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Crystal Structures of *trans*-Dichloroammine(1-methylcytosine-*N3*)platinum(II) Hemihydrate, $[PtCl_2(NH_3)(C_5H_7N_3O)]\cdot{}^1/_2H_2O$, and *trans*-Diamminebis(1-methylcytosine-*N3*)platinum(II) Dinitrate. Evidence for the Unexpected Lability of NH_3 in a *cis*-Diammineplatinum(II) Complex

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Two trans-ligand-platinum(II) complexes have been isolated and investigated. *trans*-Dichloroammine(1-methylcytosine-*N3*)platinum(II) hemihydrate, $[Pt(NH_3)Cl_2(C_5H_7N_3O)]\cdot{}^1/_2H_2O$ (A), has the space group $C2/c$ with a = 14.697 (6) Å, b = 6.816 (1) Å, c = 23.225 (4) Å, β = 112.03 (2)°, and eight formula units in the unit cell. *trans*-Diamminebis(1-methylcytosine-*N3*)platinum(II) dinitrate, $[Pt(NH_3)_2(C_5H_7N_3O)_2](NO_3)_2$ (B), has space group $P2_1/c$ with a = 6.834 (2) Å, b = 10.315 (2) Å, c = 13.349 (3) Å, β = 107.90 (2)°, and two formula units in the unit cell. Data for both compounds were collected with use of Mo Kα radiation and a Syntex $P2_1$ diffractometer. Both crystal structures were determined by standard methods. A was refined to R_1 = 0.0612 and R_2 = 0.0775 on the basis of 2503 independent reflections. The final R_1 = 0.0346 and R_2 = 0.0410 for B were based on 1687 independent reflections. A has normal bond distances (Pt–Cl = 2.288 (5), 2.296 (5) Å; Pt–N(pyrimidine) = 2.03 (1) Å; Pt–N(ammonia) = 2.04 (1) Å) and angles, and the pyrimidine ring is at an angle of 64° to the ligand square plane. A is formed from chloro-*cis*-diammine(1-methylcytosine-*N3*)platinum(II) chloride in aqueous solution at room temperature. A mechanism is proposed for its formation, and possible implications with regard to the binding properties of *cis*-$Pt(NH_3)_2Cl_2$ are discussed. B also has normal bond distances (Pt–N(ammonia) = 2.067 (10) Å; Pt–N(pyrimidine) = 2.023 (8) Å) and angles; the pyrimidine–square-plane dihedral angle is larger (78°).

Introduction

The discovery of the antitumor activity of *cis*-$Pt(NH_3)_2Cl_2$ by Rosenberg and co-workers[2] has stimulated great interest in platinum–nucleic acid interactions. There appears to be wide agreement that *cis*-$(NH_3)_2Pt^{II}$ is acting as a bifunctional electrophile with cross-linking of DNA.[3,4] The sites of platinum coordination are still under discussion, but a kinetically controlled preference for guanine has been found.[5] *trans*-$(NH_3)_2Pt^{II}$, although acting as a bifunctional electrophile and cross-linking DNA as well,[6] does not show antitumor activity. No satisfactory explanation for this finding has been suggested.

With respect to the Pt species actually binding to the nucleobases, it has generally been assumed that activation of *cis*-$Pt(NH_3)_2Cl_2$ proceeds via hydrolysis with partial or complete replacement of the chloro ligands.[7] It is assumed the *cis*-diammine arrangement is retained.

We herewith present X-ray structural evidence for the unexpected lability of the NH_3 group in *cis*-$[PtCl(NH_3)_2$(1-methylcytosine)]Cl. This compound releases ammonia at room temperature in aqueous solution with formation of *trans*-$PtCl_2(NH_3)$(1-methylcytosine). This reaction has been observed before by Roos, Thomson, and Eagles in a mass spectroscopic study.[8] Our findings, that this reaction occurs in aqueous solution even at room temperature, opens up the interesting possibility of *cis*-$Pt(NH_3)_2Cl_2$ binding to more than two biomolecules at the same time.

We further report on the X-ray structure of *trans*-diamminebis(1-methylcytosine)platinum(II) dinitrate and compare the two structures. This work is the continuation of our efforts to systematically synthesize and characterize *cis*- and *trans*-diammineplatinum(II) complexes with nucleobase model compounds in order to get a better understanding of the interaction of cis Pt^{II} and trans Pt^{II} with DNA.[9-13]

Experimental Section

Preparation of the Compounds. (a) ***trans*-$[Pt(NH_3)_2(C_5H_7N_3O)_2](NO_2)_2$.** Formation of this compound originally had been observed upon reaction of "*cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$"[14] with 2 equiv of 1-methylcytosine in water.[12] Yields varied between 2 and 5% depending on the *cis*-$(NH_3)_2Pt^{II}$ product used. Separation of the trans product from the other cis products was achieved because of the extremely low solubility of this compound in water. It could be either filtered from the concentrated reaction mixture (after 2–3 days at room temperature) or obtained from the mixture of crystallized compounds by addition of water. The trans product was left as the most insoluble product.

Because of the very low solubility of the title compound in H_2O, we are almost certain that the yields obtained are "real". We do not have any evidence for a cis–trans isomerization and therefore assume that formation of the trans product was a consequence of a small contamination of *trans*-$Pt(NH_3)_2Cl_2$ in the bulk material of *cis*-$Pt(NH_3)_2Cl_2$ (obtained from Degussa, FRG).

Formation of the title compound in 85% yield was achieved by reacting *trans*-$Pt(NH_3)_2Cl_2$[15] with 2 equiv of $AgNO_3$ (0.6 g of *trans*-$Pt(NH_3)_2Cl_2$, 0.675 g of $AgNO_3$, 50 mL of H_2O, 40 h, 40 °C), filtration of AgCl, and subsequent reaction of the filtrate with 2 equiv of 1-methylcytosine (500 mg, 40 mL of H_2O, 5 h, 80 °C, pH 5, stoppered flask). Upon slow concentration to a 10-mL volume, colorless, transparent crystals (up to 3 mm in length) were obtained. Recrystallization was from boiling water. Anal. Calcd: C, 19.9; H, 3.4; N, 23.2; Pt, 32.3. Found: C, 20.1; H, 3.5; N, 22.9; Pt, 32.2.

(b) ***trans*-$[PtCl_2(NH_3)(H_5N_7N_3O)]\cdot{}^1/_2H_2O$.** Formation of this compound was observed when a sample of *cis*-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl\cdot H_2O$[16] was recrystallized from H_2O or D_2O at either 50 or 22 °C. Since selected single crystals of the almost colorless

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(12) Faggiani, R.; Lippert, B.; Lock, C. J. L.; Speranzini, R. A. *J. Am. Chem. Soc.*, in press.
(13) Lippert, B.; Lock, C. J. L.; Speranzini, R. A., submitted for publication in *Inorg. Chem.*
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(15) *trans*-$Pt(NH_3)_2Cl_2$ was prepared according to: Kauffman, G. B.; Cowan, D. O. *Inorg. Synth.* **1963**, *7*, 239.

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cis complex had been used, formation of yellow crystals of the trans compound was discovered.

This compound has also been isolated from the reaction mixture of *cis*-$Pt(NH_3)_2Cl_2$ and 1-methylcytosine (1:1) in water which gave *cis*-$[Pt(NH_3)_2Cl(C_5H_7N_3O)]Cl\cdot H_2O$ as the major product.[16]

Yields of *trans*-$[PtCl_2(NH_3)(C_5H_7N_3O)]\cdot{}^1/_2\,H_2O$ were increased by addition of NaCl or HCl to an aqueous solution of *cis*-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl\cdot H_2O$. No attempts were made to optimize the yields. However, preliminary results indicate that more frequent filtration of the precipitated compound substantially increases the yields. Crystals obtained from NaCl solution are considerably larger than those obtained from HCl solution.

A 160-mg sample of *cis*-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl\cdot H_2O$[16] and 200 mg of NaCl were dissolved in 5 mL of H_2O at 40 °C and then kept at room temperature in an open flask (pH 5.25). Within 4–6 days well-shaped yellow columns of the title compound had formed (pH 5.5). The crystals were filtered, washed with some water, and dried in air (first crop 15 mg). The solution was kept at 5-mL volume, and every 5 days the precipitate was filtered off. After 3 weeks a total of 36 mg had been collected (24% yield). The pH of the yellow solution at that time was 7.3. Recrystallization was from water.

In an analogous procedure a few drops of 0.2 N HCl was added instead of NaCl (pH 2.0) and the solution kept at 5-mL volume. Yellow crystals of the title compound were collected every few days. The yield within 3 weeks was 31%. pH at that time was 2.05. Recrystallization was from water. Anal. Calcd: C, 14.3; H, 2.6; N, 13.3; Pt, 46.4. Found: C, 14.5; H, 2.9; N, 13.2; Pt, 45.5.

(c) *cis*-$[Pt(NH_3)_2(C_5H_7N_3O)_2]Cl_2\cdot 4H_2O$. A 200-mg sample of *cis*-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl\cdot H_2O$[16] was dissolved in 4 mL of H_2O at room temperature (pH 5.4). A 56-mg sample of 1-methylcytosine was added, and the colorless solution was kept in a 80 °C waterbath for 7 h (stoppered flask). Then the solution was transferred into an open beaker and kept at room temperature (pH 6.4). After 2 days, 90 mg of colorless needles of *cis*-$[Pt(NH_3)_2(C_5H_7N_3O)_2]Cl_2\cdot 4H_2O$ were filtered off, washed with 0.5 mL of H_2O, and briefly dried in air. After another day yellow crystals of *trans*-$[PtCl_2(NH_3)(C_5H_7N_3O)]$ had formed and so had more colorless crystals of the cis product. Separation was by addition of 4 mL of H_2O: 5 mg of the yellow crystals of *trans*-$[PtCl_2(NH_3)(C_5H_7N_3O)]$ remained undissolved. Concentration of the solution yielded 130 mg of *cis*-$[Pt(NH_3)_2(C_5H_7N_3O)_2]Cl_2\cdot 4H_2O$. Crystals of the title compound lose water slowly when kept in air and quickly if dried in vacuo. Loss of water is accompanied by a loss of transparency. Identification of the cis compound was by IR and Raman spectra[17] and elemental analysis. Anal. Calcd: C, 19.3; H, 4.5; N, 18.0; Pt, 31.3. Found: C, 19.4; H, 4.6; N, 17.6; Pt, 32.0.

(d) *trans*-$Pt(NH_3)_2Cl_2$ from $[Pt(NH_3)_3Cl]Cl$. $[Pt(NH_3)_3Cl]Cl$ was prepared according to the published procedure.[18] A 300-mg sample of $[Pt(NH_3)_3Cl]Cl$ was dissolved in 3 mL of H_2O (pH of the pale yellow, clear solution 3.45) and kept in a stoppered flask in a 40 °C water bath for 24 h and then at room temperature. After 1 day at room temperature, the pH had risen to 5.20 and some yellow crystalline precipitate had formed. After 5 days, the pH was 6.5 and the precipitate was filtered off. It consisted of deep yellow crystals of *trans*-$Pt(NH_3)_2Cl_2$ and colorless microcrystals of unknown composition. Brief treatment of the precipitate with 3 mL of dimethylformamide removed the colorless microcrystals, leaving 15 mg of *trans*-$Pt(NH_3)_2Cl_2$. Indentification was by IR spectroscopy.

After 2 more weeks at room temperature, more crystals of *trans*-$(NH_3)_2PtCl_2$ had formed. No attempts were made to optimize the yield of *trans*-$(NH_3)_2PtCl_2$.

Apparatus. pH measurements were performed with a Radiometer 20 pH meter and a combination electrode. IR spectra were recorded on a Perkin-Elmer 580 (Nujol mulls); Raman spectra on a Coderg PH1 with krypton laser (647.1-nm) excitation.

Collection of the X-ray Diffraction Data. Crystals of the two compounds were selected after examination under a polarizing microscope for homogeneity. The pale yellow crystal of *cis*-dichloroammine(1-methylcytosine-*N3*)platinum(II) hemihydrate (A) was mounted roughly along *b*. Precession photographs showed the crystal was monoclinic with the systematic absences of *C2/c* or *Cc*. The centric cell was chosen for initial work: the choice was justified by the successful solution of the structure. The colorless crystal of *cis*-diamminebis(1-methylcytosine-*N3*)platinum(II) dinitrate (B) was mounted roughly along *a*. Precession photographs showed the crystal was monoclinic with the systematic absences of $P2_1/c$. Unit cell parameters for each crystal were obtained from a least-squares fit of χ, ϕ, 2θ for 15 well-centered reflections in the range $20° < 2\theta < 35°$ recorded on a $P2_1$ diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71069 Å at 22 °C). Crystal data and other numbers related to data collection are summarized in Table I. Densities were obtained by flotation in a diiodomethane–iodoethane mixture. Intensities were measured on the Syntex $P2_1$ diffractometer using a coupled θ(crystal)–2θ(counter) scan. The methods of selection of scan rates and initial data treatment have been described.[14b,19] Corrections were made for Lorentz–polarization effects and absorption.

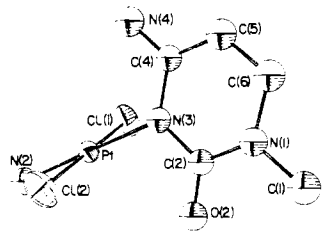

Figure 1. The molecule *trans*-dichloroammine(1-methylcytosine-*N3*)platinum(II), showing the atom numbering.

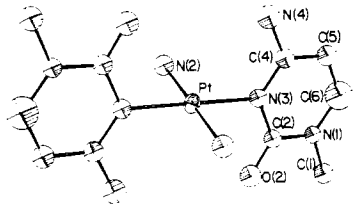

Figure 2. The molecular cation *trans*-diamminebis(1-methylcytosine-*N3*)platinum(II), showing the atom numbering.

Solution of the Structure. Both structures were solved in the same way. The coordinates of the platinum atoms were found from three-dimensional Patterson syntheses, and a series of full-matrix least-squares refinements, followed by three-dimensional electron density difference syntheses, revealed all the nonhydrogen atoms. After refinement the temperature factors of the platinum and chlorine atoms, which were previously isotropic, were made anisotropic. Tests were made to show the use of increased parameters was significant.[20] Further refinement using full-matrix least squares and minimizing $\sum w(|F_o| - |F_c|)^2$ was terminated when the maximum shift/error was <0.01. Secondary extinction was applied with use of the method of Larson.[21] Throughout, the scattering curves were taken from ref 22, and anomalous dispersion corrections from ref 23 were applied to the curves for platinum and chlorine. The parameters of nonhydrogen atoms are listed in Tables II and III.[24]

Results and Discussion

The molecule and molecular cation of the title compounds

(16) We shall report on the preparation and the X-ray structure of *cis*-$[PtCl(NH_3)_2(1\text{-methylcytosine})]Cl\cdot H_2O$ shortly.

(17) The cis configuration of the NH_3 ligands can be deduced from comparison of IR and Raman spectra of *cis*-$[Pt(NH_3)_2(C_5H_7N_3O)_2]Cl_2$ and *trans*-$[Pt(NH_3)_2(C_5H_7N_3O)_2](NO_3)_2$: cis product ($C_2$ or C_1 symmetry) ν(Pt–NH_3) ≃ 530 vw, sh cm^{-1} (IR, solid), 538 s, 529 m (Raman solid); trans product (C_i symmetry): ν(Pt–NH_3) = 515 w (IR, solid) cm^{-1} 533 s cm^{-1} (Raman, solid).

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(23) Cromer, D. T. Reference 22, Table 2.3.1, pp 149–150.

(24) All calculations were carried out on a CDC-6400 computer. The programs DATCOS, ABSORB, and DATRDN were from the XRAY-76 package and were used for preliminary data treatment. The full-matrix least-squares program CUDLS, Fourier program SYMFOU, and least-squares program PALS were written locally by J. S. Stephens, J. S. Rutherford, and P. G. Ashmore, respectively. Diagrams were prepared by using the program ORTEP-II by: Johnson, C. K. U.S. Atomic Energy Commission Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, Tenn., 1976.

Table I

compd	$C_5H_{11}Cl_2N_4O_{1.5}Pt$	$C_{10}H_{20}N_{10}O_8Pt$
fw	417.1	603.3
cryst size	cylinder; r = 0.083 mm, l = 0.40 mm	cylinder, r = 0.062 mm, l = 0.25 mm
systematic absences	hkl, $h + k = 2n + 1$	$0k0$, $k = 2n + 1$
	$h0l$, $l = 2n + 1$	$h0l$, $l = 2n + 1$
space group	$C2/c$ (No. 15)	$P2_1/c$ (No. 14)
unit cell parameters (Å and deg)	a = 14.697 (6)	a = 6.834 (2)
	b = 6.816 (1)	b = 10.315 (2)
	c = 23.225 (4)	c = 13.349 (3)
	β = 112.03 (2)	β = 107.90 (2)
V, Å^3	2157 (1)	895.5 (4)
Z	8	2
ρ_{calcd}, g cm^{-3}	2.57	2.24
ρ_{obsd}, g cm^{-3}	2.55 (2)	2.22 (2)
linear abs coeff, cm^{-1}	141.4	83.09
transmission coeff limits	5.97–6.86	2.26–2.29
max 2θ, quadrant	50°; $h,k,\pm l$	45°; $h,k,\pm l$
std reflctns	(1) −2,0,−12; (2) −1,−1,−12	(1) 3,3,−3; (2) 1,−2,−2
overall esd, %	(1) 1.35; (2) 1.36	(1) 2.1; (2) 2.3
temp, °C	22	22
no. of independent reflctns	2503	1687
no. with $I > 3\sigma(I)$	1795	1055
$3\sigma(I) > I > \sigma(I)$ where $F_c > F_o$	103	73
$3\sigma(I) > I > \sigma(I)$ where $F_c < F_o$	146	180
$I < \sigma(I)$ (rejected)	459	379
final R_1[a]	0.0612	0.0346
final R_2[a]	0.0775	0.0410
final shift in esd, max	0.015	0.006
av	0.002	0.0003
g (secondary extinction)	1.67×10^{-7}	3.49×10^{-7}
final difference map		
highest peak; location	2.99 e/Å^3; 0.15, 0.05, 0.37	1.09 e/Å^3; 0.40, 0.05, 0.42
lowest valley; location	−2.74 e/Å^3; 0.20, 0.05, 0.29	−0.89 e/Å^3; 0.40, 0.40, 0.20
weighting	$1/w = 69.34 - 1.083\|F_o\| + 0.00804\|F_o\|^2$	$1/w = 9.947 - 0.232\|F_o\| + 0.00238\|F_o\|^2$

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

Table II. Atom Parameters and Temperature Factors (Å^2) for *trans*-Dichloroammine(1-methylcytosine-*N3*)platinum(II) Hemihydrate

	x	y	z	U
Pt	217.13 (4)	50.79 (6)	328.45 (2)	*a*
Cl(1)	76.3 (3)	−64.3 (6)	336.7 (2)	*a*
Cl(2)	355.9 (3)	170.4 (7)	317.6 (2)	*a*
N(2)	136 (1)	158 (2)	242.2 (6)	46 (3)
N(1)	389.6 (9)	19.2 (6)	519 (2)	38 (2)
C(1)	428 (1)	158 (2)	570.0 (7)	48 (3)
C(2)	335 (1)	83 (2)	461.9 (6)	35 (3)
O(2)	317.9 (7)	257 (2)	452.2 (4)	41 (2)
N(3)	297.4 (8)	−52 (1)	414.7 (5)	32 (2)
C(4)	312 (1)	−250 (2)	427.1 (6)	36 (3)
N(4)	272 (1)	−374 (2)	381.2 (6)	46 (3)
C(5)	373 (1)	−313 (2)	486.8 (7)	46 (3)
C(6)	409 (1)	−180 (2)	530.6 (7)	44 (3)
O(1)	0	498 (5)	250	101 (8)

[a] Anisotropic temperature U_{ij} were obtained from $\beta_{ij} = 2\pi^2\mathbf{b}_i\mathbf{b}_jU_{ij}$ where β_{ij}'s occur as a temperature effect of the form $\exp[-(\beta_{11}h^2 + ... + 2\beta_{12}hk + ...)]$ and $\mathbf{b}_i$ and $\mathbf{b}_j$ are the reciprocal lattice vectors. For Pt, U_{11} = 37.6 (3), U_{22} = 26.5 (3), U_{33} = 23.9 (3), U_{12} = 1.7 (2), U_{13} = 9.5 (2), and U_{23} = 1.9 (2). For Cl(1), U_{11} = 43 (2), U_{22} = 61 (2), U_{33} = 37 (2), U_{12} = −10 (2), U_{13} = 9 (1), and U_{23} = 12 (2). For Cl(2), U_{11} = 46(2), U_{22} = 64 (2), U_{33} = 66 (2), U_{12} = −2 (2), U_{13} = 25 (2), and U_{23} = 22 (2).

Table III. Atom parameters and Temperature Factors (Å^2) for *trans*-Diamminebis(1-methylcytosine-*N3*)platinum(II) Dinitrate

	x	y	z	U
Pt	0.0	0.0	0.0	*a*
N(2)	117 (1)	27.3 (8)	−123.4 (6)	34 (2)
N(1)	431 (1)	273.2 (7)	174.3 (6)	25 (2)
C(1)	649 (2)	264 (1)	238.6 (8)	37 (2)
C(2)	343 (1)	162.1 (9)	120.5 (7)	27 (2)
O(2)	443 (1)	65.7 (8)	120.7 (6)	38 (2)
N(3)	130 (1)	168.6 (8)	65.8 (6)	26 (3)
C(4)	25 (1)	278.6 (9)	64.3 (7)	28 (2)
N(4)	−181 (1)	278 (1)	12.4 (7)	41 (2)
C(5)	116 (2)	392 (1)	114.8 (8)	36 (2)
C(6)	325 (2)	386 (1)	173.4 (8)	70 (3)
N(10)	264 (1)	144 (1)	365.8 (8)	43 (2)
O(11)	89 (2)	174 (1)	318.5 (8)	66 (2)
O(12)	317 (3)	30 (2)	367 (1)	133 (6)
O(13)	386 (1)	229 (1)	414.1 (8)	60 (2)

[a] Anisotropic temperature U_{ij} were obtained from $\beta_{ij} = 2\pi^2\mathbf{b}_i\mathbf{b}_jU_{ij}$ where β_{ij}'s occur as a temperature effect of the form $\exp[-(\beta_{11}h^2 + ... + 2\beta_{12}hk + ...)]$ and $\mathbf{b}_i$ and $\mathbf{b}_j$ are the reciprocal lattice vectors. For Pt, U_{11} = 25.0 (3), U_{22} = 25.5 (3), U_{33} = 22.4 (3), U_{12} = −7.5 (3), U_{13} = 4.2 (2), U_{23} = −5.2 (3).

are illustrated in Figures 1 and 2, and selected interatomic distances are given in Tables IV and V. The structure of *trans*-dichloroammine(1-methylcytosine-*N3*)platinum(II) (A) is very similar to that of *trans*-dichloro(diisopropyl sulfoxide-*S*)(1-methylcytosine-*N3*)platinum(II)[25] and dichloro(dimethyl sulfoxide-*S*)(1-methylcytidine-*N3*)platinum(II).[26]

Equivalent bond distances and angles do not differ significantly from those in the sulfoxide complexes except for the Cl–Pt–N(3) and Cl(1)–Pt–Cl(2) angles. The Cl–Pt–N(3) angles are significantly larger in A (average 90.8 (4) vs. 84.6 (3) and 88.1 (5)°) such that now the chlorine atoms are bent away from the pyrimidine ring (Cl(1)–Pt–Cl(2) 181.6 (4) vs. 174.3 (1) and 176.1 (1)°). This is probably because the NH_3 group is much less bulky than the organic sulfoxides, and the chloride–ammonia repulsion will not be as great as the chloride–sulfoxide repulsion.[25] The dihedral angle between the plane of the pyrimidine ring and the plane of the four ligand atoms is only 64.4°, compared to the much larger angles (84.4, 77.4°) in the sulfoxide complexes.

(25) Lock, C. J. L.; Speranzini, R. A.; Powell, J. *Can. J. Chem.* **1976**, *54*, 53.
(26) Melanson, R.; Rochon, F. D. *Inorg. Chem.* **1978**, *17*, 679.

Table IV. Selected Interatomic Distances (Å) and Angles (Deg) for *trans*-Dichloroammine(1-methylcytosine-*N3*)platinum(II) Hemihydrate[a]

		Distances			
Pt-Cl(1)	2.288 (5)	Pt-Cl(2)	2.296 (5)	Pt-N(2)	2.04 (1)
Pt-N(3)	2.03 (1)	N(1)-C(1)	1.45 (2)	N(1)-C(2)	1.34 (2)
C(2)-O(2)	1.22 (2)	C(2)-N(3)	1.38 (2)	N(3)-C(4)	1.38 (2)
C(4)-N(4)	1.32 (2)	C(4)-C(5)	1.41 (2)	C(5)-C(6)	1.32 (2)
C(6)-N(1)	1.39 (2)				
		Possible Hydrogen Bond Distances			
N(4)-O(2)^{iv}	2.94 (2)	O(1)-N(2)	3.11 (3)	O(1)-N(2)^{i}	3.11 (3)
O(1)-Cl(2)^{ii}	3.29 (1)	O(1)-Cl(2)^{iii}	3.29 (1)	N(2)-Cl(1)^{i}	3.33 (1)
		Angles			
Cl(1)-Pt-N(2)	89.4 (4)	Cl(1)-Pt-Cl(2)	178.4 (1)	Cl(1)-Pt-N(3)	90.5 (4)
N(2)-Pt-Cl(2)	89.1 (5)	N(2)-Pt-N(3)	179.1 (6)	Cl(2)-Pt-N(3)	91.1 (4)
Pt-N(3)-C(2)	117.6 (8)	Pt-N(3)-C(4)	122.1 (8)	C(1)-N(1)-C(2)	120 (1)
C(1)-N(1)-C(6)	119 (1)	C(6)-N(1)-C(2)	121 (1)	N(1)-C(2)-O(2)	120 (1)
N(1)-C(2)-N(3)	119 (1)	O(2)-C(2)-N(3)	121 (1)	C(2)-N(3)-C(4)	120 (1)
N(3)-C(4)-N(4)	118 (1)	N(3)-C(4)-C(5)	120 (1)	N(4)-C(4)-C(5)	122 (1)
C(4)-C(5)-C(6)	118 (1)	C(5)-C(6)-N(1)	122 (1)		
		Possible Hydrogen Bond Angles			
C(4)-N(4)-O(2)	99.1 (9)	C(2)-O(2)-N(4)	158 (1)	N(2)-O(1)-N(2)^{i}	83.5 (9)
N(2)-O(1)-Cl(2)^{ii}	72.3 (3)	N(2)-O(1)-Cl(2)^{iii}	146.8 (8)	Cl(2)^{ii}-O(1)-Cl(2)^{iii}	138 (1)
Pt-N(2)-O(1)	111.3 (6)	Pt^{ii}-Cl(2)-O(1)	133.1 (5)	Pt-N(2)-Cl(1)^{i}	117.3 (6)
Pt^{i}-Cl(1)^{i}-N(2)	119.2 (3)	Pt-Cl(1)-N(4)	63.2 (3)	C(4)-N(4)-Cl(1)	85.2 (9)

[a] Atoms are related to those given in Table II as follows: (i) $-x, y, {}^1/_2 - z$; (ii) $x - {}^1/_2, {}^1/_2 + y, z$; ((iii) ${}^1/_2 - x, {}^1/_2 + y, {}^1/_2 - z$; (iv) $x, y - 1, z$.

The structure of the *trans*-diamminebis(1-methylcytosine-*N3*)platinum(II) cation (B) is normal and very similar to that of Pd(1-methylcytosine-*N3*)$_2$Cl$_2$.[33] Pt–NH$_3$ distances (2.07 (1) Å) are very similar to those we have found previously[9-14] as are the Pt–N(3) distances (2.023 (8) Å).[25,26] Distances and angles within the pyrimidine rings do not differ except for C(5)–C(6). This is different in B (1.41 (1) Å) and A (1.32 (2) Å), although it is not different from those in other compounds.[25,26,33] We see no reason for this difference. The dihedral angle between the pyrimidine rings and square plane of the four ligand atoms is 78.2° larger than in A and closer to previous values.[25,26]

The packing of A in the crystal is shown in Figure 3. The pyrimidine rings of one molecule and another related by the *b* translation are hydrogen bonded through N(4)–H···O(2), giving a chain of pyrimidine rings along *b*. Down *a* there are two sets of four of these chains within the translational repeat, giving sheets of parallel pyrimidine rings centered at $z = 0$ and ${}^1/_2$. Molecules of one chain in the sheet are related to those in adjacent chains along *a* by the inversion operation so that the pyrimidine rings of molecules in one chain are interleaved with those of molecules in adjacent chains. Within this region there are no hydrogen bonds along *a*; interaction is solely van der Waals, arising principally from the π–π interactions of adjacent rings. There is, however, considerable hydrogen-bonding interaction with the other end of the molecule, the Cl(1)Cl(2)N(2) fragment. Hydrogen bonding between molecules in the sheets at $z = 0$ and ${}^1/_2$, which also gives bonding in the *a* direction, occurs between the water molecule, O(1), and the N(2)s of a pair of molecules related by the twofold rotation. This pair is also hydrogen bonded directly through two N(2)–H···Cl(2) hydrogen bonds. A pair of similar O(1)–Cl(2) interactions occurs with another pair of molecules related by the twofold rotation. One of the molecules in the first pair is related to one in the second pair by the 2_1 operation.

The packing of B within the crystal is shown in Figure 4. The pyrimidine rings of molecules at the origin are interleaved with those of molecules centered at ${}^1/_2, {}^1/_2, 0$ giving a buckled sheet of cations centered along the *ab* plane. The nitrate ions are intercalated between adjacent pyrimidine rings along the *a* direction, giving pyrimidine–nitrate–pyrimidine–nitrate

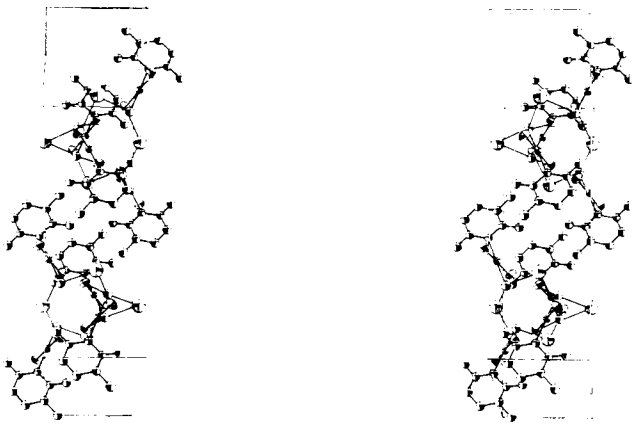


Figure 3. The unit cell contents of *trans*-dichloroammine(1-methylcytosine-*N3*)platinum(II) hemihydrate. *b* and *c* are parallel to the bottom and side of the page, respectively. The view is down *a*.* Hydrogen bonds are shown by a single line.

stacks at roughly $y = {}^1/_4, z = {}^1/_4$, and $y = -{}^1/_4, z = -{}^1/_4$. This will maximize π–π interactions between the nitrate ions and the pyrimidine rings. Because of the large dihedral angle between the pyrimidine ring and the ligand atom square plane, the ammonia groups on a cation are in a position to hydrogen bond to the nitrate groups above and below the pyrimidine ring. This gives bonding interaction both up *a* along the stacks and also provides cross bonding in the *b* direction. Bonding in the *c* direction is provided primarily by hydrogen bonds between N(4) of a cation and O(13) of a nitrate ion and between N(2) of one cation and O(2) of its nearest centrosymetrically related neighbor along *c*.

Formation of *trans*-[PtCl$_2$(NH$_3$)(C$_5$H$_7$N$_3$O)]·${}^1/_2$H$_2$O from *cis*-[PtCl(NH$_3$)$_2$(C$_5$H$_7$N$_3$O)]Cl in aqueous solution was unexpected. *cis*-Pt(NH$_3$)$_2$Cl$_2$, for example, does not show any signs of NH$_3$ release in aqueous solution and has to be heated under reflux with 4–6 N HCl to give [Pt(NH$_3$)Cl$_3$]$^-$.[27] Roos, Thomson, and Eagles,[8] who first observed the interconversion of *cis*-[PtCl(NH$_3$)$_2$(C$_5$H$_7$N$_3$O)]Cl into *trans*-[PtCl$_2$-

(27) (a) Drew, H. D. K.; Pinkard, F. W.; Wardlaw, W.; Cox, E. G. *J. Chem. Soc.* **1932**, 988. (b) Gel'man, A. D. *Izv. Plat. 1949*, 17, 13.

Table V. Selected Interatomic Distances (Å) and Angles (Deg) for *trans*-Diamminebis(1-methylcytosine-*N3*)platinum(II) Dinitrate[a]

		Distances			
Pt-N(2)	2.067 (10)	Pt-N(3)	2.023 (8)	N(1)-C(1)	1.48 (1)
N(1)-C(2)	1.39 (1)	C(2)-O(2)	1.21 (1)	C(2)-N(3)	1.42 (1)
N(3)-C(4)	1.34 (1)	C(4)-N(4)	1.37 (1)	C(4)-C(5)	1.40 (1)
C(5)-C(6)	1.41 (1)	C(6)-N(1)	1.37 (1)	N(10)-O(11)	1.21 (1)
N(10)-O(12)	1.22 (2)	N(10)-O(13)	1.25 (1)		
		Possible Hydrogen Bond Distances			
N(2)-O(11)^{i}	3.30 (1)	N(2)-O(11)^{ii}	3.16 (1)	N(2)-O(13)^{ii}	3.06 (1)
N(2)-O(2)^{iii}	3.15 (1)	N(4)-O(13)^{iii}	2.85 (1)		
		Angles			
N(2)-Pt-N(2)^{i}	180.0 (4)	N(2)-Pt-N(3)	90.3 (3)	N(2)-Pt-N(3)^{i}	89.7 (3)
N(3)-Pt-N(3)^{i}	180.0 (5)	Pt-N(3)-C(2)	115.4 (6)	Pt-N(3)-C(4)	123.9 (6)
C(1)-N(1)-C(2)	117.0 (8)	C(1)-N(1)-C(6)	119.7 (8)	C(6)-N(1)-C(2)	123.3 (8)
N(1)-C(2)-O(2)	121.3 (8)	N(1)-C(2)-N(3)	116.4 (8)	O(2)-C(2)-N(3)	122.3 (8)
C(2)-N(3)-C(4)	120.6 (8)	N(3)-C(4)-N(4)	117.8 (9)	N(3)-C(4)-C(5)	123.0 (8)
N(4)-C(4)-C(5)	119.2 (9)	C(4)-C(5)-C(6)	117 (1)	C(5)-C(6)-N(1)	119.6 (9)
		Possible Hydrogen Bond Angles			
Pt-N(2)-O(11)^{i}	111.8 (4)	N(10)^{i}-O(11)^{i}-N(2)	111.2 (8)	Pt-N(2)-O(11)^{ii}	108.7 (4)
N(10)^{ii}-O(11)^{ii}-N(2)	98.7 (7)	Pt-N(2)-O(13)^{ii}	110.1 (4)	N(10)^{ii}-O(13)^{ii}-N(2)	102.8 (7)
Pt-N(2)-O(2)^{iii}	123.7 (3)	C(2)^{iii}-O(2)^{iii}	142.4 (7)	C(4)-N(4)-O(13)^{iv}	176.9 (8)
N(10)^{iv}-O(13)^{iv}-N(4)	130.8 (8)	O(11)^{i}-N(2)-O(11)^{ii}	116.0 (4)	O(11)^{i}-N(2)-O(13)^{ii}	137.4 (4)
O(11)^{i}-N(2)-O(2)	89.6 (3)	O(11)^{ii}-N(2)-O(13)^{ii}	39.8 (3)	O(11)-N(2)-O(2)	106.5 (4)
O(13)^{ii}-N(2)-O(2)	73.8 (3)				

[a] Atoms are related to those given in Table III as follows: (i) $-x, -y, -z$; (ii) $x, {}^1/_2 - y, z - {}^1/_2$; (iii) $1 - x, -y, -z$; (iv) $x - 1, {}^1/_2 - y, z - {}^1/_2$.

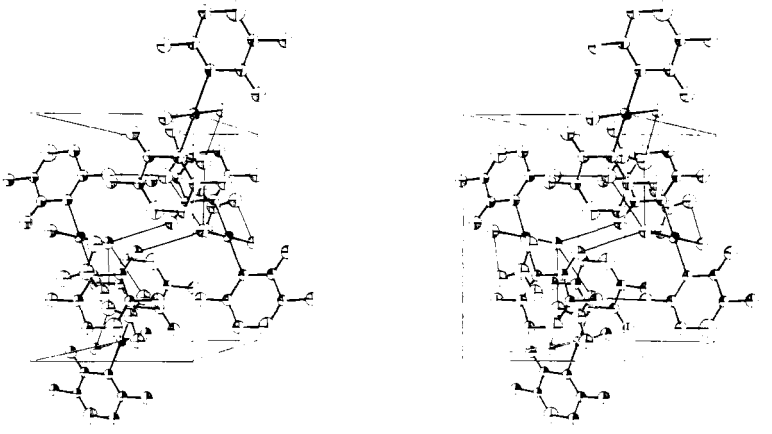
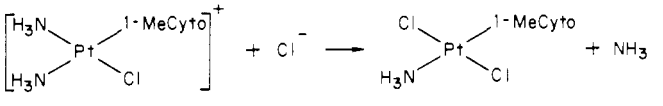


Figure 4. The unit cell contents of *trans*-diamminebis(1-methylcytosine-*N3*)platinum(II) dinitrate. *b* and *c* are parallel to the side and bottom of the page, respectively. The view is down *a*.* Hydrogen bonds are shown by a single line. The atoms of the nitrate ion are represented by spheres of arbitrary size.

$(NH_3)(C_5H_7N_3O)]$ in a mass spectroscopic study, did not draw any conclusions concerning the possible implications of their observations. Probably they did not assume that conditions in the mass spectrometer source could be relevant for aqueous solutions. We have now found that the reaction



takes place in an aqueous solution at room temperature. The mechanism of this reaction is consistent with expectations on the kinetic trans effect in square-planar platinum complexes with the trans effect order $Cl^- > NH_3$.[28] We also considered another possible pathway for this reaction, namely, replacement of the NH_3 ligand trans to 1-methylcytosine followed by an isomerization step and uptake of chloride with formation of the trans product. The rationale behind this idea was the observation of NH_3 release during formation of "platinum pyrimidine blues" from "*cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$" and uracil and thymine.[29] This release of ammonia cannot be a consequence of the trans effect of H_2O or OH^- ligands in the "platinum blues" since their ability to labilize NH_3 should be too weak. One is left, therefore, with the possibility that the pyrimidine ligands are exercising the trans-labilizing effect and consequently are leading to the release of NH_3. The cytosine ligand might be expected to have a similar effect to the uracil and thymine anions in "platinum blues". However, when we reacted *cis*-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl$ with additional 1-methylcytosine in water, we observed formation of major quantities of *cis*-$[Pt(NH_3)_2(C_5H_7N_3O)_2]Cl_2$[17] and only a small amount of *trans*-$[PtCl_2(NH_3)(C_5H_7N_3O)]\cdot{}^1/_2H_2O$. This finding indicates that the trans influence of 1-methylcytosine cannot be strong, because then a compound of composition *trans*-$[PtCl(NH_3)(C_5H_7N_3O)_2]Cl$ should have been obtained in substantial yield.

Direct replacement of NH_3 by Cl^- as a consequence of the higher trans effect of chloride over NH_3 is used in the preparation of *trans*-$Pt(NH_3)_2Cl_2$ from $[Pt(NH_3)_4]Cl_2$.[15] Heating of $[Pt(NH_3)_3Cl]Cl$ to 200 °C[8] or HCl treatment of this compound[30] results in the formation of *trans*-$Pt(NH_3)_2Cl_2$.

(28) Appleton, T. G.; Clark, H. C.; Manzer, L. E. *Coord. Chem. Rev.* **1973**, *10*, 335.

(29) Lippard, S. J., unpublished results; quoted in his talk at the Conference on "Chimie de coordination et chimotherapie des Cancers", Toulouse 1978.

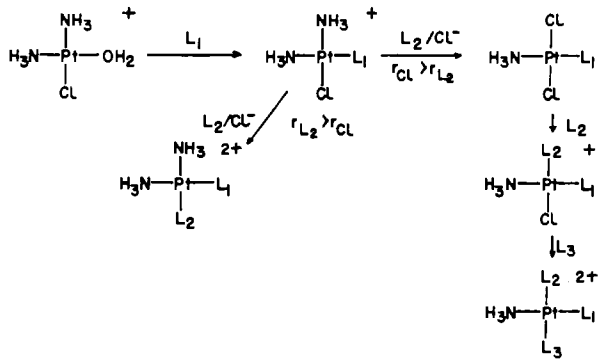


Figure 5. Possible reaction pathways of a *cis*-$[PtCl(NH_3)_2(H_2O)]^+$ species with ligands L_1, L_2, L_3, or Cl^-.

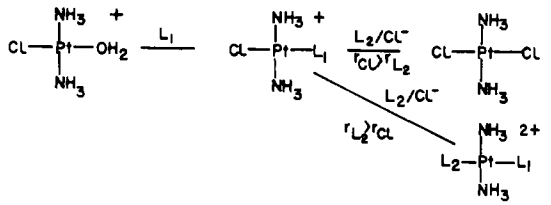


Figure 6. Possible reaction pathways of *trans*-$[PtCl(NH_3)_2(H_2O)]^+$ species with ligands L_1, L_2, or Cl^-.

We observed formation of *trans*-$Pt(NH_3)_2Cl_2$ from $[Pt(NH_3)_3Cl]Cl$ in aqueous solution without addition of chloride, although in very low yield only (cf. Experimental Section).

Our findings on the *cis*-$[PtCl(NH_3)_2$(1-methylcytosine)]Cl → *trans*-$[PtCl_2(NH_3)$(1-methylcytosine)] interconversion open up an interesting alternative to the generally accepted electrophilic attack of *cis*-$Pt(NH_3)_2Cl_2$ on *two* bases of DNA. If we assume a reactive species of the kind *cis*-$[PtCl(NH_3)_2(H_2O)]^{+}$[31] to bind to a ligand L_1[32] giving *cis*-$[PtCl(NH_3)_2L_1]^+$, it depends upon the relative rates of the substitution reaction with a second ligand L_2 and that of the NH_3 replacement trans to Cl^- whether *cis*-$[Pt(NH_3)_2L_1L_2]^{2+}$ or $[PtCl(NH_3)L_1L_2]^+$ (see Figure 5) is formed. The former should be formed predominantly when reaction with L_2 is fast. If reaction with L_2 is slow, the reaction leading to NH_3 release might be competitive and eventually lead to the second product. The latter could bind to a third ligand (L_3) to give the final product $[Pt(NH_3)L_1L_2L_3]^{2+}$ (Figure 6). Provided this second pathway could occur inside a cell, it would imply that *one* platinum atom could, at the same time, form inter- and intrastrand cross-links or cross-link DNA and bind to a protein, for example. This kind of simultaneous binding to three biomolecules would be unique for *cis*-$[PtCl(NH_3)_2(H_2O)]^+$ and possibly *cis*-$[PtCl(OH)(NH_3)_2]$. It would be expected neither for *trans*-$Pt(NH_3)_2Cl_2$ and any of its aquation products which would give only *trans*-$[PtCl(NH_3)_2C_5H_7N_3O]^+$ or *trans*-$[Pt(NH_3)_2(C_5H_7N_3O)_2]^{2+}$ (see Figure 6) nor for *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$, unless one postulates a high trans effect of the incoming ligand(s) for the latter (cf. preceeding discussion). Reaction between *cis*-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl$ and 1-methylcytosine (1:1) leads not only to *cis*-$[Pt(NH_3)_2(C_5H_7N_3O)_2]Cl_2$ but also to a small amount of *trans*-$[PtCl_2(NH_3)(C_5H_7N_3O)]$. This clearly indicates that substitution of chloride by the incoming ligand and cis–trans interconversion with release of ammonia are competitive under our reaction conditions, although the former is favored. The results are completely consistent with similar reactions involving pyridine instead of the pyrimidine.[34] It is feasible that, in a system imposing steric restrictions for fast reactions, e.g., with the highly ordered DNA, the possibility for the second pathway leading to a binding of three new ligands to platinum can actually occur.

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Registry No. A, 76068-65-0; B, 76068-67-2; *cis*-$[Pt(NH_3)_2(C_5H_7N_3O)_2]Cl_2$, 76123-94-9; *cis*-$[PtCl(NH_3)_2(C_5H_7N_3O)]Cl$, 75659-46-0; *trans*-$Pt(NH_3)_2Cl_2$, 14913-33-8; $[Pt(NH_3)_3Cl]Cl$, 13815-16-2.

Supplementary Material Available: Tables of observed and calculated structure factors for *trans*-dichloroammine(1-methylcytosine-*N3*)platinum(II) hemihydrate and *trans*-diamminebis(1-methylcytosine-*N3*)platinum(II) dinitrate (15 pages). Ordering information is given on any current masthead page.

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(31) The existence of such a hydrolysis product of *cis*-$Pt(NH_3)_2Cl_2$ has been proposed. See, e.g.: Drobnik, J.; Horacek, P. *Chem.-Biol. Interact.* **1973**, *7*, 223.
(32) For simplicity in the following and in Figure 5 L_1, L_2, L_3 are assumed to be neutral.
(33) Sinn, E.; Flynn, C. M.; Martin, R. B. *Inorg. Chem.* **1977**, *16*, 2403.
(34) Basolo, F.; Pearson, R. G. "Mechanisms of Inorganic Reactions", 2nd ed.; Wiley: New York, 1967; p 352 ff.