# X-Ray-Diffraction Study and Determination of Absolute Configuration of the Anticancer Drug S(−)Cyclophosphamide (Endoxan, Cytoxan, NSC-26271)

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S(−) Cyclophosphamide, Absolute Configuration, X-Ray Diffraction Methods

(−) Cyclophosphamide (**1**) crystallized from tetrachloromethane in the triclinic space group P1 with cell dimensions $a = 10.500\ (4)$ Å, $b = 10.490\ (4)$ Å, $c = 10.761\ (4)$ Å, $\alpha = 110.0\ (2)°$, $\beta = 110.0\ (2)°$, $\gamma = 108.9\ (2)°$. Three molecules are contained in the unit cell. The X-ray analysis was based on diffractometer measurement of 2635 independent reflections and the structure was solved by Patterson and direct methods. The final $R$ and $R_w$ factors after full-matrix least-squares refinement are 0.0717 and 0.0677, respectively. The absolute configuration is S based on Hamilton's $R$-factor ratio test. The oxazaphosphorinane ring exists in a chair form with the bis-$\beta$-chloroethylamino group in equatorial position and about perpendicular to and bisecting the O−P−N plane.

The structure is similar to that found in racemic **1** except a different conformation about one ethylamino N−C bond.

## Introduction

Cyclophosphamide (**1**, Cytoxan, Endoxan, NSC-26271, 2-(bis-$\beta$-chloroethyl) amino-2-oxo-1,3,2-oxazaphosphorinane is a powerful, clinically tested and applied cancerostatic agent [1]. The stereoselective consumption of I by humans [2] and differentiated cytotoxic activity of its enantiomeric forms [3] against ADJ/PC6 plasma cell tumour in mice [4] suggest that the configuration around phosphorous atom is an important factor in the metabolic process of **1**. These results prompted us to carry out the below described single crystal X-ray analysis of (−)**1** in order to supply information about structure – function relationships. An X-ray study of racemic **1** has been described previously [5].

## Experimental

(−)**1** crystallized from tetrachloromethane in the form of stout, irregular prisms. Space group symmetry and cell constants were derived by photographic and diffractometer techniques and are gathered in Table I. Owing to rather high thermal motion of the molecules in the crystal lattice, the X-ray intensities fell of rapidly with glancing angle $\Theta$ and therefore only 2635 data could be collected ($\Theta_{max} = 58°$) using an automated STOE four circle diffractometer equipped with a fine focus tube (Cu $K_\alpha$, Ni-filter). Data were corrected for geometrical factors but not for absorption (size of crystal only $0.3 \times 0.3 \times 0.5$ mm$^3$), standard deviations were assigned according to counting statistics [6] and the data were finally converted to normalized structure amplitudes. The structure was solved by direct methods (MULTAN [7]), but since only the positions of P and Cl atoms were apparent from an E-map, they were confirmed against a sharpened Patterson map and then successive Fourier maps were calculated which finally allowed us to deduce the whole structure. In order to establish the absolute con-

Table I. Crystallographic data.

| | |
|---|---|
| Chemical formula: | $C_7H_{15}N_2O_2Cl_2P$ |
| Space group: | P 1 |
| Cell constants: | $a = 10.500\ (4)$ Å |
| | $b = 10.490\ (4)$ Å |
| | $c = 10.761\ (4)$ Å |
| | $\alpha = 110.0\ (2)$ Å |
| | $\beta = 110.0\ (2)$ Å |
| | $\gamma = 108.9\ (2)$ Å |
| $Z = 3$ | |
| $D_{cal} = 1.27$ g/cm$^3$ | |

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figuration of (−)**1**, coordinates and anisotropic temperature factors were refined by least squares techniques [8] for both models $(x, y, z)$ and the enantiomorph $(\bar{x}, \bar{y}, \bar{z})$ with proper inclusion of anomalous scattering contributions from Cl and P atoms [9]. Final weighted discrepancy indices

$$R_w = [\Sigma w(|F_{obs}| - |F_{calc}|)^2 / \Sigma w |F_{obs}|^2]^{1/2}$$

are 7.28% for model $(x, y, z)$ and 6.77% for model $(\bar{x}, \bar{y}, \bar{z})$ *. On the basis of Hamilton's $R$-factor ratio test [10], model $(x, y, z)$ can be excluded at a significance level $<0.005$, see Table II.

Table II. Determination of the absolute configuration of (−)−**1** using Hamilton's significance test.

For both models 1 $(\bar{x}, \bar{y}, \bar{z})$ and 2 $(x, y, z)$ the R-factors are:

Model 1. $R_1 = 0.0717$ $R_{w1} = 0.0677$

Model 2. $R_2 = 0.0766$ $R_{w2} = 0.0728$

where $R = \Sigma ||F_{obs}| - |F_{cal}|| / \Sigma |F_{obs}|$

$R_W = [\Sigma w(|F_{obs}| - |F_{cal}|)^2 / \Sigma w |F_{obs}|^2]^{1/2}$

$R$ and $R_w$ are a measure of the agreement between a set of observed structure amplitudes $F_{obs}$ and a set of calculated structure amplitudes $F_{cal}$; $w$ is a set of weights; $w = 1/\sigma^2$, where $\sigma^2$ is the variance of $F_{obs}$.

The $R$-factor ratios are: $\mathcal{R} = R_2/R_1 = 1.06834$

$\mathcal{R}_W = R_{w2}/R_{w1} = 1.07533$

In our case for the "dimension of hypothesis", $b = 1$; the "number of reflections", $n = 2635$; the "number of refined parameters", $n = 376$; and "significance level", $\alpha = 0.005$.

$$\mathcal{R}_{b,n-m,\alpha} = \mathcal{R}_{1,2259,0.005} = 1.0018 .$$

From the "table of significance points of the $R$-factor ratio" [10] for $b = 1$, $\alpha = 0.005$, $N = 2000$ and $N_2 = 3000$ we get:

$$\mathcal{R}_{1,2000,0.005} = 1.0020$$

$$\mathcal{R}_{1,3000,0.005} = 1.0013$$

Since $N_1 = m - n = 2259$ is between 2000 and 3000 the value 1.0018 was obtained using the following formula [10]: for $N_0 < N_1 < N_2$

$$\mathcal{R}_{b,N_1,\alpha} \simeq \frac{1}{N_1(N_2 - N_0)} \times [(N_1 - N_0) N_2 \mathcal{R}_{b,N_2,\alpha} + (N_2 - N_1) N_0 \mathcal{R}_{b,N_0,\alpha}] .$$

Both $R$-factor ratios $\mathcal{R}$ and $\mathcal{R}_w$ are greater than the $\mathcal{R}$-factor ratio of 1.0018. Therefore for $N_1 = 2259$ and $\alpha = 0.005$, model 2 can be rejected at a level $<0.005$ (99.5% probability).

## Results and Discussion

Final atomic coordinates for (−)**1** are listed in Table III. Tables IV to VI display geometrical data calculated from the entries in Table III. The structure of (−)**1** is presented in Fig. 1. The configuration around the phosphorous atom is S, the complete description of the molecule is S(−)cyclophosphamide. The packing of the molecules within the unit cell is described in the stereo view Fig. 2.

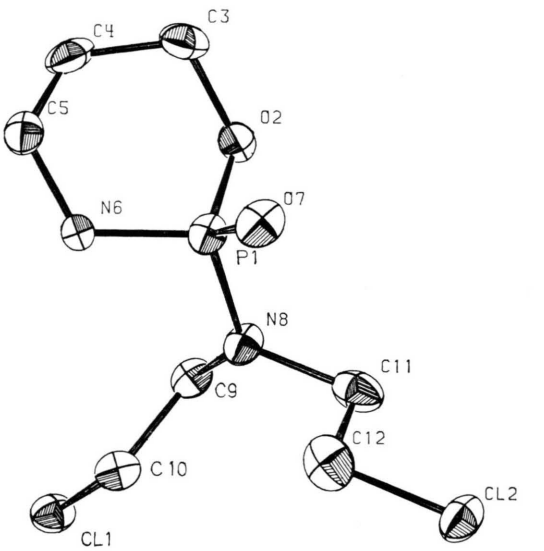


Fig. 1. A plot of S(−)I showing thermal ellipsoids of the atoms the 20% probability level.

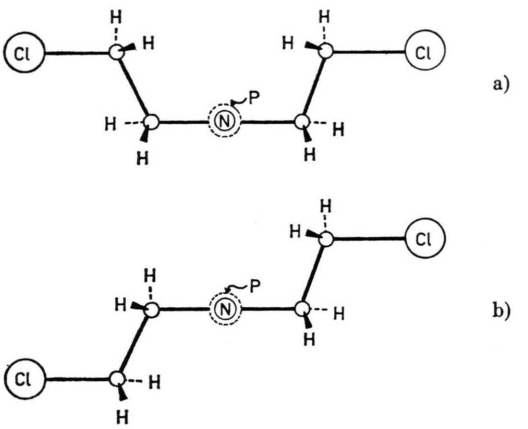


Fig. 2. Schematic drawing of a view along the N−P bond in a) S(−)**1** of this crystal structure and in b) the structure of racemic (±)**1**. Note that in a) the two $\beta$-chloroethyl groups are related by m symmetry while diad symmetry is observed in b).

It is remarkable that within the unit cell (= the asymmetric unit in this space group) three independent molecules are assembled which show identical conformations with torsion angles not deviating more

* A list of observed and calculated structure factors may be obtained from the authors.

than 3 $\sigma$. The molecules are linked via hydrogen bonds

N(6) – H···O(7″), 2.891 Å;
N(6′) – H···O(7), 2.893 Å and
N(6″) – H···O(7′), 2.878 Å,

*i. e.* each molecule acts simultaneously as a hydrogen bond donor and acceptor.

The cyclophosphamide molecules in the present investigation have similar geometry as discussed for the crystal structure of the racemate[5] with only one torsion angle different. The 1,3,2-oxazaphosphorinane rings display chair conformation with the bis-$\beta$-chloroethylamino substituent in equatiorial orientation. The latter is approximately perpendicular tot he O(2) – P(1) – N(6) plane, the torsion angles with the C(9) – N(8) – C(11) planes being 83.4°, 85.6°, and 86.1° for molecules, A, B and C. This conformation results from partial double bond character of the P – N(8) bond which is shortened by 0.119 Å with respect to a normal single bond of 1.769 Å. Similarly, the configuration about N(8) is nearly planar, with the sum of angles around N(8) at 357.5°. Further it is noticeable that the P(1) – N(6) distance, 1.636 Å, indicates partial double bond character as well, *i. e.* the hydrogen atom at N(6) is rather acidic.

Table III. Fractional atomic coordinates and anisotropic temperature factors of the non-hydrogen atoms with standard deviations in parantheses. Temperature factors are in the form $T = \exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

| Atom | X | Y | Z | B(11) * 10000. | B(22) * 10000. | B(33) * 10000. | B(12) * 10000. | B(13) * 10000. | B(23) * 10000. |
|---|---|---|---|---|---|---|---|---|---|
| P1 | −.7657(4) | −.5713(3) | −.9948(4) | 166(5) | 117(4) | 148(4) | 45(4) | 63(4) | 69(4) |
| O2 | −.6915(8) | −.6604(9) | −1.0670(9) | 153(14) | 213(15) | 189(15) | 96(12) | 83(12) | 111(13) |
| C3 | −.6630(15) | −.6303(16) | −1.1798(17) | 182(23) | 234(25) | 245(27) | 79(20) | 144(22) | 116(22) |
| C4 | −.8147(17) | −.6862(17) | −1.3133(15) | 226(27) | 265(27) | 154(21) | 36(22) | 115(21) | 106(21) |
| C5 | −.8973(14) | −.6040(14) | −1.2721(15) | 174(19) | 172(19) | 187(22) | 56(17) | 74(18) | 109(18) |
| N6 | −.9152(9) | −.6063(10) | −1.1468(9) | 130(14) | 213(16) | 143(13) | 89(12) | 69(11) | 100(12) |
| O7 | −.6499(9) | −.4074(8) | −.8771(9) | 259(16) | 127(12) | 202(15) | 37(11) | 100(14) | 74(12) |
| N8 | −.8408(10) | −.6672(9) | −.9211(10) | 173(15) | 137(13) | 154(14) | 22(12) | 60(13) | 84(12) |
| C9 | −.9719(13) | −.8284(11) | −1.0202(12) | 211(19) | 141(15) | 161(17) | 90(14) | 103(16) | 89(14) |
| C10 | −1.1221(14) | −.8246(13) | −1.0330(14) | 224(22) | 125(17) | 201(21) | 83(16) | 126(19) | 82(16) |
| C11 | −.7349(13) | −.6050(13) | −.7409(14) | 258(19) | 288(19) | 419(21) | 185(16) | 228(17) | 255(17) |
| C12 | −.7952(19) | −.5209(17) | −.6862(20) | 311(32) | 227(27) | 355(39) | 184(26) | 165(31) | 171(29) |
| CL1 | −1.2856(4) | −1.0212(4) | −1.1546(4) | 183(5) | 164(5) | 182(5) | 56(4) | 100(5) | 79(5) |
| CL2 | −.6636(5) | −.4271(4) | −.4655(4) | 260(8) | 234(7) | 157(6) | 82(6) | 86(6) | 92(5) |
| P1′ | −.6221(4) | −.0035(4) | −.7584(4) | 122(4) | 184(5) | 147(5) | 75(4) | 65(4) | 80(4) |
| O2′ | −.5346(9) | .1617(9) | −.7392(9) | 175(14) | 170(14) | 152(14) | 108(13) | 66(13) | 86(13) |
| C3′ | −.5674(16) | .1563(17) | −.8871(18) | 197(24) | 260(28) | 291(32) | 145(23) | 119(24) | 208(26) |
| C4′ | −.5063(16) | .0658(18) | −.9593(15) | 196(23) | 297(31) | 164(22) | 127(23) | 90(20) | 165(23) |
| C5′ | −.5898(14) | −.1014(16) | −1.0035(13) | 159(20) | 233(25) | 102(17) | 97(19) | 32(16) | 78(18) |
| N6′ | −.5872(10) | −.1151(11) | −.8708(11) | 138(15) | 172(16) | 144(16) | 76(13) | 58(13) | 74(14) |
| O7′ | −.7904(9) | −.0523(12) | −.8048(11) | 107(13) | 380(23) | 230(19) | 115(15) | 83(14) | 157(18) |
| N8′ | −.5279(11) | .0191(13) | −.5880(11) | 123(15) | 288(22) | 118(15) | 115(15) | 66(13) | 108(16) |
| C9′ | −.3660(12) | .0456(14) | −.5249(13) | 112(16) | 181(20) | 139(19) | 47(15) | 58(15) | 66(17) |
| C10′ | −.3711(12) | −.1018(14) | −.5427(14) | 96(16) | 195(21) | 179(22) | 51(16) | 47(16) | 92(19) |
| C11′ | −.5897(17) | .0595(17) | −.4749(19) | 203(27) | 219(28) | 228(29) | 71(23) | 7(24) | 106(26) |
| C12′ | −.6776(18) | −.0911(15) | −.5012(21) | 273(31) | 143(22) | 304(36) | 70(22) | 105(29) | 100(24) |
| CL1′ | −.1734(4) | −.0739(4) | −.4683(4) | 152(5) | 238(6) | 212(6) | 101(5) | 97(5) | 141(5) |
| CL2′ | −.7670(4) | −.0450(5) | −.3733(4) | 214(7) | 361(9) | 212(7) | 144(6) | 147(6) | 160(7) |
| P1″ | −.1898(0) | −.4279(0) | −.0884(0) | 202(5) | 151(4) | 196(5) | 110(4) | 130(5) | 109(4) |
| O2″ | −.3558(9) | −.5052(9) | −.2388(9) | 159(13) | 180(14) | 154(13) | 75(11) | 83(11) | 73(12) |
| C3″ | −.3500(16) | −.5338(14) | −.3797(14) | 255(25) | 150(20) | 149(21) | 97(19) | 56(19) | 44(17) |
| C4″ | −.2604(19) | −.3813(17) | −.3631(15) | 343(35) | 261(27) | 173(23) | 199(27) | 177(25) | 138(22) |
| C5″ | −.0921(16) | −.2964(14) | −.2361(15) | 238(25) | 172(21) | 219(24) | 119(19) | 151(22) | 111(19) |
| N6″ | −.0780(10) | −.2770(10) | −.0888(11) | 152(15) | 146(15) | 184(17) | 69(12) | 89(14) | 89(13) |
| O7″ | −.1452(11) | −.5477(10) | −.0871(11) | 307(18) | 219(16) | 284(19) | 187(15) | 211(17) | 191(15) |
| N8″ | −.2111(12) | −.3538(11) | .0605(11) | 257(20) | 182(16) | 202(17) | 149(16) | 169(16) | 135(15) |
| C9″ | −.2376(13) | −.2223(14) | .0943(14) | 173(18) | 189(19) | 192(20) | 109(17) | 126(17) | 126(17) |
| C10″ | −.0904(14) | −.0715(14) | .2284(14) | 197(21) | 184(20) | 148(20) | 107(17) | 89(18) | 62(17) |
| C11″ | −.2508(17) | −.4564(19) | .1332(18) | 198(27) | 363(38) | 210(28) | 115(27) | 96(24) | 4(27) |
| C12″ | −.1051(16) | −.3988(17) | .2539(20) | 186(24) | 263(28) | 271(31) | 103(22) | 104(24) | 88(26) |
| CL1″ | −.1203(4) | .0912(4) | .2703(4) | 230(6) | 186(5) | 194(5) | 124(5) | 110(5) | 110(4) |
| CL2″ | −.1485(5) | −.5305(5) | .3384(5) | 313(8) | 293(8) | 284(8) | 192(7) | 190(7) | 214(7) |

Table IV. Fractional atomic coordinates for the hydrogen atoms.

| Atom | X | Y | Z |
|---|---|---|---|
| H3 1 | −.6097 | −.6991 | −1.2222 |
| H3 2 | −.5829 | −.5072 | −1.1303 |
| H4 1 | −.8899 | −.8106 | −1.3616 |
| H4 2 | −.7947 | −.6682 | −1.4000 |
| H5 1 | −.8292 | −.4813 | −1.2374 |
| H5 2 | −1.0111 | −.6567 | −1.3711 |
| H6 1 | −1.0299 | −.6323 | −1.1534 |
| H9 1 | −.9870 | −.8741 | −1.1371 |
| H9 2 | −.9507 | −.8987 | −.9749 |
| H11 1 | −.6109 | −.5324 | −.6988 |
| H11 2 | −.7543 | −.7020 | −.7194 |
| H12 1 | .0739 | .3800 | .2696 |
| H12 2 | .2232 | −.4200 | .2854 |
| H10 1 | −.1378 | .2600 | −.0972 |
| H10 2 | −.1311 | .2200 | .0622 |
| H3′ 1 | −.5080 | .2762 | −.8645 |
| H3′ 2 | −.6927 | .1033 | −.9619 |
| H4′ 1 | −.3830 | .1149 | −.8808 |
| H4′ 2 | −.5213 | .0686 | −1.0636 |
| H5′ 1 | −.5345 | −.1613 | −1.0476 |
| H5′ 2 | −.7112 | −.1561 | −1.0924 |
| H6′ 1 | −.5605 | −.2016 | −.8497 |
| H9′ 1 | −.2926 | .1375 | −.4073 |
| H9′ 2 | −.3164 | .0791 | −.5933 |
| H11′1 | −.4944 | .1469 | −.3546 |
| H11′2 | −.6688 | .1084 | −.5083 |
| H10′1 | −.4191 | −.1357 | −.4770 |
| H10′2 | −.4423 | −.1938 | −.6627 |
| H12′1 | .3452 | −.1820 | .4251 |
| H3″ 1 | −.2927 | −.6017 | −.3986 |
| H3″ 2 | −.4681 | −.5950 | −.4778 |
| H4″ 1 | −.3125 | −.3091 | −.3346 |
| H4″ 2 | −.2643 | −.4001 | −.4700 |
| H5″ 1 | −.0301 | −.1838 | −.2224 |
| H5″ 2 | −.0381 | −.3664 | −.2681 |
| H6″ 1 | .0066 | −.1612 | .0191 |
| H9″ 1 | −.3301 | −.2439 | .1209 |
| H9″ 2 | −.2737 | −.2108 | −.0079 |
| H10″1 | −.0550 | −.0849 | .3278 |
| H10″2 | .0011 | −.0515 | .1991 |
| H11″1 | −.3289 | −.4416 | .1736 |
| H11″2 | −.2996 | −.5812 | .0511 |
| H12″1 | −.0582 | −.2730 | .3720 |

The bis-$\beta$-chloroethylamino group displays nearly mirror-symmetry, Fig. 2. The torsion angles about the N – C bonds, P(1) – N(8) – C(9) – C(10) and P(1) – N(8) – C(11) – C(12) are opposite, at – 104° and 97° but the orientations about the ethyl bonds, N – $CH_2$ – $CH_2$ – Cl, are both *trans*.

From the close structural relationship between the three S(–)**1** molecules one could conclude that they exist in a rather constrained conformation. A comparison with the crystal structure of the racemic (±)**1** (Tables V – VII) shows that the six-membered oxazaphosphorinane ring and its substituents N(8), C(9) and C(11) have nearly identical geometry but the conformation about the N(8) – C(9) bond is different, with the torsion angle P(1) – N(8) – C(9) – C(10) at 103°. This brings the two $\beta$-chloroethyl groups into a propeller-like orientation with nearly twofold rotational symmetry, Fig. 2. Thus the oxazaphosphorinane moiety appears to be rather rigid but rotation does accur about the N – C bonds.

Table V. Bond distances (Å), with standard deviations in parentheses.

| Bond | Molecule A | Molecule B | Molecule C | Ref. 5 |
|---|---|---|---|---|
| P(1) – O(2) | 1.570(11) | 1.580(10) | 1.613(07) | 1.580(4) |
| O(2) – C(3) | 1.453(24) | 1.486(23) | 1.469(20) | 1.466(4) |
| C(3) – C(4) | 1.489(20) | 1.465(27) | 1.485(22) | 1.520(10) |
| C(4) – C(5) | 1.474(26) | 1.495(23) | 1.520(19) | 1.488(8) |
| C(5) – N(6) | 1.431(21) | 1.477(21) | 1.475(22) | 1.481(7) |
| N(6) – P(1) | 1.659(10) | 1.606(13) | 1.644(11) | 1.623(5) |
| P(1) – O(7) | 1.474(06) | 1.510(10) | 1.477(12) | 1.466(4) |
| P(1) – N(8) | 1.650(13) | 1.648(13) | 1.652(13) | 1.623(5) |
| N(8) – C(9) | 1.476(11) | 1.487(17) | 1.444(20) | 1.457(7) |
| C(9) – C(10) | 1.551(22) | 1.473(22) | 1.530(12) | 1.512(8) |
| C(1) – Cl 1 | 1.812(10) | 1.832(14) | 1.770(16) | 1.769(6) |
| N(8) – C(11) | 1.622(16) | 1.564(25) | 1.565(27) | 1.483(6) |
| C(11) – C(12) | 1.335(27) | 1.418(25) | 1.384(21) | 1.513(7) |
| C(12) – Cl 2 | 1.956(18) | 1.931(24) | 1.918(23) | 1.798(5) |

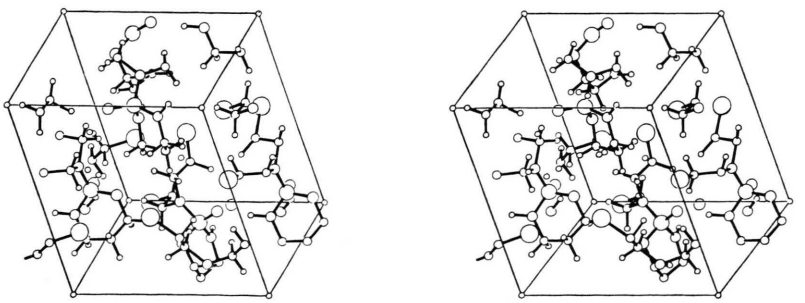

Fig. 3. A stereo view of the structure along a-axis.

Table VI. Bond angles (°) with standard deviations in parentheses.

| Angle | Molecule A | Molecule B | Molecule C | Ref. 5 |
|---|---|---|---|---|
| O(2) —P(1) —N(6) | 103.0 (0.5) | 105.0 (0.6) | 103.6 (0.5) | 103.1 (0.2) |
| O(2) —P(1) —O(7) | 112.0 (0.6) | 114.4 (0.6) | 110.2 (0.5) | 113.8 (0.2) |
| O(2) —P(1) —N(8) | 105.8 (0.5) | 104.7 (0.6) | 106.6 (0.5) | 104.4 (0.2) |
| N(6) —P(1) —O(7) | 117.7 (0.6) | 117.5 (0.7) | 120.1 (0.6) | 117.3 (0.3) |
| N(6) —P(1) —N(8) | 106.2 (0.5) | 107.2 (0.6) | 105.4 (0.6) | 106.7 (0.2) |
| O(7) —P(1) —N(8) | 111.1 (0.6) | 110.2 (0.7) | 110.1 (0.6) | 110.4 (0.2) |
| P(1) —O(2) —C(3) | 115.7 (0.9) | 113.3 (0.9) | 114.7 (0.8) | 118.8 (0.4) |
| O(2) —C(3) —C(4) | 108.8 (1.3) | 108.9 (1.4) | 108.5 (1.2) | 108.9 (0.5) |
| C(3) —C(4) —C(5) | 112.6 (1.4) | 112.0 (1.4) | 111.2 (1.4) | 112.1 (0.6) |
| C(4) —C(5) —N(6) | 112.9 (1.2) | 110.8 (1.2) | 112.5 (1.3) | 110.5 (0.5) |
| P(1) —N(6) —C(5) | 119.4 (0.9) | 119.8 (1.9) | 118.3 (0.9) | 121.5 (0.4) |
| P(1) —N(8) —C(9) | 120.8 (0.9) | 120.9 (1.0) | 120.6 (1.0) | 121.7 (0.4) |
| P(1) —N(8) —C(11) | 117.5 (0.8) | 118.7 (1.0) | 117.7 (1.0) | 122.1 (0.4) |
| C(9) —N(8) —C(11) | 118.7 (1.0) | 118.2 (1.2) | 119.3 (1.2) | 116.3 (0.5) |
| N(8) —C(9) —C(10) | 108.2 (1.0) | 108.4 (1.1) | 111.5 (1.2) | 110.6 (0.5) |
| C(9) —C(10) —Cl 1 | 109.2 (1.0) | 109.6 (1.0) | 112.1 (1.0) | 110.3 (0.5) |
| N(8) —C(11) —C(12) | 98.4 (1.2) | 100.3 (1.4) | 101.4 (1.5) | 117.7 (0.4) |
| C(11) —C(12) —Cl 2 | 101.6 (1.3) | 100.7 (1.3) | 102.3 (1.3) | 107.2 (0.4) |

Table 7. Torsional angles* (°) and standard deviations in parentheses.

| Angles | Molecule A | Molecule B | Molecule C | Ref. 5 |
|---|---|---|---|---|
| P(1) —O(2) —C(3) —C(4) | −63.6 (1.5) | −64.5 (1.5) | −65.5 (1.4) | −59.6 |
| P(1) —N(6) —C(5) —C(4) | 44.2 (1.6) | 44.2 (1.6) | 45.6 (1.6) | 45.8 |
| P(1) —N(8) —C(9) —C(10) | −104.4 (1.1) | −101.9 (1.2) | −103.7 (1.2) | 102.8 |
| P(1) —N(8) —C(11) —C(12) | 97.2 (1.3) | 96.8 (1.4) | 97.4 (1.4) | 90.8 |
| O(2) —P(1) —N(6) —C(5) | −40.3 (1.1) | −40.7 (1.2) | −41.3 (1.1) | −38.0 |
| O(2) —P(1) —N(8) —C(9) | −65.2 (1.0) | −68.5 (1.1) | −67.5 (1.1) | −54.4 |
| O(2) —P(1) —N(8) —C(11) | 95.0 (0.9) | 94.3 (1.2) | 94.9 (1.1) | 123.6 |
| O(2) —C(3) —C(4) —C(5) | 61.9 (1.7) | 65.5 (1.7) | 64.3 (1.6) | 61.9 |
| C(3) —O(2) —P(1) —N(6) | 49.6 (1.1) | 49.2 (1.1) | 50.9 (1.0) | 44.9 |
| C(3) —C(2) —P(1) —O(7) | −77.9 (1.1) | −79.0 (1.1) | −78.8 (1.0) | −83.3 |
| C(3) —O(2) —P(1) —N(8) | 160.9 (1.0) | 161.9 (1.0) | 161.8 (1.0) | 159.2 |
| C(3) —C(4) —C(5) —N(6) | −53.0 (1.8) | −54.5 (1.8) | −55.0 (1.9) | −55.0 |
| C(5) —N(6) —P(1) —O(7) | 83.5 (1.1) | 83.7 (1.2) | 82.1 (1.1) | 88.0 |
| C(5) —N(6) —P(1) —N(8) | −151.4 (1.0) | −151.7 (1.0) | −153.1 (1.0) | −147.6 |
| N(6) —P(1) —N(8) —C(9) | 43.9 (1.1) | 42.6 (1.2) | 42.1 (1.2) | 44.9 |
| N(6) —P(1) —N(8) —C(11) | −155.9 (0.9) | −154.6 (1.1) | −155.5 (1.1) | −127.6 |
| O(7) —P(1) —N(8) —C(9) | 173.0 (0.9) | 171.5 (1.0) | 173.1 (1.0) | −177.2 |
| O(7) —P(1) —N(8) —C(11) | −26.8 (1.0) | −25.7 (1.3) | −24.6 (1.3) | 0.9 |
| N(8) —C(9) —C(10) —Cl 1 | 179.9 (0.9) | 179.2 (0.9) | 179.5 (1.0) | −175.9 |
| N(8) —C(11) —C(12) —Cl 2 | −175.9 (0.9) | −176.0 (1.0) | −176.9 (1.0) | 176.7 |
| C(9) —N(8) —C(11) —C(12) | −102.1 (1.4) | −99.9 (1.6) | −100.1 (1.6) | −91.1 |
| C(10) —C(9) —N(8) —C(11) | 95.6 (1.2) | 95.2 (1.5) | 94.3 (1.5) | −75.4 |

* Definition: The angles A—B—C—D are defined zero when the bonds A—B and C—D are cis planar. They are counted positive when, looking along the central B—C bond, the far bond is rotated clockwise with respect to the near bond.

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