

Structure and Conformation of Amino Acids Containing Sulfur. III.* The Crystal Structure and Absolute Configuration of 3,3,3',3'- Tetramethyl-D-cystine (D-Penicillamine Disulfide) Dihydrochloride: An Unusually Short Intramolecular N-H···S Contact Distance

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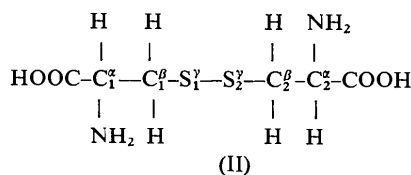
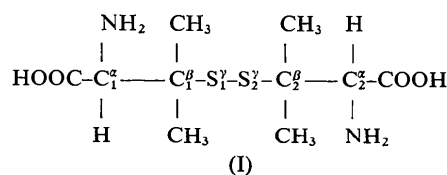
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Crystals of 3,3,3',3'-tetramethyl-D-cystine dihydrochloride (C₁₀H₂₀N₂O₄S₂·2HCl) are orthorhombic, space group *P*2₁2₁2₁. Unit-cell constants [$\lambda(\text{Cu } K\alpha_1) = 1.54051 \text{ \AA}$, $T = 22 \pm 3^\circ\text{C}$] are $a = 10.507$ (1), $b = 26.419$ (2), and $c = 6.101$ (1) \AA ; $V_o = 1693.5 \text{ \AA}^3$, and $Z = 4$. $D_{\text{obs}} = 1.46$ (1) (flotation), $D_{\text{calc}} = 1.448 \text{ g cm}^{-3}$, and $\mu(\text{Cu } K\alpha) = 57.6 \text{ cm}^{-1}$. The structure, solved by the heavy-atom method, was refined by least-squares calculations to an R of 0.043, using 1593 intensity measurements that had been corrected for absorption. An unusually short intramolecular N₂-H···S₂' contact distance of 2.43 (13) \AA is accompanied by a 15° conformational twist about the valence bond C₂ ^{β} -C₂ ^{α} , relative to the nearly perfect staggering about C₁ ^{β} -C₁ ^{α} . This H···S₂' contact is directed nearly normal to the plane through the sulfide group S₁'-S₂'-C₂ ^{β} , suggesting an attraction between the electropositive hydrogen atom and S₂'s unshared pair of 3*p* electrons. The torsion angle about the disulfide bond is 115°. The carboxyl carbon atoms are anti-periplanar to the sulfur atoms. Each of five amino hydrogen atoms has two contacts with electro-negative atoms, and lies in the plane through these atoms and its bonded nitrogen atom.

Introduction

3,3,3',3'-Tetramethyl-D-cystine (I) (3,3'-dithiodi-D-valine) is an amino acid analogous to L-cystine (II).



(I) is the disulfide derivative of D-penicillamine, a degradation product of penicillin (Crooks, 1949), and (unlike (II)) is not found in proteins. 3,3,3',3'-Tetramethyl-D-cystine dihydrochloride (TMC) was studied as part of a general structural comparison of amino acids containing sulfur (Rosenfeld, 1974), which complements the electron-spin-resonance studies of Box and his coworkers (Box, Freund, Lilga & Budzinski, 1970; Budzinski & Box, 1971).

Experimental

Crystals of TMC (C₁₀H₂₀N₂O₄S₂·2HCl), kindly provided by Box & Budzinski, were found to be slightly cloudy. They were dissolved in water and recrystallized by slow evaporation at room temperature ($22 \pm 3^\circ\text{C}$), producing needles that were colorless and transparent. One crystal (Fig. 1) was cut normal to the needle (c) direction and mounted with the *c** axis parallel to the φ axis of the goniostat. It was orthorhombic, space group *P*2₁2₁2₁ (axial reflections with odd indices were absent).

The unit-cell parameters, $a = 10.507$ (1), $b = 26.419$ (2), $c = 6.101$ (1) \AA , and $V_o = 1693.5 \text{ \AA}^3$, were obtained with Cu $K\alpha$ radiation [$\lambda(\text{Cu } K\alpha_1) = 1.54051 \text{ \AA}$] on a G.E. XRD-5 diffractometer at room temperature, and were refined by the least-squares method from 39 2 θ measurements of reflections for which the peaks from Cu $K\alpha_1$ and Cu $K\alpha_2$ could be resolved. The calculated crystal density, D_{calc} , is 1.448 g cm^{-3} , with $Z = 4$; and the observed density, D_{obs} , is 1.46 (1) g cm^{-3} , measured by flotation.

Intensity data were collected (Cu $K\alpha$, $2\theta \leq 160^\circ$) using the stationary-crystal stationary-counter technique (Furnas & Harker, 1955) with balanced Ni-Co Ross filters. Of the 2156 unique reflections measured, 1601 were selected for the structural refinement on the criterion that their intensity (Ni-filtered minus Co-filtered) was at least equal to the average background (Co-filtered) value. Intensities of the remaining, 'weak' reflections were fixed at half the average background

* For Part II, see Rosenfeld & Parthasarathy (1974).

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value. Lorentz, polarization, and α_1 - α_2 splitting corrections were made. A correction for absorption (Coppens, 1970) was computed, based on the geometry of

the crystal (Fig. 1) and on the linear absorption coefficient, $\mu = 57.6 \text{ cm}^{-1}$, calculated from the values of μ_a in *International Tables for X-ray Crystallography* (1968). The transmission coefficients varied from 0.49 to 0.76.

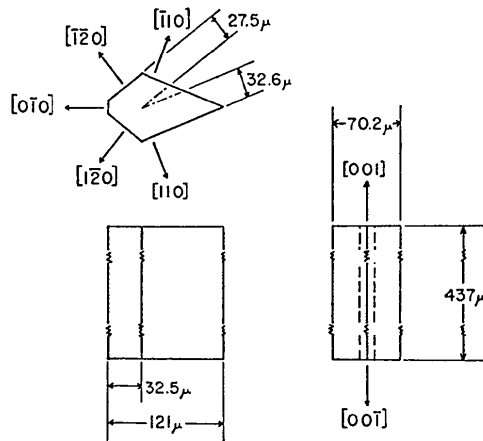


Fig. 1. Size and shape of the cut crystal of 3,3,3',3'-tetramethyl-D-cystine dihydrochloride used in this study.

Table 1. Results of the final cycle of structural refinement by least-squares calculations: a test of absolute configuration

Range of data, $\sin \theta/\lambda$	Number of reflections	R value in each range of data	
		D Enantiomorph	L Enantiomorph*
0.0-0.1	12	0.035	0.035
0.1-0.2	71	0.025	0.029
0.2-0.3	161	0.027	0.032
0.3-0.4	265	0.031	0.038
0.4-0.5	364	0.033	0.044
0.5-0.6	497	0.055	0.062
0.6-0.7	223	0.121	0.127
0.0-0.7	1593†	0.043	0.050

* $\Delta f''$ corrections for Cl⁻, S, and O were made negative.
† Eight of the 1601 reflections used to refine the structure showed relatively large differences between $|F_{\text{H}}^{\text{obs}}|$ and $|F_{\text{H}}^{\text{calc}}|$, and were removed prior to this final refinement.

Table 2. Final atomic fractional coordinates and thermal parameters

E.s.d.'s as determined from the least-squares matrix, are given in parentheses and refer to the last digit. The anisotropic thermal factor for an atom is given by the expression $\exp[-\{b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl\}]$.

IUPAC name*	$x \times 10^4$	$y \times 10^4$	$z \times 10^3$	$b_{11} \times 10^4$	$b_{22} \times 10^5$	$b_{33} \times 10^3$	$b_{12} \times 10^4$	$b_{13} \times 10^3$	$b_{23} \times 10^4$
Cl(1)	1522 (2)	-2190.1 (6)	118.2 (3)	55 (1)	75 (2)	15.6 (4)	-1.1 (8)	-3.1 (4)	-2 (2)
Cl(2)	2431 (2)	1246.5 (6)	145.4 (3)	75 (2)	77 (2)	18.9 (4)	-6.9 (10)	-0.1 (5)	-3 (2)
S(1)	S ₁ ^γ	1650 (2)	3587.3 (6)	92.3 (3)	51 (1)	92 (2)	18.6 (4)	14.8 (9)	-6.7 (5)
S(2)	S ₂ ^γ	1170 (2)	3727.8 (6)	412.1 (3)	47 (1)	77 (2)	18.4 (4)	5.2 (8)	1.4 (4)
O(1)	O ₁ ^γ	5550 (5)	2567 (2)	87 (1)	40 (4)	134 (8)	25 (2)	3 (3)	1 (2)
O(2)	O ₂ ^γ	5732 (5)	3095 (2)	368 (1)	50 (4)	132 (8)	22 (2)	7 (3)	-10 (2)
O(3)	O ₃ ^γ	-2626 (6)	4852 (2)	376 (1)	72 (5)	111 (8)	29 (2)	20 (4)	4 (2)
O(4)	O ₄ ^γ	-896 (5)	5304 (2)	296 (1)	61 (5)	63 (6)	37 (2)	12 (3)	-3 (2)
N(1)	N ₁	3035 (5)	2560 (2)	115 (1)	47 (4)	65 (7)	16 (2)	-1 (3)	-1 (2)
N(2)	N ₂	-1579 (5)	3975 (2)	333 (1)	35 (4)	74 (7)	20 (2)	2 (3)	2 (2)
C(1)	C ₁	5110 (7)	2863 (3)	215 (1)	54 (6)	77 (9)	12 (2)	0 (4)	-2 (2)
C(2)	C ₂ ^α	3701 (6)	2994 (2)	213 (1)	35 (5)	76 (8)	13 (2)	5 (3)	-1 (2)
C(3)	C ₃ ^β	3414 (6)	3506 (2)	92 (1)	46 (5)	88 (8)	13 (2)	7 (4)	1 (2)
C(4)	C ₄	-1542 (7)	4888 (2)	327 (1)	68 (6)	76 (8)	10 (2)	0 (4)	-4 (2)
C(5)	C ₅ ^α	-733 (6)	4414 (2)	286 (1)	48 (5)	70 (8)	10 (2)	-3 (4)	-3 (2)
C(6)	C ₆ ^β	542 (6)	4388 (2)	415 (1)	42 (5)	53 (7)	13 (2)	4 (3)	1 (2)
C(7)	C ₇ ^{β1}	4126 (7)	3939 (3)	197 (1)	50 (6)	73 (8)	24 (2)	-1 (4)	0 (2)
C(8)	C ₈ ^{β2}	3746 (8)	3474 (3)	-155 (1)	88 (8)	103 (10)	15 (2)	27 (5)	2 (2)
C(9)	C ₉ ^{γ1}	1520 (7)	4750 (2)	319 (1)	63 (6)	68 (8)	22 (2)	-8 (4)	5 (2)
C(10)	C ₁₀ ^{γ2}	324 (7)	4490 (3)	662 (1)	49 (6)	144 (12)	11 (2)	1 (4)	-3 (2)

IUPAC name*	$x \times 10^3$	$y \times 10^3$	$z \times 10^2$	$B(\text{\AA}^2)\dagger$	IUPAC name*	$x \times 10^3$	$y \times 10^3$	$z \times 10^2$	$B(\text{\AA}^2)\dagger$	
H(1)	H ₁ ^γ	654 (12)	298 (4)	40 (2)	7	H(12)	H ₁₂ ^γ	-131 (7)	555 (3)	31 (1)
H(2)	H ₂ ^γ	343 (5)	308 (2)	38 (1)	0	H(13)	H ₁₃ ^γ	-50 (5)	437 (2)	14 (1)
H(3)	H ₃ ^γ	227 (8)	263 (3)	6 (1)	2	H(14)	H ₁₄ ^γ	-112 (12)	369 (4)	36 (2)
H(4)	H ₄ ^γ	346 (10)	245 (4)	-2 (2)	5	H(15)	H ₁₅ ^γ	-216 (6)	406 (2)	45 (1)
H(5)	H ₅ ^γ	300 (9)	229 (3)	19 (2)	4	H(16)	H ₁₆ ^γ	-217 (9)	389 (3)	21 (2)
H(6)	H ₆ ^{γ11}	383 (10)	427 (4)	12 (2)	5	H(17)	H ₁₇ ^{γ11}	237 (6)	472 (2)	40 (1)
H(7)	H ₇ ^{γ12}	397 (8)	398 (3)	37 (1)	3	H(18)	H ₁₈ ^{γ12}	167 (9)	467 (3)	17 (2)
H(8)	H ₈ ^{γ13}	506 (10)	390 (4)	16 (2)	5	H(19)	H ₁₉ ^{γ13}	125 (6)	512 (2)	31 (1)
H(9)	H ₉ ^{γ21}	344 (8)	379 (3)	-22 (1)	3	H(20)	H ₂₀ ^{γ21}	112 (11)	451 (4)	71 (2)
H(10)	H ₁₀ ^{γ22}	461 (9)	335 (3)	-16 (2)	4	H(21)	H ₂₁ ^{γ22}	-7 (10)	483 (4)	68 (2)
H(11)	H ₁₁ ^{γ23}	313 (11)	322 (4)	-21 (2)	6	H(22)	H ₂₂ ^{γ23}	-23 (7)	427 (3)	72 (1)

* In this column atoms are labeled according to the criteria of the IUPAC-IUB Commission on Biochemical Nomenclature (1970), except for the numbering of the hydrogens of the amino and methyl groups. The lowest numbered hydrogen of each group has the principal torsion angle of largest magnitude.

† The average e.s.d. for the isotropic thermal parameters is 2\AA^2 .

Solution and refinement of the structure

The structure was solved by the heavy-atom method. Atomic parameters were refined by the method of block-diagonal least-squares calculations, minimizing $\sum w_{\mathbf{H}}(|F_{\mathbf{H}}|^{\text{obs}} - (1/k)|F_{\mathbf{H}}|^{\text{calc}}|)^2$, where $w_{\mathbf{H}} = (1/f_{\text{oxy}})$. Scatter-factor values for Cl^- , S, O, N, and C were obtained from *International Tables for X-ray Crystallography* (1968), and for H from Stewart, Davidson & Simpson (1965). With individual anisotropic thermal factors for the non-hydrogen atoms, the structure was refined to an R of 0.066. An electron-density difference synthesis showed the positions of the hydrogen atoms at an average peak height of $0.4 \text{ e } \text{Å}^{-3}$, and the succeeding structural refinement included the hydrogens with individual isotropic thermal factors.

Anomalous dispersion corrections (*International Tables for X-ray Crystallography*, 1968) were applied to the scattering factors of Cl^- , S, and O. The absolute configuration of the molecule, determined by the R value technique (Hamilton, 1965), agrees with Fischer conventions. Atomic coordinates for the D and L enantiomorphs lead to final R values of 0.043 and 0.050, respectively; and the D coordinates yield lower R values than the L coordinates in every $\sin \theta/\lambda$ range of data, except the lowest range, in which the R values are equal (Table 1). In the final cycle of refinement, the non-hydrogen parameters shifted by less than a tenth of their estimated standard deviation (e.s.d. determined from the least-squares matrix), and the hydrogen parameters by no more than a third. The final atomic parameters are listed in Table 2.*

During the last stages of the structural refinement, eight reflections which showed relatively large differences between $|F_{\mathbf{H}}|^{\text{obs}}$ and $|F_{\mathbf{H}}|^{\text{calc}}$ were removed. Three of these reflections were attenuated presumably by extinction effects ($|F_{\mathbf{H}}|^{\text{obs}} < |F_{\mathbf{H}}|^{\text{calc}}$, $|F_{\mathbf{H}}|^{\text{obs}} > 100$, and $\sin \theta/\lambda < 0.33$). Very large differences between $|F_{\mathbf{H}}|^{\text{obs}}$ and $|F_{\mathbf{H}}|^{\text{calc}}$ also occurred for 4,10,3 ($|F_{\mathbf{H}}|^{\text{obs}} = 9.6$, $|F_{\mathbf{H}}|^{\text{calc}} = 56.0$) and 2,21,0 ($|F_{\mathbf{H}}|^{\text{obs}} = 20.1$, $|F_{\mathbf{H}}|^{\text{calc}} = 47.3$). The 'weak' reflections 446, 11,14,2, and 805 ($3.6 \leq |F_{\mathbf{H}}|^{\text{obs}} \leq 5.3$, $27.0 \leq |F_{\mathbf{H}}|^{\text{calc}} \leq 30.6$) and three additional reflections also had $|F_{\mathbf{H}}|^{\text{obs}}$ much less than $|F_{\mathbf{H}}|^{\text{calc}}$, suggesting that these reflections showing large discrepancies resulted from errors in setting the diffractometer by hand. None of the data could be remeasured at the time errors were discovered, for the crystal had become cloudy. The absence of all these reflections is judged to have an insignificant effect on the final atomic parameters and on the test of absolute configuration.

Bond lengths and angles

In the divalent cation of 3,3,3',3'-tetramethyl-D-cystine, most of the valence bond lengths and angles not involving hydrogen atoms (Fig. 2) agree with those found in previously reported structures of amino acids containing sulfur and with the corresponding average values (about C^{α}) reported by Marsh & Donohue (1967). The C(3)–C(2) and C(6)–C(5) bond lengths, 1.571 (9) and 1.556 (9) Å, are longer than the average C^{β} – C^{α}

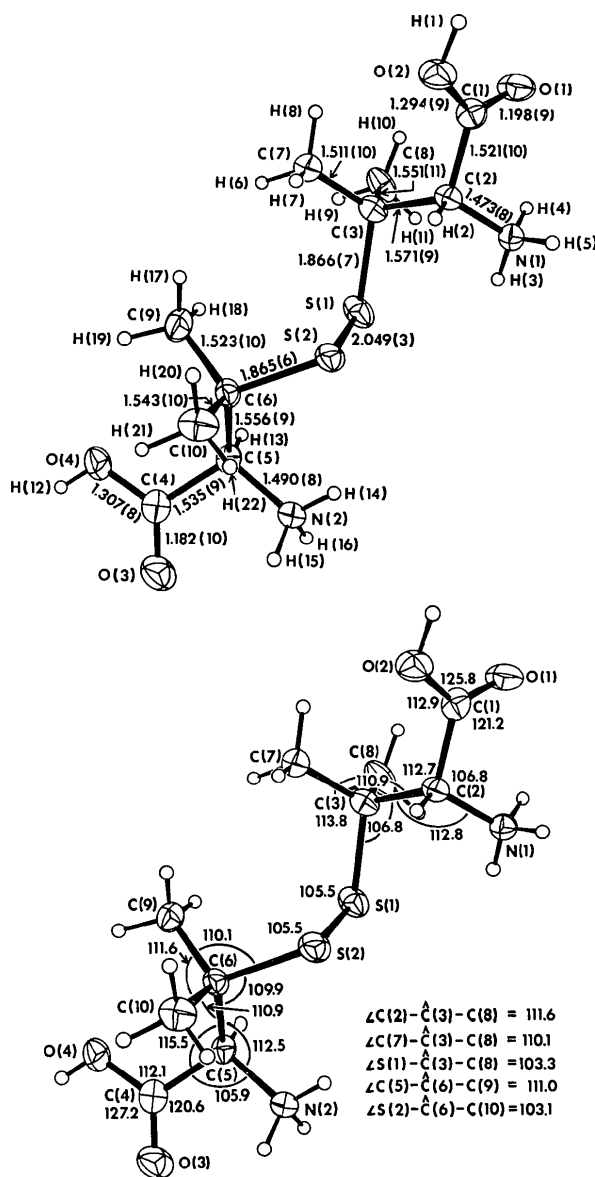


Fig. 2. Valence bond lengths (Å) and bond angles (°), excluding those with hydrogen atoms. E.s.d.'s for the lengths are shown in parentheses; for the angles about sulfur they are 0.2° , and about the other atoms they are 0.4 – 0.7° . These diagrams and those in Fig. 7 were made with the ORTEP program, using 50% probability ellipsoids for the non-hydrogen atoms and 0.08 Å radii for the hydrogens.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30691 (17 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

bond length, 1.525 Å, reported by Marsh & Donohue; and the S(1)–C(3)–C(2) and S(2)–C(6)–C(5) bond angles, 106.8 (4) and 109.9 (4)°, are smaller than the mean $S^{\gamma}-C^{\beta}-C^{\alpha}$ bond angle, 113.0 (8)°, found by the authors from three crystal structures of the divalent cation of L-cystine (Steinrauf, Peterson & Jensen, 1958; Peterson, Steinrauf & Jensen, 1960; Rosenfield & Parthasarathy, 1975). The average N–H and C–H bond lengths, 0.93 (5) and 0.99 (6) Å, respectively, are about

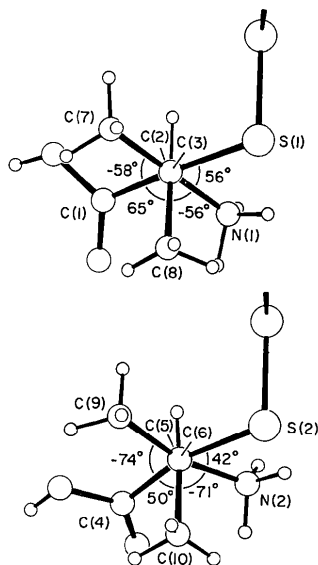


Fig. 3. Torsion angles about the $C^{\beta}-C^{\alpha}$ [C(3)–C(2) and C(6)–C(5)] bonds, as seen by projecting the molecule onto planes normal to these bonds. The conformation about the bond C(6)–C(5) is twisted 15°, relative to the nearly perfectly staggered conformation about C(3)–C(2). These diagrams and those in Figs. 4–6 were made with the *ORTEP* program, using atomic radii of 0.20 Å for S and Cl⁻, 0.15 Å for N, O, and C, and 0.08 Å for H.

0.1 Å shorter than those usually found in neutron-diffraction studies (Hamilton & Ibers, 1968).

The bond angles S(1)–C(3)–C(8) and S(2)–C(6)–C(10) [following the IUPAC–IUB Commission on Biochemical Nomenclature (1970), $S_i^{\gamma}-C_i^{\beta}-C_i^{\alpha}$; $i=1,2$] are both 103.2(5)°, which is significantly smaller than the tetrahedral value, 109.5°. Four short $C_i^{\gamma^2}-H \cdots S_i^{\gamma}$ contact distances accompany these small bond angles (discussed below).

There is good agreement between the dimensions of the two halves of the molecule, with equivalent bond lengths and angles differing by 1.5 e.s.d.'s on the average. Indeed, only three dimensions differ by more than 2 e.s.d.'s; the angles C(3)–C(2)–C(1) and C(6)–C(5)–C(4) (4 e.s.d.'s), S(1)–C(3)–C(2) and S(2)–C(6)–C(5) (5 e.s.d.'s), and S(1)–C(3)–C(7) and S(2)–C(6)–C(9) (6 e.s.d.'s).

Conformation of the molecule

The torsion angles in 3,3,3',3'-tetramethyl-D-cystine are listed in Table 3. They show approximate twofold symmetry between the halves of the molecule-ion. Twofold molecular symmetry, either *exact* or *approximate*, is also found in every previously reported structure of L-cystine and its bis derivatives. The torsion angle about the disulfide bond (χ^3) of 115° in this D enantiomorph contrasts with values near -80° found in the divalent cation of L-cystine (Steinrauf *et al.*, 1958; Peterson *et al.*, 1960; Rosenfield & Parthasarathy, 1975). This conformational difference in the tetramethyl derivative cannot be accounted for in terms of steric repulsion between the methyl groups, since C(7) and C(9) are 3.555 (10) Å apart and the three shortest C(7)–H \cdots H–C(9) distances, 2.5–2.6 (1) Å, are longer than the accepted H \cdots H van der Waals contact distance of 2.4 Å (Pauling, 1960).

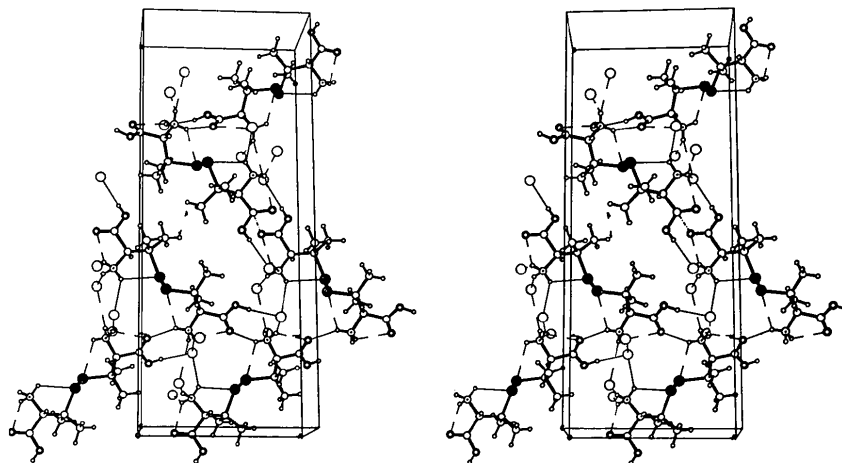


Fig. 4. Packing diagram of TMC; a stereo pair, viewed 12° from the *c* direction. Sulfur atoms are completely blackened, oxygens are blackened about their perimeter, and nitrogens are blackened at their center. Thin continuous lines represent hydrogen bonds, and thin broken lines represent weaker hydrogen interactions. Arrows show the twofold screw axes at $(x, \frac{1}{4}, 0)$ and $(\frac{1}{4}, \frac{1}{2}, z)$, and the line - - - shows the intermolecular contact between O(3) and C(4) (see text).

The conformation angles about the $C^\beta-C^\alpha$ [C(3)-C(2) and C(6)-C(5)] bonds (Table 3, Fig. 3) show (1) that the carboxyl carbon atoms are anti-periplanar [nomen-

Table 3. *Torsion angles*

Torsion angle description	IUPAC-IUB (1970) designation	Torsion angle value (°)
$\tau(C_2^\beta-S_2^\gamma-S_1^\gamma-C_1^\beta)$	χ^3	115
$\tau_2(S_2^\gamma-S_1^\gamma-C_1^\beta-C_2^\beta)^*$	(χ_1^1, χ_2^2)	(70, 67)
$\tau_2(S_1^\gamma-C_1^\beta-C_1^\alpha-N_1)$	(χ_1^1, χ_2^2)	(56, 42)
$\tau_2(S_1^\gamma-C_1^\beta-C_1^\alpha-C_1)$		(177, 164)
$\tau_2(N_1-C_1^\alpha-C_1=O_1)$	(ψ_1^1, ψ_2^2)	(25, -3)

* $\tau_2(S_2^\gamma-S_1^\gamma-C_1^\beta-C_2^\beta)$ designates the two equivalent torsion angles $\tau[S(2)-S(1)-C(3)-C(2)]$ and $\tau[S(1)-S(2)-C(6)-C(5)]$, in that order; hence the subscript '2'.

clature of Klyne & Prelog (1960)] to the γ -sulfur atoms, a conformation not usually found in previously reported structures of L-cystine and L-cysteine (Lakshminarayanan, Sasisekharan & Ramachandran, 1967); and (2) that the conformation about the C(6)-C(5) bond is twisted about 15° with respect to the nearly perfectly staggered conformation about the C(3)-C(2) bond.

Hydrogen bonding

Both carboxyl hydrogen atoms form relatively strong hydrogen bonds to the chloride ions (Table 4), one hydrogen bond being linear and the other bent. Each of five of the amino hydrogen atoms lies in the plane through two contacting atoms and its bonded nitrogen, as seen by the sum of the angles about the hydrogen

atom (Table 4). Such planar N-H configurations, where H is electropositive and A_1 and A_2 are electro-

negative, have been observed in other structures (Nilsson, Liminga & Olovsson, 1968; Parthasarathy, 1969; Rosenfield & Parthasarathy, 1974).

Five of the contacts with the amino groups appear

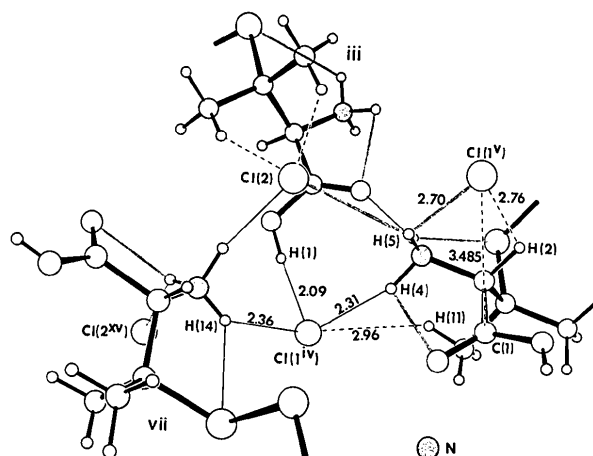


Fig. 5. The environment of Cl(1). Hydrogen bonds (thin black lines), weaker hydrogen interactions (gray lines), and van der Waals contacts (dashed lines) are shown.

Table 4. *Contacts with the carboxyl and amino hydrogen atoms*

D is the donor and A is a possible acceptor atom. The following superscripts distinguish atoms related by symmetry operations to those in Table 2: none x, y, z ; i $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; ii $-x, \frac{1}{2}+y, \frac{1}{2}-z$; iii $-\frac{1}{2}+x, \frac{1}{2}-y, -z$; iv $\frac{1}{2}-x, -y, -\frac{1}{2}+z$; v $\frac{1}{2}-x, -y, \frac{1}{2}+z$; vi $-\frac{1}{2}+x, \frac{1}{2}-y, 1-z$; vii $\frac{1}{2}+x, \frac{1}{2}-y, -z$; viii $-\frac{1}{2}-x, 1-y, \frac{1}{2}+z$; xi $\frac{1}{2}+x, \frac{1}{2}-y, 1-z$; xii $\frac{1}{2}-x, 1-y, -\frac{1}{2}+z$; xiii $\frac{1}{2}-x, 1-y, \frac{1}{2}+z$; xiv $1+x, y, z$; xv $x, y, -1+z$; xvi $-1+x, y, z$.

D-H...A	Distance (Å)		Angle (°)		$A_1 \cdots H \cdots A_2$ (Sum)†
	H...A	D...A	D-H...A	D-H...A	
O(2)-H(1) ... Cl(1 ⁱ)	2.09 (12)*	2.984 (5)	163 (12)		
O(4)-H(12) ... Cl(2 ⁱⁱ)	2.21 (7)*	2.988 (5)	178 (7)		
D—H...A ₁	H...A ₁	D...A ₁	D-H...A ₁		
D—H...A ₂	H...A ₂	D...A ₂	D-H...A ₂		
N(1)-H(3) ... O(1 ⁱⁱⁱ)	2.08 (8)*	2.907 (8)	152 (6)	94 (3)	
N(1)-H(3) ... S(1)	2.61 (7)	3.084 (5)	114 (6)	(360)	
N(1)-H(4) ... Cl(1 ^{iv})	2.31 (12)*	3.217 (6)	153 (9)	108 (5)	
N(1)-H(4) ... O(1)	2.31 (11)	2.648 (7)	99 (8)	(360)	
N(1)-H(5) ... Cl(1 ^v)	2.70 (10)	3.257 (6)	127 (8)	91 (3)	
N(1)-H(5) ... Cl(2)	2.85 (9)	3.532 (5)	142 (8)	(360)	
N(2)-H(14) ... Cl(1 ^{vi})	2.36 (12)*	3.093 (5)	137 (10)	102 (5)	
N(2)-H(14) ... S(2)	2.43 (13)*	3.000 (6)	120 (9)	(359)	
N(2)-H(15) ... Cl(2 ^{vii})	2.65 (7)	3.397 (6)	136 (5)	116 (3)	
N(2)-H(15) ... O(3)	2.20 (6)	2.579 (7)	103 (5)	(355)	
N(2)-H(16) ... Cl(2 ^{viii})	2.27 (11)*	3.155 (6)	151 (8)		

* A hydrogen bond.

† Sum = angle (D-H...A₁ + D-H...A₂ + A₁...H...A₂).

to be hydrogen bonds (Table 4), while the remaining contacts are weaker hydrogen interactions (Parthasarathy, 1969; Koetzle, Hamilton & Parthasarathy, 1972). The hydrogen-bonding distances are 0.3 Å or more shorter than the sum of the H and A van der Waals radii, using Pauling's (1960) values for S, Cl⁻ and O and Baur's (1972) value (1.0 Å) for polar H. H(14) appears to participate in bifurcated hydrogen bonding. Both contact distances to H(14) are 0.4 Å shorter than the van der Waals contact distance, and both N(2)-H(14)···A contact angles are considerably more bent than the angles (150°) of the other three amino hydrogen bonds.

Packing

The packing of TMC is illustrated in Fig. 4. The hydrogen bonds and weaker hydrogen interactions, al-

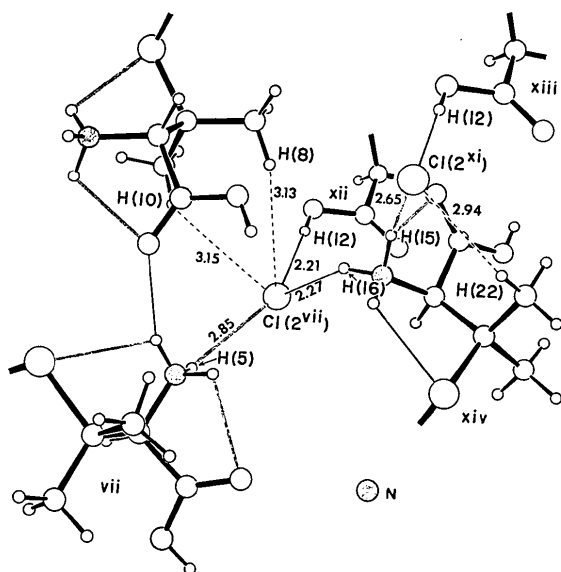


Fig. 6. The environment of Cl(2).

ready described (Table 4), form a three-dimensional network. A hydrophilic region extends in the *a* direction, centered on the twofold screw axis at $(x, \frac{1}{4}, 0)$; and a hydrophobic tunnel (formed by the methyl groups) extends in the *c* direction, centered on the twofold screw axis at $(\frac{1}{4}, \frac{1}{2}, z)$. In this hydrophobic region, the shortest intermolecular H···H distances are 2.5 (1) Å. In TMC, the shortest intermolecular contact distance not involving hydrogen atoms is 2.970 (9) Å, between O(3) and C(4^{viii}).

The environments of the chloride ions are illustrated in Figs. 5 and 6. Hydrogen bonds and weaker hydrogen interactions are shown, as well as six van der Waals contacts of the type Cl⁻···H-C and Cl⁻···C(carboxyl).

There is a short intramolecular contact distance of 2.31 (6) Å between O(4) and H(19).

Environment of the sulfur atoms

Eight intramolecular S^γ···H contacts are listed in Table 5 and illustrated in Fig. 7. The first six S^γ···H contacts in the table have already been pointed out and involve the amino groups and the γ 2-methyl groups. These six S^γ···H distances are significantly shorter than the van der Waals contact distance, using van der Waals radii of 1.85 Å for S (Pauling, 1960), 1.0 Å for polar H (Baur, 1972), and 1.2 Å for nonpolar H (Pauling, 1960; Bondi, 1964). As shown in Table 5 and Fig. 7, each of the two S^γ···H-N_{*i*} (*i* = 1 or 2) contacts is directed along the *normal* to the sulfide group S^γ-S^γ-C^β (*j* = 1 or 2, *i* = 1 or 2, and *i* ≠ *j*); in contrast, each of the four S^γ···H-C^γ contacts lies nearly *in* the S^γ-S^γ-C^β sulfide plane.

Assuming that S₁^γ and S₂^γ have unhybridized 3*p* orbitals, the unshared pair of S^γ's (*i* = 1 or 2) 3*p* electrons lies in an orbital extending normal to each side of the plane through the atoms S^γ-S^γ-C^β, with the plane itself a nodal surface of this orbital (Price & Oae, 1962). The maximal electron density in the orbital lies 0.81 Å from

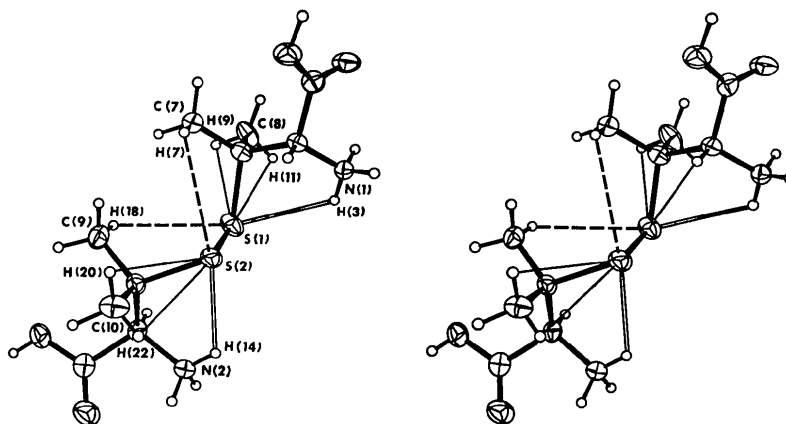


Fig. 7. Environment of the sulfur atoms; a stereo pair. Short S^γ···H-N_{*i*} contact distances (thin double lines), short S^γ···H-C^γ contact distances (thin single lines), and van der Waals S^γ···H-C^γ contact distances (dashed lines) are shown, along with the direction of each contact.

Table 5. *Contacts with sulfur*

$S_i \cdots H-X$	Distance $S_i \cdots H$	Angle between the direction of $S_i \cdots H$ and the direction normal to the plane through the sulfide group $S_i-S_i-C_i^f$
$S(1) \cdots H(3)-N(1)$	2.61 (7) Å	25°
$S(2) \cdots H(14)-N(2)$	2.43 (13)	18
$S(1) \cdots H(9)-C(8)$	2.75 (9)	68
$S(1) \cdots H(11)-C(8)$	2.58 (11)	79
$S(2) \cdots H(20)-C(10)$	2.74 (11)	69
$S(2) \cdots H(22)-C(10)$	2.78 (8)	79
$S(1) \cdots H(18)-C(9)$	2.90 (9)	19
$S(2) \cdots H(7)-C(7)$	3.03 (8)	17

S_i^f (Slater, 1965) on either side of the $S_i-S_i-C_i^f$ sulfide plane, while in the vicinity of this plane the electron density from the orbital should be quite small.

Thus, the $S(1) \cdots H(3)$ and $S(2) \cdots H(14)$ contacts may each indicate an attraction between the sulfur atom's unshared pair of $3p$ electrons and the polar hydrogen atom; while the $S(1) \cdots H(9)$, $S(1) \cdots H(11)$, $S(2) \cdots H(20)$, and $S(2) \cdots H(22)$ contacts may each reflect a reduced van der Waals radius for S_i^f in the $S_i-S_i-C_i^f$ sulfide plane, the orbital nodal plane of S_i^f 's unshared pair of $3p$ electrons (Rosenfield & Parthasarathy, 1974).

The last two $S_i^f \cdots H$ contacts in Table 5 are van der Waals contacts involving the γ 1-methyl hydrogen atoms, and are directed nearly normal to the plane through $S_i-S_i-C_i^f$. These appear to be the only intramolecular contacts that can sterically oppose a smaller χ^3 torsion angle in this molecule. If the value of χ^3 were slightly smaller, there would be (in each half of the molecule) still closer, and less favored, proximity between the γ 1-methyl hydrogen atom and the orbital of S_i^f 's unshared pair of $3p$ electrons.

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