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Caffeine Complexes of Platinum(II): Crystal Structure of *Cis*-$[Pt(C_8H_{10}N_4O_2)_2Cl_2]\cdot 0.4H_2O$

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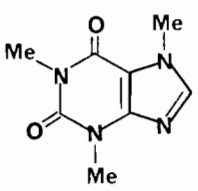
The preparations are reported of cis-*[Pt(caffeine)$_2$Cl$_2$]·0.4H$_2$O, Pd(caffeine)$_2$Cl$_2$, the methanol adduct of the previously known compound K[Pt(caffeine)Cl$_3$], and Pt(caffeine)(cytidine)Cl$_2$. Crystals of [Pt(caffeine)$_2$Cl$_2$]·0.4H$_2$O are tetragonal* P4$_2$/n *with* a = *13.156(2)* Å, c = *12.734(2)* Å, Z = *4. The structure was refined on 945 reflections to* R = *0.025. The molecule is* cis *with a crystallographic two-fold axis bisecting the Cl–Pt–Cl and N–Pt–N angles. The Pt is square planar with Pt–N and Pt–Cl bonds of 2.029(5)* Å *and 2.271(2)* Å *respectively. There is a 5.4° dihedral angle between the imidazole and pyrimidine rings, and the imidazole ring is rotated away from the coordination plane by 86.4°. Symmetry related caffeine units pack parallel to each other with an inter-ring separation of 3.45* Å.

Introduction

An important aspect of cancer research is the study of the lesions formed on DNA by cytotoxic, mutagenic, or carcinogenic chemicals and of the subsequent repair processes available to the cell. The ability of an anti-cancer drug, or combination of drugs, to overcome natural repair processes, which might otherwise permit the cell to build up drug resistance is an important factor in clinical use. Moreover, the activity of a particular drug may be enhanced by the co-administration of another compound which can block, or delay, repair processes.

Caffeine(I) has been found to inhibit postreplication repair of both UV and chemically induced



(I)

damage in DNA [1, 2]. Roberts and co-workers have shown that caffeine is particularly effective in enhancing the effects of the DNA lesions caused by *cis*-$[Pt(NH_3)_2Cl_2]$ (or its aquated or hydrolysed products) and have proposed that, in so doing, the caffeine inhibits a process which would normally permit replication to proceed past these lesions [2].

In view of this, and the continuing interest in the potential anti-cancer activity of analogues of *cis*-$[Pt(NH_3)_2Cl_2]$, one of us (RTR) explored in 1979 the possibility of forming platinum complexes of caffeine. The compounds obtained at that time had stoichiometries $Pt(caffeine)_2Cl_2\cdot nH_2O$ (n ~ 0.5) and $K[Pt(caffeine)Cl_3]\cdot CH_3OH$. While that work was in progress, Cramer and his co-workers reported their synthesis of the $[Pt(caffeine)Cl_3]^-$ ion, as the potassium salt, which was shown to have anti-cancer activity, and as the triphenylmethylphosphonium salt, on which an X-ray structural determination was carried out [3]. We have subsequently obtained crystals of the 2:1 complex, and have determined its structure. We report here the results of this work and synthetic details for some related compounds.

Experimental

Preparations

[Pt(caffeine)$_2$Cl$_2$]·0.4H$_2$O and K[Pt(caffeine)Cl$_3$]·CH$_3$OH. We first obtained these by the following method. A solution of K_2PtCl_4 (4.20 g) in water (50 cm^3), after shaking with charcoal and filtering, was added slowly to one of caffeine (3.90 g) in water (80 cm^3) and HCl (40 cm^3 of 0.5 *M* solution). The resulting orange-red solution was warmed (60 °C, 1 hr) and then left to stand for two days. The 2:1 complex separated as a pale yellow solid and this was filtered off, washed with water, and dried *in vacuo* at 40 °C overnight (yield 0.34 g). *Anal.* Found: C, 28.58; H, 2.97; N, 16.62; Pt, 29.40%. Calcd. for $[Pt(caffeine)_2Cl_2]\cdot 0.4H_2O$: C, 29.04; H, 3.17; N, 16.94; Pt, 29.49%. IR, ν(Pt–Cl) 350 cm^{-1}.

The orange yellow filtrate remaining after separation of the 2:1 complex was evaporated to dryness and the residue recrystallised twice from refluxing methanol to give orange-yellow crystals (4.89 g) of

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$K[Pt(caffeine)Cl_3]\cdot CH_3OH$. *Anal.* Found: C, 19.06; H, 2.39; N, 10.20; Cl, 18.47; O, 8.15; Pt, 34.50%. Calcd. for $K[Pt(caffeine)Cl_3]\cdot CH_3OH$: C, 19.07; H, 2.49; N, 9.89; Cl, 18.76; O, 8.49; Pt, 34.42%. IR, ν(Pt–Cl) 320 sh, and 330 cm^{-1}.

Subsequently, a quicker, more direct route to $K[Pt(caffeine)Cl_3]\cdot CH_3OH$ was employed: A mixture of K_2PtCl_4 (4.20 g) and caffeine (1.94 g) was slurried in methanol (100 cm^3) and HCl (20 cm^3 of 1 *M* aqueous solution) and gently refluxed for 4–5 hrs. The black solution obtained was treated with charcoal and filtered. The orange-yellow complex separated in 59% yield on cooling the filtrate in a fridge overnight and was obtained as orange crystals on recrystallisation from a hot methanol/dil. HCl mixture. *Anal.* Found: C, 18.82; H, 2.40; N, 9.85%. The ^1H NMR and IR spectra of this product were identical to those of the sample obtained by the original method. The presence of methanol of solvation was supported by ^{13}C NMR in D_2O (resonance at 48.91 ppm from external TMS). Acetone can also be used in place of methanol for the initial reflux stage and the product recrystallised from methanol/HCl as above.

The crystals of *cis*-$[Pt(caffeine)_2Cl_2]\cdot 0.4H_2O$ used in the X-ray study were obtained by the method outlined previously but on a one-quarter scale and allowing crystallisation to continue for 3 days.

Pt(caffeine)(cytidine)Cl₂. A sample of $K[Pt(caffeine)Cl_3]\cdot CH_3OH$ was treated with an equimolar amount of cytidine in a water/ethanol mixture to give a yellow solid (26% yield). *Anal.* Found: C, 28.75; H, 3.29; N, 13.66; Cl, 9.84%. Calcd: C, 29.03; H, 3.30; N, 13.94; Cl, 10.08%.

Pd(caffeine)₂Cl₂. A solution of $PdCl_2$ (1.77 g) in water (100 cm^3) was slowly added to one of caffeine (3.90 g) in water (80 cm^3) and HCl (40 cm^3 of 0.5 *M* solution). A pale yellow precipitate was formed immediately. The mixture was allowed to stand for 1 hr, filtered off, washed thoroughly with hot acetone, and dried *in vacuo* at 40 °C (3 g yield). *Anal.* Found: C, 33.74; H, 3.56; N, 19.38%. Calcd. for Pd(caffeine)$_2Cl_2$: C, 33.94; H, 3.58; N, 19.81%. IR, ν(Pd–Cl) 347 cm^{-1}.

X-Ray Study

$[Pt(caffeine)_2Cl_2]\cdot 0.4H_2O$ crystallises as pale yellow columns elongated along *c*. The crystals have a tendency to craze, probably due to loss of water of crystallisation. The crystal data are: $Pt(C_8H_{10}N_4O_2)_2Cl_2\cdot 0.4H_2O$, tetragonal, a = 13.156(2) Å, c = 12.734(2) Å, V = 2204 Å^3 space group $P4_2/n$, Z = 4, mol. wt. 661, D_c = 2.00 g cm^{-3}, μCu-K$_\alpha$ = 146 cm^{-1}. Refined unit cell parameters were obtained by centering 20 reflections on a Nicolet R3m diffractometer. 1135 independent reflections ($\theta \leq 50°$) were measured with Cu-K$_\alpha$ radiation (graphite monochromator) using the omega-scan measuring routine. Of these 945 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. Lorentz, polarisation and a numerical absorption correction were applied.

Predominance of reflections of the type *hkl*, $l = 2n$ indicated that the Pt was in the two-fold position at 3/4, 1/4, z. (The origin was taken at $\bar{1}$). The positions of the Pt and Cl atoms were determined from a sharpened Patterson map. The remaining non-hydrogen atoms were located in the ensuing ΔF map. This map also revealed a partial occupancy water molecule. Refinement of the occupancy of the water oxygen atom gave a value of 0.41(1). The C(8) hydrogen atom position was idealised. The positions of the hydrogen atoms of the three methyl groups were found in a ΔF map. The methyl groups were idealised and allowed to refine as rigid bodies. All C–H distances were fixed at 0.96 Å. Although indications of the positions of the water protons were obtained from the ΔF map, these atoms would not refine and were therefore omitted. The non-hydrogen atoms were refined anisotropically; the hydrogen atoms were assigned isotropic thermal parameters, U(H) = 1.2 Ueq (C). Refinement was by block-cascade least-squares to $R = R_\omega = 0.025$, ($\omega^{-1} = \sigma^2(F) + 0.00011F^2$). Computations were carried out on an Eclipse S140 computer using the SHELXTL program system [4]. Scattering factors were from reference [5].

The fractional atomic coordinates and isotropic thermal parameters are listed in Table I. Table II lists the bond lengths and angles.

Discussion

The reaction between caffeine and K_2PtCl_4 in 2:1 mole ratio in acidified aqueous solution yields both $Pt(caffeine)_2Cl_2$ and the $[Pt(caffeine)Cl_3]^-$ ion, with the latter predominating under the conditions we employed (see Experimental section). Although Cramer *et al.* report [3] that they used the potassium salt of the mono-caffeine complex for anti-cancer tests, they did not quote experimental details for its isolation, though they infer that they obtained it without solvent of crystallisation. Our experimental procedure involved the use of methanol and we consistently found that the solid potassium salt had the stoichiometry $K[Pt(caffeine)Cl_3]\cdot CH_3OH$. The methanol of crystallisation, whose presence is shown by NMR and by analysis, was lost at 160 °C when the compound was subjected to thermogravimetric analysis.

Our interest centred particularly on the compound of stoichiometry $Pt(caffeine)_2Cl_2$ because of its potential similarity to *cis*-$Pt(NH_3)_2Cl_2$ and the currently favoured 'second generation' drugs of that stoichiometry [6]. Its IR spectrum showed only one

TABLE I. Atom Coordinates ($\times 10^4$) and Temperature Factors ($Å^2 \times 10^3$).

Atom	*x*	*y*	*z*	U_{eq}
Pt	12500	7500	−1963(1)	47(1)*
Cl	11906(1)	6412(1)	−3204(1)	63(1)*
C(1)	9580(6)	6927(7)	467(6)	67(3)*
O(1)	8843(5)	7471(5)	502(4)	89(2)*
N(2)	9712(5)	6154(5)	1207(5)	68(2)*
C(2)	8930(8)	6063(7)	2031(7)	104(4)*
C(3)	10530(7)	5502(6)	1288(5)	68(3)*
O(3)	10598(5)	4856(4)	1971(4)	94(2)*
C(4)	11256(5)	5689(5)	469(5)	53(3)*
C(5)	11176(5)	6433(5)	−248(5)	50(2)*
N(6)	10310(4)	7016(4)	−305(4)	54(2)*
C(6)	10075(6)	7722(6)	−1163(6)	86(4)*
N(7)	12197(4)	5249(4)	297(4)	61(2)*
C(7)	12675(7)	4406(6)	881(6)	86(4)*
C(8)	12625(6)	5764(6)	−477(5)	59(3)*
N(9)	12026(4)	6513(4)	−840(4)	51(2)*
O	9668(11)	5247(12)	4171(12)	106(7)*

Hydrogen Coordinates ($\times 10^4$) and Temperature Factors ($Å^2 \times 10^3$)

Atom	*x*	*y*	*z*	*U*
H(2a)	8753	5365	2154	120
H(2b)	8332	6437	1840	120
H(2c)	9217	6348	2659	120
H(6a)	9386	7637	−1395	102
H(6b)	10518	7754	−1761	102
H(6c)	10131	8340	−766	102
H(7a)	13132	4669	1402	106
H(7b)	13052	4026	369	106
H(7c)	12184	3971	1211	106
H(8)	13290	5619	−749	69

*Equivalent isotropic *U* defined as one third of the trace of the orthogonalised U_{ij} tensor.

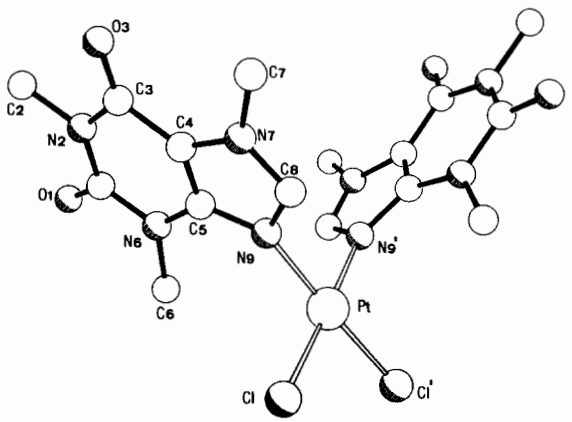

Fig. 1. Perspective view of the molecular structure of Pt-(caffeine)$_2$Cl$_2$.

TABLE II. Bond Lengths (Å) and Bond Angles (deg.).

Pt–Cl	2.271(2)
Pt–Cl′	2.271(2)
C(1)–O(1)	1.206(10)
C(1)–N(6)	1.379(9)
N(2)–C(3)	1.381(10)
C(3)–C(4)	1.435(10)
C(4)–N(7)	1.384(9)
C(5)–N(9)	1.353(8)
N(7)–C(7)	1.476(10)
C(8)–N(9)	1.344(9)
Pt–N(9)	2.029(5)
Pt–N(9′)	2.029(5)
C(1)–N(2)	1.397(10)
N(2)–C(2)	1.475(11)
C(3)–O(3)	1.219(9)
C(4)–C(5)	1.343(9)
C(5)–N(6)	1.375(8)
N(6)–C(6)	1.467(9)
N(7)–C(8)	1.322(9)
Cl–Pt–N(9)	89.0(1)
N(9)–Pt–Cl′	177.8(2)
N(9)–Pt–N(9′)	90.4(3)
O(1)–C(1)–N(2)	120.4(7)
N(2)–C(1)–N(6)	117.1(7)
C(1)–N(2)–C(3)	126.8(6)
N(2)–C(3)–O(3)	122.9(7)
O(3)–C(3)–C(4)	126.1(7)
C(3)–C(4)–N(7)	129.7(6)
C(4)–C(5)–N(6)	120.5(6)
N(6)–C(5)–N(9)	127.7(6)
C(1)–N(6)–C(6)	116.0(6)
C(4)–N(7)–C(7)	128.0(6)
C(7)–N(7)–C(8)	125.4(6)
Pt–N(9)–C(5)	134.2(4)
C(5)–N(9)–C(8)	103.6(5)
Cl–Pt–Cl′	91.7(1)
Cl–Pt–N(9′)	177.8(2)
Cl′–Pt–N(9′)	88.9(1)
O(1)–C(1)–N(6)	122.4(7)
C(1)–N(2)–C(2)	116.9(7)
C(2)–N(2)–C(3)	116.1(6)
N(2)–C(3)–C(4)	111.0(6)
C(3)–C(4)–C(5)	124.5(6)
C(5)–C(4)–N(7)	105.5(6)
C(4)–C(5)–N(9)	111.8(6)
C(1)–N(6)–C(5)	119.5(6)
C(5)–N(6)–C(6)	124.5(6)
C(4)–N(7)–C(8)	106.5(6)
N(7)–C(8)–N(9)	112.5(6)
Pt–N(9)–C(8)	122.1(4)

ν(Pt–Cl) band but this does not provide an unambiguous assignment of molecular geometry as two closely spaced ν(Pt–Cl) absorptions from a *cis*-PtL_2Cl_2 arrangement may not be resolved.

The X-ray analysis showed (Fig. 1) the molecule to be *cis* with a crystallographic two-fold axis bisecting the Cl–Pt–Cl′ and N(9)–Pt–N(9′) angles. The Pt is

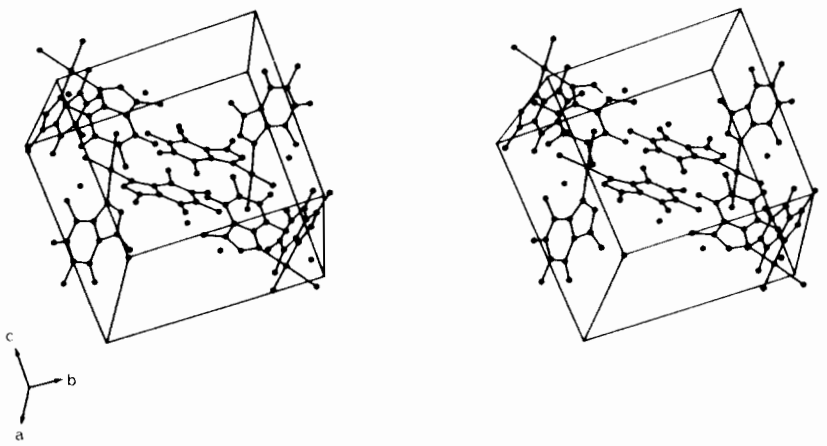

Fig. 2. Stereoscopic view of the packing of the molecules in the structure of $[Pt(caffeine)_2Cl_2]\cdot 0.4H_2O$.

essentially square planar with all the angles at Pt within 1.7° of 90°. There is however, a small twist (3°) of the Cl–Pt–Cl′ plane relative to that of N(9)–Pt–N(9′). The Pt–N distance [2.029(5) Å] is, within statistical significance, the same as observed in the $[PtCl_3(caffeine)]^-$ ion [3], but that for Pt–Cl [2.271-(2) Å] is significantly shorter than the average distance (2.301 Å) found in [3].

All the bond lengths and angles in the caffeine moiety are, within the limits of accuracy of the determination, identical to those observed in [3]. Also the angles at N(9) to the Pt [122.1(4) and 134.2(4)°] are very close to those in [3] [119.4(4) and 135.8-(4)°].

The imidazole ring is planar with a maximum deviation from the least squares plane, of 0.011 Å for C(4) and C(5). The pyrimidine ring shows larger deviations from planarity with C(5) and N(6) displaced 0.034 and 0.038 Å respectively from the plane. Re-calculation of the mean plane omitting N(6) shows a marked improvement in planarity with a maximum deviation of 0.015 Å, for C(4); N(6) is 0.074 Å from this plane and C(6), 0.28 Å. There is a characteristic [3, 7] non-zero dihedral angle between the imidazole and pyrimidine rings of 5.4°. The imidazole ring is rotated away from the coordination plane by 86.4° (*cf.* 73.5° in [3]).

An interesting feature of the packing (Fig. 2) is a parallel arrangement of symmetry related caffeine molecules (Fig. 3) very similar to that observed in [3]. The planes of the molecules are separated by 3.45 Å (*cf.* 3.31 Å in [3]). There are six other intermolecular contacts of less than 3.5 Å. Five of these are to Cl: C(1) 3.32, N(6) 3.36, C(5) 3.41, N(7), 3.43 and N(2) 3.48 Å. The other, 3.26 Å is between C(6) and O(3). The closest contacts to the water molecule are 3.10 to O(3), 3.16 to O(1) 3.18 to C(8) and 3.25 Å to Cl.

The formation of *cis*-$[Pt(caffeine)_2Cl_2]$, as well as $[Pt(caffeine)Cl_3]^-$ suggested that mixed ligand

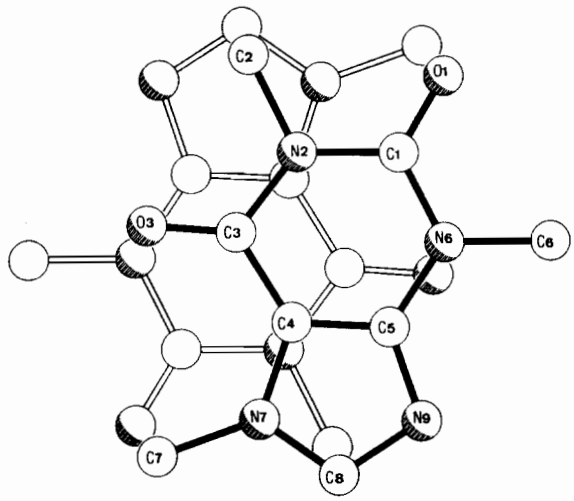

Fig. 3. Projection onto the mean plane of the purine showing the overlap between the parallel symmetry related caffeine units in the structure.

complexes $Pt(caffeine)LCl_2$ could also be obtained. We found that when $K[Pt(caffeine)Cl_3]\cdot CH_3OH$ was reacted with an equimolar amount of cytidine in aqueous methanol a complex of stoichiometry Pt-(caffeine)(cytidine)Cl_2 was obtained. However, attempts to prepare analogous complexes with guanosine, uridine, uracil, 5′-CMP, or 5′-GMP gave partial or extensive reduction to platinum, and a similar reaction using 5′-UMP caused formation of a 'blue'.

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