

e.s.d.'s of bond lengths are *ca.* 0.04 Å, the results are not directly comparable.

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A Single-Crystal Structure Determination of DL-6-Thioctic Acid, C₈H₁₄O₂S₂

BY R. M. STROUD*† AND C. H. CARLISLE

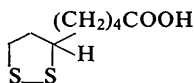
The Crystallographic Laboratory, Birkbeck College, London W.C. 1, England

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Single crystals of DL-6-thioctic acid, (α -DL-lipoic acid), {5-[3(1,2-dithiolanyl)] pentanoic acid}, were obtained by recrystallization of a racemic mixture of DL-6-thioctic acid from cyclohexane. The crystals are predominantly twinned, and show a high degree of disordering. The space group is $P2_1/c$ with $a=11.744$, $b=9.895$, $c=9.246$ Å, and $\beta=109^\circ 35'$. There are four molecules per unit cell, and the structure was solved by the heavy-atom technique. Hydrogen atoms were located using difference Fourier syntheses. The molecules are held together by hydrogen bonds between pairs of carboxyl groups, and by van der Waals contacts between sulphur atoms. Karle, Estlin & Britts (*Acta Cryst.* (1967) **22**, 567) previously solved the crystal structure of the twinned crystal of DL-6-thioctic acid, using a restricted data set. This single-crystal study reports more accurate bond distances and angles for the same molecule.

Introduction

Lipoic acid possesses fat soluble and acidic characteristics.



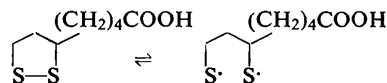
The current view suggests that it is concerned directly in photosynthesis, carrying energy from activated


* Present address: Norman W. Church Laboratory of Chemical Biology, California Institute of Technology, Pasadena, California, U.S.A.

† This work was submitted as part of a Ph. D. thesis at London University (Stroud, 1968).

chlorophyll in illuminated chloroplasts (Calvin, Bartlop & Hayes, 1954), and then reducing pyridine nucleotides. Lipoic acid also acts to decarboxylate and, at the same time, dehydrogenate pyruvic acid in mammalian carbohydrate metabolism (Wagner & Folkers, 1964).

Many properties of α -lipoic acid accrue from the ease with which it can be reduced or oxidized according to:



and the present study was undertaken principally to find the conformation of the  ring.

Crystallographic studies

Several months after completing this study of lipoic acid, Karle, Estlin & Britts (1967) reported they were unable to grow any single crystals and published the structure determination of the twinned crystal of lipoic acid. Several significant differences between this analysis and that of Karle *et al.* were observed, probably reflecting the limitations of data collected from intimately twinned crystals and the use of a partial data set ($l=0$ to 5 only). The study of Karle *et al.* gave rise to two very unusual bond lengths and a negative temperature factor for one of the atoms, which were not observed in the present study. Some differences in cell dimensions and planarity of the side chain that were observed are discussed.

Experimental

Synthetic α -DL-lipoic acid was obtained from the Sigma Chemical Company. Several attempts were made to recrystallize the material from a warm saturated solution of lipoic acid in ethyl alcohol. These attempts resulted, invariably, in the formation of twinned crystals of tabular habit.

Several single crystals were obtained by slow cooling of a warm saturated solution of α -lipoic acid in cyclohexane for 14 days. The crystals were tabular parallel to (100). They showed very high birefringence, and the almost universal twinned crystals could readily be separated because they revealed no true extinction between crossed polars.

X-ray data were collected from two single crystals on equi-inclination Weissenberg photographs. Cell parameters were determined by comparing high-angle reflexions with the superimposed diffraction from a stationary copper wire (Stroud, 1968):

$$\begin{aligned} a &= 11.744 (8) \text{ \AA} \\ b &= 9.895 (8) \\ c &= 9.246 (6) \\ \beta &= 109.6 (1)^\circ. \end{aligned}$$

These agree with the values of Karle *et al.*, within their somewhat larger standard deviations.

In all these calculations, the wavelength of $\text{Cu } K\alpha_1$ radiation was used as the standard (ASTM Index) and was taken to be $\lambda_{\text{Cu}K\alpha_1} = 1.54051 \text{ \AA}$.

The density of the crystals was measured by flotation in an aqueous solution of potassium iodide, to which a few drops of detergent were added as a wetting agent. One difficulty in making this measurement was that lipoic acid has a somewhat fatty nature, while it is soluble both in aqueous and in organic solvents. Karle *et al.* (1967) report they were unable to determine the density, due to these properties.

Density was found to be $D_o = 1.343 \text{ g.cm}^{-3}$ at a room temperature of 21°C . The molecular weight of lipoic acid ($\text{C}_8\text{H}_{14}\text{O}_2\text{S}_2$) is 206.320, and the calculated density

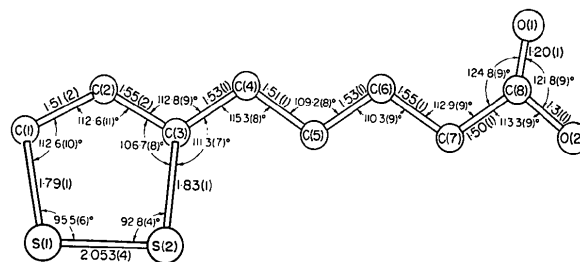


Fig. 1. Bond lengths (\AA) and angles in one molecule of lipoic acid, together with standard deviations.

for lipoic acid, based on four molecules per cell, is 1.349 g.cm^{-3} . The density calculated on this basis is not significantly different from the measured density, suggesting that ideally there are four molecules per unit cell.

The Laue group for these crystals is $2/m$. Systematic absences occurred in the $h0l$ reflexions for l odd, and in the $0k0$ reflections for k odd; hence, the space group was identified as $P2_1/c$.

Data were collected around the b axis from the zero layer to the eighth, and around the c axis from the zero and first layers only. Due to strain in the second crystal, X-ray diffraction maxima recorded from this crystal showed wide systematic variation in the measure of related intensities, and a separate spot-shape correction was applied to these data. Intensities were measured by optical comparison with a standardized intensity scale. In all, 1319 independent non-zero data were recorded, representing 56% of the copper sphere. The data were corrected for absorption (Stroud, 1968), spot shape, spot size (Phillips, 1954), Lorenz and polarization factors. They were scaled together and placed on an absolute scale (Wilson, 1942). Computer programs were written by one of us (Stroud, 1968) to carry out these corrections on the London Atlas computer.

Solution of the structure

Positions of both sulphur atoms in the asymmetric unit were located unambiguously from a sharpened three-dimensional Patterson synthesis. The trial sulphur positions were used to calculate structure factors, whose signs were used with the observed $F_{(hkl)}$ to calculate a three-dimensional electron density synthesis. About 15% of the data were omitted on statistical grounds. Two further cycles of Fourier refinement revealed the complete structure. These atomic positions were refined using a block-diagonal approximation to the least-squares process, together with Hughes's (1941) weighting scheme. The function minimized was $R_1 = \sum_{hkl} w \times (|F_o| - |F_c|)^2$. Refinement was terminated after eight cycles using anisotropic temperature factors, at which point positional shifts were all less than 0.1 standard deviations. The index $R = \sum |F_o - F_c| / \sum |F_o|$ was 0.12.

The final set of atomic coordinates and their standard deviations are listed in Table 1; corresponding vibrational parameters with their standard deviations are given in Table 2. Bond distances and angles in one molecule are shown in Fig. 1; the O...O hydrogen bond distance between two carboxyl groups in the dimer is 2.64 (1) Å. Observed and calculated structure factors are available from author RMS upon request.

Table 1. *Lipoic acid-atomic positions of the heavy atoms in one molecule, and their standard deviations, in fractional coordinates*

	<i>x</i>	<i>y</i>	<i>z</i>
S(1)	0.4041 (3)	1.0896 (3)	0.1177 (4)
S(2)	0.3789 (2)	1.1256 (3)	0.3235 (3)
C(1)	0.3993 (14)	0.9088 (11)	0.1301 (16)
C(2)	0.3383 (12)	0.8614 (11)	0.2418 (13)
C(3)	0.2794 (9)	0.9791 (10)	0.3024 (10)
C(4)	0.2597 (8)	0.9453 (10)	0.4534 (10)
C(5)	0.2026 (8)	1.0556 (9)	0.5178 (10)
C(6)	0.1749 (9)	1.0013 (10)	0.6577 (10)
C(7)	0.1114 (10)	1.1116 (10)	0.7228 (11)
C(8)	0.0674 (8)	1.0594 (10)	0.8475 (10)
O(1)	0.0706 (6)	0.9435 (7)	0.8858 (7)
O(2)	0.0172 (6)	1.1527 (7)	0.9065 (7)

Location of hydrogen-atom positions in the molecule was attempted by calculating a difference Fourier electron density synthesis, whose coefficients were ($F_o - F_c$) (Lipson & Cochran, 1953). The map shows no variations greater than $\pm \frac{1}{2}$ mean peak height of a carbon atom at this scale. Anticipated positions of 13 of the 14 hydrogen atoms in the molecule were calculated, assuming a covalent C-H bond length of 1.0 Å; these positions are listed in Table 3. All hydrogen atoms except H(1) occur in positive regions of the map and generally lie on positive peaks; however, there is considerable background noise in the map, and a more accurate location of the hydrogen atoms was not attempted. Positions for atoms H(1) to H(13) were included in a calculation of the structure factors and they reduced the discrepancy factor *R* by 0.008, to 0.111. Atom H(14) was omitted from the calculation, since it lay in the hydrogen bond. The map shows no other

larger variations than these, indicating that the molecule had been correctly located and refined.

Table 3. *Calculated positions of the hydrogen atoms, based on tetrahedral angles and a C-H bond length of 1.0 Å*

	<i>x</i>	<i>y</i>	<i>z</i>
H(1)	0.484	0.874	0.165
H(1')	0.353	0.872	0.026
H(2)	0.400	0.817	0.331
H(2')	0.274	0.795	0.188
H(3)	0.197	0.998	0.228
H(4)	0.340	0.924	0.531
H(4')	0.206	0.864	0.436
H(5)	0.126	1.085	0.438
H(5')	0.260	1.134	0.550
H(6)	0.252	0.975	0.739
H(6')	0.120	0.921	0.626
H(7)	0.040	1.147	0.637
H(7')	0.170	1.186	0.766
H(0)*	---	---	---

* Atom in hydrogen bond.

Discussion

The equation for the least-squares plane through the C(4)-C(5)-C(6)-C(7) chain is:

$$8.8698x + 3.0486y + 2.9069z = 6.473. \quad (1)$$

Deviations from this plane (Table 4) indicate that C(2) and C(3) are significantly displaced from this plane. In the analysis of Karle *et al.* (1967), C(3) was included in the least-squares calculation, which account for the apparently large deviations from their published plane and for the apparent difference between their equation to the plane and this one.

The least-squares plane for the carboxyl group is

$$8.2455x + 1.7316y + 3.8371z = 5.623, \quad (2)$$

and deviations of the four atoms used in the calculation are listed in Table 4. No four atoms in the five-membered ring are coplanar, and the dihedral angle in the CSSC group is 35.0°. The dihedral angle between the plane of the carboxyl group and the plane of the chain is 5.29°.

Table 2. *Lipoid acid-final anisotropic thermal vibrational parameters ($\times 10^4$) and their standard deviations*

Form of the temperature correction is: $T = \exp [-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{23}kl + \beta_{31}hl + \beta_{12}hk)]$.

	β_{11}	β_{22}	β_{33}	β_{23}	β_{31}	β_{12}
S(1)	202 (4)	172 (5)	240 (5)	011 (7)	321 (8)	-050 (7)
S(2)	120 (2)	120 (2)	204 (4)	-033 (6)	176 (5)	-037 (5)
C(1)	292 (21)	111 (15)	386 (29)	-020 (30)	568 (45)	041 (27)
C(2)	194 (14)	158 (16)	236 (18)	-072 (27)	312 (28)	035 (24)
C(3)	127 (10)	128 (13)	186 (14)	-022 (22)	199 (20)	-055 (18)
C(4)	117 (9)	132 (12)	171 (13)	021 (20)	201 (19)	028 (17)
C(5)	119 (9)	104 (11)	179 (14)	052 (20)	190 (19)	009 (17)
C(6)	142 (10)	135 (14)	189 (14)	020 (21)	254 (22)	005 (18)
C(7)	153 (11)	122 (13)	193 (14)	011 (22)	242 (22)	-004 (19)
C(8)	113 (9)	123 (12)	164 (13)	-025 (20)	167 (18)	-032 (17)
O(1)	155 (7)	134 (9)	213 (11)	-014 (16)	268 (16)	010 (13)
O(2)	161 (8)	113 (8)	205 (11)	-007 (15)	234 (16)	-011 (13)

Table 4. *Deviations of atoms from the least-squares planes*

Atoms labelled with an asterisk were not used to derive the planes.

C(4)–C(5)–C(6)–C(7)		C(7)–C(8) $\begin{smallmatrix} \sphericalangle \\ \sphericalangle \end{smallmatrix} \begin{smallmatrix} \text{O(1)} \\ \text{O(2)} \end{smallmatrix}$	
Equation (1)		Equation (2)	
Δ		Δ	
C(2)*	–0.201	C(7)	–0.006
C(3)*	–0.178	C(8)	0.020
C(4)	–0.014	O(1)	–0.008
C(5)	0.013	O(2)	–0.006
C(6)	0.014		
C(7)	–0.013		
C(8)*	–0.193		

Several significant differences are apparent between this analysis and that of Karle *et al.* (1967) who noted that all the crystals they examined were twinned, and they have suggested an interesting mechanism of formation for the twin crystal in terms of their structure analysis.

They report that the temperature factor for atom C(7) persisted in becoming negative during refinement, and that no hydrogen atoms could be located on a difference map, probably reflecting the limitations of data collected from an intimately twinned crystal. They also report a large difference between the two C–C bond lengths in the ring: C(1)–C(2), 1.464; C(2)–C(3), 1.581 Å. These distances would be unlikely for a C–C bond, and in the present analysis they fall within the normal expected limitations for such bonds: C(1)–C(2), 1.514 ± 0.020 ; C(2)–C(3), 1.553 ± 0.016 Å. Standard deviations of the parameters, as obtained from the normal equations matrix, were much lower in this single-crystal study. They were generally much lower

in the parameters related to the *c* direction, notably in the *z* and β_{33} parameters, and less so in β_{13} and β_{23} , reflecting the restriction of data collection in the *c* direction of Karle *et al.*

Temperature factors of all atoms in the single-crystal study reported here fall within expected values; they reveal the heavy anisotropy of this structure, indicating that thermal vibration is greatest in directions approximately normal to the planes of the side chain. The closest non-bonded S–S contacts [obtained here as 3.858 (4) Å] are S(1)–S(2') contacts between molecules related by glide planes. The S(1)–S(2'') distances between molecules related by a 2_1 axis are 5.191 and 5.830 Å.

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