data for the Fe_2S_4 subcell c'' axis *versus* Ba concentration and by extrapolation we obtain $c'' = 5 \cdot 88$ Å. Thus $c = 17 \cdot 64$ Å and the Ba—Ba repeat distance is $4 \cdot 41$ Å in this phase. Attempts to prepare those two compounds, $BaFe_2S_4$ and $Ba_{1 \cdot 333}Fe_2S_4$, to confirm the above are currently underway.

The basic structure principles for $Ba_9Fe_{16}S_{32}$ can be extended to postulate the approximate structures of all other members of the series $Ba_p(Fe_2S_4)_q$ where p and q are integers (Table 5).

It had been proposed that this system presents a model system for testing current theories which postulate that quenched high-temperature structures represent frozen 'quantum states' of the periodic thermal vibrations of the atoms (Grey, 1974). We made a study of the X-ray powder diffraction pattern at temperatures up to 535°C. Only the normal thermal expansion was observed up to approximately 450°C. Above this temperature the sample began to decompose slowly. No phase transformations were observed.

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Activated Cyclophosphamide Anticancer Drugs: Molecular Structure of 4-Hydroperoxycyclophosphamide

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4-Hydroperoxycyclophosphamide is an active cytostatic agent closely related to an active metabolite of the antitumor drug cyclophosphamide. $C_7H_{15}Cl_2N_2O_4P$, monoclinic, $P2_1/c$; $a = 14 \cdot 229$ (4), $b = 7 \cdot 706$ (3), $c = 11 \cdot 891$ (3) Å, $\beta = 103 \cdot 06$ (2)°, $Z = 4$, $D_x = 1 \cdot 533$ g cm^{-3}; $T = -5$°C. The structure was solved by direct methods and refined by full-matrix least-squares methods to $R = 0 \cdot 055$ for 1957 observed reflections. The configuration at the P atom is phosphoryl O axial and dialkyamino group equatorial. The peroxide group attached to C(4) is axial and is thus *cis* to the phosphoryl O.

Introduction

Cyclophosphamide (CPA) (Fig. 1), an antitumor alkylating agent, is one of the most widely used drugs in the treatment of many types of cancer. Though it is an effective antineoplastic agent against many tumors, CPA has virtually no cytotoxic activity against mammalian cell cultures (Arnold, Bourseaux & Brock, 1958); *in vivo* pharmacological activity requires conversion of CPA to alkylating substances by the mixed function oxidase system of liver microsomes (Brock & Hohorst, 1963; Cohen & Jao, 1970). It is becoming increasingly clear that mono-oxidation at C(4) is responsible for activation of CPA with the first step being production of 4-hydroxycyclophosphamide (HCPA) (Hohorst, Ziemann & Brock, 1971; Hill, Laster &
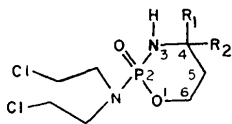
Fig. 1. Structural formula for: CPA, $R_1 = R_2 = H$; HCPA, $R_1 = OH$, $R_2 = H$; KCPA, R_1, $R_2 = O$; HPCPA, $R_1 = OOH$, $R_2 = H$.

Struck, 1972; Takamizawa, Matsumoto, Iwata, Katagiri, Tochino & Yamaguchi, 1973; Takamizawa *et al.*, 1975). It had been thought that HCPA was the active antitumor alkylating agent, but recent evidence (Colvin, Padgett & Fenselau, 1973; Connors, Cox, Farmer, Foster & Jarman, 1974) suggests that it undergoes decomposition to yield acrolein and phosphoramide mustard, with the latter being the ultimate cytostatic cyclophosphamide metabolite. We have previously determined the molecular structure of one of the metabolic end products of CPA, 4-ketocyclophosphamide (KCPA) (Camerman & Camerman, 1973), but neither these results nor those of CPA (Garcia-Blanco & Perales, 1972; Clardy, Mosbo & Verkade, 1972) yield information about the important configuration at C(4) of the hydroxylated antitumor species. Recently, Takamizawa *et al.* (1975) synthesized HCPA and HPCPA. They found that both synthetic products exhibit pronounced *in vitro* and *in vivo* cytostatic activities and that HPCPA can be readily converted to HCPA by chemical and by biological reduction. HCPA is highly unstable and is not amenable to crystallographic studies so we have chosen to determine the crystal and molecular structure of HPCPA in order to elucidate the configuration about C(4) in these synthetic CPA derivatives. As they exhibit high cytostatic activity, it is likely that these compounds will have the same C(4) configuration as the active HCPA metabolite; thus, stereochemical results for HPCPA may provide valuable aid in understanding steps in cyclophosphamide metabolic pathways.

Experimental

Crystals of 4-hydroperoxycyclophosphamide (HPCPA) exhibited moderate deterioration and a slight change in cell dimensions on exposure to X-radiation. The rate of deterioration was considerably reduced by cooling the crystals in a stream of cool dry air. Cell dimensions and space group information were determined from X-ray photographs and diffractometer measurements on a colorless tabular crystal of dimensions $0.20 \times 0.44 \times 0.52$ mm. Systematic absences $h0l$, $l \neq 2n$ and $0k0$, $k \neq 2n$ confirm the space group $P2_1/c$. Intensities of all independent reflections having a 2θ (Mo $K\alpha) < 50°$ (corresponding to a minimum interplanar spacing of 0.84 Å) were measured on an automated four-circle diffractometer at $-5\,°C$ using Nb-filtered Mo radiation ($\lambda = 0.71069$ Å, $\theta-2\theta$ scan, scan width $= 1.7°$, scan speed $2°$ min^{-1}). 10 s background counts were taken at each end of the scan range.

Three standard reflections, monitored periodically, showed steady decline in intensity during the period of data collection to a maximum of 44% reduction. A quadratic decomposition curve, fitted by least squares to a plot of standard intensity *versus* reflection number, was used to calculate scale factors as a function of the serial order of collection. Approximately one-half of the data set – those intensities needing the largest correction for decomposition – were recollected in reverse serial order. This partial data set was merged into the complete data set by applying a single scale factor calculated from the ratios of the overlapping reflections and averaging corresponding intensities. The agreement of the two data sets was $R = \Sigma |I_1 - I_2|/\Sigma I_{av} = 0.10$, where I_1 and I_2 are scaled intensities from corresponding reflections in the two data sets. The largest intensities were recollected at a lower X-ray tube current to eliminate error due to saturation of the counter circuit. Of the 2472 reflections in the range recorded, 1957 had intensities greater than twice their standard deviations and were used in structure refinement. Since the linear absorption coefficient was relatively small ($\mu = 6.39$ cm^{-1}) and the rotation of the crystal around the φ axis at $\chi = 90°$ showed little variation in intensity of a reflection along the φ axis, no absorption corrections were applied to the data set. Although some low-angle, high-intensity reflections were calculated greater than observed, no extinction corrections were made. Normalized structure amplitudes $|E|$ were obtained by the Wilson plot method.

Structure determination

The structure was solved with the multiple-solution tangent formula program *MULTAN* (Germain, Main & Woolfson, 1971), using 200 normalized structure factors with $E > 1.6$. The phase of one reflection, $10,0,\bar{2}$, was determined by the Σ_1 relation at a 0.95 probability level. The three origin-specifying reflections and three additional reflections were automatically selected as the starting set by the program; with these as input, eight sets of phases for the data were derived from the Sayre relation. The E map calculated from the phase set with the highest figure of merit (1.28) and lowest residual (19.9%) revealed all 16 non-hydrogen atoms. With these atoms in the model, the discrepancy index, $R = \Sigma |F_o| - |F_c|/\Sigma |F_o|$, was 0.33.

The atomic positional and anisotropic thermal parameters were refined by full-matrix least squares, where the function minimized was $\Sigma w(|F_o| - |F_c|)^2$. Unit weights were initially chosen, but for final refinement statistical weights, $w = 1/\sigma_F^2$, were used. Atomic

scattering factors for H from Stewart, Davidson & Simpson (1965) and for the other atoms from Cromer & Mann (1968) were used. Computations were done with the X-RAY system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972). A difference Fourier map, computed after several cycles of least-squares refinement, showed the positions of all 15 H atoms. Further refinement of all atom positions with anisotropic tem-
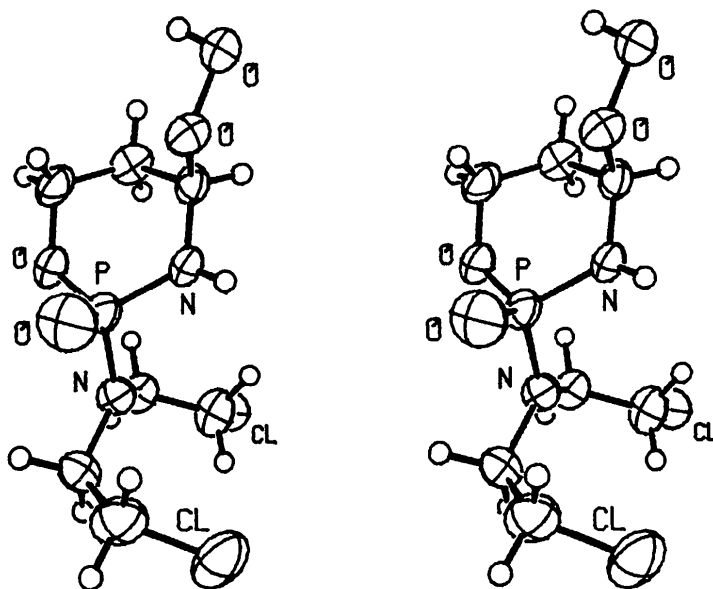

Fig. 2. Stereoscopic drawing of 4-hydroperoxycyclophosphamide showing the molecular conformation. The thermal ellipsoids of the non-hydrogen atoms are drawn at the 50% probability level. Carbon and hydrogen atoms are not labeled.

Table 1. *Fractional coordinates and thermal parameters for atoms of HPCPA*

The fractional coordinates have been multiplied by 10^5 for P and Cl atoms; 10^4 for C, N and O; 10^3 for H. The form of anisotropic thermal ellipsoid is $\exp[-2\pi^2 (U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$. The values of U_{ij} (U) have been multiplied by 10^4 for P and Cl; 10^3 for C, N and O; 10^2 for H. Numbers in parentheses here and throughout the paper are estimated standard deviations in the least significant digits.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	3030 (2)	2511 (4)	2104 (2)	62 (2)	68 (2)	45 (1)	−9 (1)	10 (1)	20 (1)
P(2)	30823 (7)	6373 (13)	26464 (8)	504 (5)	463 (5)	387 (5)	−12 (4)	199 (4)	−42 (4)
N(3)	3690 (2)	977 (4)	3977 (3)	50 (2)	43 (2)	40 (2)	−2 (1)	12 (1)	12 (1)
C(4)	4435 (3)	2243 (5)	4293 (3)	52 (2)	47 (2)	32 (2)	−2 (2)	14 (1)	−0 (1)
C(5)	4185 (3)	3925 (5)	3638 (3)	58 (2)	38 (2)	64 (3)	2 (2)	23 (2)	−1 (2)
C(6)	3880 (3)	3595 (6)	2360 (3)	60 (3)	56 (2)	57 (2)	−3 (2)	19 (2)	22 (2)
O(7)	5283 (2)	1470 (3)	4036 (2)	48 (1)	44 (1)	53 (1)	−1 (1)	16 (1)	4 (1)
O(8)	3469 (2)	−680 (5)	1986 (3)	74 (2)	90 (2)	80 (2)	0 (2)	40 (2)	−36 (2)
N(9)	1996 (2)	145 (4)	2753 (2)	51 (2)	39 (1)	46 (2)	−2 (1)	18 (1)	−6 (1)
C(10)	1451 (3)	1361 (5)	3325 (3)	53 (2)	44 (2)	51 (2)	6 (2)	19 (2)	1 (2)
C(11)	1411 (4)	736 (6)	4506 (4)	75 (3)	57 (3)	56 (2)	12 (2)	32 (2)	−1 (2)
Cl(12)	7019 (7)	21925 (15)	51516 (9)	635 (6)	685 (7)	621 (6)	12 (5)	291 (5)	−192 (5)
C(13)	1436 (3)	−1169 (5)	1982 (4)	65 (3)	54 (2)	51 (2)	−11 (2)	11 (2)	−10 (2)
C(14)	1708 (4)	−3005 (6)	2293 (5)	95 (4)	49 (3)	80 (3)	−11 (2)	35 (3)	−15 (2)
Cl(15)	14180 (12)	−36829 (15)	36080 (12)	1417 (12)	455 (6)	910 (9)	−19 (7)	481 (8)	56 (6)
O(16)	6114 (2)	2443 (4)	4675 (3)	56 (2)	71 (2)	52 (2)	−13 (1)	5 (1)	20 (1)

	x	y	z	U		x	y	z	U
H(3)	381 (2)	12 (5)	438 (3)	4 (1)	H(11, 1)	212 (3)	65 (6)	504 (4)	8 (1)
H(4)	458 (3)	244 (5)	512 (4)	6 (1)	H(11, 2)	114 (3)	−42 (7)	443 (4)	10 (2)
H(5, 1)	476 (3)	471 (5)	386 (3)	5 (1)	H(13, 1)	70 (3)	−112 (6)	199 (3)	9 (1)
H(5, 2)	365 (3)	440 (5)	390 (3)	5 (1)	H(13, 2)	160 (3)	−101 (5)	114 (4)	9 (1)
H(6, 1)	367 (3)	469 (6)	197 (3)	7 (1)	H(14, 1)	142 (4)	−394 (7)	176 (5)	13 (2)
H(6, 2)	443 (2)	291 (4)	206 (3)	4 (1)	H(14, 2)	249 (3)	−318 (6)	242 (4)	10 (1)
H(10, 1)	84 (3)	167 (5)	286 (3)	6 (1)	H(16)	621 (3)	296 (6)	417 (4)	8 (1)
H(10, 2)	186 (3)	249 (6)	337 (3)	8 (1)					

perature parameters for non-hydrogen atoms and iso-tropic parameters for the H atoms resulted in a final R of 0·055 [omitting reflections with $I < 2\sigma(I)$]. A computed Fourier difference map showed no misplaced electron density. Atomic fractional coordinates and thermal parameters are given in Table 1.*

Discussion

Fig. 2 is a stereoscopic drawing showing the three-dimensional molecular structure of HPCPA. The six-

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32086 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

membered ring is in the chair conformation, and the configuration about the P atom has the bis(chloro-ethyl)amine group equatorial and the phosphoryl O atom axial, the same as that found in KCPA and CPA. The major difference between these inactive compounds and activated HCPA and HPCPA is the hydroxy (or hydroperoxy) group at C(4). The significant finding in our structure determination of HPCPA is that this group is situated axial to the ring and thus is *cis* to the phosphoryl O and *trans* to the bis(chloro-ethyl)amine group. The distance between the C(4) oxygen atom and the phosphoryl oxygen is 3·54 Å; the same distance would of course pertain for synthetic HCPA.

Bond lengths and angles in HPCPA are shown in Figs. 3 and 4. The distances and angles are in essential
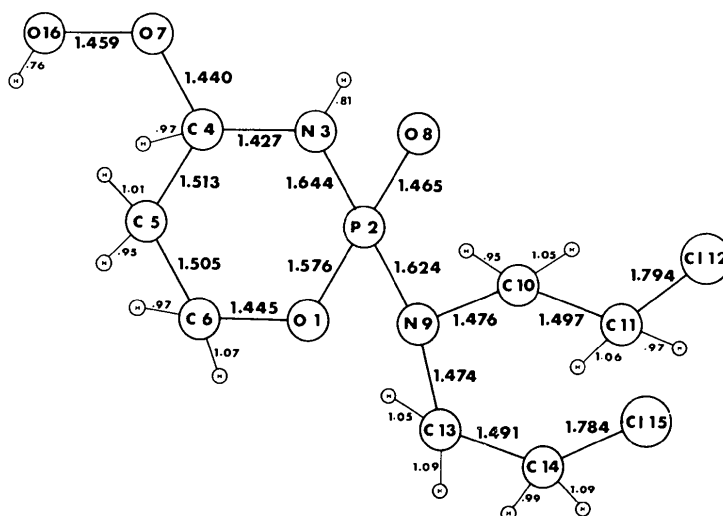

Fig. 3. Bond lengths (Å) in HPCPA. Estimated standard deviations are 0·006 Å for 'heavy' atom bonds and 0·05 Å for bonds involving hydrogen atoms.
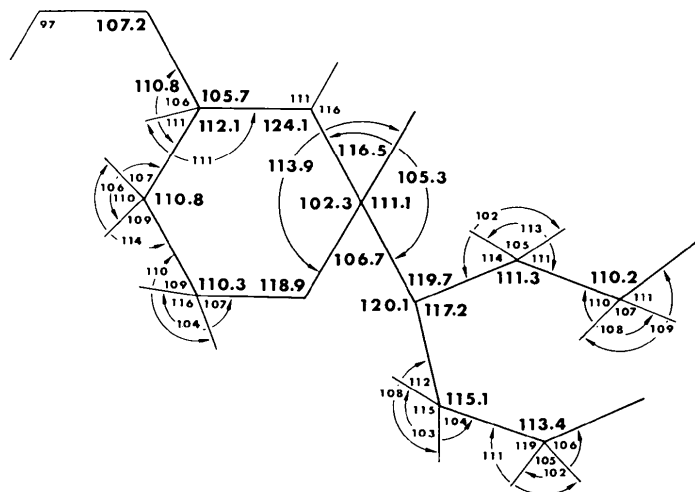

Fig. 4. Bond angles (°) in HPCPA. Estimated standard deviations are 0·04° for 'heavy' atom angles and 2–4° for angles involving hydrogen atoms.
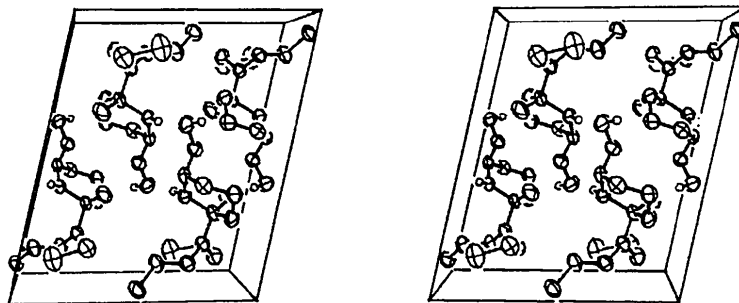
Fig. 5. Stereoscopic diagram of the molecular packing. The origin is at the top left-hand corner with y pointing away from the viewer, x down and z to the right. The only hydrogen atoms shown are those which form hydrogen bonds.

agreement with the corresponding values reported for cyclophosphamide. The only significant differences involve C(4) and the adjacent ring nitrogen, N(3). Where the present structure deviates from the cyclophosphamide structure, the HPCPA distance or angle is generally different in the same direction as in the KCPA structure. The length of the P(2)—N(3) ring bond undergoes a progressive increase in the series CPA, HPCPA, KCPA with values of 1·625, 1·644 and 1·668 Å respectively. Similarly the N(3)—C(4) bond is shortened in this series with values of 1·472 for CPA, 1·427 for HPCPA and 1·385 Å for KCPA. These changes are explained by the presence of an electron-withdrawing group on C(4), which shifts electron density into the N(3)—C(4) bond at the expense of the N(3)—P(2) bond. The C(4)—C(5) bond is 0·019 (9) Å shorter in CPA than in HPCPA. Also, the ring angle at the endocyclic nitrogen, N(3), becomes progressively larger for the series CPA, HPCPA, KCPA with values of 121·9, 124·1, 127·1° respectively. All other corresponding bond distances and angles are essentially the same for the CPA, KCPA and HPCPA structures. The C—O bond of the peroxide group has a length of 1·440, which is comparable to the C—O bonds of the peroxide linkage in 4-peroxycyclophosphamide (PCPA), where lengths of 1·44 and 1·42 Å were found (Sternglanz, Einspahr & Bugg, 1974). The O—O bond distance of 1·459 Å is slightly shorter in HPCPA than in PCPA.

The spatial packing of the molecules is displayed in Fig. 5. In the crystal the molecules are connected by intermolecular hydrogen bonds between the O(16) hydrogen and the phosphoryl oxygen, O(8), on the screw-axis-related molecule. The H(16)···O(8) distance is 1·86 Å [the O(16)···O(8) distance is 2·62 Å] and the O—H···O angle is 175°. These chains of hydrogen-bonded molecules are weakly interconnected by a bifurcated hydrogen bond between the N(3) hydrogen and the two peroxide oxygens, O(7) and O(16), on the molecule situated across the center of symmetry at $(\frac{1}{2},0,\frac{1}{2})$. The H(3)···O(7) and H(3) ···O(16) distances are 2·36 and 2·26 Å respec-

tively; the N(3)···O(7) and N(3)···O(16) distances are 3·12 and 3·06 Å; and the N—H···O angles are 157 and 170° for O(7) and O(16). All other intermolecular contacts correspond to normal van der Waals distances.

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The Crystal Structure of Tetra(3-methylphenyl)tin

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The crystal structure of tetra(3-methylphenyl)tin, $(3-CH_3C_6H_4)_4Sn$, has been determined from three-dimensional X-ray intensity data collected by counter methods on a computer-controlled diffractometer. The compound crystallizes in the tetragonal space group $I4_1/a$ (C_{4h}^6) with unit-cell dimensions $a = 17.370$ (13), $c = 8.285$ (9) Å and $Z = 4$. The structure was refined by a full-matrix least-squares procedure to a conventional R index of 0.031 for 1102 independent reflections. The crystal structure consists of discrete molecules with crystallographically imposed $\bar{4}$ symmetry, separated by normal van der Waals contacts. The observed Sn–C and C(aryl)–C(methyl) distances are 2.150 (3) Å and 1.517 (5) Å respectively. The methyl group is twofold disordered. Rotation of the aryl ring plane from the C–Sn–C plane is 41° which differs considerably from the value of 140.3° predicted by a geometrical analysis [Maly & Teply, Chem. Zvesti, (1953), 7, 553–562].

Introduction

We have been interested in the crystal structures of aryl Group IVa compounds of the type (aryl)$_4$M in order to provide accurate structural parameters for use in a continuing study of the crystal packing and energetics of such molecular compounds. Of particular interest are those derivatives which retain molecular $\bar{4}$ symmetry in crystals of tetragonal symmetry (Kitaigorodsky, 1961; Karipides, Forman, Thomas & Reed, 1974). This paper is concerned with the structural investigation of one such derivative, tetra(3-methylphenyl)tin (Teply & Maly, 1953).

Experimental

Tetra(3-methylphenyl)tin was prepared following the procedure described by Krause & Becker (1920) and suitable crystals were obtained by recrystallization from ethanol. A single crystal, approximately 0.28 × 0.28 × 0.36 mm, mounted along the longest dimension (c*) was used. The tetragonal space group was uniquely determined to be $I4_1/a$ from indexed Weissenberg photographs based on the systematic absences $h +$

$k + l = 2n + 1$ for hkl; $h(k) = 2n + 1$ for $hk0$; $l = 4n + 1$ for $00l$. Accurate values of the unit-cell dimensions were obtained from the least-squares refinement of the angular settings of 12 reflections carefully measured on a Picker FACS-I automated diffractometer. The experimental density was determined by flotation in an aqueous solution of KI. The pertinent crystal data are presented in Table 1.

Three-dimensional X-ray intensity data were collected on the diffractometer already mentioned using Zr-filtered Mo $K\alpha$ ($\lambda = 0.71069$ Å) radiation. 1327 reflections out to 50° in 2θ were recorded by the θ–2θ scan technique with a 1° min^{-1} scan rate and a scan range of $2\theta(\text{Mo } K\alpha_1) - 1.0°$ to $2\theta(\text{Mo } K\alpha_2) + 1.0°$. A background count for 20 s at the start and end of each scan was taken. During the data collection the intensities of

Table 1. Crystal data for tetra(3-methylphenyl)tin

$(3-CH_3C_6H_4)_4Sn$	Space group $I4_1/a$ (C_{4h}^6)
$a = 17.370$ (13) Å	$M_r = 483.2$ g mol^{-1}
$c = 8.285$ (9)	$F(000) = 984$
$\lambda(\text{Mo } K\alpha) = 0.17069$ Å	$\mu(\text{Mo } K\alpha) = 10.4$ cm^{-1}
$Z = 4$	$D_o = 1.30$ g cm^{-3}
$V = 2500$ Å^3	$D_c = 1.284$