

- KITAIGORODSKY, A. I. (1973). *Molecular Crystals and Molecules*. New York, London: Academic Press.
- KUMAKURA, S., IWASAKI, F. & SAITO, Y. (1967). *Bull. Chem. Soc. Jpn*, **40**, 1826-1833.
- LE BARS-COMBE, M., CHION, B. & LAJZÉROWICZ-BONNETEAU, J. (1979). *Acta Cryst.* **B35**, 913-920.
- LE BARS-COMBE, M. & LAJZÉROWICZ-BONNETEAU, J. (1981). *Acta Cryst.* **B37**, 1707-1712.
- MACFARLANE, R. M. & USHIOA, S. (1977). *J. Chem. Phys.* **67**, 3214-3220.
- MIRSKY, K. (1978). *Proceedings of an International Summer School on Crystallographic Computing*. Twente: Delft Univ. Press.
- MIRSKY, K. & COHEN, M. D. (1978). *Acta Cryst.* **A34**, 346-348.
- POLAK, M. (1977). *J. Chem. Phys.* **67**, 5572-5576.
- SHMUELI, U. & GOLDBERG, I. (1973). *Acta Cryst.* **B29**, 2466-2471.
- TSUCHIYA, H., MARUMO, F. & SAITO, Y. (1972). *Acta Cryst.* **B28**, 1935-1941.
- WRIGHT, J. D., YAKUSHI, K. & KURODA, H. (1978). *Acta Cryst.* **B34**, 1934-1938.

Acta Cryst. (1982). **B38**, 168-171

Structures of Inorganic Rings as Antitumor Agents.

II. Structure of the Benzene Clathrate of 2,2,4,4,6,6-Hexa(1-aziridinyl)cyclotri(phosphazene), $N_3P_3az_6$

BY T. STANLEY CAMERON*

Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J3

AND JEAN-FRANÇOIS LABARRE AND MARCEL GRAFFEUIL

Laboratoire Structure et Vie, Université Paul Sabatier, 118 Route de Narbonne, 31400 Toulouse, France

(Received 15 August 1980; accepted 27 May 1981)

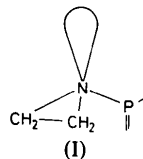
Abstract

$2C_{12}H_{24}N_9P_3 \cdot C_6H_6$, $M_r = 852.71$, is rhombohedral, space group $R\bar{3}$, with $a = 10.266(1) \text{ \AA}$, $\alpha = 79.21(1)^\circ$, $Z = 1$, $D_c = 1.374 \text{ Mg m}^{-3}$, $\lambda(\text{Mo } K\alpha_1) = 0.70926 \text{ \AA}$, $\mu = 0.260 \text{ mm}^{-1}$, $T = 288 \pm 0.05 \text{ K}$. The structure was solved by the heavy-atom method. $R = 0.026$ for 1206 independent reflections. The two cyclotri(phosphazene) molecules are related by the symmetry centre, the benzene is at the centre, and all three molecules lie on the crystallographic C_3 axis; in the cyclotri(phosphazene), the geminal aziridinyl groups adopt an unusual *cis* conformation.

Introduction

The considerable antitumor activity of the aziridinyl-cyclo(phosphazenes) $N_3P_3az_6$ and $N_4P_4az_8$ [az = aziridinyl = $-\text{N}(\text{CH}_2)_2$] (I) against many animal leukemias (P388 and L1210), melanoma (B16), sar-

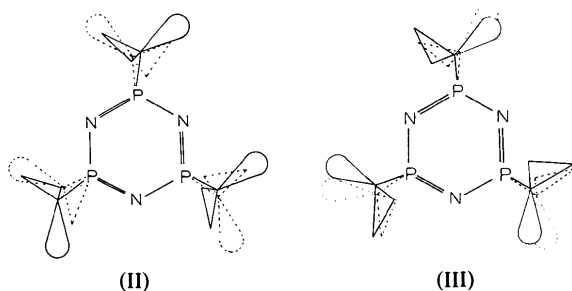
comas (colon, Lewis lung, Yoshida) and other tumors (P815 mastocytoma, ependymoblastoma) has been reported recently (Labarre *et al.*, 1978; Labarre, Faucher, Levy, Sournies, Cros & Francois, 1979). A greatly enhanced activity against some of these tumors (P388, L1210, B16) has also been observed for the three aziridinylcyclo(phosphathiazene) derivatives, $N_3P_2S(O)Raz_4$ ($R = \text{F, Ph, az}$) (Labarre, Sournies, van de Grampel & van der Huizen, 1979). These inorganic ring systems apparently do not need any intermediate metabolization to be effective and thus it is reasonable to look at the relationship between the *in vitro* geometric structure of the molecules and their *in vivo* antitumor activity.



One of the most promising of these drugs seems to be $N_3P_3az_6$. This molecule is exceedingly soluble in water (Sournies, 1980) and so far has not been

* To whom correspondence should be addressed.

successfully recrystallized from this medium. When it is recrystallized from CCl_4 , it forms a complex, $\text{N}_3\text{P}_3\text{az}_6 \cdot 3\text{CCl}_4$; this structure has already been determined (Galy, Enjalbert & Labarre, 1980). When recrystallized from *m*-xylene, $\text{N}_3\text{P}_3\text{az}_6$ forms an orthorhombic unsolvated crystal, while crystallization from CS_2 produces a monoclinic unsolvated crystal. The structure of the cyclotri(phosphazene) molecule in each of these three crystal forms is very similar (Cameron, Labarre & Graffeuil, 1982) and the conformations (II) of the aziridinyl groups are those that would be expected from simple VSEPR considerations (Gillespie, 1963). When, however, $\text{N}_3\text{P}_3\text{az}_6$ is recrystallized from benzene, it forms a very stable complex, $2(\text{N}_3\text{P}_3\text{az}_6) \cdot \text{C}_6\text{H}_6$, with a most unusual conformation (III) at the geminal aziridinyl groups. The structure of this complex is reported here.



Experimental

The crystals were obtained by a slow evaporation (three weeks) at room temperature of a saturated benzene solution.

The absence of systematic extinctions indicated space group $R\bar{3}$. 1206 independent reflections, of which 908 had $I > 3\sigma(I)$, were measured on a CAD-4 diffractometer.

The preliminary cell data were derived from equi-inclination Weissenberg photographs and the cell dimensions were subsequently refined from the CAD-4 circle angles of 25 general reflections with the Bragg angle θ in the range 15–17°. The data were reduced by normal procedures which are described in detail in Cameron & Cordes (1979); neither absorption nor extinction corrections were applied.

Solution and refinement

The crystal was indexed in a rhombohedral system with no systematic absences. Initially, the E statistics did not clearly distinguish between centrosymmetric and non-centrosymmetric systems, and thus possible space groups were $R3$ (C_3^4 , No. 146), $R32$ (D_3^7 , No. 155), $R3m$ (C_{3v}^5 , No. 160), $R\bar{3}$ (C_{3i}^2 , No. 148) and $R\bar{3}m$ (D_{3d}^5 , No. 166). The three-dimensional Patterson function, sharpened to point atoms at rest, contained a series of peaks which could be interpreted as the $\text{P}\cdots\text{P}$ vectors of a cyclotri(phosphazene). Unfortunately, these vec-

tors were consistent with a solution for the structure in each of the five possible space groups. A three-dimensional Fourier synthesis was calculated phased on the positions of two of the P atoms of two cyclotri(phosphazene) rings in space group $R3$. From this and subsequent Fourier maps the positions of the C and N atoms were determined. The conformations of the aziridinyl groups of the cyclotri(phosphazene) were not disordered, and their configuration precluded space groups $R32$, $R3m$ and $R\bar{3}m$. The structure was refined in space group $R3$, with isotropic temperature factors on all atoms, and converged at $R = 0.04$. A difference Fourier synthesis calculated at this stage clearly showed all the H atoms, and refinement continued with isotropic temperature factors on these H atoms and anisotropic temperature factors on the rest. The refinement converged with $R = 0.028$, $R_w = 0.029$ for the 1448* unique reflections in space group $R3$. The structure was similarly refined in space group $R\bar{3}$, where it converged with $R = 0.12$. The lower R factor for the non-centrosymmetric system was apparently significant (Hamilton, 1965), but the final structure had some disturbing irregularities (Cameron, Chan, Labarre & Graffeuil, 1980); normally equivalent P–N bond lengths differed by 20 e.s.d.'s without obvious reason; the contacts between the two cyclotri(phosphazene) molecules and the benzene ring looked very similar, but the benzene was displaced towards one cyclotri(phosphazene) molecule; the cyclotri(phosphazene) and benzene rings themselves were significantly non-planar. A powdered sample was examined with a Guinier–Lenné X-ray camera [the powder pattern is projected through a narrow slit onto an X-ray film, while the film cassette is moving behind the slit synchronously with the smoothly varying sample temperature (Lenné, 1961)]. The photograph showed a slight change in pattern at about 295 K, and the detail started to become very blurred at about 308 K. The temperature in the room where the data were collected can vary between 293–298 K so the crystal was cooled to a temperature below 295 K but just above the dew-point to avoid condensation. The X-ray reflection data were recollected with the CAD-4 variable temperature system set to give a controlled crystal temperature of 288 ± 0.05 K. The coordinates derived from the previous attempt were refined again in space groups $R3$ and $R\bar{3}$, converging at $R = 0.024$ and 0.026 respectively. The lower R factor in the non-centrosymmetric space group is now not significant (Hamilton, 1965) and the structure is best represented in space group $R\bar{3}$. In the final stages of refinement, the weighting scheme was $w = (\sigma^2 |F_o| + 0.000696 F_o^2)^{-1}$ where σ is the individual e.s.d. for each reflection calculated from

* The structure has 1448 independent reflections in $R3$ when the data are collected as though the crystal system were triclinic, but only 1206 independent reflections in $R\bar{3}$, where Friedel pairs can be averaged.

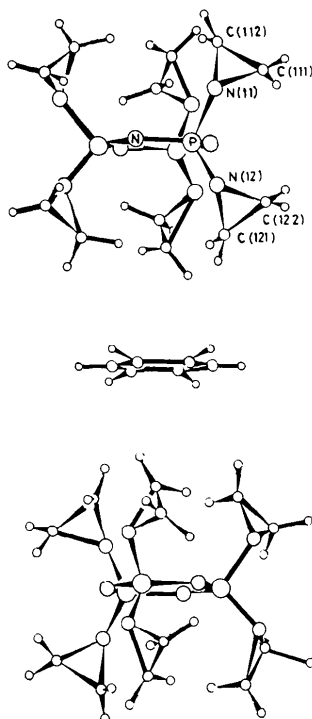
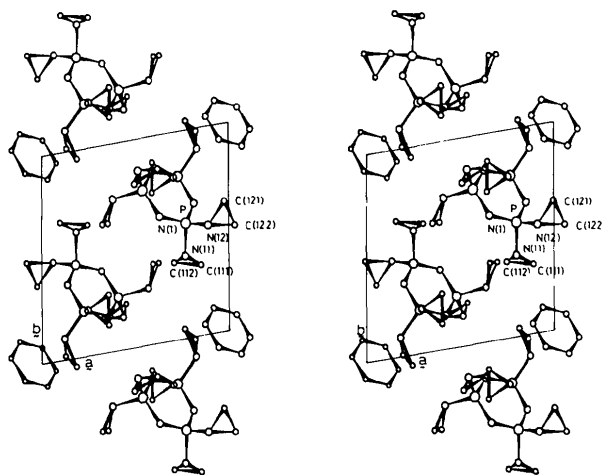
Table 1. Atomic parameters ($\times 10^4$ except $\times 10^5$ for phosphorus)
$$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33}).$$

	x	y	z	U_{eq} (\AA^2)
P(1)	44585 (5)	25194 (5)	21585 (5)	2570 (2)
N(1)	3921 (2)	1695 (2)	3566 (2)	290 (8)
N(11)	2695 (2)	2183 (2)	6038 (2)	360 (9)
N(12)	1518 (2)	985 (2)	4750 (2)	418 (9)
C(111)	3817 (3)	1286 (3)	6613 (3)	495 (12)
C(112)	3824 (3)	2734 (3)	6269 (3)	578 (14)
C(121)	1609 (4)	142 (3)	3722 (4)	707 (15)
C(122)	2127 (3)	-441 (3)	4963 (4)	632 (15)
C(1)	9291 (3)	1211 (3)	9499 (3)	546 (15)

Table 2. Interatomic distances (\AA) and interbond angles ($^\circ$)

P(1)—N(1)	1.590 (2)	N(12)—C(121)	1.465 (4)
P(1)—N(1 ¹)	1.597 (2)	N(12)—C(122)	1.474 (4)
P(1)—N(11 ¹)	1.670 (2)	C(111)—C(112)	1.463 (4)
P(1)—N(12)	1.677 (2)	C(121)—C(122)	1.454 (5)
N(11)—C(111)	1.476 (3)	C(1)—C(1 ^{1b})	1.379 (4)
N(11)—C(112)	1.456 (4)		
N(1)—P(1)—N(1 ¹)	116.6 (1)	C(111)—N(11)—C(112)	59.9 (2)
N(1)—P(1)—N(11 ¹)	107.7 (1)	P(1 ^{1b})—N(12)—C(121)	118.6 (2)
N(1)—P(1)—N(12)	108.8 (1)	P(1 ^{1b})—N(12)—C(122)	118.7 (2)
N(1 ¹)—P(1)—N(11 ¹)	111.8 (1)	C(121)—N(12)—C(122)	59.3 (2)
N(1 ¹)—P(1)—N(12)	111.4 (1)	N(11)—C(111)—C(112)	59.4 (2)
N(11)—P(1)—N(12)	99.1 (1)	N(11)—C(112)—C(111)	60.7 (2)
P(1)—N(1)—P(1 ^{1b})	123.3 (1)	N(12)—C(121)—C(122)	60.7 (2)
P(1 ^{1b})—N(11)—C(111)	119.4 (2)	N(12)—C(122)—C(121)	60.0 (2)
P(1 ^{1b})—N(11)—C(112)	118.6 (2)	C(1 ^{1b})—C(1)—C(1 ^{1a})	120.0 (3)

Symmetry code: (i) z, x, y ; (ii) y, z, x ; (iii) $-y + 1, -z + 1, -x + 2$; (iv) $-z + 2, -x + 1, -y + 1$.

Fig. 1. View of the molecules almost perpendicular to the C_3 axis.Fig. 2. Unit cell viewed along c .

the diffractometer counting statistics. The final atomic coordinates are given in Table 1.* The atomic scattering factors used were those recorded in *International Tables for X-ray Crystallography* (1974), and were corrected for the real part of the anomalous-dispersion effect. The interatomic distances and bond angles are given in Table 2. Fig. 1 shows the arrangement around the threefold axis and Fig. 2 illustrates the molecular packing. All calculations were computed with the Sheldrick (1976) *SHELX* system.

Results and discussion

The crystal is constructed from two centrosymmetrically related molecules of the cyclotri(phosphazene) and a single molecule of benzene positioned at the symmetry centre. All three molecules contain at least C_3 symmetry and are located in the unit cell with the molecular and crystal C_3 axes coincident. The planes of the three rings are thus parallel. The distances between the least-squares best planes are 6.365 (2) \AA from the benzene rings to the cyclotri(phosphazenes), and 8.118 (3) \AA between the two cyclotri(phosphazenes) in the contact where there is no benzene between them. The benzene–cyclotri(phosphazene) contact distances are too long for any intermolecular charge-transfer interactions, and an examination of Fig. 1 shows that the benzene is held as a simple clathrate.

Neither the cyclotri(phosphazene) nor the benzene ring is required to be planar by symmetry. The cyclotri(phosphazene) is very slightly puckered with the P atom 0.016 (1) \AA on one side (and the N atoms the same distance on the other side) of the least-squares

* Lists of structure factors, thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36268 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

best plane through the P_3N_3 ring. In the benzene ring the mean deviation from coplanarity is 0.001 (1) Å.

The cyclotri(phosphazene) contains two unique exocyclic and two unique endocyclic P–N bonds. The endocyclic bond lengths are 1.590 (2) and 1.597 (2) Å, which compare with mean values of 1.589 (2) Å in $N_3P_3az_6 \cdot 3CCl_4$ (Galy *et al.*, 1980), 1.595 (3) Å in the orthorhombic form of $N_3P_3az_6$, and 1.575 (3) Å in $N_3P_3Cl_6$ (Bullen, 1971). The length of the endocyclic bond seems to be well established at 1.593 (1) Å. This is not significantly longer than the mean endocyclic P–N bond length of 1.588 (3) Å in hexakis(dimethylamino)cyclotri(phosphazene) (Rettig & Trotter, 1973) but is obviously much longer than the lengths observed in cyclo(phosphazene) chlorides.

The two exocyclic bond lengths are 1.670 (2) and 1.677 (2) Å. These compare with mean lengths of 1.676 (3), 1.676 (4) and 1.652 (4) Å in $P_3N_3az_6 \cdot 3CCl_4$, orthorhombic $P_3N_3az_6$ and hexakis(dimethylamino)cyclotri(phosphazene) respectively.

The aziridinyl (az) groups are acutely pyramidal (I); the sums of the interbond angles at nitrogen have values of 287.9 (4) and 296.6 (4)° for N(11) and N(12). The N atoms themselves are 0.675 (3) and 0.566 (3) Å respectively from the plane of three atoms bonded to them. In hexakis(dimethylamino)cyclotri(phosphazene), the mean sum of the interbond angles at the amino N atoms is 358.2 (4)° (Rettig & Trotter, 1973) and the differences in exocyclic P–N bond lengths between the aziridinyl and dimethylamino compounds could be largely attributed to the difference in covalent radii of a predominantly sp^2 and a decisively sp^3 nitrogen (Coulson & McWeeny, 1979).

The aziridinyl group has a prominent electron lone-pair orbital (I) which occupies space within the crystal lattice, and efficient packing of these lone pairs must be a factor in the crystallization of the compound. The molecule, though, has two aziridinyl groups bonded to each P atom, and so intra- as well as intermolecular lone-pair interactions become significant.

For the purpose of considering the conformations of the aziridinyl groups it is worth examining the 'torsional' angle between the axes of the lone-pair orbitals of geminal aziridinyl N atoms. This is the angle between the orbital axes when the two aziridinyl groups are viewed in projection along the N...N contact. The angle cannot be determined directly but is estimated approximately as the angle between the planes of the three atoms bonded to each of the two N atoms. There are two readily discernible conformations, the *cis* (III) with a torsional angle of 0° and the *trans* (II) with an angle of 90°. Simple VSEPR considerations (Gillespie, 1963) suggest that the staggered conformation (II) is the most favorable since this places the lone pair on one nitrogen between the methylene H atoms and the lone pair of the other N atom. The torsional angles in the

unsolvated $N_3P_3az_6$ crystals and in the cyclo(phosphathiazenes) (Cameron *et al.*, 1980) are in the range 97–133° with a mean of 107 (12)°, all groups thus having essentially the *trans* conformation (II). The torsional angle in this benzene-solvated sample is however 7.3 (8)°, it having therefore the *cis* conformation (III). The axes of the lone-pair orbitals at N(11) and N(12) have torsional angles of 8 and 4° with P(1)–N(1) about the P(1)–N(11) bond. The lone-pair orbitals are thus not only *cis* but are also arranged with their axes almost parallel to the plane of the P_3N_3 ring. There is, at the moment, no ready explanation for the adoption of this unusual conformation.

The actual dimensions of the aziridinyl group are not unexpected. The four N–C distances have a range of 1.456 (3)–1.476 (3) Å and the two C–C distances are 1.463 (4) and 1.454 (5) Å; these compare with mean N–C and C–C distances of 1.466 (6) and 1.465 (7) Å in the CCl_4 -clathrated sample (Galy *et al.*, 1980).

We thank the Natural Sciences and Engineering Research Council for a grant in aid of research to TSC and for a visiting Professorship to J.-F.L.

References

- BULLEN, G. J. (1971). *J. Chem. Soc. A*, pp. 1450–1453.
 CAMERON, T. S., CHAN, C., LABARRE, J.-F. & GRAFFEUIL, M. (1980). *Z. Naturforsch. Teil B*, **35**, 784–785.
 CAMERON, T. S. & CORDES, R. E. (1979). *Acta Cryst.* **B35**, 748–750.
 CAMERON, T. S., LABARRE, J.-F. & GRAFFEUIL, M. (1982). *Acta Cryst.* **B38**. To be published.
 COULSON, C. A. & MCWEENY, R. (1979). *Coulson's Valence*, pp. 221–223. Oxford Univ. Press.
 GALY, J., ENJALBERT, R. & LABARRE, J.-F. (1980). *Acta Cryst.* **B36**, 392–397.
 GILLESPIE, R. J. (1963). *J. Chem. Educ.* **40**, 295–301.
 HAMILTON, W. C. (1965). *Statistics in Physical Science*, pp. 157–162. New York: Ronald Press.
International Tables for X-ray Crystallography (1974). Vol. IV, pp. 99 and 149. Birmingham: Kynoch Press.
 LABARRE, J.-F., CROS, S., FAUCHER, J.-P., FRANCOIS, G., LEVY, G., PAOLETTI, C. & SOURNIES, F. (1978). Proc. 2nd Int. Symp. on Inorganic Ring Systems (IRIS), Göttingen, p. 44.
 LABARRE, J.-F., FAUCHER, J.-P., LEVY, G., SOURNIES, F., CROS, S. & FRANCOIS, G. (1979). *Eur. J. Cancer*, **15**, 637–643.
 LABARRE, J.-F., SOURNIES, F., VAN DE GRAMPPEL, J. C. & VAN DER HUIZEN, A. (1979). French patent No. 79 17336.
 LENNÉ, H.-U. (1961). *Z. Kristallogr.* **116**, 3–6.
 RETTIG, S. J. & TROTTER, J. (1973). *Can. J. Chem.* **51**, 1295–1302.
 SHELDRIK, G. M. (1976). *SHELX*. X-ray system report, Univ. Chemical Laboratory, Lensfield Road, Cambridge, England.
 SOURNIES, F. (1980). Doctorat d'Université n° 350, Paul Sabatier Univ. Toulouse, France.