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Tris(1-methylcytosine-N3)ammineplatinum(II) Perchlorate Monohydrate, a Model for Simultaneous Binding of Three Nucleobases to a Single Metal Ion

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Abstract

A Pt(II) complex containing three 1-methylcytosine ligands (*C*), [Pt(NH$_3$)*C*$_3$](ClO$_4$)$_2$·H$_2$O], has been prepared starting with *cis*-Pt(NH$_3$)$_2$Cl$_2$, and its crystal structure has been determined. The title compound represents a model of a hypothetical interaction of *cis*-Pt(II) with three biomolecules which proceeds via an intermediate monochloro complex, *cis*-[Pt(NH$_3$)$_2$-*C*Cl]Cl, and loss of ammonia from this compound. [Pt(NH$_3$)*C*$_3$](ClO$_4$)$_2$·H$_2$O crystallizes in space group $P2_1/c$ (No. 14) with a = 15.296(3), b = 14.666(3), c = 14.025(2) Å, β = 122.61(1)° and has 4 formula units in the unit cell. Data were collected with use of a Syntex P2$_1$ diffractometer and MoKα radiation. The crystal structure was determined by standard methods and refined to R_1 = 0.043 and R_2 = 0.056 based on 2925 independent reflections. The compound contains the three 1-methylcytosine ligands bound through N(3) with the three ligands almost perpendicular to the Pt coordination plane. The two *C* ligands *trans* to each other have identical orientations with respect to the platinum square plane whereas the cytosine *trans* to NH$_3$ has the opposite orientation. Bond lengths and angles are normal.

Introduction

Cis-Pt(NH$_3$)$_2$Cl$_2$, Cisplatin, represents a powerful antitumor agent that is presently undergoing extensive clinical use in the treatment of cancer [1]. Its mode of action generally is believed to involve a bifunctional attack on nucleobases of DNA with guanine being the preferred initial binding site [2]. The unexpected lability of a NH$_3$ group in the model nucleobase complex *cis*-[Pt(NH$_3$)$_2$*C*Cl]Cl (*C* = 1-methylcytosine) which causes formation of *trans*-Pt(NH$_3$)*C*Cl$_2$ [3, 4], has lead us to speculate on the possible biological implications of this finding [4, 5]. To summarize these ideas briefly, it has been pointed out that in principle it is possible to bind three biomolecules simultaneously to a single platinum(II) atom by starting out with *cis*-Pt(NH$_3$)$_2$Cl$_2$, and that such a possibility would be unique for monochloro complexes of *cis*-Pt(II). In order to test this idea, model complexes containing three nucleobases bound to Pt have been prepared, and ^{1}H NMR spectroscopic evidence has been presented for their existence [5]. We now report the crystal and molecular structure of one of the isolated complexes, tris(1-methylcytosine-N3)ammineplatinum(II) diperchlorate monohydrate, which can be considered a model for the interaction of a transition metal with DNA in an inter- and intrastrand fashion at the same time.

Experimental

The title compound has been prepared, starting with *cis*-Pt(NH$_3$)$_2$Cl$_2$, via *cis*-[Pt(NH$_3$)$_2$*C*Cl]Cl·H$_2$O and *trans*-Pt(NH$_3$)*C*Cl$_2$ as described [5]. It has previously been formulated as 1.5 hydrate on the basis of C, H, N elemental analysis because of a slightly better agreement between found and calculated C values as compared with a monohydrate. *Anal.* Found: C, 21.98; H, 3.33; N, 17.55. Calcd. for [Pt(NH$_3$)(C$_5$H$_7$N$_3$O)$_3$](ClO$_4$)$_2$·H$_2$O: C, 22.28; H, 3.25; N, 17.33%.

Collection of the Crystal Data

Precession photographs of the colourless crystal showed it was monoclinic and unit cell parameters were obtained for a least squares fit of χ, ϕ and 2θ for 15 reflections for the compound in the range $19.8° < 2\theta < 24.6°$ recorded on a Syntex P2$_1$ diffractometer with use of graphite-monochromated MoKα radiation (λ 0.71069 Å), Crystal data and other numbers related to data collection are summarized in Table I. The density was obtained by flotation in a

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TABLE I. Crystal Data.

Formula	$[Pt(NH_3)(C_5H_7N_3O)_3](ClO_4)_2 \cdot H_2O$, $C_{15}H_{26}Cl_2N_{10}O_{12}Pt$	
Formula weight	804.4	
Crystal size (mm)	cylinder $r = 0.10$, $l = 0.40$	
Space group, syst. absence	$P2_1/c$, No. 14, $h0l$, $l = 2n + 1$, $0k0$, $k = 2n + 1$	
Cell parameters, Å, deg.	$a = 15.296(3)$ $b = 14.666(3)$ $c = 14.025(2)$	$\beta = 122.61(1)$
Volume (Å^3)	2650.3(8)	
Z	4	
ρ_{calc}, ρ_{obs} (g cm^{-3})	2.016, 2.00(1)	
Linear absorption coeff. (cm^{-1})	58.5	
Absorp. Corr. factor limits	2.64–2.69	
Max. 2θ, reflctns. collected	45°, $h, k + 1$	
Standard reflctns, (e.s.d. %)	4 3 4 (1.22)	6 6 −2 (1.23)
Temperature (°C)	22	
No. of independent reflctns.	3450	
No. with $I > 3\sigma(I)$	2653	
$3\sigma(I) > I > 0, F_c > F_o$	267	
$3\sigma(I) > I > 0, F_c < F_o$	332	
$I < \sigma(I)$, rejected	198	
Final R_1, R_2[a]	0.043, 0.056	
Final shift/error max., ave.	0.090, 0.012	
g(secondary extinction)	7.81×10^{-8}	
Final difference map		
Highest peak, eÅ^{-3}; location	0.45; 0.80, 0.00, 0.30	
Lowest valley, eÅ^{-3} location	−0.42; 0.15, 0.45, 0.30	
Weighting	$w = (\sigma^2 + (0.03\ F_o)^2)^{-1}$	
Error in an obs. of unit wt.	1.43	

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_2 = \{\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2\}^{1/2}$.

carbon tetrachloride-bromoform mixture. Intensities were also measured with use of the Syntex $P2_1$ diffractometer and a coupled θ (crystal)–2θ (counter) scan. The methods of selection of scan rates and initial data treatment have been described [6, 7]. Corrections were made for Lorentz-polarization effects and absorption.

Solution of the Structure

The coordinates of the platinum atom were found from a three-dimensional Patterson synthesis and a series of full-matrix least-squares refinements, followed by three-dimensional electron difference syntheses, revealed all the non-hydrogen atoms. Further refinement, with anisotropic temperature factors for Pt and Cl, minimizing $\Sigma w(|F_o| - |F_c|)^2$ was terminated when the maximum/shift error was <0.25. Attempts were made to locate hydrogen atoms. Peaks in chemically acceptable positions were found for about half the expected number, but the peaks were comparable to others in the background. No attempt was made to refine the hydrogen atoms which were located. Corrections were made for secondary extinction using the method of Larson [8]. Throughout the refinement, the scattering curves were taken from reference [9], and anomalous disperse ion corrections from reference [10] were applied to the curves for Pt and Cl. The parameters for non-hydrogen atoms are listed in Table II.**

Results and Discussion

The molecular cation is shown in Fig. 1. The planes of the cytosine rings are roughly at right angles to the platinum square plane (dihedral angles, 96.5(8)°, 87.5(8)°, 89.2(8)°) and to each other (86.7(8)°, 85.5(8)°). The two *trans* cytosine rings are roughly

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**All calculations were carried out on CYBER 170/730 and 170/815 computers. The programs DATCO5, ABSORB and DATRDN from the XRAY-76 package (11) were used for initial data treatment. The full-matrix least-squares program CUDLS and Fourier program SYMFOU were written locally by J. S. Stephens and J. S. Rutherford respectively. Diagrams were prepared with ORTEP [12] and planes calculations were performed with use of NRC-22 [13].

TABLE II. Atomic Positional Parameters.

Atom	x	y	z
Pt	1342.3(3)	1000.5(3)	1829.1(3)
Cl(1)	5304(2)	4009(2)	7932(2)
Cl(2)	1387(3)	421(2)	7388(3)
O(11)	4478(13)	4351(13)	6954(15)
O(12)	6017(10)	4721(9)	8446(11)
O(13)	5685(11)	3309(11)	7606(12)
O(14)	4881(13)	3768(11)	8558(15)
O(21)	1464(8)	1044(6)	8195(8)
O(22)	1068(11)	935(10)	6378(14)
O(23)	626(9)	−264(8)	7142(10)
O(24)	2342(10)	24(9)	7721(11)
N(1)	3192(7)	−1000(6)	1580(8)
C(2)	2446(8)	−359(7)	1340(9)
N(3)	2436(6)	19(6)	2251(7)
C(4)	3144(9)	−263(8)	3335(9)
C(5)	3867(10)	−963(9)	3531(11)
C(6)	3900(10)	−1316(9)	2638(11)
C(1)	3271(10)	−1321(9)	659(11)
O(2)	1822(6)	−104(5)	370(6)
N(4)	3085(8)	110(7)	4158(9)
N(1A)	3575(6)	3095(6)	3502(7)
C(2A)	2919(7)	2390(7)	3274(8)
N(3A)	2406(6)	2013(6)	2201(6)
C(4A)	2628(7)	2318(6)	1447(8)
C(5A)	3290(8)	3067(8)	1689(9)
C(6A)	3740(8)	3440(7)	2719(9)
C(1A)	4152(11)	3504(10)	4666(11)
O(2A)	2751(5)	2090(5)	3988(6)
N(4A)	2162(6)	1911(6)	418(7)
N(1B)	−1155(7)	2811(6)	−176(7)
C(2B)	−377(7)	2179(7)	199(8)
N(3B)	174(6)	1944(6)	1315(6)
C(4B)	−73(8)	2318(7)	2039(9)
C(5B)	−911(9)	2932(9)	1629(10)
C(6B)	−1424(9)	3194(8)	526(10)
C(1B)	−1708(10)	3097(10)	−1360(11)
O(2B)	−176(5)	1835(5)	−475(6)
N(4B)	483(7)	2070(7)	3124(7)
N	296(7)	−3(6)	1488(7)
O	1490(8)	487(8)	4714(9)

co-planar (7.7(8)°). However, the rings do not have the same orientation with respect to the platinum square plane. The two *trans* cytosines have the amine group on the same side of the plane but the cytosine *cis* to both has the amine group on the opposite side of the plane. Intramolecular hydrogen bonding is not the reason for this arrangement; it is presumably because of intermolecular hydrogen bonding requirements. Bond lengths and angles within the cation agree well with values found previously for platinum–ammine–cytosine complexes [14, 15 and references therein].

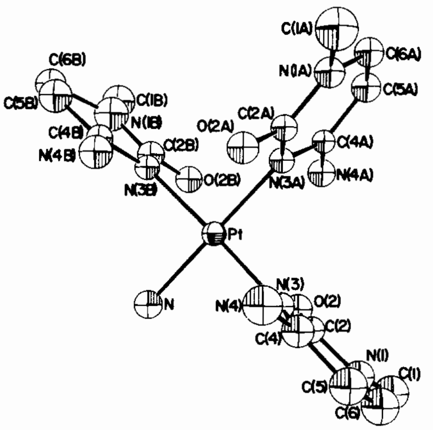

Fig. 1. The cation tris(1-methylcytosine-N3)ammineplatinum(II) showing the atom numbering.

The unit cell packing is shown in Fig. 2. Cytosine–cytosine π–π interactions are rare in the structure. There is only one such pair of interactions between N(1) and N(1B) rings of cations related by the inversion centre at 0 1/2 1/2. This is reinforced by N···O(2) and N···O(2B) hydrogen bonds between the cations. All other ring–ring π–π interactions are prevented by the ClO_4^- ions which fit between the rings. The cation pairs mentioned above, the water molecule and the $Cl(1)O_4^-$ ions form layers about the *a* faces bound in the *c* direction by a hydrogen bonding network of medium to weak hydrogen bonds. These nets at roughly $z = 0, 1/2$ involve the exocyclic N4 and O2 groups, the water molecule and O(22) and O(23) of the $Cl(1)O_4^-$ ion. The layers are separated in the a direction by the $Cl(2)O_4^-$ ions lying in the $x = 1/2$ plane, which are involved only in ionic or van der Waals interactions with the ions in the layers.

We have previously commented on the chances of forming tris(nucleobase) complexes out of a *cis*-

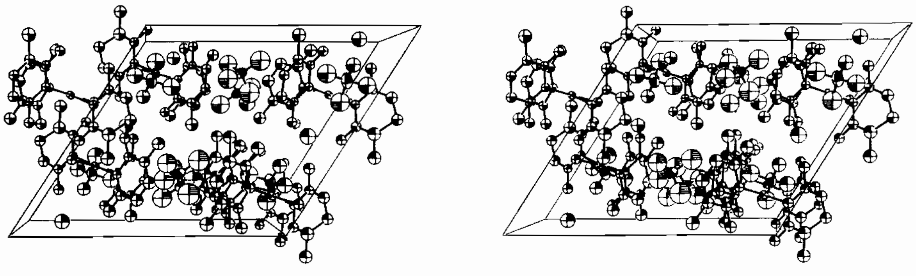

Fig. 2. The packing within the unit cell. *a* and c^* are parallel to the bottom and side of the page and the view is down *b*.

TABLE III. Selected Interatomic Distances (Å) and Angles (deg).

Pt–N(3)	2.039(9)	Pt–N(3A)	2.052(9)	Pt–N(3B)	2.059(8)
N(1)–C(2)	1.37(2)	N(1A)–C(2A)	1.35(1)	N(1B)–C(2B)	1.37(1)
C(2)–N(3)	1.40(2)	C(2A)–N(3A)	1.38(1)	C(2B)–N(3B)	1.36(1)
N(3)–C(4)	1.37(1)	N(3A)–C(4A)	1.35(2)	N(3B)–C(4B)	1.37(2)
C(5)–C(5)	1.42(2)	C(4A)–C(5A)	1.40(2)	C(4B)–C(5B)	1.37(2)
C(5)–C(6)	1.39(3)	C(5A)–C(6A)	1.34(2)	C(5B)–C(6B)	1.36(2)
C(6)–N(1)	1.36(1)	C(6A)–N(1A)	1.35(2)	C(6B)–N(1B)	1.37(2)
N(1)–C(1)	1.44(2)	N(1A)–C(1A)	1.50(2)	N(1B)–C(1B)	1.46(2)
C(2)–O(2)	1.23(1)	C(2A)–O(2A)	1.24(2)	C(2B)–O(2B)	1.25(2)
C(4)–N(4)	1.33(2)	C(4A)–N(4A)	1.36(1)	C(4B)–N(4B)	1.33(1)
Pt–N	2.033(9)	Cl(1)–O(11)	1.36(2)	Cl(1)–O(12)	1.40(1)
Cl(1)–O(13)	1.38(2)	Cl(1)–O(14)	1.39(3)	Cl(2)–O(21)	1.41(1)
Cl(2)–O(22)	1.44(2)	Cl(2)–O(23)	1.43(1)	Cl(2)–O(24)	1.40(2)
Hydrogen Bonds					
O(2)···N[a]	2.865(9)	O(2A)···N(4A)[b]	2.99(2)	O(2B)···N[a]	3.00(1)
O(2B)···O(4B)	3.10(2)	O···O(22)	2.81(3)	O···O(23)[d]	2.88(1)
O···N(4)	2.98(2)	O···N(4B)	3.01(1)	N···O(23)[c]	2.96(2)
N–Pt–N(3)	88.6(4)	N–Pt–N(3A)	179.0(4)	N–Pt–N(3B)	88.8(4)
N(3)–Pt–N(3A)	91.3(4)	N(3)–Pt–N(3B)	176.4(3)	N(3A)–Pt–N(3B)	91.3(3)
Pt–N(3)–C(2)	115.2(6)	Pt–N(3A)–C(2A)	118.2(8)	Pt–N(3B)–C(2B)	117.1(8)
Pt–N(3)–C(4)	124.7(9)	Pt–N(3A)–C(4A)	122.7(6)	Pt–N(3B)–C(4B)	122.8(6)
C(6)–N(1)–C(2)	125(1)	C(6A)–N(1A)–C(2A)	122(1)	C(6B)–N(1B)–C(2B)	122.3(9)
N(1)–C(2)–N(3)	117.6(8)	N(1A)–C(2A)–N(3A)	118(1)	N(1B)–C(2B)–N(3B)	119(1)
C(2)–N(3)–C(4)	120(1)	C(2A)–N(3A)–C(4A)	119.1(9)	C(2B)–N(3B)–C(4B)	120.1(9)
N(3)–C(4)–C(5)	120(1)	N(3A)–C(4A)–C(5A)	121.5(9)	N(3B)–C(4B)–C(5B)	120(1)
C(4)–C(5)–C(6)	119(1)	C(4A)–C(5A)–C(6A)	118(1)	C(4B)–C(5B)–C(6B)	119(1)
C(5)–C(6)–N(1)	118(1)	C(5A)–C(6A)–N(1A)	121(1)	C(5B)–C(6B)–N(1B)	119(1)
C(6)–N(1)–C(1)	118(1)	C(6A)–N(1A)–C(1A)	119(1)	C(6B)–N(1B)–C(1B)	119(1)
C(2)–N(1)–C(1)	117.7(9)	C(2A)–N(1A)–C(1A)	119(1)	C(2B)–N(1B)–C(1B)	119(1)
N(1)–C(2)–O(2)	122(1)	N(1A)–C(2A)–O(2A)	122(1)	N(1B)–C(2B)–O(2B)	120.0(9)
N(3)–C(2)–O(2)	121(1)	N(3A)–C(2A)–O(2A)	120(1)	N(3B)–C(2B)–O(2B)	121.1(9)
N(3)–C(4)–N(4)	117(1)	N(3A)–C(4A)–N(4A)	118.6(9)	N(3B)–C(4B)–N(4A)	118(1)
C(5)–C(4)–N(4)	120(1)	C(5A)–C(4A)–N(4A)	120(1)	C(5B)–C(4B)–N(4B)	121(1)
O(11)–Cl(1)–O(12)	107(1)	O(11)–Cl(1)–O(13)	106(1)	O(11)–Cl(1)–O(14)	104(1)
O(12)–Cl(1)–O(13)	112(1)	O(12)–Cl(1)–O(14)	111(11)	O(13)–Cl(1)–O(14)	116(1)
O(21)–Cl(2)–O(22)	106.7(8)	O(21)–Cl(2)–O(23)	110.6(9)	O(21)–Cl(2)–O(24)	112.4(7)
O(22)–Cl(2)–O(23)	109.3(8)	O(22)–Cl(2)–O(24)	107(1)	O(23)–Cl(2)–O(24)	110.9(8)

$Pt(NH_3)_2(II)$ species inside a cell, and considered such a possibility as rather unlikely [5]. On the other hand, it has been pointed out by us that in the plasma, via a loss of NH_3 from a *cis*-$[Pt(NH_3)_2ClX]$ species, binding of three biomolecules might be feasible. We do not, at present, want to further speculate on the likelihood of such a reaction pathway under physiological conditions, although the fact that, for example, the trifunctional $[Pt(NH_3)Cl_3]^-$ species reacts with DNA [16] and shows antitumor activity [17], is appealing in this respect.

From a structural point of view, the tris(1-methylcytosine) complex exemplifies in an impressive manner the drastic distortion of DNA to be expected if binding of three bases occurred to a single metal of square-planar coordination geometry. While in bis(nucleobase) complexes of *cis*-Pt(II) some base overlap can occur because of the possibility of the bases to slightly tilt from perpendicular positions relative to the metal coordination plane [15, 17, 18], in the tris(base) complex the bases are forced in almost perpendicular positions in order to minimize mutual repulsion.

Binding of three nucleobases, if it were to occur in DNA, should cause loop formation of one DNA strand by binding to two adjacent and a further removed base, or to a simultaneous inter- and intrastrand crosslinking.

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