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The Structure of a Platinum(II) Complex of 1-(β-D-Arabinofuranosyl)cytosine

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The structure of a complex, arapen, formed between Pt ethylenediamine dichloride ($PtenCl_2$) and 1-(β-D-arabinofuranosyl)cytosine (ara-C) is described. The sugar puckering is C(2′)-*endo*, and an intramolecular hydrogen bond connecting O(2′) to O(5′) in the sugar moiety is observed, a feature seen in the structure of neutral ara-C. The possible implications of the structure to reactivity studies of the complex with nucleic acid components are discussed. [Crystal data: $(C_{11}H_{21}N_5O_5PtCl)^+Cl^-$, space group $P2_12_12$, $a = 24{\cdot}440$ (2), $b = 10{\cdot}388$ (2), $c = 6{\cdot}700$ (1) Å, $Z = 4$.]

Introduction

1-(β-D-Arabinofuranosyl)cytosine (ara-C) is a nucleoside antimetabolite with potent antileukaemic and antiviral activity (Suhadolnik, 1970).

In vitro tests have shown that ara-C can inhibit DNA replication by two mechanisms: in the first the triphosphate derivative competitively inhibits the utilization of the corresponding deoxyribonucleoside triphosphate in the DNA polymerase reaction. In the second ara-C is actually incorporated into DNA probably impeding further chain synthesis. Recent *in vivo* studies have shown the latter mechanism to be the dominant (Rashbaum & Cozzarelli, 1976). The chemotherapeutic value of ara-C is limited, since it is rapidly deaminated by cytidine deaminase to the inactive antimetabolite ara-U (Pizer & Cohen, 1960).

cis-Pt ethylenediamine dichloride ($PtenCl_2$) is a cytotoxic Pt coordination complex and is in particular an effective antitumour agent (Rosenberg, Van Camp, Trosko & Mansour, 1969). It was suggested (Robins, 1976) that a complex formed between $PtenCl_2$ and ara-C could possibly inhibit deamination of the latter.

A crystallographic study was undertaken to investigate the conformational properties of the Pt–nucleoside complex with reference to its interactions with nucleic acid components (Robins, 1976).

Experimental

Arapen was prepared from a mixture of ara-C and $PtenCl_2$ (Robins, 1976). It was crystallized from the solution and not subjected to electrophoretic purification. The colourless, long thin needles of the complex showed parallel extinction. Photographs revealed the crystals to be orthorhombic. Systematic absences, $h00$ and $0k0$ with h and $k = 2n + 1$ respectively, uniquely identified the space group as $P2_12_12$. Cell dimensions were obtained from diffractometer measurements.

Crystal data

$(C_{11}H_{21}N_5O_5PtCl)^+Cl^-$, $M_r = 569{\cdot}10$. Orthorhombic needles, elongated along **c**. $a = 24{\cdot}440$ (2), $b = 10{\cdot}388$ (2), $c = 6{\cdot}700$ (1) Å, $V = 1711{\cdot}5$ Å^3, $D_o = 2{\cdot}22$ (by flotation), $D_c = 2{\cdot}209$ g cm^{-3} for $Z = 4$. $F(000) = 1088$, $\mu = 176{\cdot}18$ cm^{-1} for Cu $K\alpha$ radiation ($\lambda_{K\alpha} = 1{\cdot}54178$ Å). Space group $P2_12_12$.

Intensities were collected manually on a Supper–Pace two-circle equi-inclination diffractometer for layers $hk0$–$hk6$, to a θ limit of 65° for Cu $K\alpha$ radiation. 1494 intensities were measured, their standard deviations being taken (Eisenberg & Ibers, 1966) as $\sigma(I) = [I + 2B + (0{\cdot}03I)^2]^{1/2}$ where B was the background count. 45 reflections were considered to be unobserved with $I < 2{\cdot}5\sigma(I)$. The data were corrected for absorption. The scattering factors and anomalous dispersion corrections ($\Delta f'$ and $\Delta f''$) for Pt were taken from *International Tables for X-ray Crystallography* (1962).

Structure determination and refinement

The structure was solved by the heavy-atom method. Full-matrix least-squares refinement was carried out with all non-hydrogen atoms anisotropic. Several

strong, low-sin θ reflections suffering from severe secondary extinction were removed in the later stages. Those H atoms which were located in difference syntheses had their positional and thermal parameters fixed throughout the refinement.

Refinement converged to a final R of 0·0757 ($R = \sum |F_o| - |F_c| / \sum |F_o|$ and an R_w of 0·0899 ($R_w = \sum w|F_o| - |F_c| / \sum w|F_o|$) where $w = [1{\cdot}363/\sigma^2(F_o) + 0{\cdot}003F_o^2]^{1/2}$.

All calculations were performed with programs written by Dr G. M. Sheldrick.

Tables 1 and 2 list the final positional parameters.*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33327 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Final positional parameters for the non-hydrogen atoms* (×10⁴), *with estimated standard deviations in parentheses*

	x	y	z
Pt	2591 (0)	5382 (1)	2432 (2)
Cl(1)	2896 (3)	7469 (6)	2681 (14)
Cl(2)	3234 (3)	1345 (8)	1921 (14)
N(en 1)	2272 (10)	3527 (28)	2564 (26)
N(en 2)	1794 (10)	5941 (28)	3075 (41)
C(en 1)	1671 (18)	3726 (34)	2536 (56)
C(en 2)	1466 (11)	4753 (32)	3315 (67)
N(1)	4201 (9)	3924 (22)	2034 (41)
C(2)	3734 (10)	4318 (23)	2873 (48)
O(2)	3587 (8)	4293 (23)	4516 (41)
N(3)	3309 (10)	4794 (21)	1398 (31)
C(4)	3422 (10)	4770 (32)	−347 (60)
N(4)	3058 (11)	5088 (26)	−1847 (37)
C(5)	3951 (13)	4268 (32)	−1291 (49)
C(6)	4341 (10)	3921 (31)	209 (40)
C(1′)	4618 (11)	3586 (26)	3549 (42)
O(1′)	5150 (7)	3635 (16)	2540 (38)
C(2′)	4591 (12)	2164 (28)	4377 (56)
O(2′)	4418 (9)	1291 (17)	2983 (34)
C(3′)	5183 (13)	1974 (34)	5113 (32)
O(3′)	5301 (10)	2566 (25)	6843 (42)
C(4′)	5487 (12)	2605 (28)	3320 (50)
C(5′)	5709 (12)	1881 (32)	1583 (48)
O(5′)	5288 (8)	1377 (24)	335 (29)

Table 2. *Observed positional parameters* (×10³) *for the* H *atoms, assigned a temperature factor of* 0·04 Å²

	x	y	z
H(Nen1)	215	260	272
H(Nen1)	228	346	124
H(Nen2)	206	656	254
N(Nen2)	139	638	253
N(Cen1)	164	271	270
H(Cen1)	163	353	138
N(N4)	263	542	−147
H(N4)	311	529	−326
H(C5)	418	439	−259
H(C6)	475	369	−15
H(C1′)	537	561	466
H(O2′)	45	579	807
H(C2′)	−61	322	424
H(C3′)	38	379	548
H(C5′)	82	203	896

Discussion

As seen in Figs. 1 and 2(*a*,*b*) covalent attachment of the Pt fragment to the cytosine residue is by N(3), as has been found before in metal–cytosine and metal–CMP structures (Louie & Bau, 1977). The Pt atom has the usual square-planar coordination, the presence of Cl(1) giving the molecule a net charge of +1. This charge is balanced by a Cl^- ion.

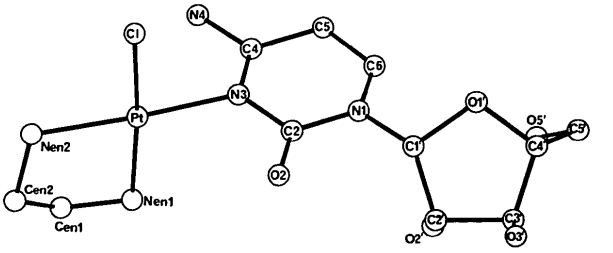
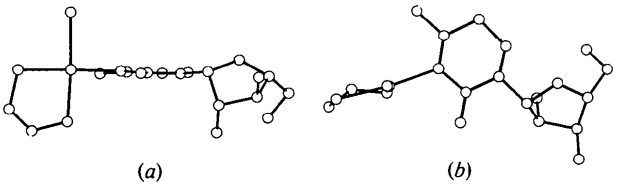


Fig. 1. A view of the molecule showing the numbering scheme.



(*a*) (*b*)

Fig. 2. Two views of the molecule (*a*) along, and (*b*) perpendicular to, the cytosine ring.

Table 3. *Bond lengths* (Å) *and angles* (°)

Standard deviations for bond lengths range from 0·032 to 0·050 Å, and for bond angles from 2·4 to 3·4°.

Pt–Cl(1)	2·30	Pt–N(en2)–C(en2)	107·3
Pt–N(en1)	2·08	N(en1)–C(en1)–C(en2)	119·7
Pt–N(en2)	2·08	N(en2)–C(en2)–C(en1)	115·7
Pt–N(3)	1·98	C(2)–N(1)–C(1′)	111·5
N(en1)–C(en1)	1·48	C(2)–N(1)–C(6)	129·5
N(en2)–C(en2)	1·48	C(6)–N(1)–C(1′)	118·6
C(en1)–C(en2)	1·29	N(1)–C(2)–O(2)	131·1
N(1)–C(2)	1·34	N(1)–C(2)–N(3)	113·9
N(1)–C(6)	1·28	O(2)–C(2)–N(3)	114·8
N(1)–C(1′)	1·49	C(2)–N(3)–C(4)	118·3
C(2)–O(2)	1·17	N(3)–C(4)–N(4)	123·9
C(2)–N(3)	1·52	N(3)–C(4)–C(5)	127·1
N(3)–C(4)	1·21	N(4)–C(4)–C(5)	108·7
C(4)–N(4)	1·39	C(4)–C(5)–C(6)	110·7
C(4)–C(5)	1·53	N(1)–C(6)–C(5)	120·0
C(5)–C(6)	1·44	N(1)–C(1′)–O(1′)	106·3
C(1′)–O(1′)	1·47	N(1)–C(1′)–C(2′)	115·8
C(1′)–C(2′)	1·58	O(1′)–C(1′)–C(2′)	103·5
O(1′)–C(4′)	1·45	C(1′)–O(1′)–C(4′)	108·0
C(2′)–O(2′)	1·37	C(1′)–C(2′)–O(2′)	112·9
C(2′)–C(3′)	1·54	C(1′)–C(2′)–C(3′)	101·2
C(3′)–O(3′)	1·35	O(2′)–C(2′)–C(3′)	115·1
C(3′)–C(4′)	1·56	C(2′)–C(3′)–O(3′)	114·8
C(4′)–C(5′)	1·49	C(2′)–C(3′)–C(4′)	98·3
C(5′)–O(5′)	1·43	O(3′)–C(3′)–C(4′)	112·1
Cl(1)–Pt–N(en2)	91·4	O(1′)–C(4′)–C(3′)	108·7
Cl(1)–Pt–N(3)	91·7	O(1′)–C(4′)–C(5′)	107·0
N(en1)–Pt–N(en2)	84·2	C(3′)–C(4′)–C(5′)	124·6
N(en1)–Pt–N(3)	93·5	C(4′)–C(5′)–O(5′)	112·7
Pt–N(en1)–C(en1)	104·0		

Table 4. *Deviations* (Å) *of atoms from various least-squares planes*

Cytosine ring		Arabinose ring	
N(1)	−0·016	C(1′)	0·000
C(2)	−0·015	O(1′)	0·000
N(3)	0·026	C(4′)	0·000
C(4)	−0·008	*C(2′)	−0·473
C(5)	−0·020	*C(3′)	0·137
C(6)	0·034	*C(5′)	−1·090
*C(1′)	0·085	*N(1)	−0·844
*O(2)	−0·041		
*N(4)	−0·096		

* Atom not included in the plane calculations.

Bond lengths and angles are listed in Table 3. The Pt–*X* distances compare well with those found in $(PtenG_2)^{2+}$ (Gellert & Bau, 1975), PtenCMP (Louie & Bau, 1977), and $PtenCl_2$ (Iball & Scrimgeour, 1974), as do the bond angles around Pt. The ethylenediamine ring also has the same conformation as in these crystal structures.

Deviations of atoms from defined least-squares planes are listed in Table 4. The cytosine ring is planar within experimental error. As has been found in other ara-C derivatives (Sherfinski & Marsh, 1973; Birnbaum, Darżynkiewicz & Shugar, 1975; Tougard & Lefebvre-Soubeyran, 1974), the relatively large deviation of C(1′) from the pyrimidine ring reflects the close contact of 2·86 Å between N(1) and O(2′).

A recent presentation of the average distances and angles for the arabinose moiety in several structures (Bunick & Voet, 1974) shows that the values found here correspond well to these averages.

Molecular conformation

Table 5 lists several important torsion angles; the first of these corresponds to the glycosidic angle χ (Sundaralingam, 1969). The base shows the *anti* conformation which is common to most pyrimidine nucleosides but the value of $\chi = 14{\cdot}1°$ is smaller than values reported for the arabinosylpyrimidine structures, whose χ values range from 24·1 to 36°. The small value found here may be due to an electrostatic interaction between the Cl^- ion and O(2′). The sugar puckering is C(2′)-*endo* (Table 3) as seen also in ara-C (Tougard & Lefebvre-Soubeyran, 1974; Chwang & Sundaralingam, 1973), ara-C HCl (Sherfinski & Marsh, 1973), ara-U (Tollin, Wilson & Young, 1973) and 3′-*O*-methyl-ara-C (Birnbaum, Darżynkiewicz & Shugar, 1975).

Table 5. *Torsion angles* (°)

The torsion-angle convention used is that given by Sundaralingam (1969).

C(6)–N(1)–C(1′)–O(1′)	14·1	χ
Arabinosyl ring torsion angles		
C(4′)–O(1′)–C(1′)–C(2′)	−20·4	τ_0
O(1′)–C(1′)–C(2′)–C(3′)	40·7	τ_1
C(1′)–C(2′)–C(3′)–C(4′)	−42·8	τ_2
C(2′)–C(3′)–C(4′)–O(1′)	32·5	τ_3
C(3′)–C(4′)–O(1′)–C(1′)	−7·6	τ_4
Exocyclic torsion angles		
O(5′)–C(5′)–C(4′)–O(1′)	−58·2	
O(5′)–C(5′)–C(4′)–C(3′)	70·0	ψ

Again, as in ara-C and ara-U the presence of an energetically favoured intramolecular hydrogen bond O(2′)–H···O(5′) of length 2·77 Å constrains the arabinose ring in the C(2′)-*endo* conformation. The H atom involved in the hydrogen bond, H(O2′) was one of those observed. Another constraint imposed by this hydrogen bond is the conformation about the exocyclic C(4′)–C(5′) which is *gauche–gauche*.

Detailed comparisons of sugar puckering and exocyclic bond conformations for many arabinosyl nucleosides are well documented (Birnbaum, Darżynkiewicz & Shugar, 1975; Bunick & Voet, 1974). It is apparent from them that the ara-C moiety in arapen preserves its gross conformational characteristics when coordinated to $PtenCl_2$, the principal differences compared with neutral ara-C being the degree of C(2′)-*endo* puckering and the smaller glycosidic torsion angle. Quantitatively the degree of sugar puckering can be expressed by the phase angle of pseudorotation (Altona & Sundaralingam, 1972) which for arapen is 170·9° compared with 162·7° for ara-C, implying a situation nearer the C(2′)-*endo*–C(3′)-*exo* ($P = 180°$) extreme for arapen (Table 4).

Structure and reactivity with nucleic acid components

Solution studies of the reactivity of $PtenCl_2$ and $Pt(NH_3)_2Cl_2$ with nucleic acid components (Mansy, Rosenberg & Thompson, 1975) indicate that the *cis* isomers of these antitumour agents react in a bidentate fashion with adenosine at the 6-NH_2 and N(7), or 6-NH_2 and N(1) sites; in a bidentate fashion with cytosine at 4-NH_3 and N(3), but in a monodentate fashion with guanosine at the N(7) site. Robins (1976) has investigated the reactivity of arapen towards various nucleic acid components. It is found that deoxyguanosine and cytidine monophosphate show no reaction with arapen, and that various adenine compounds all react at about the same rate, which is 10–20 times slower than with $PtenCl_2$.

It has been suggested (Robins, 1976) that steric limitations possibly inhibit the reactivity of deoxyguanosine towards arapen in view of the fact that this nucleoside is very reactive towards $PtenCl_2$ itself. If coordination of deoxyguanosine to the Pt in place of

Cl(1), *via* site N(7) on the imidazole ring is sterically inhibited then adenine can still react *via* the 6-NH_2 position. However, investigation of Fig. 2(*a*) along with some model building with CPK space-filling models reveals that there is little steric hindrance for coordination of deoxyguanosine to arapen, assuming the molecular conformation for arapen as determined here. An alternative explanation could be the more remote position of 6-NH_2 from the bulk of the adenine derivative molecule which probably enhances its coordinating ability.

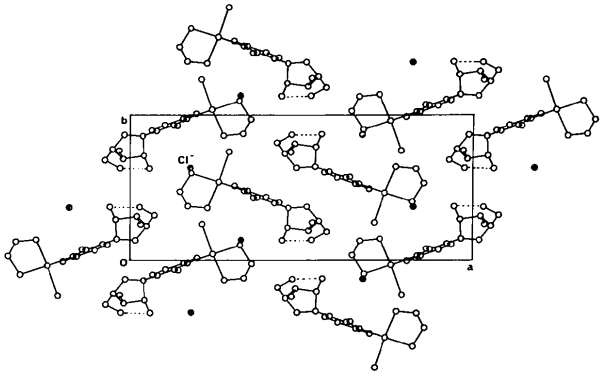


Fig. 3. The *c*-axis projection of the crystal structure. Dashed lines indicate hydrogen bonds.

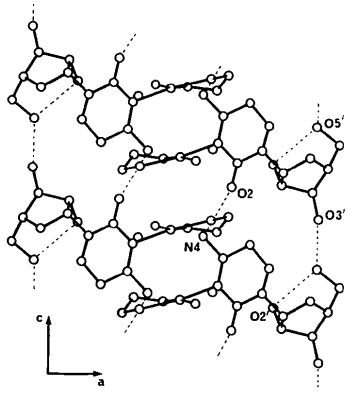


Fig. 4. The *b*-axis projection of the crystal structure.

Table 6. *Hydrogen-bonded contact distances* (Å)

Atom 1	Atom 2	Distance	Symmetry operation for atom 2
O(2')–H	O(5')	2·77	*x,y,z*
O(5')–H	O(3')	2·66	*x, y,* 1 + *z*
N(4)–H	O(2)	2·89	*x, y,* 1 + *z*

Intermolecular packing

Fig. 3 shows the *c*-axis projection of the crystal structure. Apart from the intramolecular hydrogen bond the only notable intermolecular interaction in this plane is the electrostatic one between the Cl^- ion Cl(2) and O(2'), arising from their close contact of 2·98 Å. Fig. 4 shows the *b*-axis projection and reveals the hydrogen-bonding linking equivalent molecules in an infinite chain in the **c** direction (Table 6). A similar N(4)–H···O(2) hydrogen bond was observed in the packing of ara-C molecules.

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