Acta Cryst. (1982). B**38**, 2471–2473

Structure of the Thallium Salt of Cationomycin

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(*Received* 13 *March* 1982; *accepted* 5 *April* 1982)

Abstract. $C_{45}H_{69}O_{15}Tl$, orthorhombic, $P2_12_12_1$, $a = 21{\cdot}194\ (3)$, $b = 16{\cdot}486\ (4)$, $c = 14{\cdot}130\ (3)$ Å, $U = 4937\ (2)$ Å^3, $Z = 4$, $D_c = 1{\cdot}42$ Mg m^{-3}, $R = 5{\cdot}8\%$ for 3099 independent reflections. The absolute configuration was determined by anomalous dispersion. Cationomycin is a new polyether ionophore antibiotic. The molecule has a tadpole shape. The head of the molecule surrounds the Tl atom. The Tl atom is coordinated by seven O atoms with Tl···O distances ranging from 2·79 (1) to 3·07 (1) Å. The exterior surface of the head consists of hydrophobic groups.

Introduction. Cationomycin is a new polyether ionophore antibiotic, isolated from a new species of rare actinomycete designated as *Actinomadura azurea*. The antibiotic is active against Gram-positive bacteria including mycobacteria and shows remarkable chicken-coccidiostat activity (Nakamura, Kobayashi, Sakurai & Isono, 1981).

The single crystals of the thallium salt were prepared as follows: Cationomycin free acid was distributed in ethyl acetate and 0·1 mol dm^{-3} thallium acetate, made slightly alkaline with dilute NH_4OH. The ethyl acetate layer was separated and washed several times with water, which was then concentrated *in vacuo* to dryness. The residue was crystallized from hot methanol. Recrystallization was repeated several times from the same solvent, affording single crystals of the thallium salt; m.p. 478–481K. Analysis: calculated for $C_{45}H_{69}O_{15}Tl$:C 51·25, H 6·59, Tl 19·38, found: C 51·08, H 6·80, Tl 18·59 at. %; FD/MS $(M + H)^+$ 1055, $(M + Na)^+$ 1077.

X-ray diffraction data were collected on a Rigaku automated four-circle diffractometer with graphite-monochromatized Mo $K\alpha$ radiation. Since the crystal deteriorated during the exposure to X-rays, two crystals of *ca* 0·3 × 0·3 × 0·2 mm were used for the data collection. After being corrected for Lorentz, polarization and deterioration factors, these data were combined to give 3099 independent reflections. The Tl position was determined by a Patterson map. The z coordinate was almost 0·25, and the first heavy-atom Fourier map showed a pseudo mirror plane through the Tl atom. Several groups of atoms with a reasonable shape were carefully selected from the map and the skeleton of the molecule was deduced from the successive Fourier and least-squares calculations, and the R index was reduced to 9·4%. At this stage 13 reflections with large Bijvoet differences were selected and the absolute configuration was determined from the measurement of these reflections (Table 1). Subsequent refinements with the correct chirality revealed all non-hydrogen atoms and the final R index converged to 5·8% by the block-diagonal least-squares method. Unit weight was used for all observed reflections, and anisotropic temperature factors were assigned to all non-hydrogen atoms. The atomic parameters are given in Table 2. The hydrogen-atom coordinates were calculated from these coordinates.*

* Lists of structure factors, hydrogen-atom parameters and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36850 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Determination of the absolute configuration*

h	k	l	$F_o(+)$	$F_o(-)$	$F_c(+)$	$F_c(-)$
1	1	2	284	273	285	268
1	1	3	138	154	140	153
1	3	1	89	32	84	31
1	3	2	103	57	84	39
2	2	1	103	81	152	129
2	2	2	167	119	191	141
2	2	3	122	140	125	146
2	2	4	138	122	133	114
2	4	2	203	184	204	185
3	1	1	135	113	154	136
3	1	2	178	162	198	178
3	3	2	186	194	198	212
4	6	1	235	257	220	237

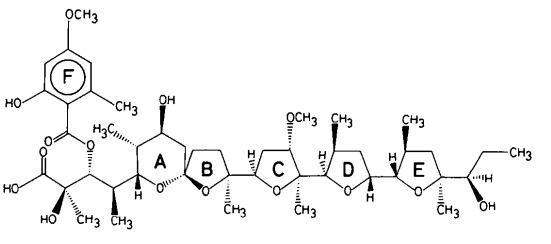

Fig. 1. The structure of cationomycin.

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Table 2. *Atomic parameters* ($\times 10^4$; $x,y \times 10^5$ *for* Tl)

The equivalent isotropic temperature factor is defined by

$$B_{eq} = \tfrac{4}{3} \sum_i \sum_j \beta_{ij} (a_i a_j).$$

	x	y	z	B_{eq}(Å^2)
Tl	23981 (3)	4773 (4)	2517 (1)	4·14 (2)
O(1)	3572 (8)	1023 (11)	1523 (15)	6·6 (6)
O(2)	3848 (8)	1591 (12)	2862 (15)	7·1 (7)
O(3)	4702 (8)	764 (10)	924 (12)	5·5 (5)
O(4)	5609 (6)	344 (9)	2285 (11)	4·2 (5)
O(5)	3877 (6)	−1214 (8)	3432 (11)	3·5 (4)
O(6)	3025 (6)	521 (9)	4255 (11)	3·9 (4)
O(7)	2801 (6)	−1051 (7)	3169 (10)	2·9 (4)
O(8)	1580 (6)	−1050 (8)	2287 (10)	3·2 (4)
O(9)	492 (7)	−2153 (9)	3459 (12)	4·2 (5)
O(10)	1128 (6)	239 (8)	3475 (11)	3·4 (4)
O(11)	1487 (6)	1744 (8)	2679 (11)	3·1 (4)
O(12)	2695 (7)	2212 (9)	2985 (11)	4·7 (5)
O(1)′	5941 (7)	496 (12)	3781 (11)	5·1 (5)
O(2)′	8604 (7)	507 (13)	1796 (13)	6·1 (6)
O(3)′	7077 (7)	685 (11)	4140 (11)	5·1 (5)
C(1)	3979 (11)	1253 (14)	2104 (18)	4·5 (7)
C(2)	4666 (11)	1064 (15)	1878 (18)	4·2 (7)
C(3)	4955 (8)	464 (12)	2621 (19)	3·1 (5)
C(4)	4675 (8)	−401 (13)	2727 (13)	3·0 (6)
C(5)	4060 (8)	−380 (12)	3298 (14)	2·7 (5)
C(6)	4103 (10)	32 (13)	4292 (16)	3·5 (6)
C(7)	3444 (10)	0 (13)	4748 (14)	3·0 (6)
C(8)	3204 (12)	−863 (16)	4768 (16)	4·8 (8)
C(9)	3265 (9)	−1327 (12)	3813 (17)	3·3 (6)
C(10)	3152 (11)	−2246 (13)	3926 (22)	5·1 (8)
C(11)	2922 (11)	−2472 (12)	2921 (17)	4·3 (7)
C(12)	2598 (9)	−1712 (10)	2597 (21)	3·6 (5)
C(13)	1859 (9)	−1780 (12)	2672 (25)	4·8 (8)
C(14)	1612 (10)	−1822 (16)	3674 (20)	4·7 (7)
C(15)	923 (9)	−1501 (13)	3552 (16)	3·2 (6)
C(16)	927 (8)	−1015 (12)	2600 (23)	3·8 (6)
C(17)	785 (9)	−99 (12)	2720 (14)	3·0 (6)
C(18)	87 (9)	192 (13)	2848 (16)	3·8 (6)
C(19)	217 (10)	1053 (14)	3134 (18)	4·2 (7)
C(20)	822 (10)	989 (12)	3777 (17)	3·4 (6)
C(21)	1298 (10)	1695 (12)	3654 (17)	3·6 (6)
C(22)	1046 (12)	2538 (13)	3910 (19)	4·6 (7)
C(23)	1498 (11)	3040 (14)	3351 (20)	4·6 (8)
C(24)	1677 (9)	2592 (11)	2400 (23)	3·7 (6)
C(25)	2395 (10)	2535 (11)	2209 (16)	4·2 (7)
C(26)	2681 (13)	3372 (14)	1954 (24)	7·2 (10)
C(27)	3357 (13)	3280 (17)	1572 (28)	7·5 (11)
C(28)	5030 (12)	1895 (14)	1949 (20)	5·2 (8)
C(29)	4603 (12)	−887 (14)	1779 (18)	4·5 (7)
C(30)	4601 (10)	−401 (18)	4894 (16)	4·7 (7)
C(31)	2728 (13)	−1530 (15)	1477 (18)	5·2 (8)
C(32)	316 (13)	−2479 (18)	4341 (24)	6·5 (10)
C(33)	508 (12)	−1374 (16)	1799 (20)	5·1 (8)
C(34)	−262 (10)	−262 (16)	3617 (20)	4·9 (8)
C(35)	991 (14)	2699 (14)	4918 (18)	5·0 (8)
C(36)	1263 (14)	2842 (16)	1573 (22)	6·2 (9)
C(1)′	6701 (7)	411 (11)	2557 (21)	3·0 (4)
C(2)′	6868 (10)	309 (13)	1620 (16)	3·6 (6)
C(3)′	7510 (10)	309 (12)	1326 (16)	3·7 (6)
C(4)′	7985 (9)	455 (15)	2019 (16)	3·9 (6)
C(5)′	7834 (9)	596 (13)	2956 (17)	3·9 (6)
C(6)′	7207 (9)	549 (14)	3236 (15)	3·4 (5)
C(7)′	6057 (9)	420 (13)	2931 (15)	3·4 (5)
C(8)′	6408 (11)	144 (20)	725 (19)	6·3 (9)
C(9)′	8791 (14)	405 (24)	853 (19)	7·5 (11)

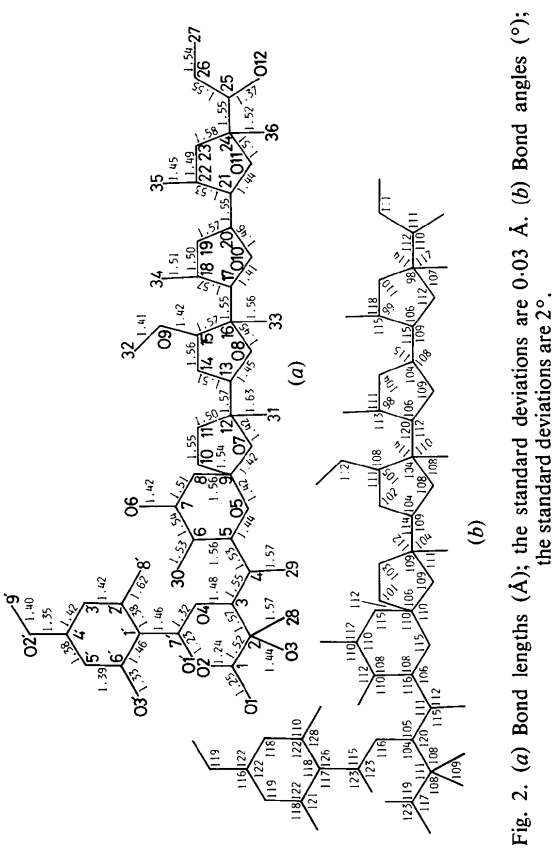

Fig. 2. (*a*) Bond lengths (Å); the standard deviations are 0·03 Å. (*b*) Bond angles (°); the standard deviations are 2°.

Discussion. The molecule is shown in Fig. 1 and bond distances and angles are in Fig. 2. The molecule has four tetrahydrofuran rings (*B–E*) and one tetrahydropyran ring (*A*) forming a spiro-acetal with one of the former (*B*). Many of the ionophore antibiotics have similar polyether ring systems. Out of more than 60 polyether antibiotics hitherto known, lasalocid A, B (Westley, Evans, Williams & Stempel, 1970), noboritomycin (Juselen, King, Kuhn, Loosli & Wartberg, 1978), CP-4461 (Tone *et al.*, 1978) and calcimycin (A-23187) (Chaney, Demarco, Jones & Occolowitz, 1974) are known to possess an aromatic acid in the backbone carbon chain. Carriomycin (Otake, Nakayama, Miyamae, Sato & Saito, 1977) and another eight antibiotics are known to possess a side-chain sugar, 2,3,6-trideoxy-4-*O*-methyl-D-*erythro*-hexopyranose. Cationomycin is unique in that this is the first example of a polyether antibiotic having an aromatic acyl side chain through an ester linkage. The molecule has a tadpole shape as shown in Fig. 3, with the planar tail consisting of 4-*O*-methyl-*o*-orsellinic acid ester. The backbone (27 carbon atoms) starts from the carboxyl group and forms a circular conformation around the Tl atom. The end of the side chain is connected by a hydrogen bond between the terminal hydroxy group O(12), and one of the oxygens, O(2), of the carboxyl group. The Tl atom is coordinated by seven O atoms with Tl···O distances ranging from 2·79 (1) to 3·07 (1) Å. The exterior surface of the head of the molecule consists of hydrophobic groups.

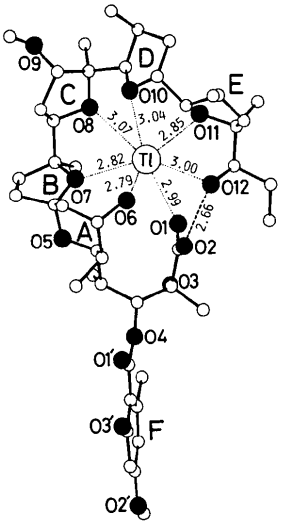

Fig. 3. The molecular shape. (Distances in Å.)

Cationomycin is of particular interest because of the exceptionally low toxicity to mice compared with other ionophore antibiotics (ID_0 200 mg kg^{-1}, intraperitoneal). In this respect, the role of the aromatic acyl tail in the biological activity may be worth further study.

Calculations were performed on a FACOM 230–75 computer of this Institute using the *UNICS* III program system (Sakurai & Kobayashi, 1979).

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Acta Cryst. (1982). B**38**, 2473–2475

Thallium Triacetate Monohydrate*

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(*Received* 5 *January* 1982; *accepted* 7 *April* 1982)

Abstract. $Tl[C_2H_3O_2]_3.H_2O$, monoclinic, $P2_1/c$, $a = 9{\cdot}311$ (4), $b = 14{\cdot}341$ (6), $c = 9{\cdot}198$ (2) Å, $\beta = 119{\cdot}69$ (2)°, $V = 1067{\cdot}0$ Å^3, $M_r = 399{\cdot}5$, $Z = 4$, $D_x = 2{\cdot}49$ Mg m^{-3}, $\mu = 15{\cdot}11$ mm^{-1}. The structure was refined by X-ray diffraction to $R = 0{\cdot}04$ for 577 observed reflections. The Tl atom is irregularly coordinated by eight O atoms (Tl–O = 2·17–2·78 Å). The angles between adjacent bonds correlate with the strengths of the bonds. The molecules are linked by a bridging acetate O atom and a hydrogen bond into columns running along **c**. There is a simple relation between the structure of the monohydrate and the anhydrous triacetate.

* *catena*-μ-Acetato-*O*, μ-*O'*-aquadiacetatothallium(III).

Introduction. Thallium triacetate monohydrate was prepared by dissolving 0·2 g of $Tl[CH_3CO_2]_3$ (Alfa Products) in 10 ml distilled water and leaving it uncovered at room temperature. Large colourless plates of the title compound appeared after several days. Since the crystals decomposed in a few hours when removed from the solution, the crystal used was ground to a cylinder and sealed in a Lindemann-glass capillary. The structure was determined by X-ray diffraction, experimental details being given in Table 1. When the structure had been fully refined with anisotropic temperature factors for Tl the largest positive and negative peaks in the residual electron density map were found in the neighbourhood of the Tl atom and were identified as arising from anisotropic extinction. Consequently the 15 strongest reflections were omitted

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