Trichloroamine Complexes of Platinum: Preparation, Crystal Structure and Solution Behavior of Cytosinium Trichlorocytosineplatinate(II)

STEFAN JAWORSKI

Anorganisch-Chemisches Institut, Technische Universität München, D-8046 Garching, F.R.G.

HELMUT SCHÖLLHORN, PETRA EISENMANN, ULF THEWALT

Sektion für Röntgen- und Elektronenbeugung, Universität Ulm, D-7900 Ulm, F.R.G.

and BERNHARD LIPPERT*

Institut für Anorganische und Analytische Chemie, Universität Freiburg, D-7800 Freiburg, F.R.G.

(Received February 4, 1988)

Abstract

A complex containing a protonated and an N3-platinated cytosine (C), $[CH][Cl_3Pt(C)]$ (**1a**) has been prepared, converted into its $K[Cl_3Pt(C)]$ (**1b**) and $NH_4[Cl_3Pt(C)]\cdot H_2O$ (**1c**) analogs, and structurally characterized (X-ray, Raman, NMR). Reaction of **1b** with L = 1-methylcytosine and with L = Me_2SO gave the neutral mixed-ligand complexes *cis*-$Cl_2Pt(C)L$. Excess NH_3 was used to convert the anion of **1b** into the cation $[(NH_3)_3Pt(C)]^{2+}$ (**3a**). The pK_a of the N(1)H proton in **3a** is 9.4, as determined by UV spectroscopy. The N(1)H is displaced by Pt(II) electrophiles even at neutral pH to give N3,N1-diplatinated cytosinato complexes, as shown by ^1H NMR (^3J coupling or ^{195}Pt at N(1) with H6, 29 Hz, and ^4J coupling of ^{195}Pt at N(3) with H5, 14Hz). The results of the X-ray structure determination of **1a** ($R = 0.031$, $R_w = 0.034$) are of relevance in that they permit a direct comparison of the effect of a proton as opposed to that of a Pt electrophile on the nucleobase geometry. Moreover, the expected decrease in C=O(2) bond length as a consequence of Pt binding is observed.

Introduction

Despite their simplicity in composition, anionic trichloro(amine) complexes of Pt(II), $[Cl_3Pt(am)]^-$, are frequently difficult to prepare or are obtained in low yields only. The main reason for this problem appears to arise from the difficulties in finding proper conditions to stop the reaction

$$[PtCl_4]^{2-} + am \longrightarrow [PtCl_3(am)]^- + Cl^-$$

at the level of the mono(amine) (am) product and to prevent hydrolysis of the Cl ligands and side reactions that may result thereof. Similarly, synthesis of $[Cl_3Pt(am)]^-$ via amine displacement according to

$$cis\text{-}Cl_2Pt(am)_2 + HCl \longrightarrow [Cl_3Pt(am)]^- + [amH]^+$$

is restricted to easily accessible bis(amine) complexes such as *cis*-$(NH_3)_2PtCl_2$ [1]. Established examples of $[Cl_3Pt(am)]^-$ complexes include, among others, those with am = NH_3 [2] and isopropylamine [3] or heterocyclic rings such as pyridine [4] or its derivatives [4, 5], theophylline [6], caffeine [7] and purine [8].

In contrast, the isolation of neutral trichloro(ligand)platinum(II) complexes $Cl_3Pt(amH)$ containing monoprotonated diamines (aliphatic [9] or heterocyclic [10, 11]) is easier and is facilitated by the expected lower solubility of the neutral species and through the very much reduced solvolysis of Cl ligands in HCl medium.

$[Cl_3Pt(am)]^-$ complexes are of interest in at least two respects. First, they are potentially antitumor-active, as demonstrated for am = NH_3 [12] and caffeine [7], for example. Interestingly, these two compounds are among the very few examples of charged platinum complexes showing antitumor activity. Activity has also been demonstrated in the case of neutral complexes containing various protonated diamines [9]. Secondly, $[Cl_3Pt(am)]^-$ complexes are, at least in theory, suitable starting materials for the synthesis of mixed amine complexes of the type *cis*-$Cl_2Pt(am)(am')$

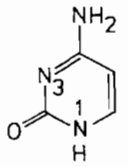
$$[Cl_3Pt(am)]^- + am' \longrightarrow cis\text{-}Cl_2Pt(am)(am') + Cl^-$$

These compounds could substantially broaden the spectrum of active Pt drugs. Good activity has indeed been demonstrated in a few cases [13, 14].

As suggested by Rochon and Kong [15], the synthetic potential of this route is limited, however, and alternative ways involving chloro- [16] and, in particular, iodo-bridged complexes [15] are superior.

*Author to whom correspondence should be addressed.

0020-1693/88/$3.50



Scheme 1.

Our effort to prepare a trichloroplatinum(II) complex containing a pyrimidine nucleobase, unsubstituted cytosine, $C_4H_5N_3O$ (Scheme 1), also originated in the idea of finding alternative routes to diammine and triammine(nucleobase) complexes of Pt(II) [17], normally prepared from *cis*-$(NH_3)_nPt(II)$ ($n = 2, 3$) precursors [18], as well as tris(nucleobase) complexes, previously obtained via *cis*-diammine complexes and loss of ammonia [19]. Reactions of Pt(II) with unsubstituted cytosine have been studied before [20] and the complexity of the reaction between $[PtCl_4]^{2-}$ and the nucleoside cytidine has been noted [21]. To our knowledge, Pt(II) complexes of unsubstituted cytosine have not been studied using X-ray analysis.

Experimental

Preparation of Compounds

[Cl_3Pt(cytosine)] complexes

Cytosine (C) (1.61 g; 14.5 mmol), dissolved in 400 ml of water, was combined with 3 g (7.2 mmol) K_2PtCl_4 and 4 g (68.4 mmol) NaCl, and the red solution was placed in a refrigerator (5 °C) for 4 days. Then 3 ml of concentrated HCl was added to the now yellow solution to bring the pH from 7 to 1. Evaporation of the solution in a stream of nitrogen gave 1.2 g (2.25 mmol) of yellow crystals which analyzed as $[CH][CPtCl_3]$ (**1a**). *Anal.* Calc. for $[C_4H_6N_3O]$-$[(C_4H_5N_3O)PtCl_3]$: C, 18.3; H, 2.1; N, 16.0; Cl, 20.3. Found: C, 17.8; H, 2.1; N, 15.9; Cl, 19.7%.

Further evaporation gave more (0.5 g) of **1a**, together with 1 g of red crystals of $[CH]_2[PtCl_4]\cdot H_2O$ (**2**). *Anal.* Calc. for $[C_4H_6N_3O]_2[PtCl_4]\cdot H_2O$: C, 16.6; H, 2.4; N, 14.5; Pt, 33.7; Cl, 24.5. Found: C, 16.0; H, 2.6; N, 14.7; Pt, 32.7; Cl, 25.2%. Evaporation to dryness yielded a mixture of KCl, NaCl, K_2PtCl_4 and [CH]Cl.

Cation exchange chromatography (K^+ and NH_4^+ form, respectively) of **1a**, followed by evaporation to dryness and recrystallization from 0.1 N HCl, gave yellow crystals of $K[CPtCl_3]\cdot H_2O$ (**1b**) and $NH_4[CPtCl_3]\cdot H_2O$ (**1c**). *Anal.* Calc. for $K[(C_4H_5$-$N_3O)PtCl_3]\cdot 3H_2O$ (**1b**): C, 10.2; H, 1.5; N, 8.9. Found: C, 10.3; H, 1.5; N, 9.0%. *Anal.* Calc. for $NH_4[(C_4H_5N_3O)PtCl_3]\cdot H_2O$ (**1c**): C, 10.7; H, 2.5; N, 12.5; Pt, 43.5. Found: C, 11.3; H, 2.5; N, 12.5; Pt, 43.1%.

Reaction with NH_3

Attempts to prepare *cis*-$PtCl_2(NH_3)C$ by adding 1 equiv. of NH_3 (from NH_4Cl and NaOH) to an aqueous solution of **1b**, heating of **1c** in water, and heating of **1c** in DMF (with NaOH added) did not yield pure materials, although ^1H NMR spectroscopy indicated that some reaction had occurred. A crystalline product was obtained, however, upon reaction of **1a** (0.3 g, 0.67 mmol) with excess NH_3 (15 ml 25% aqueous solution) at 22 °C for 15 h. Evaporation to dryness and purification by exclusion chromatography on Sephadex G10 gave 150 mg of colorless $[(NH_3)_3PtC]Cl_2$ (**3a**). *Anal.* Calc. for $[(NH_3)_3Pt$-$(C_4H_5N_3O)]Cl_2$ (**3a**): C, 11.2; H, 3.3; N, 19.6; Pt, 45.6. Found: C, 11.4; H, 3.4; N, 19.4; Pt, 45.7%. The corresponding nitrate salt **3b** was obtained from **3a** through anion exchange and evaporation as colorless crystals, which were identified by IR spectroscopy and comparison with **3a**. Alternatively, **3a** was prepared from $[(NH_3)_3PtCl]Cl$ and C (1:1 ratio, H_2O, 40 °C).

Reaction with 1-methylcytosine

Reaction of **1b** with 1-methylcytosine (1-MeC) gave two different products depending on the pH. At pH 3 (diluted HCl, heating), only exchange of K^+ by $[1\text{-MeCH}]^+$ took place, giving [1-MeCH]-$[PtCl_3C]$ (**1d**) (^1H NMR and IR spectroscopic identification). At pH 6 (3 h at 40 °C), a grayish precipitate of *cis*-$Cl_2Pt(C)(1\text{-MeC})$ (**4**) was obtained in 15% yield. *Anal.* Calc. for $PtCl_2(C_4H_5N_3O)(C_5H_7$-$N_3O)\cdot 2H_2O$ (**4**): C, 20.1; H, 3.0; N, 15.6. Found: C, 20.0; H, 2.8; N, 15.5%.

Reaction with Me_2SO

Compound **1b** (90 mg, 0.2 mmol) was dissolved in 8 ml of H_2O and 0.2 mmol of Me_2SO, dissolved in 1.5 ml of H_2O, was added. The slightly yellow solution (pH 5) was then filtered and allowed to evaporate to a small volume. A yellow–beige precipitate (40 mg) was collected and recrystallized from 1.5 ml of H_2O at 80 °C. According to the IR spectra, the sample did not undergo chemical changes on recrystallization. *Anal.* Calc. for $PtCl_2(C_4H_5N_3O)$-(C_2H_6SO) (**5**): C, 15.8; H, 2.4; N, 9.2. Found: C, 15.7; H, 2.7; N, 9.5%.

Measurements

^1H NMR spectra (D_2O) were recorded on the following instruments: Jeol JNM-FX 60, Bruker WP 80 and Bruker WM 250. Quoted shifts are relative to TSP (3.19 ppm upfield from internal standard NMe_4^+). Reactions of **3** with $[dienPt(D_2O)]^{2+}$ were performed by preparing a solution of $dienPt(D_2O)$-$(NO_3)_2$ from [dienPtI]I and $AgNO_3$ in D_2O, dissolving **3** in it, and adjusting the pD to 7 by addition of NaOD. IR spectra were recorded on a Perkin-Elmer 577 spectometer, Raman spectra on a U 1000 (Jobin Yvon) using Kr-Laser excitation (647.1 nm,

TABLE I. Atomic Coordinates and Temperature Factors for [CH][Cl_3PtC] (**1a**)

Atom	*x*	*y*	*z*	*U*
Pt1	0.3080(1)	0.3993(1)	0.0949(1)	0.014(1)
Cl1	0.3304(1)	0.2212(2)	−0.2438(2)	0.022(1)
Cl2	0.2283(1)	0.5834(2)	−0.0087(2)	0.024(1)
Cl3	0.2962(1)	0.5856(2)	0.4322(2)	0.023(1)
N1a	0.3486(4)	−0.0537(6)	0.2283(8)	0.021(4)
C2a	0.3053(5)	0.0726(7)	0.1897(9)	0.020(5)
O2a'	0.2166(3)	0.0508(5)	0.1593(7)	0.021(3)
N3a	0.3692(4)	0.2260(6)	0.1886(8)	0.017(4)
C4a	0.4665(4)	0.2494(7)	0.2297(9)	0.018(5)
N4a'	0.5223(4)	0.4006(7)	0.2290(9)	0.027(5)
C5a	0.5087(4)	0.1157(8)	0.2689(9)	0.020(5)
C6a	0.4472(5)	−0.0355(8)	0.2657(10)	0.021(5)
N1b	−0.1016(4)	0.1407(7)	0.1730(8)	0.022(4)
C2b	−0.0091(5)	0.2244(8)	0.1156(11)	0.024(6)
O2b'	0.0146(4)	0.2339(7)	−0.0577(7)	0.036(5)
N3b	0.0538(4)	0.2927(7)	0.2723(9)	0.025(5)
C4b	0.0340(5)	0.2753(8)	0.4634(10)	0.020(5)
N4b'	0.1030(4)	0.3428(8)	0.5975(9)	0.049(6)
C5b	−0.0612(4)	0.1823(9)	0.5119(10)	0.023(5)
C6b	−0.1235(4)	0.1172(9)	0.3615(10)	0.024(5)
H1	0.3047(0)	−0.1766(0)	0.1720(0)	
H2	0.4939(0)	0.4823(0)	0.1730(0)	
H3	0.5927(0)	0.4138(0)	0.2481(0)	
H4	0.5821(0)	0.1359(0)	0.2878(0)	
H5	0.4674(0)	−0.1420(0)	0.2896(0)	
H6	−0.1241(0)	0.0704(0)	0.0466(0)	
H7	0.1008(0)	0.3588(0)	0.2439(0)	
H8	0.0844(0)	0.3284(0)	0.7397(0)	
H9	0.1603(0)	0.4230(0)	0.5115(0)	
H10	−0.0790(0)	0.1713(0)	0.6389(0)	
H11	−0.1942(0)	0.436(0)	0.3755(0)	

100 mW, 1000 mic. slits) and UV spectra on a Cary 17 D. The UV spectra used for the pK_a determination of **3** displayed perfect isosbestic behavior (i.p. at 239 and 279 nm).

Crystallography

The X-ray measurements of **1a** were carried out on a Philips-PW 1100 single crystal diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71069 Å) at a temperature of −110 °C. The compound crystallizes in the triclinic space group $P\bar{1}$, $Z = 2$, $\rho_c = 2.524$ g cm^{-3}. The unit cell constants, calculated from 23 reflections ($17° < \theta < 21°$) are $a = 13.426(6)$, $b = 8.104(3)$, $c = 6.854(2)$ Å, $\alpha = 109.27(3)$, $\beta = 81.27(4)$, $\gamma = 99.51(3)°$. For the measurements a crystal fragment of 0.4, 0.2, 0.2 mm was chosen; 2431 independent reflections were measured ($2° < \theta < 25°$) using $\theta/2\theta$ scans. A set of 2360 reflections ($F_o > 2\sigma F_o$) was used for the calculations. Intensity data were corrected for Lorentz and polarization effects and, at a later stage, for absorption by using a method of Walker and Stuart [22]. The coordinates of the Pt atom were found in a 3-dimensional Patterson map. The other non-hydrogen atoms were determined by subsequent ΔF-syntheses. They were refined with anisotropic thermal parameters. All hydrogen atoms were located from ΔF maps. They were used in the F_c calculations but were not refined. The atomic parameters and the equivalent isotropic temperature factors (calculated by $U_{eq} = \frac{1}{3}\Sigma_{ij}U_{ij}a_i^*a_j^*a_i \times a_j$) are given in Table I. The final R values are $R = 0.031$ and $R_w(F) = 0.034$. Complex scattering factors for neutral atoms were taken from refs. 23 and 24. The SHELX program package was used for the calculations [25].

Results and Discussion

Formation and ^{1}H NMR Spectra of [$Cl_3Pt(C)$]$^-$

Reaction between K_2PtCl_4 and cytosine (C) in water (pH 7) and subsequent acidification (HCl, pH 1) gives two main products, cytosinium trichloro-cytosineplatinate(II) (**1a**), [CH][Cl_3PtC], and bis-(cytosinium) tetrachloroplatinate(II) (**2**), $[CH]_2[PtCl_4]$. Cation exchange converts **1a** into the corresponding potassium (**1b**) and ammonium (**1c**) salt, respectively. In **1a–c**, the Pt is bound to cytosine through N3, as evident from ^{1}H NMR (characteristic ^4J coupling between ^{195}Pt and H5 (5.99 ppm, d) of *ca.* 14.9 Hz [26], occasionally also ^5J coupling with H6 (7.44 ppm, d) of *ca.* 2.8 Hz) and from X-ray analysis (**1a**, *vide infra*). The ^{1}H NMR spectrum of **1a** exhibits two sets of C resonances due to protonated and platinated cytosine. As expected, the resonances of the cation show pH-dependent chemical shifts with signals in strongly acidic medium downfield from those of platinated cytosine. The spectra of **1a**, **1b** and **1c** undergo changes with time which are consistent with an isotopic exchange of the proton in the 5-position of platinated C *vs.* deuterium, leading eventually to a singlet for H6. The expected triplet splitting due to $I = 1$ for ^{2}H [27] is not resolved. We have previously noted the same phenomenon with *cis*-[$(NH_3)_2$Pt(1-MeC)Cl]$^+$ (1-MeC = 1-methylcytosine) [28]. As to the possible mechanism of this process, which is accompanied by a drop in pH (typically from pD 6 to pD 2 within 18 h at 30 °C) and a color change from yellow to olive-green, we note that it (i) is prevented by DCl or excess NaCl, and (ii) is prevented in strongly acidic medium (DNO_3, pD 0.5). Likewise, substitution of Cl^- by NH_3 (*vide infra*) prevents the isotopic exchange. The observations strongly suggest that solvolysis of chloro ligands *and* formation of a Pt–OH entity are necessary prerequisites for this process. With CMP [29], a HSO_3^- catalyzed isotopic

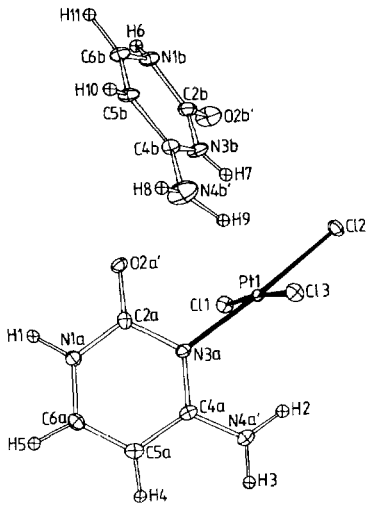


Fig. 1. View of cation (top) and anion (bottom) of [CH][Cl_3PtC] (**1a**).

exchange at the 5-position has been observed and interpreted in terms of a reversible addition of the HSO_3^- nucleophile across the C5, C6 double bond.*

Crystal Structure of ***1a***

Compound **1a** consists of discrete cytosinium cations and trichlorocytosineplatinate(II) anions (Fig. 1). Interatomic distances and angles are given in Table II. Pt–N and Pt–Cl distances within the anion are normal and compare well with data of other Cl_3Pt(am) complexes. The Pt–Cl(2) bond distance *trans* to the cytosine ligand, which is a measure of the structural *trans*-influence of the cytosine [33], is 2.309(2) Å. Thus, the influence of cytosine is at the upper limit of heterocyclic rings binding to Pt(II) through an endocyclic N donor, and therefore closest to chloride: *c.f.* 2.292 Å in the corresponding 9-methylguaninium complex [11], 2.294 Å in the theophylline compound [6] and 2.302 Å in the 9-methyladeninium analog [10] (standard deviations comparable). Planes in **1a** and deviations of atoms are listed in Table III. The dihedral angle between the Cl_3PtN(3)-plane and the cytosine ring is 104°, with Pt being considerably out of the cytosine plane (0.24 Å). There are no hydrogen-bonding interactions within the anion, yet three close contacts between anion and cation, neighboring anions, and between adjacent cations (Table IV). As can be seen from Fig. 2, the cations are stacked along the *y*-axis.

Several crystal structure determinations of protonated cytosine have been reported [34], the results of which are in good agreement with ours. As compared to neutral cytosine (anhydrous or monohydrate) [35] or neutral cytosine derivatives [36], respectively, the established [37] differences exist, which refer in particular to ring angles at N3, C4 and C2. Pt binding to N3 of cytosine has a similar, though smaller, effect than the proton. Statistically significant differences in angles between neutral cytosine [35c] and platinated cytosine in **1a** are seen in the internal ring angles at C2 (smaller on Pt binding by *ca.* 3°, 5σ**), at N3 (larger on Pt binding by 2.5°,

*We note, in this context, that we have observed irreversible reactions at the 5- and 6-positions of pyrimidine nucleobases, such as halogenation, HOCl addition [30, 31] and metal coordination [32].

TABLE II. Interatomic Distances (Å) and Angles (deg) in **1a**

(a) Pt coordination sphere			
Pt1–Cl1	2.299(2)	Cl1–Pt1–Cl2	90.1(1)
Pt1–Cl2	2.309(2)	Cl1–Pt1–Cl3	176.3(1)
Pt1–Cl3	2.305(1)	Cl1–Pt1–N3a	89.8(1)
Pt1–N3a	2.048(7)	Cl2–Pt1–Cl3	90.6(1)
		Cl2–Pt1–N3a	176.0(1)
		Cl3–Pt1–N3a	89.8(1)
(b) Cytosinium cation and cytosine ligand			
N1b–H6	0.929	N1a–H1	1.054
N1b–C2b	1.381(8)	N1a–C2a	1.370(10)
C2b–O2b'	1.206(10)	C2a–O2a'	1.215(8)
C2b–N3b	1.379(9)	C2a–N3a	1.390(8)
N3b–H7	0.802		
N3b–C4b	1.345(10)	N3a–C4a	1.348(9)
C4b–N4b'	1.327(9)	C4a–N4a'	1.328(8)
N4b'–H8	1.009	N4a'–H2	1.021
N4b'–H9	1.145	N4a'–H3	0.957
C4b–C5b	1.425(9)	C4a–C5a	1.418(11)
C5b–H10	0.897	C5a–H4	0.993
C5b–C6b	1.341(10)	C5a–C6a	1.355(9)
C6b–H11	1.043	C6a–H5	1.015
C6b–N1b	1.350(10)	C6a–N1a	1.361(9)
H6–N1b–C6b	129.1	H1–N1a–C6a	123.5
H6–N1b–C2b	103.3	H1–N1a–C2a	109.0
C6–N1b–C2b	121.9(6)	C6a–N1a–C2a	124.1(6)
O2b'–C2b–N1b	122.6(7)	O2a'–C2a–N1a	121.6(6)
O2b'–C2b–N3b	123.4(6)	O2a'–C2a–N3a	122.6(7)
N1b–C2b–N3b	114.1(7)	N1a–C2a–N3a	115.8(6)
H7–N3b–C2b	111.8	Pt1–N3a–C2a	114.9(5)
H7–N3b–C4b	121.7	Pt1–N3a–C4a	123.3(4)
C2b–N3b–C4b	125.8(6)	C2a–N3a–C4a	121.5(6)
N4b'–C4b–N3b	119.5(6)	N4a'–C4a–N3a	118.0(7)
N4b'–C4b–C5b	122.8(7)	N4a'–C4a–C5a	120.8(6)
N3b–C4b–C5b	117.7(6)	N3a–C4a–C5a	121.2(6)
H8–N4b'–C4b	116.7	H2–N4a'–C4a	118.1
H9–N4b'–C4b	101.0	H3–N4a'–C4a	118.0
H8–N4b'–H9	140.9	H2–N4a'–H3	121.9
H10–C5b–C4b	121.0	H4–C5a–C4a	118.0
H10–C5b–C6b	121.9	H4–C5a–C6a	124.5
C4b–C5b–C6b	117.1(7)	C4a–C5a–C6a	117.4(6)
H11–C6b–C5b	124.6	H5–C6a–C5a	125.8
H11–C6b–N1b	112.0	H5–C6a–N1a	114.1
C5b–C6b–N1b	123.3(6)	C5a–C6a–N1a	120.0(7)

**Average values from cytosine and cytosine monohydrate, taken from ref. 35c. σ is defined as $\sigma = (\sigma_1^2 + \sigma_2^2)^{1/2}$ with σ_1 and σ_2 being the errors to be compared.

TABLE III. Least-Squares Planes and Deviations (Å) of Atoms

(a) Deviations from best planes[a]

Pt plane

Cl1*	Cl2*	Cl3*	N3a*	Pt1
0.07	−0.07	0.07	−0.08	0.00

Plane of ring a

N1a*	C2a*	N3a*	C4a*	C5a*	C6a*	O2a′	N4a′	Pt1
0.00	0.01	−0.01	0.01	0.00	−0.01	0.03	0.01	−0.24

Plane of ring b

N1b*	C2b*	N3b*	C4b*	C5b*	C6b*	O2b′	N4b′
0.02	−0.02	0.01	0.00	0.00	−0.01	−0.10	−0.01

(b) Angle between Pt plane and plane a (deg)

104.3

[a]Atoms with an asterisk define the plane; equations of the planes refer to the *abc* basis. Pt plane: $10.785x + 3.529y - 1.358z = 4.601$ Å; plane of ring a: $-2.527x + 0.971y + 5.907z = 0.413$ Å; plane of ring b: $-6.893x + 7.029y - 0.111z = 1.647$ Å.

TABLE IV. Close Contacts (in Å and deg)[a]

H1–Cl2^{i}	2.12	N1a–H1–Cl2^{i}	167
H8–O2b′^{ii}	1.86	N4b′–H8–O2b′^{ii}	158
H6–O2a′^{iii}	1.93	N1b–H6–O2a′^{iii}	159

[a]Symmetry transformations: i = $x, -1+y, z$; ii = $x, y, 1+z$; iii = $-x, -y, -z$.

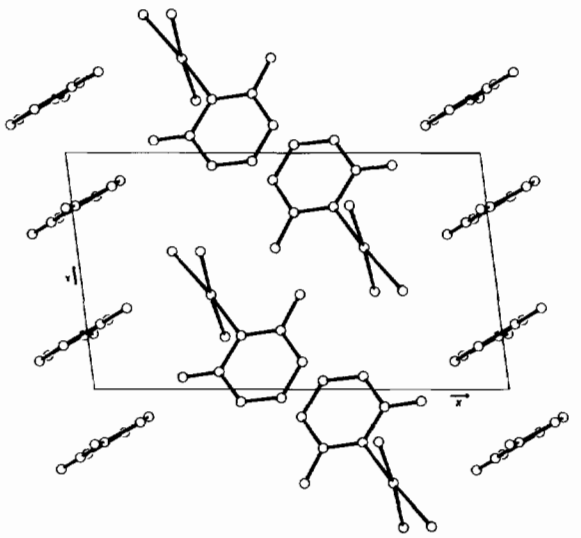


Fig. 2. Arrangement of cations and anions in the crystal of **1a**.

3.5σ, and at N1 (larger in Pt complex by 2.5°, 4σ). Of the exocyclic angles, N1–C2–O2′ decreases on Pt fixation by 2.5°, 4σ. As to changes in bond lengths, we note a slight decrease (3.6σ) in the C2–O2′ bond distance on platination (1.215(8) Å) and the cytosine ring (*c.f.* 1.241(3) Å in the anhydrous form, 1.251(2) Å in the monohydrate [35c]). Possibly this shortening reflects the expected increase in double-bond character of the C=O group as the metal 'occupies' the lone electron pair at the N3 position. The magnitude of this effect is comparable to protonation of N3 (*c.f.* C2–O2′ in the cytosinium cation in **1a** is 1.206(10) Å).

Raman Spectra of $[Cl_3Pt(C)]^-$

Raman spectroscopy represents a useful method to differentiate metal binding sites on nucleobases [38]. A comparison of Raman spectra of C [39], [CH]Cl and compounds **1a**–**1c** suggests that in particular the positions of the cytosine modes at 455, 615 and 799 cm^{-1} are good indicators for N3-platination. The corresponding modes occur for free C at 442 (skeletal mode), 597 (δ-ring) and 790 cm^{-1} (ν, δ-ring) and for CH^+ at 425 (split), 585 (split) and 789 cm^{-1}, respectively. In the spectrum of **1a**, for example, the C modes of the anion (798 cm^{-1}) and the cation (787 cm^{-1}) are readily distinguished.

Another intense Raman mode of C, the ring-stretching mode in the 1250–1300 cm^{-1} range, is not suitable because its position appears to be the subject of intermolecular interactions. Although in **1b** this mode (1256 cm^{-1}) is well separated from that in C (1274 cm^{-1}) and CH^+ (1277 cm^{-1}), in the spectrum of **1a** the mode of the CH^+ cation is virtually identical to that of the $[Cl_3Pt(C)]^-$ anion (1255 cm^{-1}).

As to the modes of the $PtCl_3N$ entity (C_{2v} symmetry with four stretching vibrations and five deformations), the three Raman bands at 314, 326 and 331 cm^{-1} in the spectrum of **1b** (Fig. 3) are assigned to the three ν(Pt–Cl) modes ($2a_1 + b_2$) since the free ligand does not have a Raman-active band of comparable intensity in this range. With $K[Cl_3Pt(NH_3)]$ only two of the three expected Pt–Cl stretching modes are resolved [40].

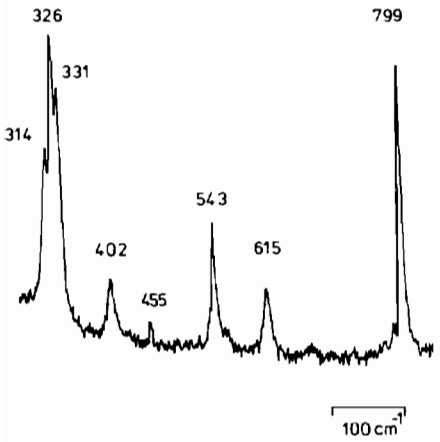


Fig. 3. Section of Raman spectrum (solid state) of K[Cl_3-PtC] (1b).

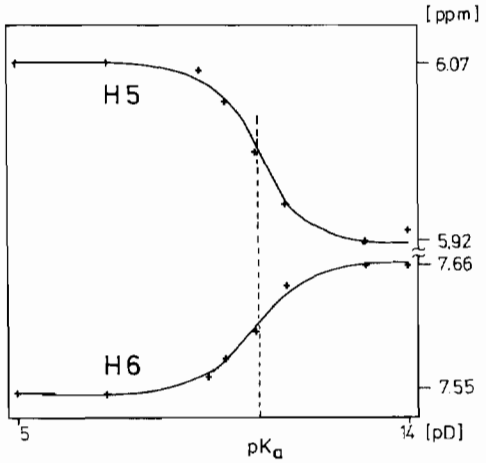


Fig. 4. ^{1}H NMR chemical shifts of H5 and H6 resonances of C ligand in 3 at different pD values.

Triammine(cytosine)platinum(II) Chloride (3)

Triammine(ligand)platinum(II) complexes are usually prepared using $[(NH_3)_3PtCl]Cl$ as starting material [41]. Since the preparation of this material is laborious [42], we have also applied alternative routes such as reaction of *cis*-$(NH_3)_2Pt(L)Cl$ [41b, 43, 44] or $Cl_3Pt(LH)$ [17] with excess NH_3. In contrast to an equivalent amount of NH_3, excess NH_3 converted $[Cl_3PtC]^-$ in a clean reaction into $[(NH_3)_3$-$PtC]Cl_2$ (3). The ^{1}H NMR spectrum of 3 indicated that the Pt binding site was unaltered (^4J between ^{1}H(5) and ^{195}Pt, 14.6 Hz), and the pH-dependence of the chemical shifts of H5 and H6 resonances showed that the N1 position was deprotonated with a $pK_a \simeq 10.4$ (uncorrected for D_2O [45]) (Fig. 4). A somewhat smaller value of 9.4, which probably is more realistic because of the much lower concentrations applied, was derived from UV spectra according to the method of Hildebrand and Reilly [46]. Compared to cytosine with a pK_a of 12.15 [47] for deprotonation at N1, platinum binding to N3 thus increases the acidity of the ligand by approximately 2.8 log units. With N3-platinated uracil (pK_a for deprotonation at N1 is 11.4 [41a]), the acidification is of the same magnitude.

The downfield shift of H6 of the cytosine ligand in 3 on deprotonation was surprising (as opposed to the 'normal' upfield shift of H5). From UV spectra of deprotonated 3 in mixtures containing various amounts of H_2O and dioxane, no indication of a tautomer equilibrium of the deprotonated cytosine ligand could be deduced, however.

Despite a pK_a of 9.4 for deprotonation of C in 3, displacement of the proton at N1 by a Pt(II) electrophile is achieved at much lower pH values. As followed by ^{1}H NMR, $(NH_3)_3Pt(II)$ or (dien)Pt(II) quantitatively coordinate to N1 at pD 6–7 to give the $[(NH_3)_3Pt(C^-)Pta_3]^{3+}$ cation (a = NH_3 or a_3 = dien) which has the anionic cytosine ring platinated at N3 and N1. The chemical shifts of the cytosine resonances in the dinuclear complex relative to 3 are upfield for H5 and downfield for H6 (Fig. 5). N1 binding of Pt to the cytosinato ring leads to a characteristic six-line pattern of the H6 resonance

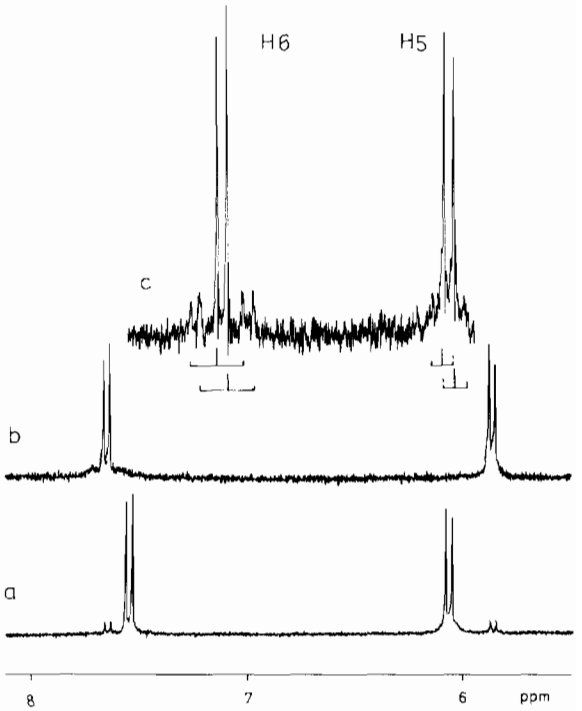


Fig. 5. ^{1}H NMR spectra (H5, H6 region only; D_2O; pD 7) of mixtures of 3b (0.06 mol l^{-1}) and $[dienPt(D_2O)](NO_3)_2$ (0.12 mol l^{-1}). (a) Immediately after sample preparation with mainly 3b and a small fraction of the N3, N1-bridged complex $[(NH_3)_3Pt(C^-)Pt(dien)]^{3+}$ present; (b) after 6 h at 60 °C with no mononuclear complex 3b left; (c) spectrum (b) recorded on an 80-MHz spectrometer instead of a 250-MHz one (spectra (a) and (b)) with ^{195}Pt–^{1}H(6) coupling clearly visible.

due to ^3J(H5–H6) and ^3J(H6–^{195}Pt) coupling with coupling constants of 6.8 and 29 Hz. The H5 resonance displays the normal pattern (doublet with ^{195}Pt satellites of *ca.* 14 Hz due to coupling with Pt at N3) very similar to **3**. As with diplatinum(II) complexes of unsubstituted uracil [43a] and unsubstituted thymine [41b], formation of the N1, N3-bridged cytosinato complex in neutral or slightly acidic medium is suggested to be due to a condensation reaction between the Pt(C) complex **3** and the hydroxo complex $[a_3Pt(OH)]^+$.

Mixed Ligand Complexes

One of our initial goals was to substantially extend the list of isolated [48] mixed-ligand complexes of type *cis*-$Cl_2Pt(L)(L')$ via reaction of Cl_3PtL^- with L', and this was not fully successful. The choice of L = cytosine proved to be disadvantageous in this respect. We believe that the possibility of condensation reactions at N1 and even N4 (*c.f.* discussion in ref. 49) between hydrolyzed **1**, $(C)Pt(Cl)_x(OH)_y$ $(x + y = 3)$, was mainly responsible for the low yields of the desired products. Out of a number of attempts to prepare and isolate *cis*-$Cl_2Pt(C)L$ complexes, only two were moderately successful: those with L = 1-MeC (complex **4**) and L = Me_2SO (complex **5**). In both cases the *cis*-geometry of the complexes was established with the classical Kurnakov test [50]. The ^{1}H NMR spectrum of **4** was consistent with N3 binding to both C and 1-MeC (^{195}Pt coupling with H5 resonances). The IR spectrum of **5** unambiguously indicated the presence of S-coordinated dimethyl sulfoxide (e.g. characteristic ν(SO) at 1142, 1120 cm^{-1}, vs; $\delta_s(CH_3)$ at 1020 cm^{-1}, vs [51]) and of two non-equivalent Cl ligands with ν(PtCl) modes around 348 cm^{-1} (Cl *trans* to C) and 320 cm^{-1} (Cl *trans* to Me_2SO). S-Coordination of Me_2SO was also evident from the ^{1}H NMR spectrum (D_2O) which showed the characteristic [51] satellites (^3J = 26 Hz) of the methyl resonances (3.56 ppm) due to coupling with the ^{195}Pt isotope. There was no indication of any fast solvolysis of the Me_2SO ligand in D_2O.

Supplementary Material

Tables of observed and calculated structure factors are available from the authors on request.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, Degussa (loan of K_2PtCl_4), and the Leonhard-Lorenz-Foundation (TU München). We thank Dr. H. Rotter for recording the Raman spectra.

References

1 (a) A. D. Gel'man, *Izv. Plat.*, *17*, 13 (1940); (b) T. S. Elleman, J. W. Reishus and D. S. Martin, Jr., *J. Am. Chem. Soc.*, *80*, 536 (1958).
2 (a) A. Cossa, *Gazzetta*, *20*, 725 (1890); (b) Y. P. Jeannin and D. R. Russell, *Inorg. Chem.*, *9*, 778 (1970).
3 F. D. Rochon, R. Melanson and M. Doyan, *Inorg. Chem.*, *26*, 778 (1987).
4 (a) A. Cossa, *Z. Anorg. Chem.*, *2*, 182 (1892); (b) A. Werner and F. Fassbender, *Z. Anorg. Chem.*, *15*, 123 (1897); (c) P.-C. Kong and F. D. Rochon, *Can. J. Chem.*, *56*, 441 (1978).
5 R. Melanson and F. D. Rochon, *Can. J. Chem.*, *54*, 1002 (1976).
6 E. H. Griffith and E. L. Amma, *J. Chem. Soc., Chem. Commun.*, *322* (1979).
7 R. E. Cramer, D. M. Ho, W. Van Doorne, J. A. Ibers, T. Norton and M. Kashiwagi, *Inorg. Chem.*, *20*, 2457 (1981).
8 (a) N. Hadjiliadis and T. Theophanides, *Inorg. Chim. Acta*, *16*, 67 (1976); (b) P.-C. Kong and F. D. Rochon, *J. Chem. Soc., Chem. Commun.*, 599 (1975). (c) G. Pneumatikakis, *Inorg. Chim. Acta*, *93*, 5 (1984).
9 (a) D. B. Brown, A. R. Khokhar, M. P. Hacker, L. Lokys, J. H. Burchenal, R. A. Newman, J. J. McCormack and D. Frost, *J. Med. Chem.*, *25*, 952 (1982); (b) S. L. Doran, A. R. Khokhar and M. P. Hacker, *Inorg. Chim. Acta*, *108*, 113 (1985).
10 (a) A. Terzis, N. Hadjiliadis, R. Rivest and T. Theophanides, *Inorg. Chim. Acta*, *12*, L5 (1975); (b) A. Terzis, *Inorg. Chem.*, *15*, 793 (1976).
11 A. Terzis and D. Mentzafos, *Inorg. Chem.*, *22*, 1140 (1983).
12 J.-P. Macquet and J.-L. Butour, *J. Nat. Cancer Inst.*, *70*, 899 (1983).
13 (a) P. D. Braddock, T. A. Connors, M. Jones, A. R. Khokhar, D. H. Melzack and M. L. Tobe, *Chem.-Biol. Interact.*, *11*, 145 (1975). (b) *U.S. Patent 4329299* (1982) to P. C. Hydes.
14 F. D. Rochon and R. Melanson, *Acta Crystallogr., Sect. C*, *42*, 1291 (1986).
15 F. D. Rochon and P.-C. Kong, *Can. J. Chem.*, *64*, 1894 (1986).
16 (a) A. J. Kunin and D. B. Brown, *J. Organomet. Chem.*, *212*, C27 (1981); (b) A. R. Khokhar, S. L. Doran, D. B. Brown and M. P. Hacker, *Inorg. Chim. Acta*, *135*, 81 (1987).
17 R. Beyerle-Pfnür, S. Jaworski, B. Lippert, H. Schöllhorn and U. Thewalt, *Inorg. Chim. Acta*, *107*, 217 (1985).
18 B. Lippert, *Gazzetta Chim. Ital.*, *118*, 153 (1988).
19 (a) B. Lippert, C. J. L. Lock and R. A. Speranzini, *Inorg. Chem.*, *20*, 808 (1981); (b) R. Faggiani, C. J. L. Lock and B. Lippert, *Inorg. Chim. Acta*, *106*, 75 (1985).
20 (a) F. Coletta, R. Ettore and A. Gambaro, *J. Magn. Reson.*, *22*, 453 (1976); (b) K. P. Beaumont, C. A. McAuliffe and M. E. Friedman, *Inorg. Chim. Acta*, *25*, 241 (1977).
21 R. Ettore, *Inorg. Chim. Acta*, *46*, L27 (1980).
22 N. Walker and D. Stuart, *Acta Crystallogr., Sect. A*, *39*, 158 (1983).
23 D. T. Cromer and J. B. Mann, *Acta Crystallogr., Sect. A*, *24*, 321 (1968).
24 D. T. Cromer and D. Liberman, *J. Chem. Phys.*, *53*, 1891 (1970).
25 G. M. Sheldrick, 'SHELX-76', Program System, University of Cambridge, 1976.
26 (a) R. Faggiani, B. Lippert and C. J. L. Lock, *Inorg. Chem.*, *21*, 3210 (1982); (b) B. Lippert, U. Thewalt, H.

Schöllhorn, D. M. L. Goodgame and R. W. Rollins, *Inorg. Chem., 23*, 2807 (1984).
27 J. A. Pople, *Mol. Phys., 1*, 168 (1958).
28 B. Lippert, C. J. L. Lock and R. A. Speranzini, *Inorg. Chem., 20*, 335 (1981).
29 K. Kai, Y. Wataya and H. Hayatsu, *J. Am. Chem. Soc., 93*, 2089 (1971).
30 R. Beyerle-Pfnür, B. Lippert, H. Schöllhorn, P. Matischok and U. Thewalt, *J. Heterocycl. Chem., 23*, 505 (1986).
31 G. Müller, J. Riede, R. Beyerle-Pfnür and B. Lippert, *J. Am. Chem. Soc., 106*, 7999 (1984).
32 H. Schöllhorn, U. Thewalt and B. Lippert, *J. Chem. Soc., Chem. Commun.*, 258 (1986).
33 G. W. Bushnell, A. Pidcock and M. A. R. Smith, *J. Chem. Soc., Dalton Trans.*, 572 (1975).
34 (a) B. L. Kindberg and E. L. Amma, *Acta Crystallogr., Sect. B, 31*, 1492 (1975); (b) M. Rossi, L. G. Marzilli and T. J. Kistenmacher, *Acta Crystallogr., Sect. B, 34*, 2030 (1978); (c) F. Fujinami, K. Ogawa, Y. Arakawa, S. Shirotake, S. Fujii and K.-I. Tomita, *Acta Crystallogr., Sect. B, 35*, 968 (1979); (d) K. Ogawa, K. Nishitani, T. Fujiwara, S. Shirotake and K.-I. Tomita, *Acta Crystallogr., Sect. B, 35*, 965 (1979); (e) P. E. Bourne and M. R. Taylor, *Acta Crystallogr., Sect. C, 39*, 430 (1983).
35 (a) D. L. Barker and R. E. Marsh, *Acta Crystallogr., 17*, 1581 (1964); (b) G. A. Jeffrey and Y. Kinoshita, *Acta Crystallogr., 16*, 20 (1963); (c) R. J. McClure and B. M. Craven, *Acta Crystallogr., Sect. B, 29*, 1234 (1973); (d) S. Neidle, A. Achari and M. Rabinovitch, *Acta Crystallogr., Sect. B, 32*, 2050 (1976).
36 R. Taylor and O. Kennard, *J. Mol. Struct., 78*, 1 (1982).
37 (a) C. Singh, *Acta Crystallogr., 19*, 861 (1965); (b) M. Sundaralingam and L. H. Jensen, *J. Mol. Biol., 13*, 930 (1965).
38 (a) M. R. Moller, M. A. Bruck, T. O'Connor, F. J. Armatis, Jr., E. A. Knolinski, N. Kottmair and R. S. Tobias, *J. Am. Chem. Soc., 102*, 4589 (1980) and refs. therein; (b) R. Faggiani, B. Lippert, C. J. L. Lock and R. A. Speranzini, *Inorg. Chem., 21*, 3216 (1982).
39 H. Susi, J. S. Ard and J. M. Purcell, *Spectrochim. Acta, Part A, 29*, 725 (1973).
40 (a) J. Hiraishi, I. Nakagawa and T. Shimanouchi, *Spectrochim. Acta, Part A, 24*, 819 (1968); (b) D. M. Adams and R. E. Christopher, *J. Chem. Soc., Dalton Trans.*, 2298 (1973).
41 (a) K. Inagaki and Y. Kidani, *Bioinorg. Chem., 9*, 157 (1978); (b) R. Pfab, P. Jandik and B. Lippert, *Inorg. Chim. Acta, 66*, 193 (1982); (c) K. Inagaki and Y. Kidani, *Inorg. Chim. Acta, 46*, 35 (1980); (d) G. Raudaschl-Sieber, H. Schöllhorn, U. Thewalt and B. Lippert, *J. Am. Chem. Soc., 107*, 3591 (1985).
42 A. Tschugaev, *J. Chem. Soc., 107*, 1247 (1915).
43 B. Lippert, *Inorg. Chem., 20*, 4326 (1981).
44 G. Raudaschl and B. Lippert, *Inorg. Chim. Acta, 80*, L49 (1983).
45 K. H. Scheller, V. Scheller-Krattiger and R. B. Martin, *J. Am. Chem. Soc., 103*, 6833 (1981).
46 G. D. Hildebrand and C. N. Reilly, *Anal. Chem., 29*, 258 (1957).
47 J. J. Christen, J. H. Rytting and R. M. Izatt, *J. Phys. Chem., 71*, 2700 (1967).
48 (a) Yu. N. Kukushkin, Y. E. Vyazmenskii and L. I. Zorina, *Russ. J. Inorg. Chem., 13*, 1573 (1968); (b) P.-C. Kong, D. Iyamuremye and F. D. Rochon, *Bioinorg. Chem., 6*, 83 (1976); (c) R. Melanson and F. D. Rochon, *Acta Crystallogr., Sect. B, 33*, 3571 (1977) and *34*, 941 (1978); (d) D. M. L. Goodgame, P. B. Hayman, R. T. Riley and D. J. Williams, *Inorg. Chim. Acta, 91*, 89 (1984).
49 J. F. Britten, B. Lippert, C. J. L. Lock and P. Pilon, *Inorg. Chem., 21*, 1936 (1982).
50 N. S. Kurnakov, *J. Russ. Phys. Chem. Soc., 25*, 565 and 693 (1893).
51 (a) F. A. Cotton, R. Francis and W. D. Horrocks, Jr., *J. Phys. Chem., 64*, 1534 (1960); (b) B. B. Wayland and R. F. Schramm, *Inorg. Chem., 8*, 971 (1969).