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The Crystal and Molecular Structure of Trofosfamide {3-(2-Chloroethyl)-2-[bis (2-chloroethyl)amino]perhydro-2H-1,3,2-oxazaphosphorine 2-Oxide, C₉H₁₈Cl₃N₂O₂P}

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Crystals of trofosfamide are monoclinic, space group $P2_1/c$ with cell dimensions: $a = 13.701$, $b = 13.913$, $c = 8.019$ Å and $\beta = 100.36^\circ$, with $Z = 4$. The crystal and molecular structure has been determined by single-crystal X-ray diffraction analysis. The structure was solved by direct methods and Fourier difference synthesis. The parameters were refined by full-matrix least-squares methods with individual anisotropic temperature factors to give the final R value of 0.074 for 2077 observed reflexions. Significant short distances of the P–N bonds are observed. Van der Waals interactions provide for the packing of the crystals.

Introduction

Trofosfamide, or ixoten, (Fig. 1) was developed in the research Laboratories of Asta-Werke, Wetsfallen (W. Germany). Trofosfamide is chemically a congener of endoxan (cyclophosphamide); its main advantage is its wide safety margin and consequently its markedly good tolerance to oral administration. Chemosensitive tumours, such as haemoblastoses and lymphoreticular tumours, may be treated with trofosfamide as initial therapy for induction of tumour remission and subse-

quently treated with the same drug to maintain remission.

Similarly to endoxan, trofosfamide is a primarily inactive transport form, thereafter to become activated in the body of the patient. The present study was undertaken to obtain a deeper insight into the configuration of this relevant drug.

Experimental

A powder sample of trofosfamide was kindly provided by Asta-Werke Laboratories. The sample was crystallized from an ether solution prepared by means of ether extraction in a Soxhlet apparatus, and subsequent cooling of the solution to a temperature of -10°C . The crystal data are collected in Table 1. Preliminary Weissenberg and precession photographs obtained with Cu $K\alpha$ radiation showed that the crystals are monoclinic, symmetry $2/m$, and systematic absences $0k0$ with k odd and $h0l$ with l odd suggested the space group $P2_1/c$. The intensity data were collected on an automatic four-circle Philips PW 1100 diffractometer with graphite-monochromatized Mo $K\alpha$ radiation and the $\omega/2\theta$ scan mode to a limit of $2\theta = 25^\circ$; 2656 independent reflexions were measured of which 2077 had intensities greater than 2σ , where $\sigma^2(I) = C_p + C_b + (0.04)^2 I^2$. C_p and C_b are peak and background counts respectively. Reflexions with intensities less than 2σ

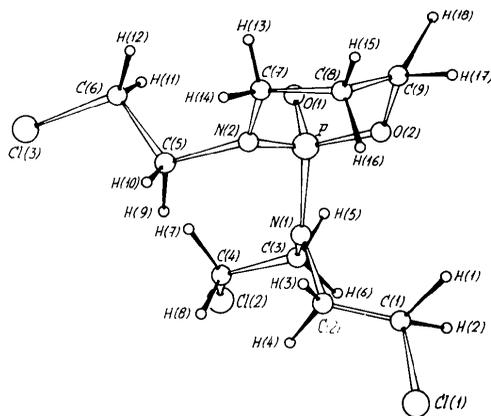


Fig. 1. The trofosfamide molecule.

Table 1. *Crystal data*

Lattice constants were determined by centring 30 reflexions and subsequent least-squares refinement

Molecular formula	$C_9H_{18}N_2O_2PCl_3$
Molecular weight	323.585
Monoclinic	Space group $P2_1/c$
$Z = 4$	Crystal size: $0.4 \times 0.35 \times 0.3$ mm
$a = 13.701(2) \text{ \AA}$	$V = 1502.5 \pm 3 \text{ \AA}^3$
$b = 13.913(2)$	$D_c = 1.37 \text{ g cm}^{-3}$
$c = 8.019(1)$	$\mu = 6.751 \text{ cm}^{-1}$
$\beta = 100.36(1)^\circ$	$\lambda(\text{Mo } K\alpha) = 0.7107 \text{ \AA}$

were classed as unobserved. The data were corrected for Lorentz and polarization effects, but not for absorption. An overall temperature factor ($B = 4.079 \text{ \AA}^2$) and scale factor were calculated from a Wilson plot and used to compute normalized structure factors (E) (Karle & Hauptman, 1956). The statistics of the E 's confirmed a centrosymmetric structure.

Structure determination and refinement

The structure was solved by direct methods with the multiresolution tangent formula program *MULTAN* (Main, Woolfson, Lessinger, Germain & Declercq, 1974). Phases of 150 reflexions with $E > 1.5$ were used. The solution with the highest figure of merit yielded an E map containing peaks corresponding to 11 of the expected 17 non-hydrogen atoms, and those remaining were located from a three-dimensional difference synthesis. The atomic positions, obtained from the E map and Fourier synthesis, were refined by a full-matrix least-squares method. Initially, individual isotropic temperature factors were used for all atoms, unit weights for the observed structure amplitudes and zero weights for the unobserved. An R value of 0.14 was obtained after three cycles of refinement. Another three cycles with anisotropic temperature factors reduced R to 0.10. At this stage, the positions of the H atoms, calculated from the molecular geometry assuming a C—H bond of 1.00 \AA and a H—C—H angle of 100.0° , were included. A three-dimensional difference synthesis also showed the location of the H atoms and the two were compared; some of the H atom positions varied slightly. Their isotropic thermal parameters were

assigned as those of the atoms to which the H's are bonded (Hamilton, 1959). The final least-squares calculations were made including the H atoms, but the latter were not refined. The final R value is 0.074. The weighting scheme is $w = kw_1w_2$ with $w_1 = 1/\sigma_f^2$ and $w_2 = 1/\sigma_s^2$, and σ_f, σ_s are as given in Table 2. After a new cycle of refinement $R' [= (\sum w\Delta^2/\sum w|F_o|^2)^{1/2}]$ for the observed reflexions is 0.073.

Table 3. *Positional ($\times 10^4$) parameters for non-hydrogen atoms*

Estimated standard deviations are given in parentheses.

	x	y	z
Cl(1)	-269 (2)	6925 (2)	353 (3)
Cl(2)	1225 (2)	4573 (2)	-6138 (2)
Cl(3)	3577 (2)	2193 (1)	301 (3)
P	3129 (1)	5744 (1)	-451 (2)
O(1)	3806 (3)	5600 (4)	-1650 (6)
O(2)	3199 (3)	6765 (3)	441 (5)
N(1)	1931 (3)	5683 (4)	-1442 (5)
N(2)	3208 (4)	5005 (3)	1187 (6)
C(1)	804 (6)	6814 (6)	-589 (9)
C(2)	1146 (4)	5792 (5)	-553 (7)
C(3)	1732 (5)	5624 (5)	-3301 (7)
C(4)	1550 (6)	4604 (5)	-3868 (8)
C(5)	2973 (5)	3961 (5)	869 (8)
C(6)	3867 (6)	3489 (6)	513 (14)
C(7)	3855 (5)	5219 (5)	2818 (8)
C(8)	3722 (6)	6255 (5)	3320 (8)
C(9)	3928 (5)	6936 (5)	1994 (8)

Table 4. *Positional and thermal parameters ($\times 10^3$) and bond distances (\AA) for the hydrogen atoms*

	x	y	z	U	C—H
H(1)	139	725	-2	74	1.05
H(2)	69	710	-176	74	0.87
H(3)	140	558	64	129	1.00
H(4)	62	538	-114	129	0.97
H(5)	221	558	-378	60	0.90
H(6)	118	599	-373	60	0.93
H(7)	215	424	-351	104	0.96
H(8)	99	435	-329	104	1.04
H(9)	237	389	-7	67	1.01
H(10)	271	367	182	67	0.99
H(11)	408	373	-56	99	1.01
H(12)	447	360	134	99	0.98
H(13)	457	508	276	73	1.01
H(14)	376	476	372	73	0.99
H(15)	420	640	445	85	1.04
H(16)	306	636	362	85	1.00
H(17)	392	761	236	72	0.99
H(18)	466	684	179	72	1.06

Table 2. *Weighting scheme*

s is $\sin \theta/\lambda$ and $K = 0.9972$.

$$\begin{aligned} \sigma_f &= (1.2806 - 0.1146 |F_o|) \text{ if } 0 < |F_o| < 2.1 \\ \sigma_f &= (0.7277 + 0.2050 |F_o|) \text{ if } 2.1 < |F_o| < 4.8 \\ \sigma_f &= (2.6652 - 0.2197 |F_o|) \text{ if } 4.8 < |F_o| < 8.2 \\ \sigma_f &= (0.8896 - 0.0008 |F_o|) \text{ if } 8.4 < |F_o| < 16.6 \\ \sigma_f &= (0.5331 - 0.0182 |F_o|) \text{ if } 16.8 < |F_o| < 38.00 \\ \sigma_s &= (2.088 - 3.6945 s) \text{ if } 0 < |F_o| < 0.39 \\ \sigma_s &= (0.3786 + 1.0079 s) \text{ if } 0.39 < |F_o| < 0.59 \\ \sigma_s &= (0.9452 + 0.2462 s) \text{ if } 0.59 < |F_o| < 0.70 \end{aligned}$$

The atomic coordinates for the non-hydrogen atoms are listed in Table 3.* Table 4 gives the atomic positions and isotropic temperature factors for H atoms, and C—H bonds.

The scattering factors used are those of *International Tables for X-ray Crystallography* (1974). The scattering factors were corrected for anomalous scattering by Cl and P with the following coefficients: Cl $\Delta f' = 0.1$, $\Delta f'' = 0.2$; P $\Delta f' = 0.1$, $\Delta f'' = 0.2$. All calculations were performed with the X-RAY system of crystallographic programs and carried out on a Univac 1108 Computer.

Results and description of the structure

Bond lengths and angles are collected in Table 5. The P coordination sphere is not different from that in similar compounds. The P—N bonds in trofosfamide are of different lengths and both are shorter than a single P—N bond.

It is considered that in cyclic phosphazenes and phosphates all the atoms attached to the P atom are allowed to participate in a molecular π -bonding system (Cruikshank, 1961; Craig & Paddock, 1962). When amino groups are attached to P the electrons from the N atom are transferred to the vacant 3d orbitals of P, and as a result shorter P—N bonds are expected. In a

number of amino-substituted cyclic phosphazenes, shorter exocyclic P—N bonds (1.62–1.68 Å, Ahmed & Pollard, 1972) than those accepted for a P—N single bond (1.77 Å) have been observed. In trofosfamide the two amino groups attached to the P atom also show short P—N bonds (1.63–1.65 Å); consequently a π -interaction along the P—N bond is expected. In this context it is interesting to consider that the chemical activity, and presumably the biological potency, of nitrogen mustard gas is known to depend on the basicity of the N atom. *N*-Phosphorylation might be expected to give products significantly less toxic than the parent mustard gas. Loss of basicity of the N atom in the phosphamidic link, owing to the inductive effect of the PO₂N₂ group (Friedman & Seligman, 1954) and possibly to resonance of:



would inhibit intramolecular cyclization to the ethyleneiminium ion necessary for high chemical activity (Ross, 1945).

It is worthwhile to consider the environment of the two N atoms: N(1) shows a trigonal planar character (see angles in Table 5) and is only displaced by 0.05 Å from the plane of the three atoms which are bonded to it. N(2) is, on the other hand, less planar and is displaced by 0.19 Å from the plane containing P, C(5), C(6). A relevant feature too is the difference between

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32338 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 5. Bond lengths (Å) and angles (°) for non-hydrogen atoms

Cl(1)—C(1)	1.780 (9)	O(1)—P—O(2)	115.2 (3)
Cl(2)—C(4)	1.793 (8)	O(1)—P—N(1)	110.1 (2)
Cl(3)—C(6)	1.846 (8)	O(1)—P—N(2)	118.6 (3)
P—O(1)	1.468 (8)	O(2)—P—N(2)	102.1 (2)
P—O(2)	1.585 (4)	O(2)—P—N(1)	103.9 (3)
P—N(1)	1.627 (9)	N(1)—P—N(2)	105.7 (3)
P—N(2)	1.656 (5)	P—N(1)—C(2)	121.9 (4)
N(1)—C(2)	1.465 (9)	P—N(1)—C(3)	121.4 (4)
N(1)—C(3)	1.468 (8)	C(2)—N(1)—C(3)	116.4 (4)
N(2)—C(5)	1.497 (9)	P—N(2)—C(5)	119.1 (4)
N(2)—C(7)	1.469 (10)	P—N(2)—C(7)	121.3 (4)
C(1)—C(2)	1.496 (9)	C(5)—N(2)—C(7)	115.1 (5)
C(3)—C(4)	1.496 (9)	Cl(1)—C(1)—C(2)	110.8 (6)
C(5)—C(6)	1.468 (11)	C(1)—C(2)—N(1)	111.0 (6)
C(7)—C(8)	1.517 (10)	N(1)—C(3)—C(4)	110.9 (5)
C(8)—C(9)	1.490 (8)	C(3)—C(4)—Cl(2)	109.1 (5)
C(9)—O(2)	1.463 (11)	N(2)—C(5)—C(6)	107.9 (6)
		C(5)—C(6)—Cl(3)	106.5 (6)
		N(2)—C(7)—C(8)	110.3 (5)
		C(7)—C(8)—C(9)	111.6 (6)
		C(8)—C(9)—O(2)	108.3 (5)
		C(9)—O(2)—P	120.3 (4)

Table 6. Conformation about the β -chloroethylamine chains

O(1)—P—N(1)—C(2)	179.4 (5) ^o
P—N(1)—C(2)—C(1)	92.8 (5)
N(1)—C(2)—C(1)—Cl(1)	175.3 (4)
O(1)—P—N(1)—C(3)	-7.7 (5)
P—N(1)—C(3)—C(4)	97.5 (5)
N(1)—C(3)—C(4)—Cl(2)	178.9 (4)
O(1)—P—N(2)—C(5)	-64.3 (5)
P—N(2)—C(5)—C(6)	83.8 (6)
N(2)—C(5)—C(6)—Cl(3)	175.6 (3)

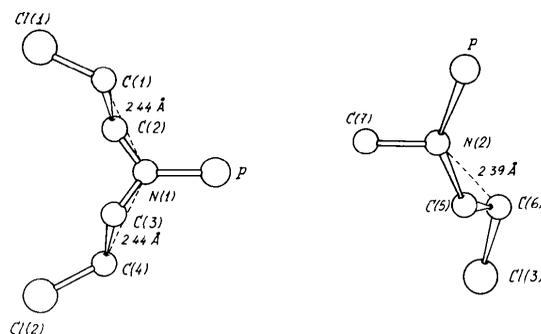


Fig. 2. Interatomic distances in the β -chloroethylamine chains.

Table 7. *Least-squares planes and deviations of the atoms (Å)*

The equations of the planes are expressed in orthogonal space as $PI + QJ + RK = S$.

Plane I	$0.8774I - 0.1733J - 0.4474K = 2.0443$
Plane II	$0.9828I + 0.1403J - 0.1201K = 5.4836$
Plane III	$0.4498I + 0.1558J + 0.8794K = 1.5828$
Plane IV	$0.9939I - 0.0974J - 0.0509K = 2.2067$
Plane V	$0.1473I - 0.1489J + 0.9778K = 0.4656$
Plane VI	$0.0269I + 0.9955J - 0.0908K = 8.1063$
Plane VII	$0.9281I - 0.2632J - 0.2619K = 2.0306$

Plane I		Plane II	
N(2)	0.0362	P	-0.0396
C(7)	-0.0367	O(2)	0.0450
O(2)	-0.0366	C(7)	0.0408
C(9)	0.0371	C(8)	-0.0463
P*	0.5496	N(2)*	-0.4695
N(1)*	-0.3373	C(9)*	0.6718
O(1)*	1.9688	C(5)*	-0.9048
Plane III		Plane IV	
Cl(4)	-0.0275	Cl(2)	-0.0063
Cl(4)	0.0273	C(4)	0.0061
C(2)	0.0336	C(3)	0.0081
N(1)	-0.0335	N(1)	-0.0078
Plane V		Plane VI	
Cl(3)	0.0266	C(2)	0.0000
C(6)	-0.0258	C(3)	0.0000
C(5)	-0.0338	P	0.0000
N(2)	0.0330	N(1)*	-0.0519
Plane VII			
C(5)	0.0000		
C(7)	0.0000		
P	0.0000		
N(2)*	-0.1924		

* Not included in the calculation of the plane.

the Cl—C bonds lengths. Cl(1)—C(1) and Cl(2)—C(4) are usual for a Cl—C_{aliphatic} bond (1.77–1.78 Å). Cl(3)—C(6) is, however, significantly longer (1.846 Å) and the C(6)—C(5) adjacent bond is consequently shorter (1.46 Å), most likely because of the high thermal parameters obtained for these atoms.

The conformation about the chloroethyl chains is given through the torsion angles in Table 6. The β -chloroethyl chains from N(1) are extended and separate from each other, the distance Cl(1)···Cl(2) being 6.77 Å. The chain which is linked to N(2) shows a coiled conformation; Fig. 2 gives the intramolecular distances in the β -chloroethyl chains.

The best planes within the molecule are given in Table 7. The hetero ring has a chair conformation.

The packing of the molecules within the unit cell is shown in Fig. 3. The shortest intermolecular contacts less than the van der Waals distances are: H(12)—O(1) 2.57; H(18)—H(11) 2.28 Å (at $-x + 1, -y + 1, -z$), and Cl(1)—H(2) 2.79 Å (at $x, -y + 1\frac{1}{2}, z + \frac{1}{2}$).

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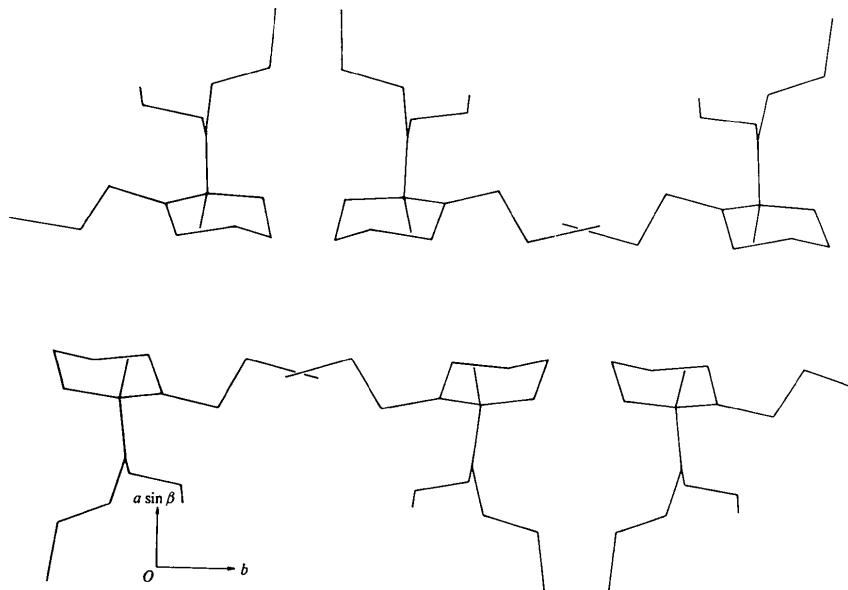


Fig. 3. Projection of the structure down c .

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The Crystal Structures of $\text{K}[\text{Mn}(\text{H}_2\text{O})_2(\text{mal})_2] \cdot 2\text{H}_2\text{O}$ and $\text{K}_3[\text{Mn}(\text{mal})_3] \cdot 2\text{H}_2\text{O}$

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The crystal structures of potassium *trans*-diaquabis(malonato)manganese(III) dihydrate and tripotassium tris(malonato)manganese(III) dihydrate were determined by single-crystal diffractometry. $\text{K}[\text{Mn}(\text{H}_2\text{O})_2(\text{mal})_2] \cdot 2\text{H}_2\text{O}$ (I) crystallizes in space group *Pbcn*, with $a = 6.842$ (3), $b = 13.491$ (7), $c = 14.115$ (6) Å; $\text{K}_3[\text{Mn}(\text{mal})_3] \cdot 2\text{H}_2\text{O}$ (II) crystallizes in *C2/c* (rather than *Cc*), with $a = 14.799$ (8), $b = 7.850$ (4), $c = 16.210$ (8) Å, $\beta = 108.51$ (4)°. The Mn–O bond distances in (II) are in the range 1.92–2.04 Å and are longer than the average Mn–O(malonate) bond length of 1.90 (1) Å in compound (I).

Introduction

Literature on the preparation, kinetics and spectra of Mn complexes with carboxylic acids is extensive. Investigations of complexes of Mn with oxalate and malonate ions are of special interest. Air-stable compounds of Mn^{III} with malonic acid (Meyer & Schramm, 1922; Cartledge & Nichols, 1940; Bullock, Patel & Salmon, 1969) have been obtained. The present paper discusses the crystal structures of $\text{K}[\text{Mn}(\text{H}_2\text{O})_2(\text{mal})_2] \cdot 2\text{H}_2\text{O}$ and $\text{K}_3[\text{Mn}(\text{mal})_3] \cdot 2\text{H}_2\text{O}$.

Experimental

Preparation

$\text{K}[\text{Mn}(\text{H}_2\text{O})_2(\text{mal})_2] \cdot 2\text{H}_2\text{O}$ was obtained by the method of Bullock, Patel & Salmon (1969) as green crystals. Red crystals of this compound prepared by the method of Bullock, Patel & Salmon were not suitable for X-ray analysis. Crystals of $\text{K}_3[\text{Mn}(\text{mal})_3] \cdot 2\text{H}_2\text{O}$ suitable for single-crystal diffractometry were obtained as follows: to a moist potassium malonate (prepared from stoichiometric proportions of potassium carbonate and malonic acid) was added well powdered, green $\text{K}[\text{Mn}(\text{H}_2\text{O})_2(\text{mal})_2] \cdot 2\text{H}_2\text{O}$. The reaction mixture was then put into an ice-box ($\sim 0^\circ\text{C}$) and after one day well formed red crystals appeared and were dried with a filter paper and ethanol.

Crystal data

$\text{K}[\text{Mn}(\text{H}_2\text{O})_2(\text{mal})_2] \cdot 2\text{H}_2\text{O}$ (I), $M_r = 370.2$, orthorhombic, $a = 6.842$ (3), $b = 13.491$ (7), $c = 14.115$ (6) Å, $V = 1302.9$ Å³; $D_m = 1.88$, $Z = 4$, $D_c = 1.89$ g cm⁻³; $\mu(\text{Cu } K\alpha) = 121.3$ cm⁻¹. Space group *Pbcn* from systematic absences.

$\text{K}_3[\text{Mn}(\text{mal})_3] \cdot 2\text{H}_2\text{O}$ (II), $M_r = 420.5$, monoclinic, $a = 14.799$ (8), $b = 7.850$ (4), $c = 16.210$ (8) Å, $\beta = 108.51$ (4)°, $V = 1785.7$ Å³; $D_m = 1.90$, $Z = 4$, $D_c = 1.91$ g cm⁻³; $\mu(\text{Cu } K\alpha) = 132.1$ cm⁻¹. Space group *Cc* or *C2/c* from systematic absences.

Intensity measurements

In both cases a Syntex P2₁ diffractometer, with Cu $K\alpha$ radiation and a graphite monochromator, was used for lattice-parameter and intensity measurements. The intensities were measured by the 2θ – ω scan technique. An irregular polyhedron of (I) with dimensions 0.15 × 0.15 × 0.10 mm was selected and 1244 independent reflexions were measured, of which 874 were ‘observed’ with $I > 1.96\sigma(I)$. In the case of (II), an almost spherical crystal with a diameter of 0.10 mm was used and 1786 independent reflexions were measured, 1456 of which were ‘observed’ with $I > 1.96\sigma(I)$. The reflexions were collected within the limit $\theta \leq 73^\circ$. The data were corrected for Lorentz and polarization effects. For (II) the absorption correction was applied as for a spherical crystal with $\mu R = 0.7$. In both cases the standard reflexion was measured every 40 reflexions; no significant changes in intensity were observed.