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The Crystal Structure of Gliotoxin

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Gliotoxin, $C_{13}H_{14}O_4N_2S_2$, a fungal product from *Gliocladium fimbriatum*, crystallizes in the monoclinic system with $a=10\cdot17$, $b=7\cdot49$, $c=18\cdot28$ Å, $\beta=100\cdot7°$ (at -150°C), $Z=4$. The space group being $P2_1$, there are two independent molecules in the asymmetric unit. The structure was determined with data (2856 reflexions) from Weissenberg photographs of 6 layers around the b axis and 7 layers around the a axis by means of a three-dimensional Patterson distribution and a Fourier synthesis, and refined by full-matrix least-squares calculations and difference syntheses to $R=0\cdot088$. The skeletal structure consists of a disulphide-bridged piperazinedione system linked through a five-membered pyrrolidine-type ring to a cyclohexadiene ring and three side groups of $-CH_3$, $-CH_2OH$ and $-OH$. The absolute configuration has been determined by the use of the anomalous dispersion of the sulphur atoms, establishing the chirality of the skew diene chromophore and of the disulphide bridge.

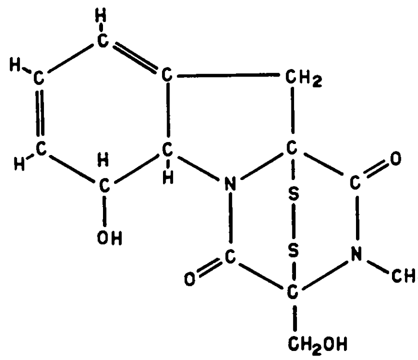
Introduction

The X-ray analysis of sporidesmin (Fridrichsons & Mathieson, 1965), the toxic metabolic agent from the fungus *Pithomyces chartarum*, revealed in its rather unusual skeletal structure some similarities to the structure proposed on the basis of chemical evidence by Bell, Johnson, Wildi & Woodward (1958) for another fungal product – gliotoxin. Gliotoxin, $C_{13}H_{14}O_4N_2S_2$, was isolated by Weindling (1941) from the fungus *Gliocladium fimbriatum*, and in view of its toxic and antibiotic properties extensive studies on its chemistry were carried out before its structure could be deduced.

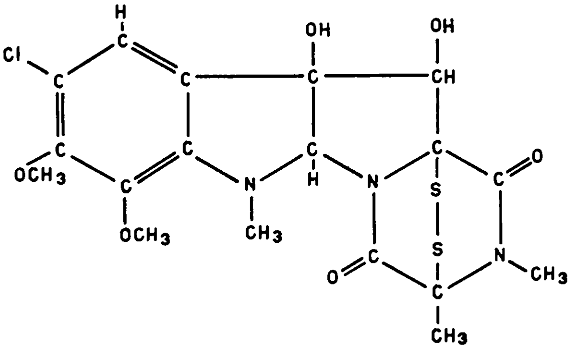
The proposed structure (I) contains a disulphide-bridged piperazinedione (diketopiperazine) system identical with that found in sporidesmin (II). As no X-ray structural work had been done on gliotoxin, apart from the determination of cell dimensions by Crowfoot & Rogers-Low (1944), and the chemical investigations did not clarify configurational detail it seemed worth while to carry out an X-ray analysis to define the structure and compare the stereochemical features of both compounds. Another point of interest in the analysis was the presence in the proposed structure of the cyclohexadiene system. If the chirality of the skew diene group could be established by determining the absolute configuration of the molecule from X-ray analysis it would be possible to compare it with predictions based on optical rotatory dispersion measurements for this chromophore (Weiss, Ziffer & Charney, 1965). Finally the analysis would provide further assessment of the suitability of sulphur as a phase-determining 'heavy atom'.

The material for the analysis was kindly provided by Dr H. Ziffer of the Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, Washington, U.S.A.

Notes on the essential features of the structure, its absolute configuration relation to that of sporidesmin (Beecham, Fridrichsons & Mathieson, 1966) and discussion of the skew diene chirality in regard to the results of circular dichroism measurements (Beecham & Mathieson, 1966) have been published, and the present paper deals only with the details and numerical data of the analysis.*



(I)



(II)

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* During preparation of the present paper we learned by private communication that a structure analysis of gliotoxin had been also carried out by G. Kartha (Center for Crystallographic Research, Roswell Park Division of Health Research Inc., Buffalo, New York 14203, U.S.A.)

Experimental

Suitable crystals for the analysis were obtained by slow recrystallization of the original material from methanol. They are lath shaped and belong to the monoclinic system, with cell dimensions at room temperature $a=10{\cdot}25$, $b=7{\cdot}52$, $c=18{\cdot}46$ Å, $\beta=100{\cdot}7^\circ$ (calibrated against a silicon standard). The space group is $P2_1$ with $Z=4$, indicating two molecules of $C_{13}H_{14}O_4N_2S_2$ in the asymmetric unit. With $M=326{\cdot}4$ and $V=1398{\cdot}2$ Å^3, the calculated density is 1·550, agreeing exactly with the measured value of $D_m=1{\cdot}550$ (by flotation in potassium iodide solution). This indicates that the crystalline material is anhydrous and excludes the possibility of a hemihydrate as suggested by Crowfoot & Rogers-Low (1944), who obtained slightly different cell dimensions ($a=10{\cdot}36, b=7{\cdot}59, c=18{\cdot}74$Å, $\beta=100^\circ$).

Data were collected at -150°C to ensure an adequate θ range (for details, see Fridrichsons & Mathieson, 1962*a*,*b*), the cell dimensions at this temperature being $a=10{\cdot}17$, $b=7{\cdot}49$, $c=18{\cdot}28$ Å, $\beta=100{\cdot}7^\circ$. Six layers around the b axis ($k=0$–5) were recorded and seven layers around the a axis ($h=0$–6), using the equi-inclination Weissenberg multiple-film technique with Cu $K\alpha$ radiation. Intensities were estimated visually against a set of timed exposures of a single reflexion and a total of 2856 independent reflexions were measured, representing *ca.* 89% of the possible number in the recorded reciprocal region.

The cross-correlated F^2 values were brought to approximately absolute scale by a Wilson (1942) statistical plot, from which an overall temperature factor $B=2{\cdot}36$ was deduced. No absorption corrections were applied. Scattering factors used were those of Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal (1955) for C, N and O, and of Dawson (1960) for S.

Analysis

The position of the two pairs of sulphur atoms of the disulphide bridges, presumed to be present in the two crystallographically independent molecules, with S–S distances of approximately 2·0–2·1 Å, were deduced by locating the respective S–S vectors in the near-origin region of a three-dimensional Patterson distribution sharpened to a point-atom condition and searching in section $P(u,\frac{1}{2},w)$ for possible Harker pair sets which would be consistent with all possible interaction vector peaks in the general distribution. Only one set led to a consistent distribution and from it the coordinates of the four sulphur atoms were determined, the y coordinate of one sulphur in molecule A being arbitrarily chosen as zero.

A direct ϱ_o synthesis phased with the sulphur contributions ($R_S=0{\cdot}51$) was inspected, and from this first three-dimensional distribution the positions of all atoms could be located with reasonable certainty and the molecular skeleton established, by consideration of permissible bond lengths, the presence of two (presumably structurally identical) molecules in the asymmetric unit proving of considerable assistance in the gradual elaboration of the skeletal model, by avoiding false interpretations (*vide e.g.* Fridrichsons, Mathieson & Sutor, 1963; Mackay & Mathieson, 1965). The molecules were found to be essentially identical in structure except for the location of the methylene hydroxyl oxygen atom, the conformation of which differed in the two molecules.

To establish the sterical aspects more precisely, refinement was carried out by means of full-matrix least-squares calculations. Although the identification of the nitrogen and oxygen atoms could have been inferred from the proposed chemical formula, an independent check was made by assuming those atoms (apart from the sulphur atoms) not clearly defined by tetrahedral coordination as carbon in the first cycle of structure factor calculations, and the differentiation of C, N and O was effected by allowing the occupancy factor for each atom to vary. The first set, on this basis, gave a reliability index $R=0{\cdot}24$ which, in the first least-squares cycle, varying all atomic coordinates and their occupancy factors, with a constant overall temperature factor $B=2{\cdot}72$, was reduced to 0·16. The oxygen and nitrogen atoms could thus be unambiguously identified, the occupancy factor changing from 1·00 to a mean value of 1·36 for the eight atoms corresponding to oxygen atoms in the proposed structure, to a mean value of 1·20 for the four nitrogen atoms and changing insignificantly for the remainder of the light (carbon) atoms. Two least-squares cycles were then carried out with the atoms differentiated as S, C, N and O, with the positional parameters and also individual (isotropic) temperature factors as variables. This step reduced R to 0·123 and a further two cycles, omitting 360 unobserved terms, gave $R=0{\cdot}112$ without significant improvement in the last cycle. As the shifts of the positional parameters in some cases still exceeded the standard deviation values, further improvement was to be expected only by the use of anisotropic temperature factors and by inclusion of the hydrogen atoms. The available computer storage permitted the refinement of only 154 variables in the full-matrix least-squares program, so the conversion to anisotropic factors and subsequent refinement was effected by splitting the 42 atoms of the two molecules into three separate groups. The S atoms were maintained common to each group and each block was refined separately. This manipulation, followed by a two-cycle refinement of positional parameters, reduced R to 0·103.

The position of the 28 hydrogen atoms of both molecules was determined with reasonable certainty from a three-dimensional difference synthesis, assisted by sterical considerations which give approximate locations for 18 of them. Inclusion of the hydrogen atoms and an interlayer rescaling of the F_o values improved the reliability index to 0·090 and a final three-block least-squares cycle with anisotropic temperature factors and positional parameters (except for the hydrogen atoms) as variables reduced it to 0·088. The shifts of the positional parameters were now much less than the standard deviations, indicating that with the present data no significant improvement by least-squares refinement could be expected. The analysis was therefore terminated with the calculation of a three-dimensional electron-density distribution, a composite map of which, with sections near atomic centres, projected down the *b* axis is shown in Fig. 1 for the two independent molecules of the asymmetric unit.

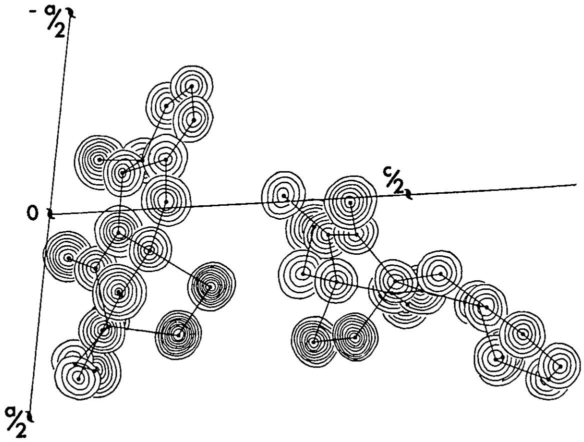

Fig. 1. Electron-density distribution for the two independent molecules, composed of sections near atomic centres, viewed down the *b* axis.

The final atomic parameters are given in Table 1. The mean standard deviation of the positional parameters according to the program output is 0·003 Å for the sulphur atoms, 0·012 Å for carbon, 0·009 Å for nitrogen and 0·008 Å for oxygen atoms. The hydrogen atom parameters were not refined and are probably reliable only to ±0·1 Å. The values of the observed and calculated structure factors are given in Table 2.

Absolute configuration

Although the anomalous dispersion contribution of sulphur for Cu $K\alpha$ radiation is relatively small ($f_S'' =$ 0·6) and the presence of four sulphur atoms in general positions would tend to diminish their combined effect, a careful inspection of the $1kl$ reflexions revealed definitely identifiable intensity differences in about 15 Bijvoet pairs $1kl$ and $1\bar{k}l$, indexed for a right-handed set of axes (Peerdeman & Bijvoet, 1956). Determination

Table 1. *Atomic parameters*

The correct absolute configuration refers to a left-handed set of axes.

	Molecule *A*			Molecule *B*		
Atom	*x/a*	*y/b*	*z/c*	*x/a*	*y/b*	*z/c*
S(1)	0·3524	0·7698	0·3838	0·3148	0·8743	0·1957
S(2)	0·3468	0·0054	0·4438	0·2012	0·0688	0·2365
C(1)	0·1971	0·6645	0·4066	0·2812	0·9529	0·0947
C(2)	0·0887	0·9375	0·4311	0·2030	0·2477	0·1100
C(3)	0·2079	0·9441	0·4938	0·1017	0·1492	0·1453
C(4)	0·8031	0·5776	0·4463	0·9794	0·2463	0·1591
C(5)	0·7123	0·4963	0·3774	0·8758	0·0993	0·1522
C(6)	0·6389	0·5702	0·3209	0·7758	0·0772	0·1892
C(7)	0·5564	0·4647	0·2660	0·6968	0·9068	0·1794
C(8)	0·5294	0·2892	0·2807	0·7409	0·7709	0·1463
C(9)	0·5835	0·2125	0·3567	0·8741	0·7703	0·1212
C(10)	0·7184	0·2930	0·3871	0·9045	0·9610	0·0969
C(11)	0·2337	0·6267	0·4883	0·1370	0·8942	0·0695
C(12)	0·1811	0·4886	0·3608	0·3740	0·8440	0·0546
C(13)	0·9824	0·7713	0·3210	0·4110	0·2201	0·0607
O(1)	0·0083	0·0616	0·4189	0·2005	0·4136	0·1070
O(2)	0·5858	0·0259	0·3484	0·8698	0·6417	0·0627
O(3)	0·7323	0·9770	0·4864	0·1065	0·7613	0·0299
O(4)	0·0617	0·4042	0·3688	0·3900	0·6663	0·0824
N(1)	0·0837	0·7827	0·3912	0·2969	0·1444	0·0888
N(2)	0·7625	0·2749	0·4689	0·0506	0·9929	0·0980
H(1)C(4)	0·925	0·567	0·453	0·000	0·300	0·208
H(2)C(4)	0·792	0·734	0·454	0·966	0·367	0·142
HC(6)	0·634	0·700	0·317	0·775	0·200	0·216
HC(7)	0·517	0·584	0·238	0·625	0·933	0·204
HC(8)	0·463	0·200	0·254	0·710	0·634	0·142
HC(9)	0·542	0·267	0·396	0·933	0·734	0·167
HC(10)	0·775	0·200	0·363	0·826	0·058	0·067
H(1)C(12)	0·238	0·367	0·367	0·359	0·836	0·002
H(2)C(12)	0·175	0·559	0·308	0·484	0·910	0·067
H(1)C(13)	0·885	0·800	0·329	0·400	0·183	0·000
H(2)C(13)	0·980	0·634	0·308	0·496	0·167	0·096
H(3)C(13)	0·017	0·835	0·284	0·413	0·383	0·071
HO(2)	0·633	0·984	0·392	0·975	0·634	0·042
HO(4)	0·058	0·258	0·388	0·333	0·550	0·092

Table 2. *Comparison of F_o and F_c values*

ℓ	F_o	F_c
	00ℓ	
1	30	24
2	65	58
3	40	40
4	111	114
6	49	51
7	70	67
8	6	6
9	16	13
10	9	8
11	22	24
13	9	9
14	8	8
15	14	14
16	21	20
17	21	20
18	7	6
19	11	10
20	12	11
21	18	18
22	4	1
23	12	12
	01ℓ	
1	62	77
2	62	66
3	54	53
4	75	74
5	41	42
6	38	41
7	38	31
8	36	35
9	39	38
10	18	16
11	32	29
12	18	17
13	9	9
14	12	13
15	19	19
16	23	23
17	11	11
18	6	7
19	10	10
20	31	25
21	13	12
22	10	8
23	8	9
	02ℓ	
0	11	12
1	46	52
2	7	5
3	44	42
4	43	41
5	29	29
6	27	29
7	19	20
8	18	17
9	54	56
10	33	36
11	33	35
12	41	39
13	30	32
14	14	16
15	28	29
16	11	12
17	10	10
19	8	8
20	11	10
22	15	13
	03ℓ	
1	21	25
2	26	33
3	38	38
4	5	7
5	61	55
6	53	47
7	52	49
8	35	35
9	38	37
10	25	26
11	12	12
12	13	13
13	12	11
14	21	25
15	10	12
16	11	12
17	10	9
18	7	6
19	6	5
20	12	10
21	8	8
22	7	8
	04ℓ	
0	42	38
1	71	61
2	47	39
3	31	29
4	32	27
5	46	39
6	4	5
7	29	27
8	39	35
9	12	11
10	19	21
11	19	21
12	18	18
13	17	17
14	18	19
15	15	17
16	6	7
17	10	12
18	20	18
19	13	11
20	6	5
21	7	8
	05ℓ	
1	17	21
2	20	21
3	50	44
4	17	18
5	21	21
6	27	26
7	5	5
8	14	13
9	13	14
10	9	10
11	13	15
12	7	7
13	5	7
14	16	20
15	8	8

ℓ	F_o	F_c
	05ℓ	
16	10	11
17	10	10
18	22	19
19	7	7
	06ℓ	
0	26	25
1	5	8
2	29	29
3	7	5
4	8	10
5	22	26
6	5	7
7	3	9
8	27	27
9	16	17
10	10	12
11	12	13
13	12	12
14	15	13
15	8	7
16	9	9
17	15	14
18	8	8
	07ℓ	
1	11	9
2	13	13
3	9	11
4	10	10
6	26	26
7	17	18
8	7	11
9	8	10
12	18	17
13	12	11
14	7	5
15	7	8
16	10	13
	08ℓ	
0	26	22
1	5	5
2	9	10
3	8	9
4	19	19
5	4	4
6	12	11
7	3	3
8	4	8
9	2	5
10	3	4
11	9	10
12	12	13
13	5	8
	09ℓ	
1	12	10
2	8	6
3	8	9
5	5	5
6	11	10
7	6	6
8	3	3
	10ℓ	
-22	6	5
-21	9	9
-20	24	20
-18	6	7
-17	12	11
-16	11	12
-15	27	28
-14	19	17
-12	29	27
-11	25	23
-10	15	16
-9	18	16
-8	11	13
-7	28	31
-6	38	38
-5	62	64
-4	31	31
-3	22	20
-2	61	57
-1	90	81
0	40	41
1	31	27
3	102	94
4	42	45
5	58	62
6	44	41
7	85	85
8	36	38
9	35	34
10	9	10
11	40	40
14	23	23
15	7	6
16	10	9
18	7	6
19	13	11
20	16	14
21	12	10
22	5	6
23	4	9
	11ℓ	
-23	6	6
-22	8	6
-21	20	18
-20	4	6
-19	18	14
-18	19	17
-17	20	17
-16	22	20
-15	16	18
-14	5	6
-12	22	23
-11	11	12
-10	34	35
-9	54	56
-8	50	47
-7	56	55
-6	36	35
-5	27	27
-4	58	54
-3	17	17
-2	58	59
-1	67	65
0	72	75
1	65	67
2	35	35

ℓ	F_o	F_c
	11ℓ	
3	27	30
4	69	72
5	86	97
6	78	83
7	28	31
8	12	11
9	37	39
10	37	35
11	9	10
12	20	19
13	42	39
14	17	16
15	19	17
16	17	14
17	22	19
18	4	3
19	11	11
20	7	7
21	3	3
22	17	15
	12ℓ	
-22	6	5
-21	16	12
-18	10	10
-17	6	7
-16	11	13
-15	21	20
-14	27	26
-13	19	18
-12	28	27
-11	27	28
-10	37	39
-9	3	4
-8	18	17
-7	24	24
-6	91	85
-5	54	49
-4	47	46
-3	56	51
-2	33	31
-1	12	15
0	12	9
1	31	27
2	9	7
3	22	19
4	30	29
5	25	26
6	19	24
7	52	52
8	36	36
9	42	42
10	11	13
11	33	31
12	16	17
13	25	27
14	15	16
15	10	10
16	16	16
17	9	10
18	12	13
19	9	9
20	11	10
21	19	17
22	5	4
	13ℓ	
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-20	10	11
-18	13	14
-17	7	6
-16	7	7
-15	21	21
-14	18	17
-13	30	29
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-11	12	11
-10	28	30
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-8	21	22
-7	41	45
-6	49	53
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-4	5	5
-3	32	39
-2	18	17
-1	70	71
0	39	36
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17	8	9
18	14	12
19	14	14
20	10	8
21	7	5
	14ℓ	
-21	4	3
-20	7	7
-19	16	14
-18	8	8
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-16	12	12
-15	19	18
-14	7	8
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-10	34	33
-9	24	25
-8	10	13
-7	4	5
-6	15	15
-5	23	21
-4	7	9
-3	57	44
-2	25	26
-1	15	15
0	11	10
1	61	52
2	19	18
3	42	38

ℓ	F_o	F_c
	14ℓ	
4	15	16
5	15	17
6	36	33
7	7	9
8	21	24
9	10	12
10	9	14
11	6	6
12	17	18
14	34	34
15	13	14
16	12	11
17	13	12
18	17	15
19	8	8
20	3	3
	15ℓ	
-20	3	3
-19	8	8
-18	17	16
-17	14	14
-16	13	12
-15	4	6
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-12	23	22
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-1	24	20
0	16	14
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11	26	28
12	9	12
13	15	14
14	14	14
15	5	5
16	5	5
17	16	15
18	9	8
	16ℓ	
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-16	8	7
-15	15	13
-14	11	10
-13	4	6
-12	4	8
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-7	21	24
-6	16	16
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-2	14	10
0	30	27
1	20	21
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-1	21	19
1	5	8
2	5	4
5	5	9
7	11	13
11	13	12
12	13	12

ℓ	F_o	F_c
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	13,0,ℓ	
-7	4	4
-6	7	9
-3	6	5
-2	5	5
	13,1,ℓ	
-5	3	3

of the sense of the inequalities for these pairs was made independently by three observers with no contradictions occurring. The differences (1)

$$D=|F_+|^2-|F_-|^2=-\frac{4f''_S}{f_S}(AB_S-BA_S) \qquad (1)$$

calculated on the basis of a right-handed set of axes for these pairs (Patterson, 1963), as can be seen from Table 3, have in all cases the opposite sign, so that the absolute configuration of the gliotoxin molecules is correctly represented by the atomic positions of Table 1, referred to a left-handed set of coordinate axes.

Table 3. *Terms used to determine the absolute configuration*

hkl	$(AB_s - BA_s)$	$F_c^2(hkl) \gtrless F_c^2(h\bar{k}l)$	$I(hkl) \gtrless I(h\bar{k}l)$
111	+1700	<	>
113	−1285	>	<
114	+3055	<	>
$11\bar{2}$	−1848	>	<
$11\bar{5}$	+868	<	>
124	−296	>	<
125	+410	<	>
126	−454	>	<
$12\bar{5}$	−1385	>	<
$12\bar{6}$	+632	<	>
$12\bar{7}$	+574	<	>
$13\bar{3}$	−712	>	<
$13\bar{6}$	−304	>	<
$13\bar{8}$	+220	<	>
$1,3,\bar{10}$	−393	>	<

Description of the structure and configurational details

The structure of the gliotoxin molecule, ignoring configurational detail, accords with the conclusion of Bell *et al.* (1958) and consists of a 1,4-disulphide-bridged 2,5-piperazinedione system, linked through a pyrrolidine-type five-membered ring to a 1,3-cyclohexadiene ring, with only three side groups (-OH, -CH_2OH, -CH_3) attached to this skeleton. The sterical disposition of one of the two crystallographically independent molecules in its correct absolute configuration is shown in Fig. 2. The bond lengths and bond angles are given in Tables 4 and 5 with the mean values for both molecules shown in Fig. 3. The differences between corresponding bonds in the two molecules do not exceed 0·03 Å, except for the three bonds in the diene system and bond N(2)-C(3). Although for these bonds the differences are between 3σ and 5σ, there do not seem to be any crystallographic or chemical reasons to regard the deviations as significant and real, their mean values, the same as for all other bonds, agreeing satisfactorily with published and accepted values for similar bond types. Particularly in analyses of this type, in which two rigid molecules of chemically identical structure permit an internal comparison of presumably equivalent interatomic dimensions, deviations of this order tend to raise questions as to either the influence of some unsuspected and not very obvious systematic error whose effect can accumulate in certain regions of the structure or the significance and validity of the standard deviations which are extracted from the least-squares refinement procedure in normal use. Owing to the low accuracy of the hydrogen positions, deduced from the difference distribution and not refined, the calculated CH and OH bond lengths (not listed in Table 4) vary from 0·91 to 1·23 Å, the mean value of the 28 bonds being 1·06 Å.

The fused rings form a rigid molecular framework, and as its structure is identical in both molecules it is

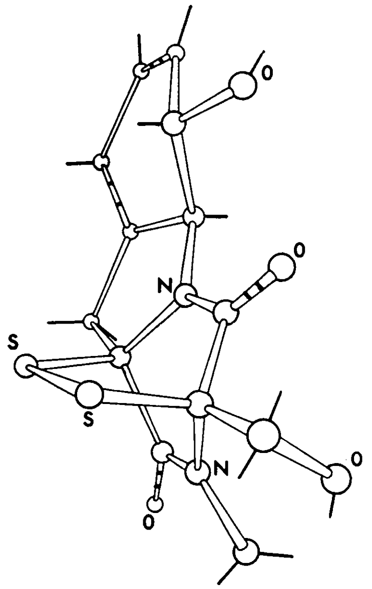

Fig. 2. Steric disposition of one molecule.

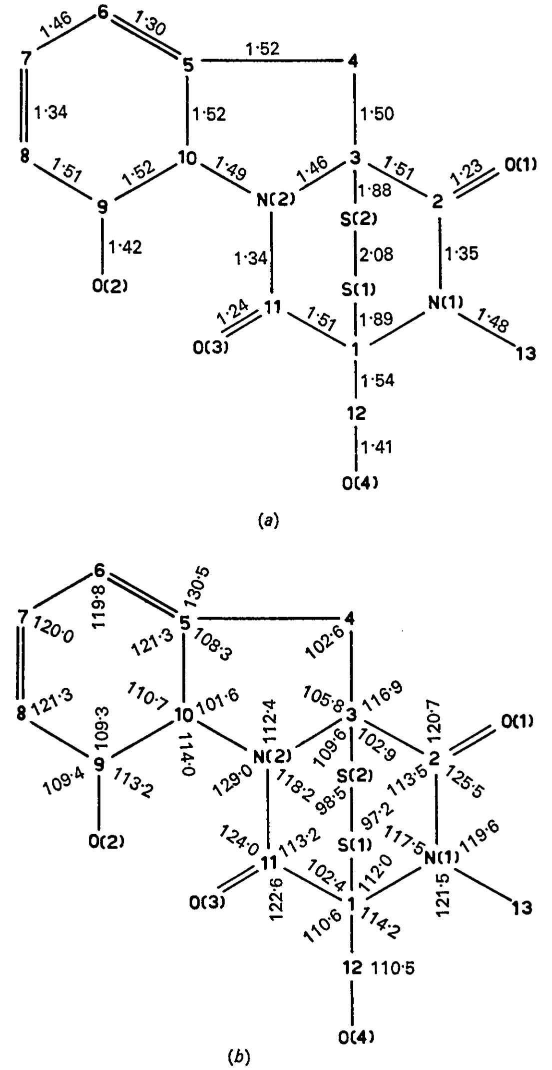

Fig. 3. Mean values of (*a*) bond lengths and (*b*) bond angles.

Table 4. *Bond lengths*

Bond	Molecule *A*	Molecule *B*
S(1)S(2)	2·08 Å	2·08 Å
C(1)S(1)	1·88	1·91
C(3)S(2)	1·88	1·88
C(1)N(1)	1·44	1·45
C(3)N(2)	1·44	1·49
C(2)N(1)	1·37	1·34
C(11)N(2)	1·35	1·33
N(1)C(13)	1·49	1·47
N(2)C(10)	1·49	1·50
C(2)O(1)	1·23	1·24
C(11)O(3)	1·24	1·24
C(12)O(4)	1·40	1·42
C(9)O(2)	1·41	1·43
C(1)C(12)	1·55	1·53
C(1)C(11)	1·50	1·52
C(2)C(3)	1·51	1·51
C(3)C(4)	1·50	1·50
C(4)C(5)	1·54	1·51
C(5)C(6)	1·28	1·33
C(6)C(7)	1·42	1·50
C(7)C(8)	1·38	1·31
C(8)C(9)	1·51	1·51
C(9)C(10)	1·51	1·54
C(10)C(5)	1·53	1·51

Table 5. *Bond angles*

Atoms	Molecule *A*	Molecule *B*
C(1)C(12)O(4)	109·4°	111·5°
C(1)S(1)S(2)	97·6	96·8
S(1)S(2)C(3)	98·4	98·6
C(11)C(1)N(1)	110·6	112·2
S(1)C(1)C(12)	104·2	106·4
C(11)C(1)S(1)	103·7	101·2
S(1)C(1)N(1)	112·0	112·0
C(11)C(1)C(12)	111·0	110·3
C(12)C(1)N(1)	114·6	113·9
C(2)C(3)N(2)	113·4	109.1
S(2)C(3)C(4)	110·9	109·4
C(2)C(3)S(2)	102·1	103·8
S(2)C(3)N(2)	109·6	109·6
N(2)C(3)C(4)	106·1	105·5
C(2)C(3)C(4)	114·7	119·2
O(1)C(2)C(3)	121·7	119·8
O(1)C(2)N(1)	126·0	125·0
N(1)C(2)C(3)	112·2	114·9
N(2)C(11)O(3)	123·5	124·5
N(2)C(11)C(1)	113·3	113·1
O(3)C(11)C(1)	122·9	122·3
C(2)N(1)C(13)	117·3	122·0
C(2)N(1)C(1)	118·0	117·1
C(1)N(1)C(13)	122·2	120·9
C(3)N(2)C(10)	113·1	111·7
C(3)N(2)C(11)	117·8	118·7
C(10)N(2)C(11)	128·8	129·2
C(3)C(4)C(5)	102·6	102·7
C(4)C(5)C(6)	131·1	129·3
C(4)C(5)C(10)	107·0	109·7
C(6)C(5)C(10)	121·8	120·9
C(5)C(10)N(2)	101·9	101·3
C(5)C(10)C(9)	109·9	111·6
C(9)C(10)N(2)	114·8	113·2
C(8)C(9)C(10)	109·8	108·9
C(8)C(9)O(2)	109·8	109·0
O(2)C(9)C(10)	113·9	112·8
C(5)C(6)C(7)	120·5	119·2
C(6)C(7)C(8)	120·3	119·7
C(7)C(8)C(9)	119·4	123·3

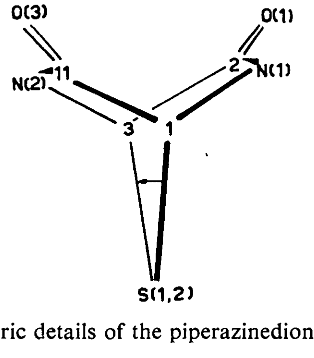

Fig. 4. Steric details of the piperazinedione system.

plausible to assume that this structure of the skeleton and its chromophore groups is also retained by the free molecules in solution.* The only atom not rigidly linked in the framework (apart from seven hydrogen atoms of the side groups) is the oxygen O(4) of the –CH$_2$OH group, which can rotate around bond C(1)-C(12). In both molecules, it is in the staggered (transoidal) configuration, but in molecule *A* it is *trans* to S(1), whereas in molecule *B* it is *trans* to N(1).

Whereas in diketopiperazine itself the piperazinedione ring system is planar (Corey, 1938; Vainshtein, 1955; Degeilh & Marsh, 1959), this ring system in gliotoxin, as in sporidesmin, is constrained to a boat form by the disulphide bridge. Owing to the steric strains imposed by this bridge and by the asymmetric link to the five-membered pyrrolidine ring, the two groups, C(1)C(11)N(2)C(3) and C(1)N(1)C(2)C(3), forming the sides of the boat are not quite planar, the dihedral angles around N(2)C(11) and C(2)N(1) being 1·4 and 3·5° in molecule *A* and 3·5 and 6·7° in molecule *B*. The mean dihedral angle between the sides of the 'boat' is 129° in *A* and 132° in *B*.

Whereas in compounds not involving strain, the CSSC dihedral angle is *ca.* 100° (Pauling, 1949; Abrahams, 1956), here it is restricted to a much lower value, being 8·8 and 15·8° in molecules *A* and *B* respectively. The difference may arise from the different disposition of the –CH$_2$OH group in both molecules, the more symmetrical disposition in *A* resulting in the smaller angle, comparable to the angle in the sporidesmin molecule (9·5°). In both molecules the chirality of the CSSC group is left-handed (Fig. 4). The contribution of the disulphide-bridged piperazinedione system can be associated with a negative peak (maximum at 233 mμ) in the circular dichroism curves of gliotoxin, sporidesmin and their derivatives containing the same system (Beecham, Fridrichsons & Mathieson, 1966)

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* Support for this contention is given by the consistent circular dichroic behaviour of gliotoxin in solution and in the solid state (Ziffer & Charney, 1966).

and it can be therefore concluded that all these compounds have the same absolute configuration.

The bond lengths in the piperazinedione system agree satisfactorily with the values obtained in the structure refinement of the diketopiperazine molecule by Degeilh & Marsh (1959), but owing to the change in conformation from planar to boat, the bond angles differ (Table 6). In view of the near agreement of the corresponding angles in both molecules of gliotoxin and also in that of sporidesmin, the mean values of the bond angles derived here can be regarded as characteristic of this sterically distorted cage structure. In the disulphide bond the SS distance of 2·08 Å indicates definitely a single bond type and the mean bond angle CSS (97·9°) is intermediate between the values for open chain (104–107°) and five-membered cyclic disulphides (92–96°) (*e.g.* Foss, Johnsen & Tverdten, 1958; Foss & Tjomsland, 1958). Although the CS distance of 1·89 Å is larger than the accepted value for a single bond (1·82Å), this bond elongation seems to be real (1·90 Å in sporidesmin) and longer CS bonds have been found also in other compounds containing a disulphide group, *e.g.*, 1·87 Å in diglycylcystine (Yakel & Hughes, 1954). The five-membered ring fused to the piperazinedione system is similar to that in sporidesmin, except that the configuration at C(10) is opposite and the three bonds at C(5) are coplanar. The molecule therefore assumes a more elongated form and not the curved one noted in sporidesmin. The group C(3)N(2)C(10)-C(5) is almost planar, with C(4) out of this plane by *ca.* 30°. The cyclohexadiene ring has identical skew-chair configuration in both independent molecules (Fig. 5), the dihedral angles of the skew diene C(5)-C(6)C(7)C(8) being 15·4 and 12·6° and the dihedral angle C(8)C(9)C(10)C(5) 44·8 and 44·7° in molecules *A* and *B* respectively. Although the corresponding bond lengths of the diene system in the two molecules reveal differences not explained (see above) the mean values of bonds $-C=C-$ (1·325 Å) and $=C-C=$ (1·46 Å) are in accord with similar bond types in other compounds (Costain & Stoicheff, 1959) and the dihedral angles are in reasonable agreement with the values of 17·5 and 45° derived in a less direct manner for cyclohexadiene itself by microwave techniques (Butcher, 1965). The chirality of the skew diene is left-handed and the implication of this result in regard to circular dichroism measurements of gliotoxin is discussed elsewhere (Beecham & Mathieson, 1966).

Packing

The disposition of the molecules in the unit cell viewed down the *b* axis is shown on Fig. 6. A particular feature is the close association of the disulphide groups and their skew relationship in which S(1) of molecule *A* is almost equidistant from S(1) and S(2) of molecule *B* and S(1) of molecule *B* is similarly disposed in relation to S(1) and S(2) of molecule *A* (Fig. 6). The possibility that interactions between disulphide groups might be of wider significance was investigated by inspecting a number of structure analyses containing this group. Certain approach distances of this type were noted, *e.g.* for 4-methyl-1,2-dithiacyclopent-4-ene-3-thione (Kehl & Jeffrey, 1958; Jeffrey & Shiono, 1959) and also in the case of a diselenide (Kruse, Marsh & McCullough, 1957) but the totality of observations does not suggest a feature of major significance in the packing of such molecules. The possibility of weak bonding between covalent sulphur and halide anions has also been noted (*e.g.* Hordvik & Kjøge, 1965).

Table 6. *Comparison of bond lengths and angles in the piperazinedione system of gliotoxin with the values in diketopiperazine*

	Gliotoxin	Diketopiperazine
C=O	1·24	1·239
C–C (keto)	1·51	1·499
C–N	1·45	1·449
N–C (keto)	1·35	1·325
C C (keto) N	113·4	118·9
C C (keto) O	121·7	118·5
N C (keto) O	124·8	122·6
C (keto) N C	117·9	126·0
C (keto) C N	111·3	115·1

The mutual disposition of the molecules is determined by numerous van der Waals contacts, some of which (< 4 Å) are indicated in Fig. 6 and listed in Table 7. The short distance between keto oxygen O(1) and hydroxyl oxygen O(4) in molecules above one another in the **b** direction (2·81 and 2·80 in *A* and *B*) indicates a hydrogen bond and an internal hydrogen bond (2·71 and 2·74 Å), connects also O(3) and O(4) in both molecules.

We would like to express our thanks to Drs P. J. Wheatley and J. J. Daly (Monsanto, Zurich) and Dr J. A. Wunderlich (Division of Applied Chemistry, C.S.I.R.O.) for the use of their crystallographic programs for initial calculations on an Elliott 803 computer, to Dr J. C. B. White (Chemistry Department, University of Melbourne) for the use of his MUFRI Fourier program and to Dr D. A. Wright (Defence Standards Laboratories, Melbourne) for the use of his adaptations of the Busing–Levy ORFLS and Shoemaker DISTAN programs to the C.S.I.R.O. CDC3600 computer. We also wish to thank Mr L. F. Power (University College, Townsville) for his assistance in the assessment of Bijvoet pair intensities and L. Mathieson for assistance in the survey of disulphide structures.

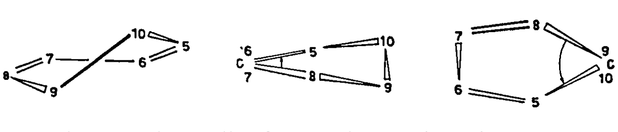

Fig. 5. Steric details of the cyclohexadiene ring.

Table 7. *Some approach distances less than* 4 Å

Single prime for molecules related by screw axes, double prime for translations along the *a* or *b* axes.

Atoms		Atoms		Atoms	
*A*S(1)*B*S(1)	3·48 Å	*A*C(13)*B*S(2)	3·68 Å	*B*S(1)*B*″C(7)	3·96 Å
*A*S(1)*B*S(2)	3·62	*A*C(13)*B*C(5)	3·94	*B*C(1)*B*′C(10)	3·32
*A*S(1)*A*′O(2)	3·21	*A*C(13)*B*C(6)	3·69	*B*C(2)*B*′O(3)	3·67
*A*S(1)*A*′C(7)	3·98	*A*C(13)*A*′C(4)	3·50	*B*C(2)*B*′O(2)	3·20
*A*S(1)*A*′C(6)	3·65	*A*C(13)*A*′C(5)	3·73	*B*C(3)*B*′O(3)	3·60
*A*S(2)*B*S(2)	3·83	*A*C(13)*A*′C(6)	3·80	*B*C(3)*B*′O(2)	3·87
*A*S(2)*A*′C(9)	3·49	*A*C(13)*B*C(9)	3·61	*B*C(4)*B*′O(3)	3·40
*A*S(2)*A*′O(2)	3·25	*A*C(13)*B*C(8)	3·65	*B*C(5)*B*′O(3)	3·58
*A*C(4)*A*′O(4)	3·46	*A*C(13)*B*C(7)	3·66	*B*C(7)*B*″S(1)	3·96
*A*C(4)*A*′N(1)	3·55	*A*O(1)*A*′C(10)	3·38	*B*C(7)*B*″C(12)	3·66
*A*C(5)*A*′O(4)	3·65	*A*O(1)*A*′N(2)	3·24	*B*C(7)*B*″O(4)	3·75
*A*C(5)*A*′C(13)	3·73	*A*O(1)*A*′O(3)	3·33	*B*C(8)*B*″C(12)	3·84
*A*C(6)*A*′C(13)	3·80	*A*O(1)*A*″O(4)	2·81	*B*C(8)*B*″O(4)	3·63
*A*C(6)*A*′S(1)	3·65	*A*O(2)*B*C(6)	3·80	*B*C(8)*B*′C(13)	3·83
*A*C(6)*B*C(8)	3·84	*A*O(2)*A*′S(1)	3·21	*B*C(10)*B*′O(1)	3·70
*A*C(6)*B*C(7)	3·74	*A*O(2)*A*″C(6)	3·51	*B*C(10)*B*′O(3)	3·22
*A*C(7)*B*S(1)	3·99	*A*O(2)*B*S(1)	3·72	*B*C(11)*B*″O(1)	3·70
*A*C(7)*B*O(4)	3·78	*A*O(2)*B*C(7)	3·59	*B*C(11)*B*′O(3)	3·91
*A*C(7)*B*C(8)	3·89	*A*O(4)*B*S(2)	3·93	*B*C(11)*B*′O(2)	3·04
*A*C(8)*B*S(2)	3·68	*A*O(4)*A*′N(2)	3·95	*B*C(12)*B*′O(2)	3·71
*A*C(8)*B*S(1)	3·95	*A*O(4)*B*C(4)	3·95	*B*C(13)*B*′O(2)	3·35
*A*C(8)*B*C(6)	3·96	*A*O(4)*A*″C(2)	3·67	*B*O(1)*B*′O(3)	3·80
*A*C(10)*A*′O(1)	3·38	*A*N(1)*B*S(2)	3·91	*B*O(1)*B*″O(4)	2·80
*A*C(10)*A*′O(4)	3·66	*A*N(1)*A*′C(4)	3·55	*B*O(1)*B*′O(2)	3·67
*A*C(11)*A*′O(1)	3·27	*A*N(2)*A*′O(1)	3·24	*B*O(3)*B*′O(2)	3·34
*A*C(12)*B*S(2)	3·91	*A*N(2)*A*′O(4)	3·95		

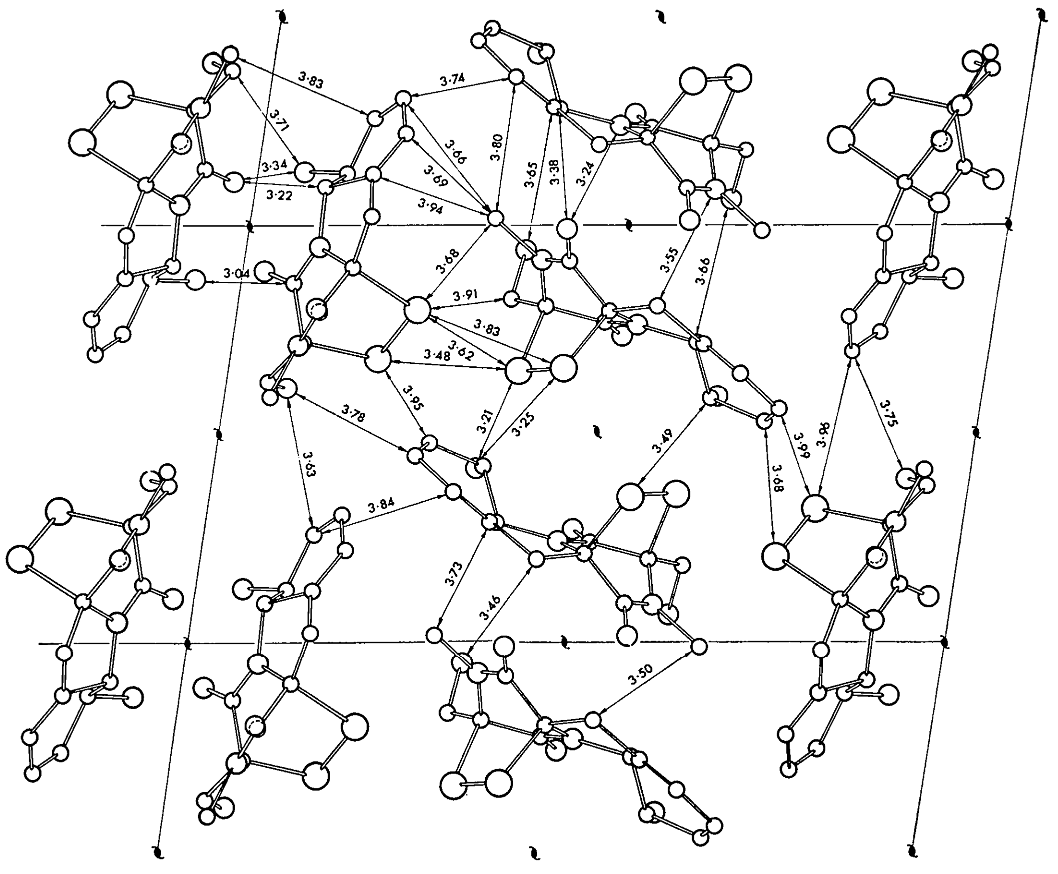

Fig. 6. Packing of the molecules and some approach distances.

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Molecular Complexes Exhibiting Polarization Bonding, X.[*] The Crystal and Molecular Structure of the 7,7,8,8-Tetracyanoquinodimethane–Bis-(8-hydroxyquinolinato)copper(II) Complex

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The 1:1 complex formed between tetracyanoquinodimethane and bis-(8-hydroxyquinolinato)copper(II) crystallizes as black triclinic crystals, space group $P\bar{1}$, with one molecule of complex in the unit cell of dimensions $a = 12{\cdot}00 \pm 0{\cdot}012$, $b = 7{\cdot}54 \pm 0{\cdot}008$, $c = 7{\cdot}12 \pm 0{\cdot}007$ Å; $\alpha = 112{\cdot}50° \pm 0{\cdot}5°$, $\beta = 88{\cdot}75° \pm 0{\cdot}5°$, $\gamma = 96{\cdot}75° \pm 0{\cdot}5°$. The structure was solved by Patterson methods and refined by least-squares methods using 2651 independent reflexions measured on a linear diffractometer. The final residual, R, was 0·068. The component molecules are stacked in a plane-to-plane manner so that the double bond adjacent to one dicyanomethylene group of the tetracyanoquinodimethane molecule lies over the 5:8 positions of one donor molecule, whilst the other double bond is similarly oriented with respect to the benzenoid ring of the centrosymmetrically related donor molecule. The perpendicular separation of the molecules, in the region of overlap, is approximately 3·2 Å.

Introduction

The powerful electron acceptor tetracyanoquinodimethane (TCNQ) was first shown by Melby, Harder, Hertler, Mahler, Benson & Mochel (1962) to form an unusual set of complexes with metal chelates acting as electron donor components. It was felt that a detailed crystallographic examination of the 1:1 complex formed between TCNQ and bis-(8-hydroxyquinolinato)copper(II) would be of interest to ascertain whether the predominant factor influencing the orientation and packing of the molecules is the charge-transfer interaction between the donor and acceptor, the coordination requirements of the copper atom, or simply general packing requirements. A direct comparison of the

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[*] Part IX, Williams & Wallwork (1967).

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