1-Methylcytosine and Cytidine Complexes of Platinum(II) stabilized by Trimethylphosphine. Synthesis and Characterization *

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The interaction of *cis*-$[Pt(PMe_3)_2(H_2O)_2]^{2+}$ with 1-methylcytosine (4-amino-1-methyl-1*H*-pyrimidin-2-one) (myct) and cytidine (4-amino-1-β-D-ribofuranosyl-1*H*-pyrimidin-2-one) (Cyd) has been investigated by ^1H and ^{31}P NMR spectroscopy. The compounds *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$ and *cis*-$[Pt(PMe_3)_2(Cyd)_2][NO_3]_2$ have been isolated and the molecular structure of the nucleobase derivative determined by single-crystal X-ray diffraction techniques. The crystals of *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$ are triclinic, space group $P\bar{1}$, with $a = 12.363(2)$, $b = 11.479(2)$, $c = 9.645(2)$ Å, $\alpha = 87.5(2)$, $\beta = 73.9(2)$, $\gamma = 84.5(2)°$ and $Z = 2$. The structure was solved by heavy-atom methods and refined by least-squares techniques to $R(F) = 0.067$ for 4112 observed reflections with $F \geqslant 7\sigma(F)$. The platinum atom is in a distorted square-planar environment with the phosphine ligands in *cis* position [P–Pt–P 94.5(3)°] and the two N(3)-bonded nucleobases in a head-to-tail arrangement. The interbase dihedral angle is 94.2(3)° and the platinum co-ordination plane forms a dihedral angle of 74.1(3)° with the pyrimidine ring planes. The Pt–P and Pt–N(3) bond distances are 2.256(5), 2.254(5) and 2.092(9), 2.108(9) Å, respectively. Strong interbase [$NH_2(4) \cdots O(2')$ 2.95(1) Å] and base–nitrate anion hydrogen bonds are observed. The ^{13}C and ^{195}Pt NMR data of these nucleobase and nucleoside adducts are also reported and discussed.

The discovery that *cis*-$[Pt(NH_3)_2Cl_2]$ (cisplatin) has cytostatic properties toward some types of tumoral cells has stimulated many studies on the reactivity of this complex with biologically important molecules such as the nucleobases.[1] The increasing amount of evidence that DNA is the main target of this drug[2] makes it desirable to understand in more detail how a metal co-ordination complex can interact with the essential components of the biological macromolecule. For instance, the importance of the ligand geometry around the metal centre in defining the stereochemistry of simple nucleobase- and/or DNA-platinum adducts has been well documented.[3]

In recent years we have become interested in the reactivity of platinum(II) phosphine complexes toward pyrimidine nucleobases and nucleosides.[4] The magnetically active ^{31}P nucleus bonded to the metal centre turned out to be a convenient probe for elucidating the stereochemistry and the molecular complexity of the adducts of these nucleic acid components. As part of these studies we have published a preliminary report on the interaction of the aqua complex *cis*-$[Pt(PMe_3)_2(H_2O)_2]^{2+}$ with 1-methyl-substituted cytosine (4-amino-1-methyl-1*H*-pyrimidin-2-one) (mcyt).[5] It has been shown that the co-ordination of the nucleobase to the metal centre is rapid and quantitative. At room temperature, complexation gives the corresponding mono- and bis-adducts, *cis*-$[Pt(PMe_3)_2(mcyt)]^{2+}$ and *cis*-$[Pt(PMe_3)_2(mcyt)_2]^{2+}$, as result of facile replacement of the solvent molecules in the metal co-ordination sphere.

In a square-planar complex containing two N(3)-bonded cytosine ligands the pyrimidine rings can be oriented, with respect to the metal co-ordination plane, in two positions, *i.e.* head-to-tail and head-to-head. In the first conformation the two nucleobases are related by a C_2 axis, in the second by a mirror plane. For the ammine complex *cis*-$[Pt(NH_3)_2(mcyt)_2][NO_3]_2$·myct crystallographic studies have shown that strong intramolecular interbase hydrogen bonds stabilize the head-to-tail conformation.[6] Moreover, the unco-ordinated nucleobase forms an intimate stacking interaction with one of the two co-ordinated mcyt ligands. Unlike the ammine analogue, the trimethylphosphine complex *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$ does not crystallize with additional nucleobase molecules. In order to verify whether the absence of the crystallization molecule has modified the steric arrangement of the co-ordinated nucleobases, a single-crystal X-ray analysis has been carried out. In this paper we report the solid-state structure of the complex *cis*-$[Pt(PMe_3)_2(mcyt)_2]^{2+}$ and its complete characterization in solution by multinuclear NMR spectroscopy. Moreover the synthesis and characterization of the corresponding nucleoside derivatives *cis*-$[Pt(PMe_3)_2(Cyd)]^{2+}$ and *cis*-$[Pt(PMe_3)_2(Cyd)_2]^{2+}$ (Cyd = cytidine = 4-amino-1-β-D-ribofuranosyl-1*H*-pyrimidin-2-one) are described.

Experimental

Instruments.—The NMR spectra were obtained with JEOL FX90Q and Bruker AM400 spectrometers. Chemical shifts are given on the δ scale and referenced as follows: internal sodium salt of 3-(trimethylsilyl)-[2,2,3,3-$^2H_4$]propionic acid in D_2O, for the proton and ^{13}C spectra; external H_3PO_4 (85% w/w) for the phosphorus spectra; external $Na_2[PtCl_6]$ (1 mol dm^{-3} in D_2O) for ^{195}Pt spectra. The ^{195}Pt NMR spectra were measured at 19.17 MHz, using a 20 kHz spectral width over 16 K data points with a 10 μs pulse. The delay time between pulses was 1 s. The ^{195}Pt–^{31}P coupling constants were measured from the ^{31}P spectra which, because of the narrower linewidth, gave more accurate values (± 2 Hz) than the ^{195}Pt spectra. The ^{31}P NMR spectra were measured at 36.23 MHz by using a 10 kHz spectral width over 16 K data points with a 8 μs pulse. The delay time between pulses was usually 1 s. For solutions containing a mixture of complexes, in order to obtain reliable integrals the pulse delay was increased to 20 s. The pH measurements were carried out with a Crison model MicroTT 2050 pH meter

* *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1993, Issue 1, pp. xxiii–xxviii.

Table 1 Crystal data for *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$

Formula	$C_{16}H_{32}N_8O_8P_2Pt$
M	721.5
Crystal dimensions/mm	0.4 × 0.4 × 0.4
Crystal system	Triclinic
Space group	$P\bar{1}$
a/Å	12.363(2)
b/Å	11.479(2)
c/Å	9.645(2)
α/°	87.5(2)
β/°	73.9(2)
γ/°	84.5(2)
Z	2
U/Å^3	1309
D_c/g cm^{-3}	1.83
μ/cm^{-1}	52.7
$F(000)$	712
No. of unique corrected reflections	4606 (up to 2θ = 50°)
No. with $F \geqslant 7\sigma(F)$	4112
No. of parameters	333
Ratio reflections : parameters	13 : 1
Final residuals R, R'	0.067, 0.066
Highest shift/e.s.d.	0.98

equipped with a microcombined pH electrode (Ingold model 10.402.3522). The thermogravimetric (TG) analysis was carried out with a Perkin Elmer TGS-2 thermobalance, operating under a nitrogen flux of 50 cm^3 min^{-1} at a heating rate of 20 °C min^{-1}.

Materials.—The complex *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ was prepared as previously described.[4d] Cytidine from Sigma was used as supplied.

Methods.—In a typical experiment, the appropriate amount of nucleoside as a solid was added to a D_2O solution of *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ (*ca.* 0.1 mol dm^{-3}) and the ^1H and ^{31}P NMR spectra obtained within a few minutes. The ratio nucleoside : platinum was then increased by addition of nucleoside and the reaction monitored again as above.

Preparation of cis-$[Pt(PMe_3)_2(Cyd)_2][NO_3]_2 \cdot H_2O$.—To a solution of *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ (0.192 g, 0.407 mmol in 5 cm^3 water) was added a solution of cytidine (0.198 g, 0.814 mmol in 5 cm^3 water). The resulting solution was stirred for 24 h at room temperature in the dark and then the solvent was vacuum evaporated. The residue was dissolved in MeOH (6 cm^3) and filtered to remove a trace amount of an insoluble material. Addition of diethyl ether gave a white precipitate which was filtered off and dried under vacuum. The yield was 0.342 g (88%). The solid contained one molecule of H_2O per molecule of complex as determined by thermal and elemental analyses (Found: C, 29.60; H, 4.70; N, 11.50. Calc. for $C_{24}H_{46}N_8O_{17}P_2Pt$: C, 29.55; H, 4.75; N, 11.50%). The thermogravimetric analysis revealed a weight loss of *ca.* 2% in the temperature range 40–120 °C. ^1H NMR (D_2O, 27 °C): δ 8.044 and 8.058 [d, J_{HH} 7.5, H(6)], 6.214 and 6.223 [d, J_{HH} 7.5, H(5)], 5.932 [d, J_{HH} 3.7, H(1')], 4.76 (br s, HOD), 4.25–3.88 [complex m, H(2'), H(3'), H(4'), H(5') and H(5'')] and 1.702 [apparent d, J_{PH} 11.2, J_{PtH} 37 Hz, $P(CH_3)_3$].

Crystallography.—The synthesis of *cis*-$[Pt(PMe_3)(mcyt)_2][NO_3]_2$ has been described in ref. 1. Large colourless crystals of the complex were obtained from an aqueous solution left to concentrate at room temperature. The elemental analysis confirmed the formation of an anhydrous compound (Found: C, 26.60; H, 4.60; N, 15.55. Calc. for $C_{16}H_{32}N_8O_8P_2Pt$: C, 26.65; H, 4.45; N, 15.55%).

Crystal data were taken at room temperature on a Philips PW 1100 four-circle diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å, θ–2θ scan mode to 2θ = 50° with scan width 1.2° and scan speed 0.02 s^{-1}). Details of the data collection, processing and refinement are given in Table 1.

Table 2 Fractional coordinates of *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$

Atom	x	y	z
Pt	0.270 56(3)	0.878 98(3)	0.921 35(3)
P(1)	0.209 4(2)	0.982 8(2)	1.125 9(3)
P(1')	0.301 1(2)	1.038 0(2)	0.775 0(3)
O(2)	0.064 7(6)	0.745 0(7)	1.031 8(1)
N(3)	0.247 8(7)	0.723 0(7)	1.042(1)
N(1)	0.114 2(8)	0.590 0(8)	1.164(1)
N(4)	0.431 2(8)	0.694 4(8)	1.050(1)
C(2)	0.137 3(8)	0.687 3(8)	1.078(1)
C(6)	0.196(1)	0.528(1)	1.210(1)
C(5)	0.301(1)	0.559(1)	1.177(1)
C(4)	0.329 1(9)	0.659 0(9)	1.086(1)
C(1)	−0.002(1)	0.553(1)	1.202(2)
O(2')	0.507 2(6)	0.789 3(7)	0.753 5(1)
N(3')	0.330 5(7)	0.771 3(7)	0.739 7(9)
N(1')	0.488 8(8)	0.691 9(8)	0.562(1)
N(4')	0.153 0(7)	0.749 4(8)	0.715(1)
C(2')	0.445 3(9)	0.753 3(9)	0.689(1)
C(6')	0.424(1)	0.652 4(9)	0.487(1)
C(5')	0.311(1)	0.673(1)	0.533(1)
C(4')	0.262 1(8)	0.731 4(8)	0.667(1)
C(1')	0.613 3(9)	0.659 5(9)	0.520(1)
C(8)	0.285(1)	1.105(1)	1.142(2)
C(9)	0.062(1)	1.034(1)	1.168(1)
C(7)	0.215(1)	0.898(1)	1.285(1)
C(8')	0.200 7(9)	1.165(1)	0.811(1)
C(9')	0.438(1)	1.090(1)	0.754(2)
C(7')	0.307(2)	1.008(1)	0.590(1)
N(5)	0.339 1(8)	0.443 5(8)	0.848(1)
O(3)	0.250 9(8)	0.491 7(9)	0.834(1)
O(4)	0.428 9(8)	0.496(1)	0.798(1)
O(5)	0.346(1)	0.351 9(9)	0.901(2)
N(6)	−0.055 9(9)	0.741(1)	0.527(1)
O(6)	0.028(2)	0.689(2)	0.518(2)
O(7)	−0.050(2)	0.838(2)	0.473(3)
O(8)	−0.150(2)	0.710(2)	0.523(2)

Lattice parameters were obtained by least-squares refinement of 25 reflections with 7 < θ < 11°. The structure was solved by the heavy-atom method and refined by full-matrix procedures, with anisotropic thermal parameters for all non-hydrogen atoms and weights $w = 1/[\sigma^2(F) + 0.008F^2]$. The programs used were those in SHELX 76.[7] Fractional coordinates are given in Table 2.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates and thermal parameters.

Results and Discussion

Crystal Structure of cis-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$.—The molecular structure of the cationic complex *cis*-$[Pt(PMe_3)_2(mcyt)_2]^{2+}$ is shown in Fig. 1 and selected interatomic distances and angles are given in Tables 3 and 4. The platinum atom is in a distorted square-planar arrangement, with the P–Pt–P angle [94.5(3)°] being larger than N–Pt–N [85.8(4)°]. The complex contains two mcyt moieties N(3)-co-ordinated to the metal atom and with the rings oriented in a head-to-tail fashion. The Pt–N(3) bond distances are 2.108(9) and 2.092(9) Å. These values are not significantly different from those observed in a dinuclear complex containing the cytosinate anion bridging two metal centres through the N(3) and N(4) atoms [2.109(9) and 2.119(8) Å].[4d] The planes containing the two pyrimidine rings form a dihedral angle of 94.2(3)° to each other and of 74.1(3)° to the ligand square plane. This orientation allows the formation of strong intramolecular hydrogen bonds between the NH_2 and the carbonyl groups [N(4)···O(2') 2.94(1), N(4')···O(2)

Table 3 Bond distances (Å) with estimated standard deviations (e.s.d.s) in parentheses of *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$

Pt–P(1)	2.256(5)	Pt–P(1')	2.254(5)
Pt–N(3)	2.092(9)	Pt–N(3')	2.108(9)
P(1)–C(8)	1.79(2)	P(1)–C(9)	1.80(1)
P(1)–C(7)	1.80(1)	P(1')–C(8')	1.80(1)
P(1')–C(9')	1.80(2)	P(1')–C(7')	1.81(1)
O(2)–C(2)	1.24(1)	N(3)–C(2)	1.41(1)
N(3)–C(4)	1.34(1)	N(1)–C(2)	1.36(1)
N(1)–C(6)	1.34(2)	N(1)–C(1)	1.48(2)
N(4)–C(4)	1.31(1)	C(6)–C(5)	1.34(2)
C(5)–C(4)	1.42(2)	O(2')–C(2')	1.22(2)
N(3')–C(2')	1.36(1)	N(3')–C(4')	1.36(2)
N(1')–C(2')	1.39(1)	N(1')–C(6')	1.34(2)
N(1')–C(1')	1.49(1)	N(4')–C(4')	1.30(1)
C(6')–C(5')	1.34(2)	C(5')–C(4')	1.43(1)
N(5)–O(3)	1.22(1)	N(5)–O(4)	1.28(1)
N(5)–O(5)	1.16(2)	N(6)–O(6)	1.13(2)
N(6)–O(7)	1.20(3)	N(6)–O(8)	1.26(3)

Table 4 Bond angles (°) for *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$

N(3)–Pt–N(3')	85.8(4)	P(1')–Pt–N(3')	89.5(3)
P(1')–Pt–N(3)	175.3(3)	P(1)–Pt–N(3')	175.7(4)
P(1)–Pt–N(3)	90.2(3)	P(1)–Pt–P(1')	94.5(3)
Pt–P(1)–C(7)	113.4(6)	Pt–P(1)–C(9)	113.4(6)
Pt–P(1)–C(8)	117.9(6)	C(9)–P(1)–C(7)	101.6(7)
C(8)–P(1)–C(7)	101.8(8)	C(8)–P(1)–C(9)	107.0(9)
Pt–P(1')–C(7')	112.6(6)	Pt–P(1')–C(9')	113.1(6)
Pt–P(1')–C(8')	119.5(5)	C(9')–P(1')–C(7')	101.7(8)
C(8')–P(1')–C(7')	101.6(8)	C(8')–P(1')–C(9')	106.2(8)
Pt–N(3)–C(4)	125(1)	Pt–N(3)–C(2)	115.1(9)
C(2)–N(3)–C(4)	120(1)	C(6)–N(1)–C(1)	121(1)
C(2)–N(1)–C(1)	119(1)	C(2)–N(1)–C(6)	121(1)
N(3)–C(2)–N(1)	119(1)	O(2)–C(2)–N(1)	122(1)
O(2)–C(2)–N(3)	119(1)	N(1)–C(6)–C(5)	122(1)
C(6)–C(5)–C(4)	119(1)	N(4)–C(4)–C(5)	122(1)
N(3)–C(4)–C(5)	119(1)	N(3)–C(4)–N(4)	118(1)
Pt–N(3')–C(4')	123.4(9)	Pt–N(3')–C(2')	115.3(9)
C(2')–N(3')–C(4')	121(1)	C(6')–N(1')–C(1')	121(1)
C(2')–N(1')–C(1')	116(1)	C(2')–N(1')–C(6')	123(1)
N(3')–C(2')–N(1')	117(1)	O(2')–C(2)–N(1')	121(1)
O(2')–C(2')–N(3')	121(1)	N(1')–C(6')–C(5')	120(1)
C(6')–C(5')–C(4')	119(1)	N(4')–C(4')–C(5')	120(1)
N(3')–C(4')–C(5')	120(1)	N(3')–C(4')–N(4')	121(1)
O(4)–N(5)–O(5)	119(1)	O(3)–N(5)–O(5)	123(1)
O(3)–N(5)–O(4)	118(1)	O(7)–N(6)–O(8)	106(2)
O(6)–N(6)–O(8)	131(2)	O(6)–N(6)–O(7)	115(2)

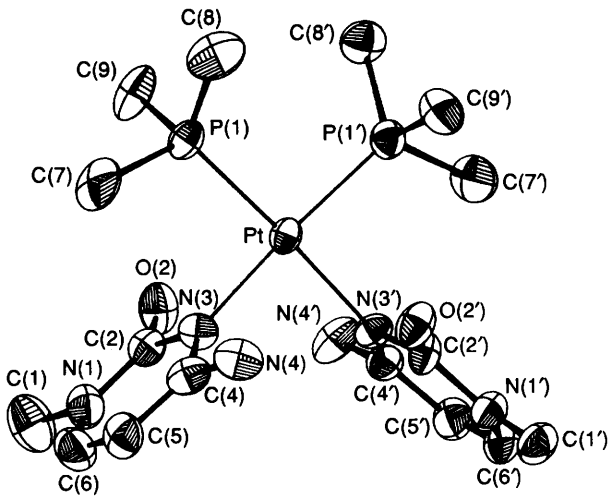

Fig. 1 An ORTEP[8] drawing of the complex *cis*-$[Pt(PMe_3)_2(mcyt)_2]^{2+}$. Thermal ellipsoids are drawn at the 50% probability level

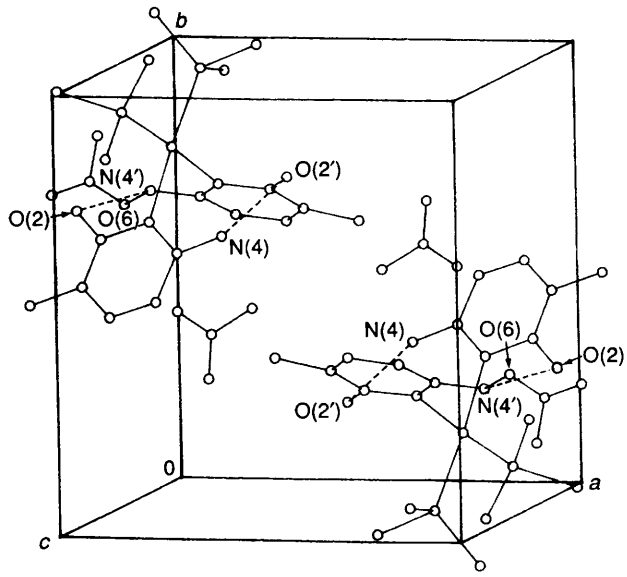

Fig. 2 Crystallographic unit cell of *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$

2.95(1) Å]. As shown in Fig. 2, one of the NH_2 groups is hydrogen bonded to a nitrate group [N(4')···O(6) 2.90(2) Å]. The NH_2 group already involved in hydrogen bonding with O(2') does not interact with the nitrate group [N(4)···O(5) > 3.5 Å]. Bond lengths and angles within the mcyt rings do not differ significantly from the values previously found,[4e] although one ring deviates slightly from planarity.

The structural features of this complex appear quite similar to those of the ammine derivative *cis*-$[Pt(NH_3)_2(mcyt)_2][NO_3]_2$·mcyt, which however contains, in addition to the N(3)-co-ordinated cytosine ligands, a cytosine molecule hydrogen bonded in the crystal lattice.[6] The replacement of the ammine with the trimethylphosphine ligands results in an increase in the Pt–N(3) bond distances, from 2.038 (average) to 2.100 (average) Å. It also causes a decrease in the N(3)–Pt–N(3') bond angle [from 92.6(3) to 85.8(4)°] with a concomitant decrease in the dihedral angle formed by the planes containing the pyrimidine rings [from 102.0(3) to 94.2(3)°]. These changes are in line with the higher steric hindrance and *trans* influence of PMe_3 with respect to NH_3 ligands. It is interesting that the decreased dihedral angle between the nucleobase rings in *cis*-$[Pt(PMe_3)_2(mcyt)_2]^{2+}$ allows a stronger *intra-ligand* hydrogen-bonding interaction. The N(4)···O(2') distance (2.94 Å) appears significantly shorter than that observed in the ammine analogue (3.04 Å).[6] Moreover, the observed reluctance of the phosphine complex to crystallize with additional molecules of mcyt, when it is prepared in the presence of an excess of nucleobase, is likely related to the unfavourable geometry of the pyrimidine rings imposed by the PMe_3 ligands.

Reactivity of cis-$[Pt(PMe_3)_2(H_2O)_2]^{2+}$ *with Cytidine. Synthesis and Characterization of cis*-$[Pt(PMe_3)_2(Cyd)_2][NO_3]_2$. —When the nucleoside is added to a water solution of *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ at room temperature its immediate co-ordination is observed with formation of mono- and bis-cytidine adducts. The reaction, followed by ^1H and ^{31}P NMR spectroscopy in D_2O solution, exhibits spectral changes very similar to those observed in the reaction of *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ with 1-methylcytosine.[5] In the proton spectrum the co-ordination of the nucleoside is evidenced by the shift of its H(6) and H(5) resonances, which occur as doublets centred at δ 8.088 and 6.275 (J_{HH} = 7 Hz) to lower field by 0.23 and 0.21 ppm, respectively, with respect to the unco-ordinated molecule. Conversely only minor variations of the ribose resonances are detectable [*e.g.* 0.024 ppm for H(1')].

In the ^{31}P NMR spectrum the monocytidine adduct is characterized by an AB multiplet, flanked by ^{195}Pt satellites,

Table 5 The ^{31}P-{^1H} and ^{195}Pt-{^1H} NMR data in D_2O at 27 °C, at autogenous pH

Complex	$\delta(^{31}P)$ (J_{PtP}/Hz) [J_{PP}/Hz]	$\delta(^{195}Pt)$	pH
cis-$[Pt(PMe_3)_2(mcyt)]^{2+}$ [a]	−23.6 (3251) [24.4] −29.0 (3710)	−4344	2.2
cis-$[Pt(PMe_3)_2(mcyt)_2]^{2+}$ [b]	−28.24 (3251)	−4430	4.65
cis-$[Pt(PMe_3)_2(Cyd)]^{2+}$ [a]	−23.39 (3286) [25.6] −28.97 (3705)	−4345	2.2
cis-$[Pt(PMe_3)_2(Cyd)_2]^{2+}$ [b]	−27.89 [c] (3260) −27.99 [c] (3262)	−4432	4.0

[a] The data refer to a 0.1 mol dm^{-3} solution of *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ containing 1 equivalent of nucleobase or nucleoside. [b] 0.1 mol dm^{-3} solution of isolated complex (nitrate salt). [c] For relative intensity see Fig. 3(*a*).

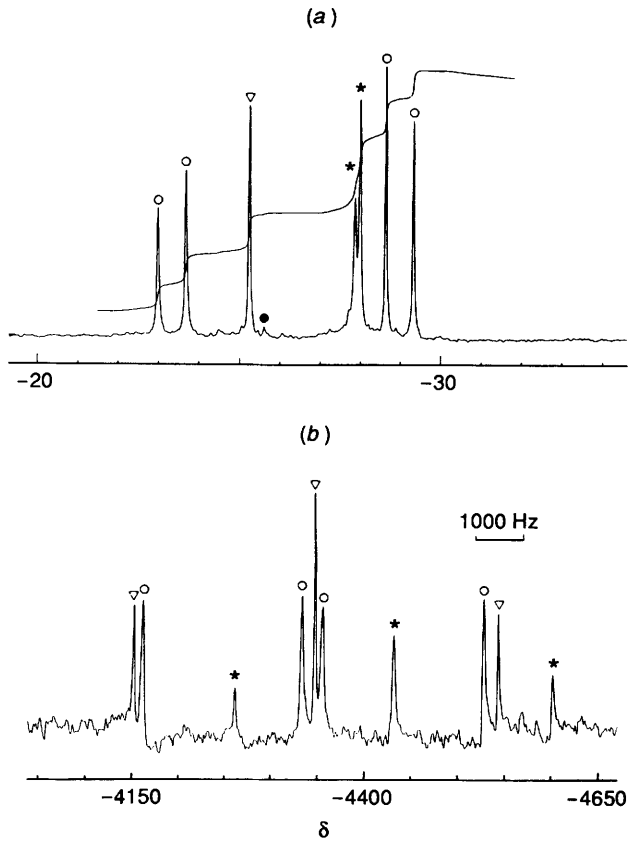

Fig. 3 The ^{31}P-{^1H} (central part) obtained at 36.23 MHz (*a*) ^{195}Pt-{^1H} NMR spectra at 19.17 MHz (*b*) of a solution of 0.35 mol dm^{-3} *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ and cytidine in D_2O at 27 °C: (▽), *cis*-$[Pt(PMe_3)_2(H_2O)_2]^{2+}$; (●), *cis*-$[\{Pt(PMe_3)_2(\mu\text{-}OH)\}_2]^{2+}$; (○), *cis*-$[Pt(PMe_3)_2(Cyd)]^{2+}$; (★), *cis*-$[Pt(PMe_3)_2(Cyd)_2]^{2+}$

centred at δ −23.39 (J_{PtP} = 3286) and −28.97 (J_{PtP} = 3705 Hz), with $^2J(PP)$ = 25.6 Hz (see Table 5). The lower-field doublet, on the basis of its lower J_{PtP} value and its larger linewidth, is attributable to the phosphine *trans* to the nucleoside N(3)-co-ordinated to the metal centre. Thus, the replacement of a water molecule by a N(3) atom of a pyrimidine ring in the aqua complex *cis*-$[Pt(PMe_3)_2(H_2O)_2]^{2+}$ (δ_P −25.25, J_{PtP} 3742 Hz)[4d] results in a deshielding of the phosphorus *trans* to the nucleoside and a concomitant decrease in its Pt–P coupling constant.

The addition of just 1 equivalent of nucleoside to a solution of *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ affords a quite respectable amount of bis(cytidine) adduct suggesting a high thermodynamic stability of these phosphine–nucleoside complexes. Accordingly, when the nucleoside: *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ ratio is increased to 2:1,

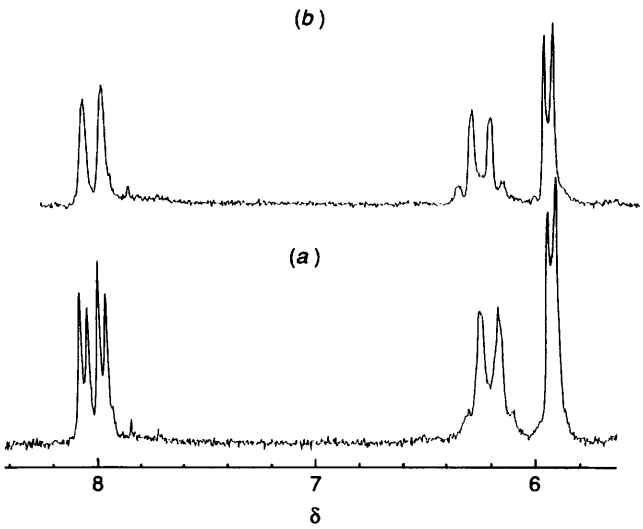

Fig. 4 The 90 MHz ^1H NMR spectra (low-field region) of *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$ in D_2O at 27 (*a*) and 45 °C (*b*)

the species *cis*-$[Pt(PMe_3)_2(Cyd)_2]^{2+}$ is the only one detectable in the resulting reaction mixture. Fig. 3(*a*) represents the central part of the ^{31}P NMR spectrum of a 0.35 mol dm^{-3} solution of *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ containing an equimolar amount of cytidine. Since the nucleoside, just as the nucleobase, acts as a monodentate ligand through its N(3)-donor atom, the formation of the bis(cytidine) adduct requires the presence of an equimolar amount of unsubstituted aqua complex in the resulting reaction mixture. The lower intensity of the resonances due to the unreacted *cis*-$[Pt(PMe_3)_2(H_2O)_2]^{2+}$ and its conjugate base *cis*-$[\{Pt(PMe_3)_2(\mu\text{-}OH)\}_2]^{2+}$ {compared with those attributable to *cis*-$[Pt(PMe_3)_2(Cyd)_2]^{2+}$ as shown in the integrals of Fig. 3(*a*)} is only the consequence of an insufficient time interval between the pulses used in the acquisition of the spectrum. By increasing the pulse delay (see Experimental section) the expected 1:1 ratio of the relative intensity of these two sets of resonances is observed. It is evident that the pyrimidine rings co-ordinated to the metal centre in the trimethylphosphineplatinum(II) complexes induce significant changes on the relaxation phenomena of the phosphorus nuclei.

The complex *cis*-$[Pt(PMe_3)_2(Cyd)_2]^{2+}$ has been isolated as its nitrato salt in quite good yield and characterized in solution by multinuclear NMR spectroscopy. The pertinent ^{31}P data are collected in Table 5 and compared with those of the corresponding nucleobase derivatives. Unlike *cis*-$[Pt(PMe_3)_2(mcyt)_2]^{2+}$, which exhibits a single resonance, the ^{31}P NMR spectrum of *cis*-$[Pt(PMe_3)_2(Cyd)_2][NO_3]_2$ at ambient temperature shows two singlets centred at δ −27.89 and −27.99 with an intensity ratio of *ca.* 1:2 [Fig. 3(*a*)] flanked by the platinum satellites, with almost equal $^1J_{PtP}$ coupling constants. These results imply the presence of the same donor atom *trans* to the phosphine ligands. When the temperature is increased to *ca.* 50 °C the two resonances merge to a single peak (δ −27.94, J_{PtP} 3267 Hz). The spectral changes are reversible although a slight decomposition of the sample occurs at higher temperature.

A similar temperature dependence is observed in the corresponding proton spectrum. At 400 MHz each pyrimidine ring proton exhibits two sets of resonances: a well resolved couple of doublets with almost equal intensity for H(6) and an apparent asymmetric triplet for H(5), respectively. At lower field [90 MHz, Fig. 4(*a*)] the latter resonance is seen as a doublet centred at δ 6.21, flanked by the ^{195}Pt satellites (J_{HH} 7.5, J_{PtH} *ca.* 9 Hz) whereas H(6) occurs as two overlapped doublets at 27 °C. When the temperature is increased these two doublets gradually broaden and finally merge to a single one (δ 8.00) at 45 °C. Since at this temperature the H(5) and PMe_3 resonances maintain their ^{195}Pt couplings, no ligand dissociation is involved in the dynamic process which makes equivalent the chemical

Table 6 Carbon-13 NMR data in D_2O at 27 °C and at autogenous pH

Compound	C(2)	C(4)	C(5)	C(6)	C(1')	C(2')	C(3')	C(4')	C(5')	N(1)CH_3	PMe_3
mcyt[a]	161.70	169.28	98.01	150.39	—	—	—	—	—	40.23	—
Cyd[b]	160.33	168.92	98.94	144.40	93.12	76.77	72.10	86.55	63.53	—	—
cis-$[Pt(PMe_3)_2(mcyt)_2]^{2+}$	156.82	166.03	96.47	149.93	—	—	—	—	—	39.31	16.39
cis-$[Pt(PMe_3)_2(Cyd)_2]^{2+}$	157.18	167.17	99.08	145.57	93.75	77.13	72.29	87.37	63.58	—	16.39
				145.09			71.93	87.02	63.35		

[a] 0.1 mol dm^{-3}, pH 8.0. [b] 0.1 mol dm^{-3}, pH 7.1.

environment of the nucleoside and phosphine ligands. These spectroscopic features are consistent with a restricted rotation about the Pt–N(nucleoside) and/or the N(1)–C(1') bonds. We have recently reported an example of slow rotation, on the NMR time-scale, of the Pt–N(3) bonds in the related complex *cis*-$[Pt(PMe_3)_2(mthy - H)_2]$, in which mthy – H is 1-methyl-substituted thymine (1,5-dimethyl-1*H*,3*H*-pyrimidin-2,4-dione) deprotonated at N(3).[5] In the case of the nucleoside complex *cis*-$[Pt(PMe_3)_2(Cyd)_2]^{2+}$, the chiral nature of the cytidine makes possible chemically different environments for the pyrimidine rings with respect to the platinum co-ordination plane and therefore the detection of stereoisomers.[9]

Carbon-13 and ^{195}Pt *NMR Spectra of cis*-$[Pt(PMe_3)_2(mcyt)_2]^{2+}$ *and cis*-$[Pt(PMe_3)_2(Cyd)_2]^{2+}$.—The isolated complexes have been further characterized by obtaining the ^{13}C and ^{195}Pt NMR spectra. Table 6 lists their ^{13}C-{^1H} NMR parameters and those of the corresponding free ligands. The ribose resonances in free cytidine have been assigned according to Tobias and co-workers.[10]

For *cis*-$[Pt(PMe_3)_2(mcyt)_2][NO_3]_2$ a single resonance for each carbon atom of the nucleobase is observed and C(5) appears to be the only carbon coupled to the platinum atom [$^3J_{PtC}$ 13 Hz). Moreover, the metal co-ordination results in upfield shifts for all the nucleobase carbon resonances, in particular for C(2) and C(4). Similar shifts are observed in the ^{13}C NMR spectrum of the corresponding nucleoside complex. Moreover, the spectrum of *cis*-$[Pt(PMe_3)_2(Cyd)_2][NO_3]_2$, obtained at 22.49 MHz, shows for each of the ribose C(4'), C(3'), C(5') and the C(6) pyrimidine nuclei two sets of resonances which appear as well resolved pairs of singlets with different intensities. These results indicate the presence of a mixture of stereoisomers as observed in the corresponding proton and ^{31}P NMR spectra.

Despite the presence of two ^{31}P NMR resonances in the spectrum of *cis*-$[Pt(PMe_3)_2(Cyd)_2][NO_3]_2$, the phosphine methyl groups exhibit a singlet set of resonances in their ^1H and ^{13}C NMR spectra. The observed patterns, although not analysed in detail, are those typical for square-planar complexes containing two trimethylphosphines in a mutual *cis* position.[11]

Both the nucleobase and nucleoside complexes are characterized by single sets of resonances in their ^{195}Pt-{^1H} NMR spectra. A binomial triplet is observed for the bis adducts, owing to coupling of the platinum with the two magnetically equivalent phosphorus ligands. As expected, a doublet of doublets is seen for the monoadduct *cis*-$[Pt(PMe_3)_2(mcyt)]^{2+}$ and the corresponding nucleoside derivative. Fig. 3(*b*) represents the spectrum of the reaction mixture resulting from the addition of 1 equivalent of cytidine to an aqueous solution of *cis*-$[Pt(PMe_3)_2(NO_3)_2]$. It is interesting that the replacement of the oxygen-donor ligands by the pyrimidine N(3) atom in the platinum co-ordination sphere of these and related phosphino complexes produces only modest changes in the ^{195}Pt chemical shifts. This is particularly evident when we consider the species *cis*-$[Pt(PMe_3)_2(H_2O)_2]^{2+}$ (δ_{Pt} –4348)[4d] and $[Pt(PMe_3)_2(Cyd)]^{2+}$ (δ_{Pt} –4345). By contrast, an analogous replacement of donor atoms in the ammine complexes *cis*-$[Pt(NH_3)_2L_2]^{n+}$ (L is H_2O or either the nitrogen or oxygen donor of the neutral or anionic α-pyridone ligand) results in platinum chemical shift differences of up to 1300 ppm.[12] As previously noticed,[4d] the ^{195}Pt resonances of the trimethylphosphine complexes are shifted to higher field in comparison with the ammine analogues {*e.g.* for *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ δ_{Pt} –1600}.[13] Apparently, the presence of two soft ligands in the *cis*-$Pt^{II}(PMe_3)_2$ unit makes the molecular parameters that influence the ^{195}Pt chemical shift much less sensitive to the nature of the remaining set of donor atoms.

Conclusion

The results of this investigation on the reactivity of *cis*-$[Pt(PMe_3)_2(NO_3)_2]$ toward mcyt and Cyd lead to the following conclusions: (*i*) the presence of the ribose moiety on the pyrimidine ring does not affect the rate of co-ordination to the metal centre; (*ii*) the formation of the bis(cytosine) adduct appears to be quantitative and rapid at ambient temperature; (*iii*) the pyrimidine N(3) atom is the only binding site to the platinum atom. Finally, the replacement of the ammine by PMe_3 ligands in *cis*-$[Pt(NH_3)_2(NO_3)_2]$ does not appear to affect strongly the stereochemistry of the adducts of these DNA-relevant molecules.

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