Crystal Structure and Molecular Conformation of 2-Deamino-L-cystine, C₆H₁₁NO₄S₂, a Mixed Disulfide

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Abstract. $M_r = 225.28$, $P1$, $a = 5.101$ (1), $b = 10.195$ (1), $c = 5.020$ (1) Å, $\alpha = 96.72$ (1), $\beta = 111.27$ (1), $\gamma = 95.63$ (1)°, $V = 238.8$ (1) Å³, $Z = 1$, $D_m = 1.61$, $D_x = 1.57$ g cm⁻³, Cu $K\alpha$, $\lambda = 1.5418$ Å, $\mu = 47.9$ cm⁻¹, $F(000) = 118$, $T = 297$ K, $R = 0.040$, $wR = 0.062$, 1944 reflections $[I \geq 2\sigma(I)]$. The title compound is a mixed disulfide of β-mercaptopropionic acid (MPA) and cysteine. The bond distances in the cysteine moiety are significantly longer than those of the MPA moiety. The $C'-C\alpha-C\beta-S\gamma$ backbone is zigzag planar in the MPA half but twisted in the cysteine half. The molecule shows short 1,4 carbon–sulfur non-bonded interactions.

Introduction. The title compound (L-2-amino-4,5-dithiaoctanedioic acid) (HDLC), a mixed disulfide of β-mercaptopropionic acid (MPA) and cysteine, is used in the synthesis of deamino-oxytocin. Deamino-oxytocin is a highly potent analog of oxytocin, the uterus-contraction hormone of the posterior pituitary (Hope, Murti & DuVigneaud, 1962). The crystal structure of HDLC was studied for three reasons: (i) to compare its conformation with those of several symmetric disulfide structures reported in the literature, *e.g.* L-cystine, D-penicillamine disulfide, *etc.*; (ii) to study short contacts from S to other atoms (Rosenfield, Parthasarathy & Dunitz, 1977; Guru Row & Parthasarathy, 1981; Chatterjee & Parthasarathy, 1983); and (iii) to examine non-bonded 1,4 carbon–sulfur interaction (Van Wart, Shipman & Scheraga, 1975).

Experimental. Compound obtained from Dr V. DuVigneaud's laboratory through Professor Scheraga, Cornell University, Ithaca; crystallized from hot water by slow evaporation. D_m from flotation in benzene/bromoform mixture. Needle-shaped crystal $0.45 \times 0.20 \times 0.15$ mm mounted along the φ axis of a CAD-4 automated diffractometer. Lattice parameters by least-squares refinement of 25 reflections $(0 < \theta < 25°)$. 1946 [1944 with $I \geq 2\sigma(I)$] reflections containing hkl and $\overline{hkl}$ with $2\theta \leq 154°$, ω-scan angle $(0.4 + 0.15 \tan\theta)°$; vertical size of slit 4 mm and width $(3.0 +$

$1.20 \tan\theta)$ mm. Three standard reflections measured after every hour of X-ray exposure, no significant intensity fluctuation, and hence no correction applied. Anisotropic absorption correction applied (North, Phillips & Mathews, 1968), 0.83 average transmission with variation from 0.65 to 0.99. Lp corrections were made. Structure solved by Patterson method; H atoms located in electron-density difference map; function minimized in least-squares procedure was $\sum w(|F_o| - |F_c|)^2$ where $w = [\sigma^2(I) + 0.05I^2]^{-1/2}$Lp (Peterson & Levy, 1957). The refinement was carried out using the full data hkl and $\overline{hkl}$ corresponding to the point group $P1$ since a pronounced anomalous-dispersion effect was observed [the R value between Bijvoet pairs was 0.06 where $R = \sum(||F| - |\bar{F}||)/\sum\frac{1}{2}(|F| + |\bar{F}|)$ and averaging Bijvoet pairs is not justified]. In final full-matrix least-squares refinement cycle $(\Delta/\sigma)_{max} = 0.15$ for non-hydrogen atoms and 0.2 for H atoms, $S = 2.48$. Computer programs from the Enraf–Nonius structure determination package; torsion-angle program by Dr S. T. Rao and *ORTEP* by Johnson (1965). Atomic scattering factors (Table 2.2B) and anomalous-dispersion factors (Table 2.3.1) from *International Tables for X-ray Crystallography* (1974).

Discussion. The final atomic parameters are listed in Table 1,† bond distances and angles in Fig. 1. The dimensions of the molecule agree with published values of dimensions for similar molecules. The molecule, as expected, exists as a zwitterion. The bond distances in the cysteine moiety are longer by ~0.02 Å (which is ~10 times their e.s.d.'s) than those of the MPA moiety. This increase in bond lengths may be caused by steric effects due to the presence of the amino group in the cysteine moiety.

The carboxylate groups are planar; C(1′) and C(2′) lie 0.010 (2) and 0.002 (2) Å, respectively, from the planes through the three atoms to which C′ is bonded. The bond angles $S\gamma(1)-S\gamma(2)-C\beta(2)$ and $S\gamma(2)-$

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† Lists of strucutre factors, anisotropic thermal parameters and bond distances and angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39941 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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$S\gamma(1)-C\beta(1)$ of 103·4 (1) and 103·9 (1)°, respectively, indicate a slight departure from sp^3 hybridization for the $S\gamma$ atoms.

Table 1. *Positional parameters, isotropic thermal parameters and their estimated standard deviations*

Atoms indicated by asterisks were refined isotropically. Anisotropically refined atoms are given in the form of the equivalent isotropic thermal parameter defined as: $\frac{4}{3}[a^2\beta(1,1) + b^2\beta(2,2) + c^2\beta(3,3) + ab(\cos\gamma)\beta(1,2) + ac(\cos\beta)\beta(1,3) + bc(\cos\alpha)\beta(2,3)]$.

|	x	y	z	$B(\text{Å}^2)$
O(11)	0·4436 (3)	−0·2411 (2)	0·3698 (3)	2·60 (3)
O(12)	0·0766 (3)	−0·3628 (2)	0·4071 (3)	2·56 (2)
C(1')	0·1850 (3)	−0·2898 (2)	0·2813 (3)	1·71 (3)
Cα(1)	−0·0048 (3)	−0·2567 (2)	−0·0106 (3)	1·78 (3)
N(1)	−0·3109 (3)	−0·2983 (2)	−0·0690 (3)	1·94 (3)
Cβ(1)	0·0481 (4)	−0·1102 (2)	−0·0385 (4)	2·33 (3)
Sγ(1)	0·000	0·000	0·250	3·62 (3)
Sγ(2)	−0·2405 (4)	0·1306 (2)	0·0385 (4)	3·91 (3)
Cβ(2)	0·0174 (5)	0·2518 (2)	−0·0091 (5)	3·16 (4)
Cα(2)	0·2547 (4)	0·3174 (2)	0·2718 (4)	2·53 (3)
C(2')	0·4645 (4)	0·4171 (2)	0·2222 (4)	2·30 (3)
O(21)	0·4341 (4)	0·4488 (2)	−0·0096 (3)	3·90 (4)
O(22)	0·6879 (3)	0·4656 (2)	0·4629 (3)	3·07 (3)
H(1Cα1)	0·026 (9)	−0·321 (5)	−0·165 (9)	4·1 (9)*
H(1N1)	−0·361 (8)	−0·264 (4)	0·035 (8)	3·3 (7)*
H(2N1)	−0·346 (9)	−0·379 (5)	−0·074 (9)	4·3 (8)*
H(3N1)	−0·410 (7)	−0·281 (4)	−0·233 (7)	2·7 (7)*
H(1Cβ1)	0·204 (9)	−0·077 (5)	−0·035 (9)	4·9 (8)*
H(2Cβ1)	−0·081 (6)	−0·100 (4)	−0·212 (6)	2·4 (6)*
H(1Cβ2)	0·089 (7)	0·206 (4)	−0·137 (7)	3·3 (7)*
H(2Cβ2)	−0·112 (8)	0·307 (4)	−0·098 (9)	3·7 (7)*
H(1Cα2)	0·362 (8)	0·251 (5)	0·348 (9)	4·2 (8)*
H(2Cα2)	0·167 (9)	0·363 (5)	0·397 (9)	4·8 (8)*
H(1O22)	0·792 (7)	0·516 (4)	0·424 (7)	3·1 (6)*
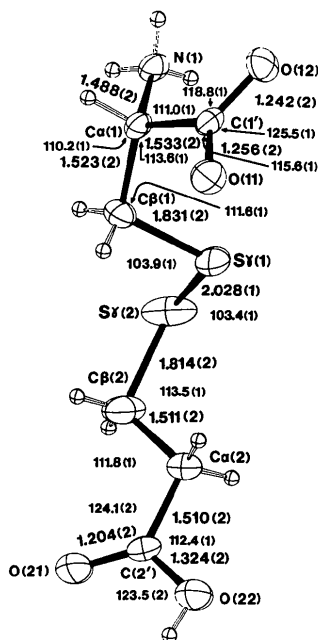
Fig. 1. Bond lengths (Å) and bond angles (°) of the HDLC molecule (for non-hydrogen atoms). The quantities in parentheses denote the e.s.d.'s. The diagrams were drawn using *ORTEP* (Johnson, 1965).

The torsion angle about $S\gamma(2)-C\beta(2)$ is −56·8 (2)°, *i.e.* g^-, as suggested from the Raman studies (Van Wart & Scheraga, 1976) and this conformation is a result of non-bonded 1,4 carbon–sulfur $[C\alpha(2)-S\gamma(1)]$ interaction (Van Wart, Shipman & Scheraga, 1975). The torsion angle χ_3 about the $S\gamma(1)-S\gamma(2)$ bond, *i.e.* $C\beta(1)-S\gamma(1)-S\gamma(2)-C\beta(2)$, for HDLC is −81·3 (2)°, which indicates that the disulfide group in this molecule has M-helical chirality (Donzel, Kamber, Wuthrich & Schwyzer, 1972), *i.e.* left-handed sense. A similar left-handed conformation is seen for disulfides in other cystine salts and derivatives, while the hexagonal and tetragonal modifications of cystine have opposite helical sense with torsion angles of +73·8 and +69·3°, respectively (for references see Rosenfield & Parthasarathy, 1974). However, both left- and right-handed conformations of disulfides have been observed in proteins (for examples see Table 6 in Jones, Bernal, Frey & Koetzle, 1974).

The angle χ', the torsion angle $N(1)-C\alpha(1)-C\beta(1)-S\gamma(1)$, is 67·9 (2)°. The location of the γ atom is found to be restricted corresponding to a small range of angles around $\chi' = 60$, 180, or 300°; the value of χ' near 300° seems to be preferred if the γ atom is not S or O (Lakshminarayanan, Sasisekharan & Ramachandran, 1967). On the other hand if the γ atom is S, as in the case of HDLC, in eight out of nine structures (Lakshminarayanan, Sasisekharan & Ramachandran, 1967), the S atom occupies only the position with $\chi' = 60°$, *i.e.* +synclinal (+*sc*) to N and −synclinal (−*sc*) to the carboxyl group (nomenclature of Klyne & Prelog, 1960). The N(1) atom is 0·253 (2) Å away from the carboxylate plane of the cysteine residue; this approximate coplanarity has been observed in many amino acids (Marsh & Donohue, 1967).

The C′−Cα−Cβ−Sγ backbone is zigzag planar in the MPA moiety but twisted in the cysteine moiety. The asymmetry in the chemical constitution is also reflected in the conformation of the two halves of the molecule.

The molecular arrangement and hydrogen-bonding interactions are illustrated in Fig. 2. This diagram shows the network of hydrogen-bonded HDLC molecular chains lying head to tail. As expected, all three H atoms of the amino group are hydrogen bonded; the distances H(1N1)···O(11), H(2N1)···O(21), H(3N1)···O(11) are 2·24 (3), 2·11 (4) and 1·97 (3) Å, respectively; the three N−H···O angles are 157 (3), 154 (3) and 167 (2)°, respectively. The O(12) oxygen atom of the carboxyl group is an acceptor for two protons, one from the unionized carboxyl group and the other from the Cα(1) carbon atom. The hydrogen H(3N1) shows short intermolecular contacts with atoms O(12) and C(1') at distances 2·58 and 2·55 Å, respectively. A short 1,4 carbon–sulfur non-bonded interaction (Van Wart, Shipman & Scheraga, 1975) is seen between Sγ(1) and Cα(2). The intramolecular distances of Sγ(1)···Cα(2)
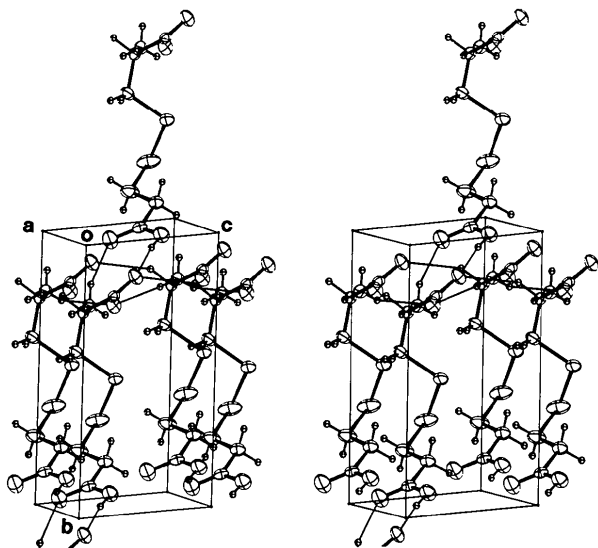
Fig. 2. A stereoview of the molecular packing and hydrogen-bonding interactions in the crystal.

and $S\gamma(1)\cdots H(1C\alpha2)$ are 3·341 (3) and 2·89 (5) Å, respectively, and the angle $S\gamma(1)\cdots H(1C\alpha2)-C\alpha(2)$ is 111 (4)°. There is no other short contact with S; the reason for the occurrence of the type of short S···S and S···X contacts (X = electrophiles or nucleophiles; Rosenfield, Parthasarathy & Dunitz, 1977) with S atoms in only some selected structures is not yet clear.

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The Structure of Phyllanthose Hexaacetate, C24H34O15*

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Abstract. O-6-Deoxy-β-D-glucopyranosyl-(1→2)-6-deoxy-α-D-glucopyranose hexaacetate. $M_r = 562·52$, monoclinic, $P2_1$, $a = 13·077$ (7), $b = 9·306$ (5), $c = 12·009$ (6) Å, $\beta = 92·33$ (2)°, $V = 1460$ (1) Å³, $Z = 2$, $D_m = 1·24$, $D_x = 1·28$ Mg m⁻³, Cu $K\alpha$, $\lambda = 1·5418$ Å, $\mu = 0·882$ mm⁻¹, $F(000) = 596$, room temperature, final $R = 0·049$ for 1930 reflections. The molecules exist as discrete monomers in the crystal. The bond