496  $hk0$  and 85  $0kl$  diffractometer  $\omega$  angle measurements.

### Structure determination and refinement

The structure was solved using the program *XCS*D, which incorporates both a pseudotangent refinement

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Table 1. *Crystal data*

$C_6H_{12}N_2O_4$ , $M_r = 176.18$
Orthorhombic, space group $P2_12_12_1$
$a = 18.053$ (6), $b = 9.389$ (4), $c = 4.858$ (3) Å
$Z = 4$ , $U = 823.4$ Å <sup>3</sup>
$\mu$ (Mo $K\alpha$ ) = $0.9$ cm <sup>-1</sup>

(Roberts, Pettersen, Sheldrick, Isaacs & Kennard, 1973) to select the starting set and also the negative quartet test NQUEST (De Titta, Edmonds, Langs & Hauptman, 1975). The best  $E$  map showed all the non-hydrogen atoms. Figures of merit were NQUEST  $-0.298$ ,  $R_\alpha$  (Roberts *et al.*, 1973)  $0.119$ ,  $R_A$  (a point-atom  $R$  factor based on observed peaks)  $0.394$ . The  $R_A$  and  $R_\alpha$  values were substantially the lowest for the successful  $E$  map; one other  $E$  map had a marginally lower NQUEST value but was incorrect. NQUEST may not be a reliable figure of merit when (as here) weak reflexions ( $<5$  c.p.s. at peak centre) are omitted from the data collection. Isotropic least-squares refinement gave  $R = 0.13$ ; anisotropic refinement (to  $R = 0.075$ ),

Table 2. *Atom coordinates* ( $\times 10^4$ )

Overall temperature factor for H atoms:  $0.054$  (3) Å<sup>2</sup>.

	$x$	$y$	$z$
C(1)	7071 (2)	8746 (4)	3697 (11)
C(2)	6570 (1)	7622 (3)	4897 (7)
C(3)	5803 (1)	7733 (3)	3624 (6)
C(4)	4495 (1)	8194 (3)	4272 (7)
C(5)	4162 (2)	6715 (3)	4048 (9)
C(6)	4037 (2)	9173 (3)	6077 (6)
N(1)	6853 (1)	6178 (2)	4296 (5)
N(2)	5255 (1)	8102 (2)	5266 (5)
O(1)	5737 (1)	7501 (3)	1137 (4)
O(2)	4120 (2)	6035 (3)	6657 (8)
O(3)	3371 (1)	9364 (2)	5356 (6)
O(4)	4330 (1)	9735 (3)	8126 (5)
H(1)	7106	8730	1477
H(2)	6887	9783	4371
H(3)	7610	8524	4561
H(4)	6596 (19)	7732 (38)	6910 (71)
H(5)	4493 (19)	8561 (39)	2522 (72)
H(6)	4503	6078	2697
H(7)	3611	6800	3198
H(8)	6604 (19)	5440 (37)	5339 (65)
H(9)	6754 (20)	5939 (35)	2438 (72)
H(10)	7376 (20)	6048 (36)	4307 (72)
H(11)	5318 (18)	8055 (36)	6846 (72)
H(12)	4684 (19)	5631 (37)	6999 (69)

followed by a difference synthesis, showed 11 of the 12 H atoms. The final stages of refinement incorporated a rigid methyl group with C—H 1.08 Å and all  $\angle\text{H—C—H}$  109.5°; C—H and  $\angle\text{H—C—H}$  were similarly constrained for the methylene group. All other H atoms refined freely with an overall isotropic temperature factor. Four reflexions clearly in error were omitted, and convergence was achieved at  $R = 0.0550$ . The corresponding  $R' = \sum w^{1/2}\Delta/\sum w^{1/2}|F_o|$  was 0.0704, with a weighting scheme  $w = 1/[\sigma^2(F) + 0.001F^2]$ ; this gave values of  $w\Delta^2$  independent of  $\sin\theta$  or  $|F_o|$ . Final atomic coordinates are given in Table 2, with derived bond lengths, bond angles and torsion angles in Tables 3–5. Diagrams of the structure are given in Figs. 1 and 2.\*

At the end of the refinement the difference map showed a large peak (1.2 e Å<sup>-3</sup>) at 0.286, 0.774, 0.045. This peak was noticed earlier and attributed to a (possibly disordered) water molecule. The preliminary density determinations showed the crystals to be of variable density. The maximum value was 1.58 g cm<sup>-3</sup> corresponding to one water molecule per asymmetric unit. Attempts to refine the structure with an isotropic O atom and with a variable site-occupancy factor (s.o.f.) resulted in an  $R$  of 0.043 with an s.o.f. of

\* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33330 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. Bond lengths (Å)

C(1)—C(2)	1.508 (6)	C(2)—C(3)	1.520 (5)
C(2)—N(1)	1.477 (5)	C(3)—N(2)	1.316 (4)
C(3)—O(1)	1.233 (5)	C(4)—C(5)	1.517 (5)
C(4)—C(6)	1.516 (5)	C(4)—N(2)	1.458 (4)
C(5)—O(2)	1.421 (6)	C(6)—O(3)	1.265 (4)
C(6)—O(4)	1.245 (5)	C(2)—H(4)	0.984 (36)
C(4)—H(5)	0.917 (36)	N(1)—H(8)	0.969 (35)
N(1)—H(9)	0.947 (36)	N(1)—H(10)	0.951 (38)
N(2)—H(11)	0.777 (36)	O(2)—H(12)	1.100 (35)

Table 4. Bond angles (°)

C(1)—C(2)—C(3)	110.0 (4)	C(1)—C(2)—N(1)	111.0 (3)
C(3)—C(2)—N(1)	107.3 (3)	C(2)—C(3)—N(2)	117.1 (3)
C(2)—C(3)—O(1)	118.3 (3)	N(2)—C(3)—O(1)	124.6 (3)
C(5)—C(4)—C(6)	112.4 (3)	C(5)—C(4)—N(2)	110.0 (3)
C(6)—C(4)—N(2)	111.0 (3)	C(4)—C(5)—O(2)	111.6 (4)
C(4)—C(6)—O(3)	116.4 (4)	C(4)—C(6)—O(4)	119.2 (3)
O(3)—C(6)—O(4)	124.4 (4)	C(3)—N(2)—C(4)	121.5 (3)
C(1)—C(2)—H(4)	106.4 (21)	C(3)—C(2)—H(4)	116.1 (21)
N(1)—C(2)—H(4)	106.0 (22)	C(5)—C(4)—H(5)	106.0 (24)
C(6)—C(4)—H(5)	107.8 (24)	N(2)—C(4)—H(5)	109.4 (23)
C(2)—N(1)—H(8)	113.1 (21)	C(2)—N(1)—H(9)	109.9 (21)
H(8)—N(1)—H(9)	104.0 (29)	C(2)—N(1)—H(10)	117.4 (21)
H(8)—N(1)—H(10)	111.4 (30)	H(9)—N(1)—H(10)	99.3 (31)
C(3)—N(2)—H(11)	118.4 (25)	C(4)—N(2)—H(11)	117.8 (25)
C(5)—O(2)—H(12)	103.9 (19)		

0.27 (1). However, this model also resulted in several very short non-bonded distances [e.g. O...C(1) = 2.86 Å]. It was decided to omit the O atom from the final refinement though the possibility of a severely disordered water molecule situated in the channels parallel to  $z$  (Fig. 2) cannot be ruled out. A factor leading to the presence of such a disordered water molecule is the lack of constraint imposed by possible hydrogen bonding

Table 5. Torsion angles (°)

The sign convention is as defined by Klyne & Prelog (1960).

C(1)—C(2)—C(3)—N(2)	-114.4 (3)
C(1)—C(2)—C(3)—O(1)	64.3 (5)
N(1)—C(2)—C(3)—N(2)	124.8 (4)
N(1)—C(2)—C(3)—O(1)	-56.5 (4)
C(2)—C(3)—N(2)—C(4)	-178.0 (3)
O(1)—C(3)—N(2)—C(4)	3.4 (5)
C(6)—C(4)—C(5)—O(2)	-61.3 (3)
N(2)—C(4)—C(5)—O(2)	62.9 (4)
C(5)—C(4)—C(6)—O(3)	-58.3 (5)
C(5)—C(4)—C(6)—O(4)	122.0 (4)
N(2)—C(4)—C(6)—O(3)	178.0 (3)
N(2)—C(4)—C(6)—O(4)	-1.7 (5)
C(5)—C(4)—N(2)—C(3)	78.1 (5)
C(6)—C(4)—N(2)—C(3)	-156.9 (3)

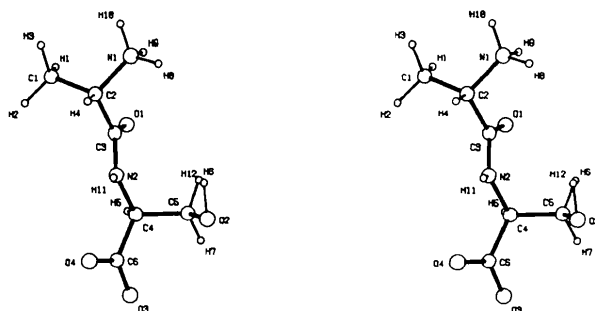


Fig. 1. Stereoview of the L-alanyl-L-serine molecule showing the atomic labelling scheme.

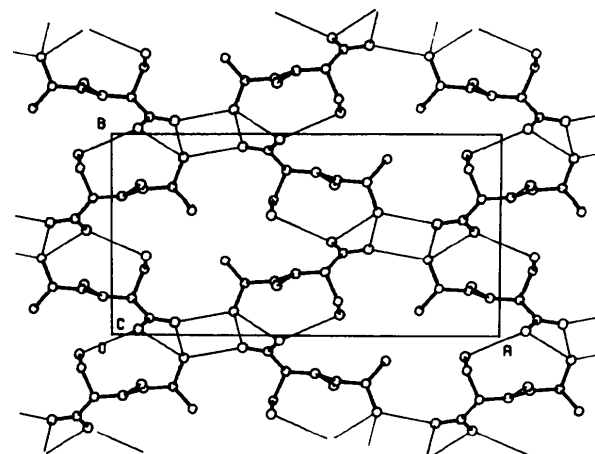


Fig. 2. Packing diagram projected down  $z$ . H atoms are omitted and hydrogen bonds shown by narrow lines.

since all available H atoms of the dipeptide molecule are already involved in hydrogen bonding. Partial occupancies for water molecules in other peptides have been reported (Leung & Marsh, 1958; Marsh & Glusker, 1961).

Attempts to refine the data from each crystal separately also resulted in the large difference peak and in view of the uncertainty about the degree of hydration we do not quote a crystallographic density for the dipeptide.

## Discussion

### Geometry of the peptide and carboxyl groups

Details of the planes containing the peptide and carboxyl groups are given in Table 6. The peptide group displays the usual *trans* geometry; the O—C—N angle of 124.6 (3)° is rather greater than 120°, as is often observed in peptides [e.g. 124.8° in glycyl-L-threonine dihydrate (Yadava & Padmanabhan, 1973), and 123.5, 122.6, 123.8, 123.5° in L-alanyl-L-alanyl-L-alanine (Fawcett, Camerman & Camerman, 1975)]. The carboxyl group is ionized, the molecule existing in the zwitterionic form.

### Torsion angles

The list of torsion angles, using the notation suggested by the IUPAC—IUB Commission on Biochemical Nomenclature (1971), is given in Table 5.

Table 6. *Least-squares planes*

The equations of the planes are of the form  $ax + by + cz + d = 0$ .

	Deviation from plane (Å)	
(i) Peptide group		
$a = 0.1561$	C(2)	-0.009
$b = 0.9679$	C(3)	-0.003
$c = -0.1968$	N(2)	0.021
$d = 8.3198$	O(1)	0.006
	C(4)	-0.015
(ii) Carboxyl group		
$a = 0.2776$	O(4)	0.001
$b = 0.7811$	O(3)	0.001
$c = -0.5593$	C(6)	-0.002
$d = 7.1006$	C(4)	0.001

The dihedral angle between planes (i) and (ii) is 24.6°.

Table 7. *Hydrogen-bonding interactions*

$D-H \cdots A$	$D \cdots A$	$H \cdots A$	Symmetry transformation of $A$
N(2)—H(11)···O(1)	3.04 Å	2.28 Å	$x, y, 1 + z$
N(1)—H(9)···O(3)	2.86	2.02	$1 - x, -\frac{1}{2} + y, \frac{1}{2} - z$
N(1)—H(8)···O(4)	2.82	1.96	$1 - x, -\frac{1}{2} + y, 1\frac{1}{2} - z$
N(1)—H(10)···O(3)	2.79	1.85	$\frac{1}{2} + x, 1\frac{1}{2} - y, 1 - z$
O(2)—H(12)···O(4)	3.06	1.97	$1 - x, -\frac{1}{2} + y, 1\frac{1}{2} - z$

The peptide assumes an extended conformation as is seen by the backbone torsion angles C(3)—N(2)—C(4)—C(6) ( $\phi_2$ ), -156.9°; N(2)—C(4)—C(6)—O(3) ( $\psi_7^2$ ), 178.0°; and C(2)—C(3)—N(2)—C(4) ( $\omega$ ), -178° (cf. fully extended chain, all 180°). The N(terminal) torsion angle N(1)—C(2)—C(3)—N(2) ( $\psi_1$ ) is, however, only 124.8°, considerably less than the fully extended value. The N(terminal)  $\phi_1$  torsion angles are -72, 44 and 157° for H(8), H(9), H(10) respectively (e.s.d. 2°).

The serine side-chain conformation is described by the angle O(2)—C(5)—C(4)—N(2) ( $\chi_{21}$ ), 62.9°, with O(2) staggered and in position I as discussed by Lakshminarayanan, Sasisekharan & Ramachandran (1967).

The carboxyl terminal torsion angle N(2)—C(4)—C(6)—O(3) ( $\psi_7^2$ , 178.0°) is rather high for a species with a  $\beta$  C atom; Sundaralingam & Putkey (1970) attribute the median value of -15° for  $\psi_7^1$  in such species to the avoidance of intramolecular contact between the  $\beta$  C and the carboxyl O. In L-alanyl-L-serine O(3)···C(5) is 2.94 Å.

### Hydrogen bonding and molecular packing

All five available H atoms take part in hydrogen bonding; a list of relevant distances is given in Table 7. As is usual in peptides, both carboxyl O atoms are acceptors to two hydrogen bonds and the peptide carbonyl to one; the -NH<sub>3</sub><sup>+</sup> group is a triple hydrogen-bond donor. Since the structure is saturated with respect to possible hydrogen-bond formation, any water of crystallization (see above) would be held by van der Waals forces only.

A packing diagram projected down  $z$  is given (Fig. 2). Hydrogen bonding of the form C=O···H—N occurs between the peptide-bond regions of adjacent molecules related by a  $c$  translation; other interactions are clearly shown in Fig. 2.

A relatively short contact (3.13 Å) exists between O(3) and N(1) (at  $1 - x, \frac{1}{2} + y, 1\frac{1}{2} - z$ ); this cannot be a hydrogen bond since N(1) is involved in the maximum of three (much shorter) hydrogen bonds (see Table 7). There are no other contacts between non-hydrogen atoms less than 3.2 Å.

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## Molekül- und Kristallstruktur von 5-(3-Dimethylaminopropyl)-10,11-dihydro-5H-dibenz[*b,f*]azepinhydrobromid (Imipraminhydrobromid). Vergleich mit der Struktur von Imipraminhydrochlorid

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Imipramine hydrobromide,  $C_{19}H_{24}N_2 \cdot HBr$ , crystallizes in the space group  $P2_1/c$  with two molecules in the asymmetric unit. The cell constants are quite similar to those of the hydrochloride [Post, Kennard & Horn, *Acta Cryst.* (1975), **B31**, 1008–1013]. The same holds for the other structural parameters, *i.e.* the two structures are isomorphous. The two molecules in the asymmetric unit have different conformations; both are of low energy.

### Einführung

Das Hydrochlorid des Imipramins findet als Psychopharmakon Verwendung und ist unter dem Namen Tofranil im Handel. Es hat eine antidepressive Wirkung. Zum ersten Mal wurde die Verbindung 1954 beschrieben (Schindler & Häfliger, 1954). Jetzt liegt davon eine Röntgeneinkristallstrukturanalyse vor (Post, Kennard & Horn, 1975). Dies ist der Anlass, unsere schon 1971 durchgeführte Röntgeneinkristallstrukturanalyse am Imipraminhydrobromid zu veröffentlichen.

Formeleinheiten enthält, müssen sich zwei Moleküle  $C_{19}H_{23}BrN_2$  in der asymmetrischen Einheit befinden.

Die Röntgenintensitäten wurden auf einem rechnergesteuerten Siemens-Einkristalldiffraktometer vermessen [Fünfwertmessung (Hoppe, 1965); Cu- $K\alpha$ -Strahlung;  $\theta_{\max} = 70^\circ$ ; 4870 Messungen: 4420 mit einem relativen prozentualen Fehler  $r < 15$ , 3204 mit  $r < 5$  und 2434 mit  $r < 3$ ].

Zuerst wurde versucht, das Strukturproblem mit der Schweratommethode zu lösen. Die beiden kristallo-

### Experimentelle Daten und Lösung des Strukturproblems

Gut ausgebildete Kristalle des Hydrobromids wurden uns von der Firma Roussel Uclaf zur Verfügung gestellt. Ein Einkristall ( $0,2 \times 0,2 \times 0,3$  mm), eingeschmolzen in ein Markröhrchen, diente zur Ermittlung der Zellkonstanten (Tabelle 1) auf einer Präzessionskamera (Cu- $K\alpha$ -Strahlung). Die systematischen Auslöschungen ( $0k0$  mit  $k = 2n + 1$ ;  $h0l$  mit  $l = 2n + 1$ ) legten eindeutig die monokline Raumgruppe  $P2_1/c$  fest. Da die Elementarzelle acht

Tabelle 1. Kristallographische Daten vom Imipraminhydrobromid (I) bzw. -chlorid (II)

	(I)	(II)
Summenformel	$C_{19}H_{23}BrN_2$	$C_{19}H_{23}ClN_2$
Molekulargewicht	361,3	316,9
Kristallsystem	monoklin	monoklin
Raumgruppe	$P2_1/c$	$P2_1/c$
<i>a</i> (Å)	11,51 (1)	11,303 (3)
<i>b</i> (Å)	29,26 (3)	29,227 (8)
<i>c</i> (Å)	14,62 (2)	14,282 (3)
$\beta$ (°)	131,0 (1)	130,91 (1)
Zellvolumen (Å <sup>3</sup> )	3716	3565,7
Zahl der Moleküle in der Elementarzelle	8	8
$D_x$ (g cm <sup>-3</sup> )	1,29	1,18