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## Studies in Molecular Structure, Symmetry and Conformation. VIII. Crystal and Molecular Structure of L-Allothreonine\*

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L-Allothreonine,  $C_4H_9NO_3$ , is orthorhombic, space group  $P2_12_12_1$ , with  $a=13.69$  (1),  $b=7.78$  (1),  $c=5.17$  (1) Å,  $Z=4$ . The structure, which is closely isomorphous with that of L-threonine, was solved from this data and has been refined to an  $R$  of 10.7% for 597 visual reflexions. The bond lengths and angles are normal.

### Introduction

A programme of studies on the structure, symmetry and conformation of organic and biomolecules is in progress in this laboratory. The major aim is to establish the molecular structure of these compounds in the solid state by X-ray methods and to correlate, if possible, the conformation and configuration through other techniques such as o.r.d., n.m.r., etc. Several simple amino acids have been X-ray analysed and their conformational and structural features studied. Recently the isomeric forms of amino acids containing more than one asymmetric carbon atom, namely threonine and isoleucine, have been studied by X-ray analysis (Srinivasan, Varughese & Swaminathan, 1973). This paper deals with the determination of the structure of L-allothreonine.

### Experimental

Crystals were obtained by slow evaporation of an aqueous solution of DL-allothreonine (supplied by Nutritional Biochemicals Corporation, Cleveland, Ohio, U.S.A.) at room temperature. On crystallization,

a racemic mixture of D- and L-forms was obtained. The same phenomenon has been reported by Shoemaker, Donohue, Schomaker & Corey (1950) in the case of DL-threonine. The crystals were well defined needles. The cell dimensions and space group were determined by rotation, Weissenberg and precession methods.

### Crystal data

$C_4H_9NO_3$ , orthorhombic,  $a=13.69$  (1),  $b=7.78$  (1),  $c=5.17$  (1) Å; space group  $P2_12_12_1$ ;  $h00$ ,  $h=2n+1$  absent;  $0k0$ ,  $k=2n+1$  absent;  $00l$ ,  $l=2n+1$  absent.  $Z=4$ ,  $M=119.1$ ,  $D_o=1.444$ ,  $D_x=1.437$  g cm $^{-3}$ ,  $\mu=10.68$  cm $^{-1}$ ,  $\lambda$  (for Cu  $K\alpha$  radiation) = 1.5418 Å.

The density was determined by flotation in a mixture of benzene and bromoform.

Intensities were collected by the equi-inclination Weissenberg technique for  $hkL$ ,  $L=0$  to 4 and  $hkl$ ,  $K=0$  and 1. The crystal had dimensions 0.2 × 0.1 × 0.1 mm. The intensities of the various reflexions were determined visually with a set of graded intensities prepared from the same crystal. The intensities were corrected for Lorentz and polarization factors, and for elongation of spots (Phillips, 1962). No absorption correction was applied ( $\mu t < 2$ ). The two sets of data were then correlated by the method of Rollett & Sparks (1960). The discrepancy index between the two sets of

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Table 1. Fractional coordinates and thermal parameters with standard deviations in parentheses

Thermal parameters are defined by  $T = \exp [-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$ . All values are multiplied by  $10^4$ .

	<i>x</i>	<i>y</i>	<i>z</i>	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
C(1)	4924 (4)	1953 (7)	2894 (15)	14 (2)	104 (9)	287 (32)	0 (8)	-18 (15)	-32 (29)
C(2)	3974 (4)	1074 (9)	3834 (15)	18 (2)	119 (9)	257 (27)	-7 (8)	-7 (13)	2 (34)
C(3)	3127 (4)	2346 (8)	3956 (15)	23 (2)	132 (10)	297 (28)	10 (9)	1 (16)	82 (36)
C(4)	3314 (5)	3891 (9)	5696 (17)	38 (3)	135 (10)	384 (40)	0 (10)	15 (22)	7 (39)
N	4144 (3)	244 (6)	6417 (10)	14 (2)	108 (7)	177 (22)	-13 (6)	-2 (10)	5 (23)
O(1)	5580 (3)	2180 (8)	4499 (11)	25 (2)	245 (12)	260 (23)	-61 (8)	-6 (11)	29 (30)
O(2)	4914 (3)	2365 (6)	545 (10)	31 (2)	159 (8)	215 (22)	-58 (8)	-1 (11)	1 (24)
O(3)	2305 (3)	1358 (6)	4853 (10)	18 (1)	144 (8)	351 (24)	12 (6)	32 (12)	0 (25)

data,  $R = \sum(|F_H|_b - |F_H|_c) / \sum \frac{1}{2}(|F_H|_b + |F_H|_c)$ , was 8.4%. Out of 725 reflexions possible in the Cu  $K\alpha$  sphere 600 independent reflexions were recorded.

### Structure determination and refinement

Since L-allothreonine differs from L-threonine only by a change in configuration at the  $C^{\beta}$  atom (Fig. 4), the cell dimensions may be expected to be close to those of L-threonine and also hopefully the two crystals may be closely isomorphous. The cell dimensions were in fact close to those of L-threonine (Shoemaker *et al.*, 1950). A statistical test of the intensities of the two crystals to determine the degree of isomorphism was carried out with the  $P(\delta)$  distribution function (Srinivasan & Ramachandran, 1965) for the  $hk0$  data. This revealed (Fig. 1) a high degree of isomorphism ( $\approx 80\%$ ) between both structures. Since the stability of such structures is essentially determined by the hydrogen bonds involving the amino and carboxyl groups, it is reasonable to suppose that the part of the structure involving  $C^{\alpha}$ ,  $NH_3^+$  and  $COO^-$  is the same in both structures. Assuming, therefore, the positions of N,  $C^{\alpha}$ ,  $COO^-$  to be the same as in L-threonine a structure-factor calculation was performed and this gave an  $R$  of 42%, which is in reasonable agreement with the theoretical value of 38.3% (Srinivasan, Sarma & Ramachandran, 1963) for  $\sigma_1^2 = 63\%$ . The remaining part of the structure was found from a difference map. As expected the peaks were close to those in the structure of L-threonine except for the change in  $CH_3$  and H positions. At this stage  $R$  with all the non-hydrogen atoms was 33%. Three cycles of full-matrix least-squares refinement were carried out on a CDC-3600 computer with the program *LALS* (Gantzel, Sparks & Trueblood, 1961) which resulted in an  $R$  of 15%. The scattering factors used were those in *International Tables for X-ray Crystallography* (1962).

At this stage a study of the variation of  $|F_o|$  with  $\sum |AF|^2$  was carried out from which the weighting scheme (Cruickshank, Bujosa, Lovell & Truter, 1961),  $W = 1/(a + |F_o| + b|F_o|^2)$  with  $a = 2.0$  and  $b = 0.03336$ , was derived. Two more cycles of refinement with this weighting scheme reduced  $R$  to 14%.

Before anisotropic refinement the hydrogen atoms were fixed from stereochemical considerations. With these included in the structure-factor calculation two

Table 2. Observed and calculated structure factors

more cycles of anisotropic refinement reduced  $R$  to 10.7%. The parameter shifts obtained in the final cycle were found to be less than  $\frac{1}{10}$ th of the estimated standard deviation. The final positional and thermal parameters are given in Table 1. The observed and calculated structure factors are listed in Table 2.

### Molecular packing and hydrogen bonding

The structure projected along **b** is shown in Fig. 2. The molecules run approximately parallel to **a** and are linked by a three-dimensional network of hydrogen bonds. Table 3 lists the various short contacts which are acceptable as hydrogen bonds from geometrical considerations (Hamilton & Ibers, 1968).

The amino acid exists as a zwitterion. There are four protons available for hydrogen-bond formation. The

three hydrogen-bond directions (at the amino group) are staggered with respect to the bonds covalently linked to C(2). In the case of L-threonine (Shoemaker *et al.*, 1950) two of the amino hydrogens are involved

in strong hydrogen bonds, while the third hydrogen is very weakly hydrogen bonded to the hydroxyl group, the N...O(3) distance being 3.10 Å and the C(2)-N...O(3) angle 132°. In the present case all three hydrogen bonds are strong. In particular the N...O(3) distance is 2.94 Å and the angle C(2)-N...O(3), 127°.

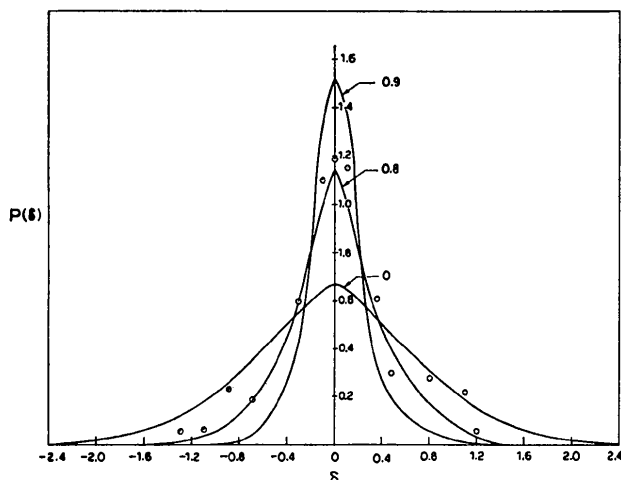


Fig. 1. Statistical test for isomorphism between L-threonine and L-allothreonine from the  $P(\delta)$  distribution function. Solid lines correspond to theoretical curves and the experimental points are shown by circles.

### Bond distances and angles

The bond distances and angles are given in Table 4 and Fig. 3. The average estimated standard deviations are 0.009 Å and 0.68° respectively. The C<sup>α</sup>-C' [C(2)-C(1)] distance of 1.541 and the C<sup>α</sup>-N [C(2)-N] distance of 1.507 Å are in agreement (within the 3σ level) with the corresponding mean values of 1.526 (4) and 1.487 (4) Å respectively (Marsh & Donohue, 1967). In the side chain the C<sup>α</sup>-C<sup>β</sup> [C(2)-C(3)] distance of 1.516 Å is in agreement with the standard value of 1.54 Å within experimental error. The C<sup>β</sup>-C<sup>γ</sup> [C(3)-C(4)] distance (1.523 Å) is in agreement with the value of Marsh & Donohue (1967). In the case of glycyl L-threonine dihydrate (Yadava & Padmanabhan, 1973), L-threonine (Shoemaker *et al.*, 1950) and L-threonyl-L-phenylalanine *p*-nitrobenzyl ester hydrobromide (Mallikarjunan, Rao, Venkatesan & Sarma, 1969) the values are 1.53, 1.50 and 1.46 Å respectively. In all the above

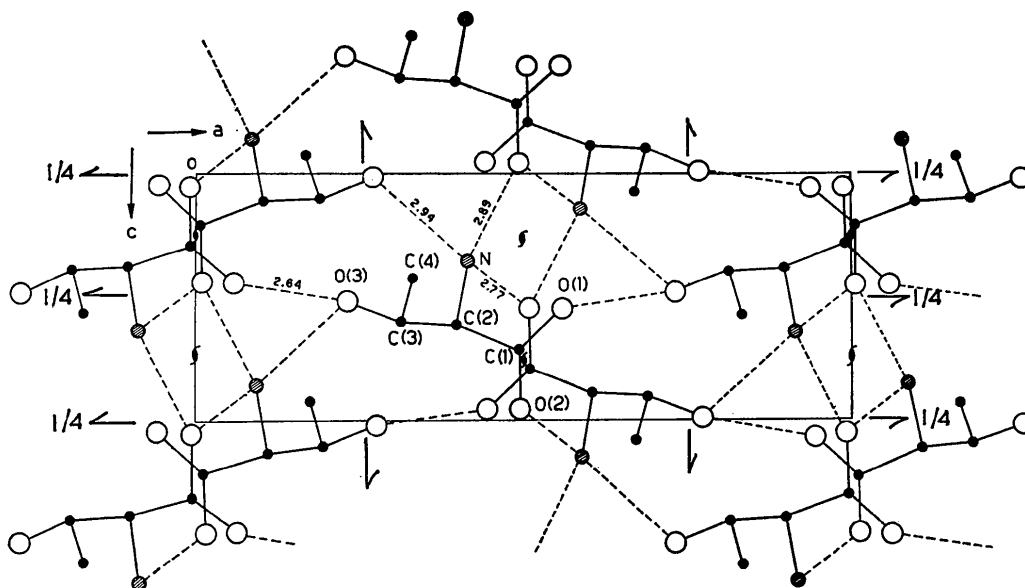


Fig. 2. Crystal structure of L-allothreonine projected down *b*.

Table 3. Hydrogen-bond lengths and angles

Donor (D)	Acceptor (A)	D...A	H...A	∠C-D...A	∠D-H...A
C(2)-N(1)...	O(2 <sup>v</sup> )	2.89 Å	2.26 Å	117.7°	135.6°
C(2)-N(1)...	O(2 <sup>iv</sup> )	2.77	1.87	95.4	166.2
C(2)-N(1)...	O(3 <sup>iii</sup> )	2.94	2.11	127.9	157.4
C(4)-O(3 <sup>iii</sup> )...	O(1)	2.64	1.86	120.5	154.8

Symmetry-code superscript: none  $x, y, z$ ; (ii)  $\frac{1}{2} - x, -y, \frac{1}{2} + z$ ; (iii)  $\frac{1}{2} + x, \frac{1}{2} - y, -z$ ; (iv)  $-x, \frac{1}{2} + y, \frac{1}{2} - z$ ; (v)  $x, y, z + 1$ .

structures the bond angles at the  $C^\beta$  atom show considerable deviation from the tetrahedral values of  $109.5^\circ$  ( $104.1, 113.4, 110.5^\circ$  in L-threonine;  $105.0, 114.1, 111.2^\circ$  in the present case;  $105.8, 113.8, 111.7^\circ$  in glycyl-L-threonine dihydrate;  $104, 109, 113^\circ$  in L-threonyl-L-phenylalanine *p*-nitrobenzyl ester HBr). Fig. 4 shows projections of the structures of L-threonine and L-allothreonine for comparison.

Table 4. Bond lengths (Å) and angles ( $^\circ$ ) with their standard deviations in parentheses

C(1)–C(2)	1.548 (9)	C(2)–C(1)–O(1)	117.69 (67)
C(1)–O(1)	1.234 (8)	C(2)–C(1)–O(2)	113.90 (67)
C(1)–O(2)	1.254 (8)	O(1)–C(1)–O(2)	128.38 (75)
C(2)–N	1.500 (8)	C(1)–C(2)–N	109.82 (67)
C(2)–C(3)	1.526 (9)	C(1)–C(2)–C(3)	111.35 (67)
C(3)–C(4)	1.523 (10)	C(3)–C(2)–N	111.31 (64)
C(3)–O(3)	1.439 (8)	C(2)–C(3)–C(4)	114.14 (67)
		C(2)–C(3)–O(3)	105.09 (68)
		C(4)–C(3)–O(3)	111.29 (71)

### Carboxyl group

The carboxyl group is in the ionized form [C(1)–O(1) = 1.234, C(1)–O(2) = 1.254 Å]. The dimensions are in agreement with the values of 1.252 (4) and 1.253 (4) Å (Marsh & Donohue, 1967).

The equation of the least-squares plane through N,  $C^\alpha$ ,  $COO^-$  is given by

$$0.3863X - 0.8919Y - 0.2354Z = 0.8914.$$

The deviation of N from the plane is 0.35 Å.

### Molecular conformation

The conformation of the amino acid is given by the angles  $\psi_1$ [N–C(2)–C(1)–O(1)] and  $\psi_2$ [N–C(2)–C(1)–O(2)] describing the torsion of the two C–O bonds about C(1)–C(2). The notation followed here is that given by Edsall *et al.* (1966). The values of  $\psi_1$  and  $\psi_2$  are  $345.1$  and  $165.8^\circ$ . The corresponding values for L-threonine (Shoemaker *et al.*, 1950) and glycyl-L-threonine dihydrate (Yadava & Padmanabhan, 1973) are  $333.8, 156.0$  and  $351.5, 169.7^\circ$  respectively. The side-chain conformation is given by the torsion angles  $\chi^{11}, \chi^{12}$  and  $\chi^{13}$  about C(2)–C(3) giving the position of the  $\gamma$  atom with respect to N (Lakshminarayanan, Sasisekharan & Ramachandran, 1967). These angles are close to  $60, 180$  and  $300^\circ$ . The  $C^\gamma$  atom moves to position I ( $65.1^\circ$ ) and the  $O^\gamma$  atom to position III ( $302.9^\circ$ ), in the present case. But in L-threonine and glycyl-L-threonine dihydrate these move to positions II and III ( $185.5, 305.2^\circ$ ) and III and I ( $298$  and  $61^\circ$ ) respectively. In L-threonyl-L-phenylalanine *p*-nitrobenzyl ester hydrobromide the  $C^\gamma$  and  $O^\gamma$  atoms take up positions II and III ( $176, 298^\circ$ ).

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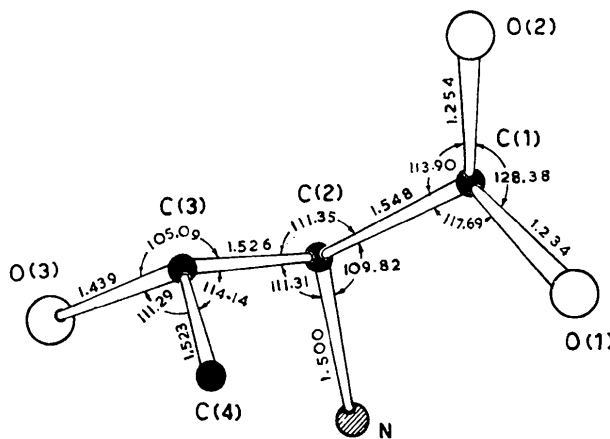


Fig. 3. Bond lengths and angles of L-allothreonine.

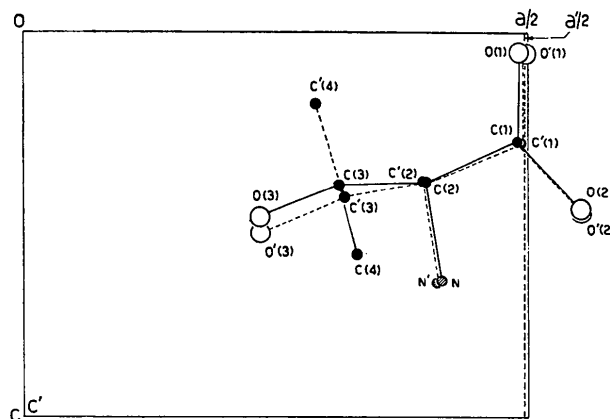


Fig. 4. Crystal structure of L-threonine (dashed line) and L-allothreonine (solid line) projected down  $b$ , with the common origin ( $O$ ).

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## Molecular Geometry of Substituted Benzene Derivatives. I. On the Nature of the Ring Deformations Induced by Substitution

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The small deformations induced by substitution in the skeletal geometry of the benzene ring are analysed in detail in a number of monosubstituted benzene derivatives. It is shown that the available structural data, which come mainly from room-temperature X-ray diffraction experiments, are unsuitable for a detailed investigation of the bond-length distribution within the ring, because of the effects of thermal motion. They are suitable, however, for a study of the internal bond angles. The observed dependence of the ring geometry upon the  $\sigma$ -electron-withdrawing or -releasing properties of the substituent and the extent of its conjugation with the ring is discussed in terms of (i) hybridization effects at the carbon atom at which substitution takes place, (ii) valence-shell electron-pair repulsions, (iii) intramolecular non-bonded interactions, and (iv) coulombic interactions between formally charged atoms. It appears that the experimental evidence is best rationalized in terms of either hybridization changes or valence-shell electron-pair repulsions. An analysis of the structural information available for *para*-disubstituted benzene derivatives has also been carried out. It is shown that the deformations induced by a substituent on the ring geometry are practically unaffected by a second substituent *para* to it, except in the case of through-conjugation.

### 1. Introduction

It has long been recognized that the regular hexagonal geometry of the carbon skeleton of the benzene ring is slightly modified when an electron-withdrawing functional group is substituted for a hydrogen atom (Bak, Christensen, Dixon, Hansen-Nygaard & Rastrup-Andersen, 1962; Bailey & Prout, 1965; Zvonkova & Khvatkina, 1965; Carter, McPhail & Sim, 1966; Nygaard, Bojesen, Pedersen & Rastrup-Andersen, 1968). The overall deformation is such as to lower the ring symmetry from  $D_{6h}$  ( $6/mmm$ ) to  $C_{2v}$  ( $2m$ ), and may be described in terms of (i) an increase of a few degrees

from  $120^\circ$  of the endocyclic bond angle,  $\alpha$ , opposite to the substituent X (Fig. 1); (ii) a minor decrease of the two adjacent endocyclic angles,  $\beta$ ; and (iii) a shortening (by some 0.01–0.02 Å) of the  $a$  bonds with respect to the adjacent  $b$  bonds. The remaining endocyclic angles,  $\gamma$  and  $\delta$ , seem to be scarcely, if at all, affected. Opposite deformations are observed with electron-releasing substituents (Zvonkova & Khvatkina, 1965; Carter, McPhail & Sim, 1966; Malone & McDonald, 1967, 1972; Di Vaira & Bianchi Orlandini, 1972).

Thanks to present-day crystal structure analysis techniques, a wealth of accurate information on the molecular geometry of the derivatives of benzene is being accumulated. In this paper we attempt a rationalization of the available data on the ring deformations, particularly for mono- and *para*-di-substituted benzenes.

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