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Platinum Purine Nucleosides. I. Interaction of K_2PtX_4 (X = Cl, Br) with Adenosine, Triacetyladenosine, Adenosine-1-oxide and 9-Methyladenine

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The reactions of K_2PtX_4, where X = Cl, Br with adenosine, triacetyladenosine, adenosine-1-oxide and 9-methyladenine have been studied in acidic, neutral aqueous solutions and in organic solvents. The isolated solid adducts have been characterized by elemental analyses, conductivity measurements, nmr and ir spectra. The results suggest that adenosine binds through N_7 to Pt(II) in neutral and weakly acidic media, whereas triacetyladenosine binds both with N_1 and N_7 sites. In adenosine-1-oxide the NH_2 group becomes an active site of bonding with the loss of a proton, the N_7 and the N_1–O groups become possible sites of chelation, too. In 9-methyladenine the N_7 is the metallation site and the N_1 the protonation site.

Introduction

The binding of transition metals to nucleosides and nucleotides is widely recognized. Evidence is rapidly accumulating about the role of transition metals in the chemistry and the reactivity of nucleic acids[1]. In this work we wish to report some reactions of purine nucleosides with platinum. The study of these coordinative interactions is important for the understanding of the discovery by Rosenberg and his collaborators of the activity of certain platinum compounds against tumours[2].

In previous papers[3–5] we have reported the preparation of complexes of adenosine and tetraacetyladenosine with platinum. The solid powders were found to be of the formula $Pt(purine)_2X_2$. Adenosine has several coordination sites; however, the most favored sites with platinum have been found to be the N_7 and N_1 nitrogen atoms of the purine ring[6,7]. The NH_2 and the sugar hydroxyl groups have been excluded from chemical evidence[5] and ir spectra[4]. The stereochemistry around the platinum atom has also been considered and a *trans*-configuration has been previously tentatively proposed on the basis of ir data and the size of the ligands[4,5]. In the present report we have re-examined the configuration around the platinum atom and present more data here on adenosine and related systems which permit a better understanding of these interactions. The *cis*-configuration seems to be favoured now for the $Pt(purine)_2X_2$ complexes on the basis of the present data. The investigation of the complexes by X-ray crystallography was not possible because we have not been able to grow single crystals in spite of numerous attempts.

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Results and Discussion

Adenosine

The coordination sites with platinum(II) in the adducts $Pt(adenosine)_2X_2$ were considered to be the N_7 and the N_1 nitrogen atoms of the purine base from nmr spectra[5]. In the case of Pt–N_1 or Pt–N_7 coordination there should be a reversal in the order of H_2 and H_8 proton signals of the free adenosine as this occurs for example in 6-substituted purines at different pH values[8]. From X-ray structure determinations[9,10] of the hydrochloric salts of adenine and adenosine it is known that protonation occurs at the N_1 nitrogen atom of the purine ring. This explains the reversal in the order of H_2 and H_8 protons in acidic media of the above bases[8]. In order to find out if coordination occurs at N_1 or N_7 it was decided to deuterate one of the two aromatic protons of the purine ring (H_8 or H_2), which leaves only one proton resonance in the nmr spectra (region of aromatic protons). The eventual shift or lack of shift of the remaining proton upon complexation should be unequivocal as to the binding site of the base. Unfortunately, no ^{195}Pt–H_8 or H_2 coupling was observed in DMSO-d_6 solutions. The aromatic proton near the coordinating site shifts downfield upon complexation as a result of delocalization of π-electron distribution of the purine ring.

Purine derivatives in general, when treated with D_2O at elevated temperatures exchange the H_8 proton with deuterium[8]. The rate of exchange and the mechanism are also known[12]. Accordingly, a solution of

adenosine in D_2O was heated at 70° C *in vacuo* for 3 days[12] and the H_8 hydrogen was deuterated. The nmr spectra in DMSO-d_6 of 50% and 100% deuteration of the H_8 of adenosine are shown in Figures 1a and 1b and the chemical shifts are given in Table I. The nmr spectrum of 35% deuteration of the adenosine–platinum chloro complex is shown in Figure 1c. The H_8 shifts substantially (~1 ppm) on complexation, obviously because of Pt–N_7 coordination (compare Figures 1b and 1c). The H_8 peak is large at the base,

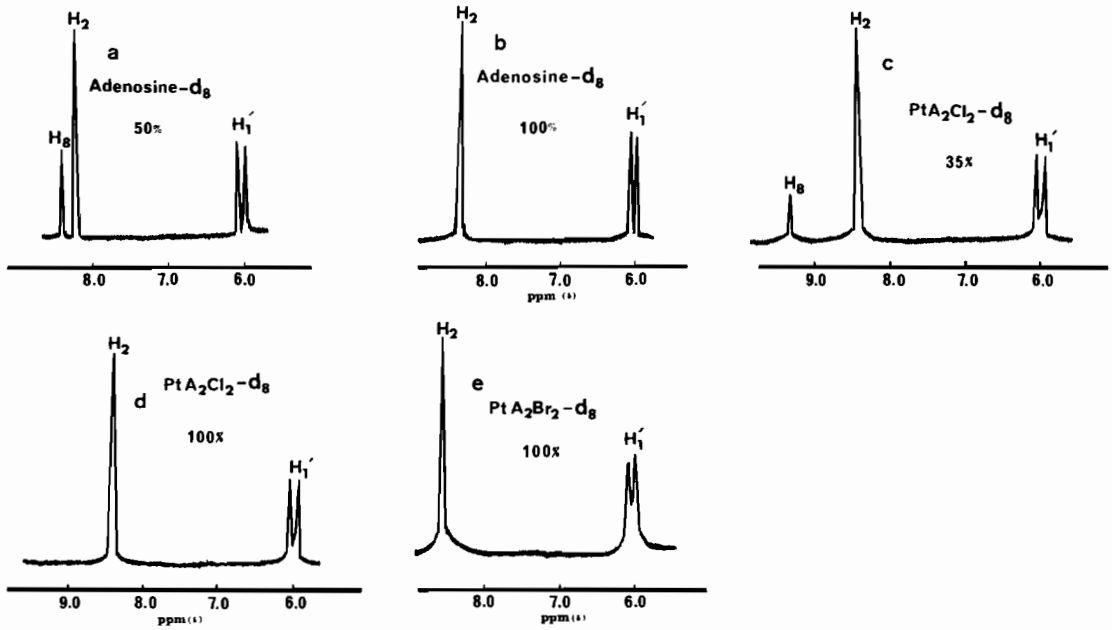


Figure 1. The nmr spectra of platinum–adenosine complexes. (a) Adenosine-d_8 (50% deuteration) after 30 hr of reaction with D_2O at 70° C under vacuum; (b) Adenosine-d_8 (100% deuteration) after three days of reaction; (c) Pt(adenosine-d_8)Cl_2 (35% deuteration); (d) Pt(adenosine-d_8)$_2Cl_2$ (100% deuteration); (e) Pt(adenosine-d_8)$_2Br_2$ (100% deuteration).

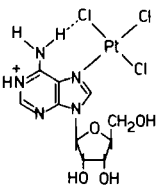
TABLE I. The Nmr Chemical shifts of Pt(II)–Adenosine Complexes in ppm (δ).

Compound	% Deuteration	H_2	H_8	H_1'	Solvent
Adenosine-d_8	50	8.25	8.41	5.99 6.08[a]	DMSO-d_6
Adenosine-d_8	100	8.33	–	5.95 6.05	DMSO-d_6
Pt(Adenosine-d_8)$_2Cl_2$	35	8.46	9.33	5.97 6.08	DMSO-d_6
Pt(Adenosinc-d_8)$_2Cl_2$	100	8.50	–	5.96 6.05	DMSO-d_6
Pt(Adenosine-d_8)$_2Br_2$	100	8.60	–	5.99 6.08	DMSO-d_6
Adenosine	0	8.43	8.52	6.03 6.13	0.3*N* DCl
Adenosine-d_8	80	8.46	8.52	6.05 6.12	0.3*N* DCl
Pt(AdenosineH)Cl_3	0	8.63	9.09	6.22 6.30	0.3*N* DCl
Pt(Adenosine-d_8H)Cl_3	80	8.68	9.14	6.17 6.25	0.3*N* DCl

[a] Doublet of H_1'.

but no clear coupling is observed. The remaining H_2 proton shifts slightly (~0.1 ppm) upon complexation with platinum as is shown in Figures 1d and 1e, both for the chloro and bromo derivatives, respectively. The above result is strong evidence of platinum–N_7 interaction in these compounds. Berger and Eichhorn reported[13] that in Cu(II) adenosine complexes in solution, both N_1 and N_7 equally participated in bonding, except in the case of 3',5'-phosphate derivatives of adenosine, where stacking of the bases favors N_7 coordination. Mansy *et al.*[14] and Robins[15] reported reactions of adenosine with *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ in which the sites N_1, N_7 and NH_2 were considered to be involved in bonding. In the present work no interaction with the NH_2 groups was observed[3–5]. Non involvement of NH_2 in bonding with platinum(II) was also reported from ^{195}Pt–H nmr coupling measurements by Kong and Theophanides[6,7]. X-ray structure determinations on complexes of adenine nucleotides with metals have clearly shown that the NH_2 group does not interact with metals[16–20]. This has been attributed to the ring participation of the NH_2 lone pair of electrons[16].

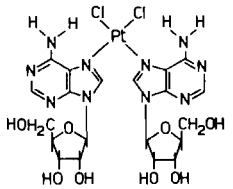
Platinum(II) interaction with the N_1 site has been observed[6,7] in the presence of excess platinum with the complex [Pt(dien)Cl]Cl and adenosine in neutral solutions. Since the yield[5] of the complexes Pt(adenosine)$_2X_2$ did not exceed 50%, the reaction of K_2PtCl_4 with adenosine and adenosine-d_8 was investigated in solution by nmr spectroscopy in 0.3*N* DCl and the nmr chemical shifts clearly indicate a lack of Pt(II)–N_1 interaction in 1:2, 1:1, 2:1 (Pt:A) molar ratios. In the 1:2 and 1:1 molar ratios the nmr of the reaction shows a mixture of compounds, but the rapid precipitation of the complex Pt(adenosine)$_2Cl_2$ prevents the identification of all the species in solution. On the other hand, when the metal was used in excess (2:1) the nmr spectra of the reaction after 3–4 hours showed one intermediate of the formula Pt(adenosineH)Cl_3 which could not be isolated and was not stable enough for further studies (see Figures 2a–d and proposed structure).



Similar compounds with Zn–adenine, Zn–guanine and Cu–guanine are known[16–19]. The isolation and crystal structure determination of the compound Pt(9-methyladenineH)Cl_3[20] also suggest the existence of Pt(adenosineH)Cl_3. The binding site with platinum is the N_7 nitrogen atom in the Pt(adenosineH)Cl_3 complex. The H_2 proton is shifted more up-field here than in the case of Pt(adenosine)$_2Cl_2$ complexes due to N_1 protonation (see Figures 2a–d and Table I).

In 0.3*N* HCl acid media the N_1 position is preferentially protonated and only the N_7 position interacts with platinum(II) under these conditions. We conclude that protonation takes place preferentially at N_1 and metallation at N_7. The reaction in neutral media could not be followed by nmr due to solubility restrictions. The compounds of the formula Pt(adenosine)$_2X_2$ prepared in neutral or weakly acidic media were identical[4,5]. The easy formation of *cis*-$[Pt(NH_3)_2(Nucl)_2]Cl_2$ and *cis*-$[Pt(en)(Nucl)_2]Cl_2$ complexes, where Nucl = nucleoside, from the reactions of *cis*-$[Pt(NH_3)_2Cl_2]$ and *cis*-$[Pt(en)Cl_2]$ with nucleosides[6,7] is in favor of a *cis*-geometry for the Pt(adenosine)$_2X_2$ complexes, obtained by a direct treatment of K_2PtCl_4 with nucleosides. The Kurnakoff test[21] was difficult to apply in this case due to solubility restrictions. However, when the complex Pt(adenosine)$_2Cl_2$ was treated with excess of thiourea in DMF for 30 minutes followed by precipitation with excess of acetone and the nmr spectrum of the precipitate was taken in D_2O the presence of free adenosine only was observed. This result indicates the formation of a $[Pt(Th)_4]Cl_2$ complex. Furthermore, when Pt(tetraacetyladenosine)$_2Cl_2$ was treated in the same manner with thiourea in DMF the product $[Pt(Th)_4]Cl_2$ was again isolated and characterized.

The above reactions indicate that the *trans*-effect of these nucleosides is comparable to that of pyridine and is smaller than the *trans*-effect of Cl^-. The unique Pt–Cl band[5] observed in the far ir spectrum of the complexes Pt(Nucl)$_2Cl_2$ cannot be always taken as evidence of *trans*-configuration[22]. In the absence of X-ray crystallographic data on Pt(adenosine)$_2X_2$ complexes the *cis*-configuration is now favored[3–5].



The *cis*-configuration of the compounds is also interesting from the point of view of antitumour activity. The existence of a weak hydrogen bonding ($NH_2 \cdots Cl$) is indicated in the spectra and is the only NH_2 interaction. An intermolecular and an intramolecular hydrogen bonding has also been found in the crystal structure of Pt(9-methyladenineH)Cl_3[20].

Triacetyladenosine

This ligand was prepared according to the method of Bredereck[23]. The reactions of triacetyladenosine

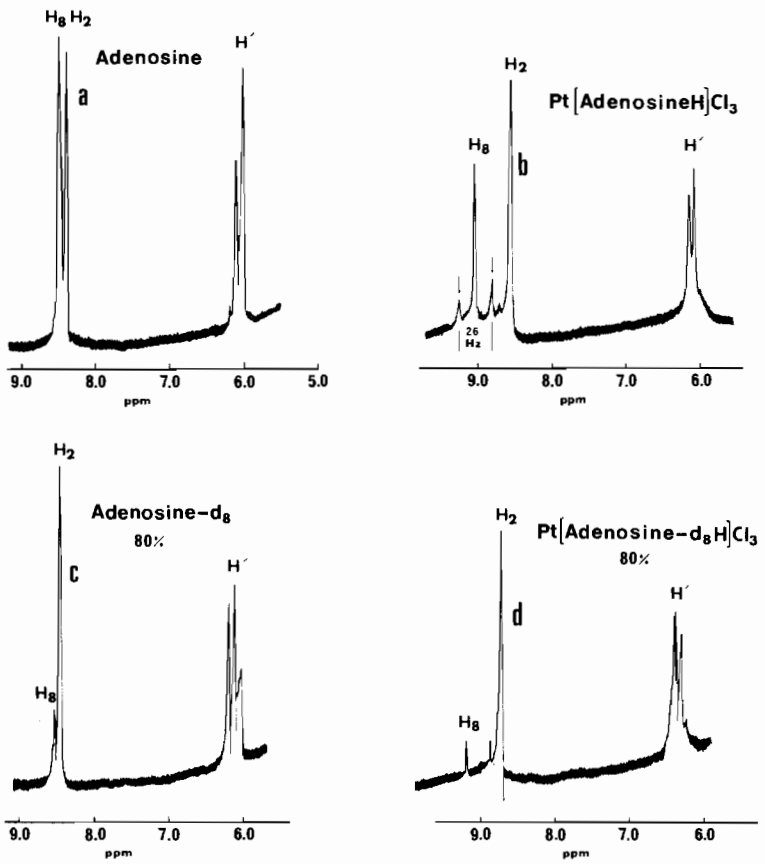


Figure 2. (a) Adenosine in 0.3*N* HCl; (b) Pt(adenosineH)Cl_3, after 3–4 hours of reaction of K_2PtCl_4 and adenosine at 2:1 ratio (0.1552 g:0.05 g in 1 ml of solvent); (c) Adenosine-d_8 (80% deuteration) in 0.3*N* HCl; (d) Pt(adenosine-d_8H)Cl_3

(TAA) with K_2PtX_4, where X = Cl,Br were attempted in order to compare them with those of adenosine and tetraacetyladenosine known to form complexes with platinum[3–5]. In this way complexes of the formula $Pt(TAA)_2X_2$, where X = Cl,Br have been isolated and characterized by chemical analyses and conductivity measurements (Table II).

The nmr spectra of these compounds in DMSO-d_6, shown in Figures 3a, b, c, d and Table III were complicated in the region of the aromatic protons and assignment of the observed peaks was very difficult. In order to facilitate the assignment the H_8 proton of the ligand (TAA-d_8) was exchanged with deuterium[8, 12]. In the nmr spectrum of $Pt(TAA)_2Cl_2$ we have observed four peaks (Figure 3c) in the aromatic proton region. In the spectrum of $Pt(TAA\text{-}d_8)_2Cl_2$ (Figure 3d) we observed only two peaks at 8.20 and 8.80 ppm(δ) and the latter was flattened. The slightly shifted peak at 8.20 ppm(δ) is assigned to the H_2 resonance of the $Pt(TAA\text{-}d_8)_2Cl_2$ complex in which the platinum atom is coordinated through the N_7 sites of the two TAA-d_8 molecules (see Figure 3d and Table III).

The second strongly shifted peak at 8.80 ppm(δ) is undoubtedly due to the H_2 proton of a species, $Pt(TAA\text{-}d_8)_2Cl_2$, in which the platinum atom is coordinated through the N_1 sites of the two TAA-d_8 molecules. A third possibility may, nevertheless, exist in which the platinum atom is coordinated through the N_1 and the N_7 sites of each TAA-d_8 molecule and the H_2 resonances may coincide with the above two. In the nmr spectrum of $Pt(TAA)_2Cl_2$, where the ligand is undeuterated (Figure 3c) the assignment may be as follows: the peaks at 8.26 and 8.89 ppm may be due to H_2 and H_8 proton resonances of the ligand coordinated through N_7 (N_7–Pt–N_7), respectively. The peaks at 8.89, 8.42 ppm(δ) are assigned to H_2 and H_8, respectively in the complex N_1–Pt–N_1 and the peaks at 8.59, 8.42 ppm to H_2 and H_8, respectively of the TAA molecule coordinated through N_1. Those at 8.26 and 8.89 ppm are assigned to H_2 and H_8 of the TAA molecule coordinated through N_7 for the species N_7–Pt–N_1. The NH_2 group does not participate in bonding and is shown at 7.36 ppm in the free ligand and at 7.43 ppm in the complex $Pt(TAA)_2Cl_2$.

TABLE II. Analytical Data and Conductivity Measurements of the Compounds.

Compound		C%	H%	N%	Pt%	X%	D.P.[a]	Molar Conductance in DMSO $ohm^{-1} cm^2 mol^{-1}$ 1 mmol Solution (20° C)
Pt(9-methyladenineH)Cl_3	Calc.	15.93	1.77	15.49	43.21	23.57		
	Found	16.33	1.78	15.96	42.76	23.01	300° C	
$[Pt(Ad\text{-}1\text{-}O\text{-}H^+)Cl]_n$	Calc.	23.35	2.52	13.60	37.97	6.90		
	Found	23.38	2.35	13.37	38.23	6.94	190–200° C	4.6
$[Pt(Ad\text{-}1\text{-}O\text{-}H^+)Br]_n$	Calc.	21.49	2.32	12.53				
	Found	21.16	2.06	12.31				
$Pt(TAA)_2Cl_2$	Calc.	36.48	3.61		18.53			
	Found	36.57	3.84		18.68		230–235° C	5.1
$Pt(TAA)_2Br_2$	Calc.	33.67	3.33	12.27	17.10	14.01		
	Found	33.51	3.50	12.04	17.58	13.75	220–225° C	
$[Pt(A\text{-}1\text{-}O\text{-}H^+)en]Cl$	Calc.				34.05			
	Found				34.32			85 in H_2O

[a] Decomposition points (D.P.).

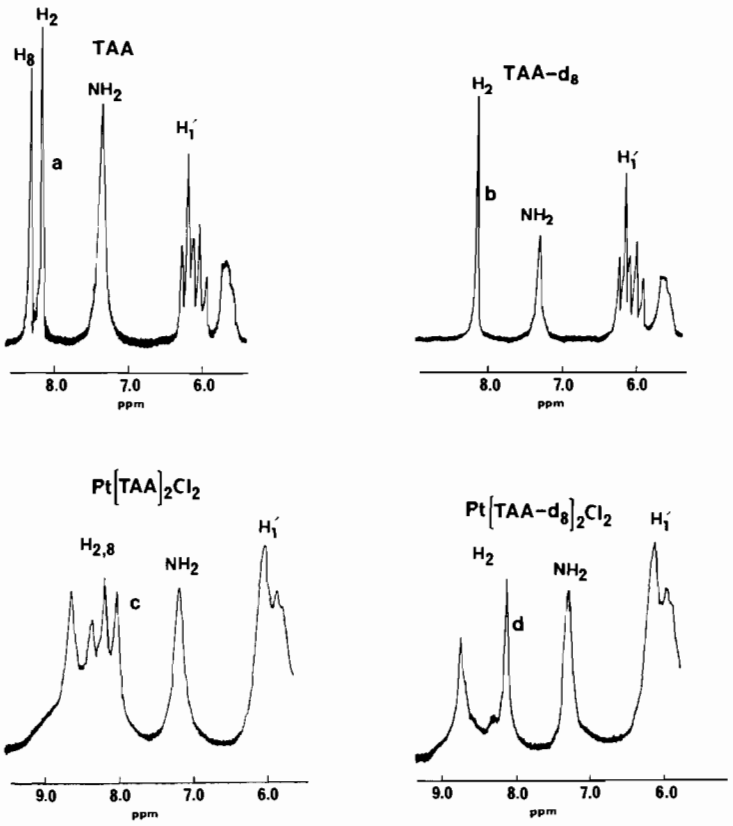


Figure 3. The nmr spectra of platinum–triacetyladenosine complexes. (a) Triacetyladenosine; (b) Triacetyladenosine-d_8 (100% deuteration; (c) $Pt(TAA)_2Cl_2$; (d) $Pt(TAA\text{-}d_8)_2Cl_2$ (100% deuteration). The spectra were taken in DMSO-d_6 solutions

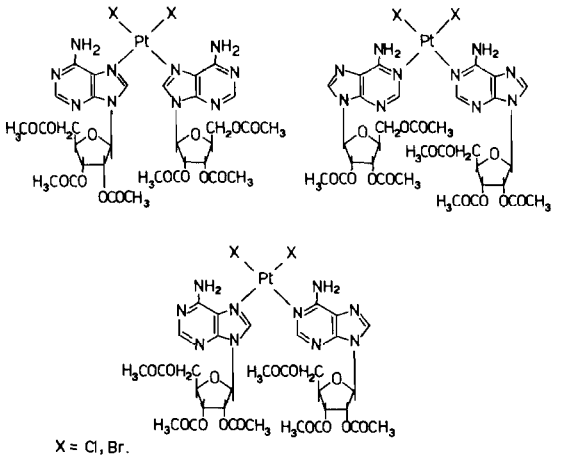
TABLE III. The Nmr Chemical Shifts of Pt(II)–TAA Complexes in ppm (δ) in DMSO-d_6.

Compound	H_2	H_8	NH_2	Assignment
TAA[a]	8.16	8.33	7.36	
TAA-d_8[b]	8.12	–	7.30	
$Pt(TAA)_2Cl_2$	8.26	8.89	7.43	N_7–Pt–N_7
	8.89	8.42		N_1–Pt–N_1
	8.26	8.89		Pt–N_7 } N_1–Pt–N_7
	8.59	8.42		Pt–N_1 }
$Pt(TAA\text{-}d_8)_2Cl_2$	8.20	–	7.30	N_7–Pt–N_7
	8.80	–		N_1–Pt–N_1
	8.20 and 8.80	–		N_1–Pt–N_7

[a]TAA = Triacetyladenosine. [b]TAA-d_8 = Triacetyladenosine-d_8, deuterated at the position 8.

In the ir spectra of $Pt(TAA)_2Cl_2$ the NH_2 appears approximately at 1655 and 1580 cm^{-1} and is coupled with the ring stretching motions in this region, as in the case of adenosine[4,24]. In triacetyladenosine the above two bands are at about 1670 and 1602 cm^{-1}, respectively. The carbonyl $\nu C{=}O$ stretching frequency does not shift and is observed near 1730 cm^{-1} in the complexes and the free ligand. The broad medium intensity band at ~330 cm^{-1} in the chloro derivatives is absent from the spectrum of the bromo derivatives and is attributed to the Pt–Cl stretching motion.

The above compounds of the general formula $Pt(TAA)_2Cl_2$ were non-electrolytes in DMSO solutions (Table II). Here, the platinum atom is most likely coordinated through N_1 and N_7 in the *cis*- configuration:

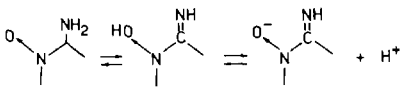


The above unusual behavior of triacetyladenosine in neutral solutions differs from that of tetraacetyladenosine in the same solution and that of adenosine in weakly acidic and neutral solutions. The strongly electron withdrawing acetyl groups are blocking the sugar hydroxyls of the nucleoside and may decrease the basicity of the N_7 nitrogen and the N_7 site is no longer the prefered site of coordination with platinum(II). In the case of tetraacetyladenosine, however, the presence of the bulky $NHCOCH_3$ group near the N_1 atom may prevent coordination with platinum through this site[4,5,7].

Adenosine-1-oxide

The N-oxides of adenine and its derivatives can act either as antimetabolites or can be metabolized to normal cellular purines[25]. Interaction of adenosine-1-oxide with K_2PtX_4 (X = Cl,Br) is therefore of biological interest. It is also interesting to compare the coordinative properties of this ligand towards platinum(II) with those of adenosine and derivatives[3–7].

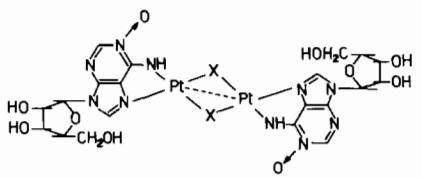
The reaction of equimolar quantities of K_2PtX_4 and adenosine-1-oxide in H_2O at 50° C or at room temperature gave green colored products after several days, corresponding to the empirical formula, $[Pt(L{-}H^+)X]_n$ where L = adenosine-1-oxide and X = Cl,Br (Table II). The reaction at 50° C was quantitative and took a shorter time (5–8 hours). During the reaction the pH decreased from 5.5 to about 2.5. This indicates a proton release from the base which may proceed according to the following reaction[26].



The pK_a value was found[26] to be 12.86. Perrin[26] on the basis of titration studies has suggested a chelate structure in metal–adenosine-1-oxide complexes taking place through O^- and NH. He observed a proton release upon complexation of the base in neutral solution (pH decreased). A similar structure has been proposed for Cu(II)–adenosine-1-oxide-5′-monophosphate complexes[27]. In the case of Cu(II)–inosine-1-oxide-5′-monophosphate complexes, however, chelation was proposed through $N_1 \rightarrow O^-$ and O_6^- atoms[28]. Weiss and Venner[29], on the other hand, concluded by a series of systematic blocking or elimination of

certain atoms that the potential binding sites in the complexes of Cu(II)–adenine-1-oxide were most likely the N_7 site and the imino group (NH^-) resulting from deprotonation of the amino group.

The green color of the products obtained in the present work is attributed to a Pt–Pt interaction (see proposed structure). Platinum(II) and several other metals are known to be bound to aromatic N-oxides *via* the O atom[30,31]. Pyridine-1-oxides when coordinated to platinum through O show a slight red shift of the νN–O frequency of the free ligand[30]. In the ir spectrum of free adenosine-1-oxide the highest band in the region of 1700 cm^{-1} was observed at 1660 cm^{-1} which may be due to the NH_2 bending vibration[32]. In the complexes $[Pt(L–H^+)X]_n$, however, the highest band is observed near 1630 cm^{-1} and was not removed upon deuteration. Therefore, this is a strong evidence of deprotonation of the NH_2 group in these complexes. The 1630 cm^{-1} band is surely then due to the skeletal vibration which is not affected on deuteration. The general ir behavior, therefore, strongly indicates the presence of an imino group and its participation in bonding with platinum. The νN–O stretching frequency may be assigned to a band near 1210 cm^{-1} in the free ligand. In the complexes a band is observed near 1195 cm^{-1} which may be due to the same motion. The band at 322 cm^{-1} is assigned to the Pt–Cl stretching in the chloro complexes since it is absent in the ir spectrum of the bromo analogs. The relatively low value of this band may indicate the presence of bridging chlorine structures[33]. The dimeric chlorine bridging structure is shown below:



cis or *trans*

Similar polymeric structures may be written. In addition, a dimeric or polymeric structure in solution involving the N_1–O atom and the NH^- group may be possible[27,28]. Previous studies, however, have shown that the N_7 site is the most favored bonding site in adenosine[3–6] and adenosine-1-oxide[7]. The complex $[Pt(L–H^+)Cl]_n$ reacted with ethylenediamine to give a water soluble complex according to the reaction:

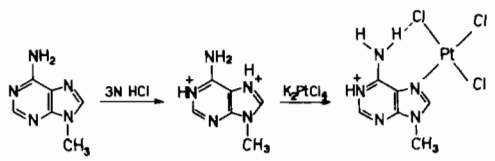
$$[Pt(L–H^+)Cl]_n + n(en) \rightarrow n[Pt(L–H^+)en]Cl$$

The platinum content of this complex fitted the above formula and the complex was found to be a 1:1 electrolyte in water (Table II). The color of the complex was green, like the starting material, indicating retention of the Pt–Pt interaction.

9-Methyladenine

In the hope to form crystalline compounds for X-ray single crystal diffraction work the reaction of K_2PtCl_4 with 9-methyladenine was attempted. This ligand does not have the sugar group, but the 9th position is occupied by a methyl group. Equimolar solutions of K_2PtCl_4 and this ligand were allowed to stand at room temperature in 3*N* HCl solution for 2 to 3 days. Slowly yellow triclinic crystals were obtained. Chemical analysis agreed with the formula, $[PtCl_3$(9-methyladenineH)] (Table II) and the structure was shown[20] to have two molecules per unit cell.

Experiments in 0.1*N* HCl gave a yellow compound with a platinum content fitting the formula, $[PtCl_2$(9-methyladenine)$]_n$. A polymeric bridging structure, where Pt is coordinated through N_1 and N_7 of the purine ligand may be possible in this case just as in the Co complexes[18]. This polymeric insoluble compound was not investigated further. In the 3*N* HCl solutions it seems that the N_1 position is preferentially protonated and bonding takes place only at the N_7 position, as follows:



Similar complexes for adenine and guanine have been reported[16,19] with Zn(II) and Cu(II) together with their X-ray structures. The nmr spectra of these two metal complexes have also been reported[34] and adenosine gave a similar compound in weak acidic aqueous solutions.

The ir spectra are consistent with the crystal structure of 9-methyladenine platinum complex.

In an ir study of a single crystal of 9-methyladenine Kyogoku and collaborators[35] assigned the 1677 cm^{-1} band to the NH_2 scissoring motion. In a KBr disk of the free base this band is shown at 1662 cm^{-1}. In the complex there is a band at the same frequency and in the partially deuterated derivative there is a strong shoulder at 1663 cm^{-1} with a maximum at 1648 cm^{-1} (see Figure 4). In the deuterated 9-methyladenine[35] (ND_2) the first band occurs at 1600 cm^{-1} which is the ring stretching. Therefore, the 1646 cm^{-1} band (ring stretching) in the $[PtCl_3$(9-methyladenineD)] indicates the protonation of the purine ring at N_1, because it shifts to higher frequencies, as in the case of purine[36] and 6-mercaptopurine riboside complexes of platinum[37]. The insolubility of the complex in suitable organic solvents did not permit us to study it in solution.

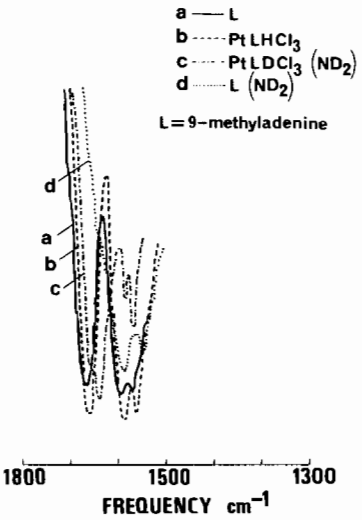


Figure 4. The ir spectra of 9-methyladenine and its platinum complex in the 1600 cm^{-1} region; a —— L = 9-methyladenine, b ---- $PtLHCl_3$, c – · – · – · – $PtLDCl_3$ (ND_2) and d · · · · L (ND_2).

Experimental

Materials

Adenosine and adenosine-1-oxide were purchased from Raylo Chemicals Ltd. and 9-methyladenine from Cyclo Chemicals Inc. All nucleosides were used without further purification.

Potassium tetrachloroplatinate(II) and potassium bromoplatinate(II) (20% aqueous solution) were from Johnson Matthey and Mallory Ltd. The aqueous or acid solutions of the platinum salts were filtered before use.

Triacetyladenosine was synthesized from adenosine by the method of Bredereck[23].

Preparation of the Complexes

Bis(triacetyladenosine)dichloroplatinum(II), $Pt(TAA)_2Cl_2$

The amount of 1 g (2.5×10^{-3} mol) of triacetyladenosine was dissolved in 70 ml of CH_3CN and to this 0.264 g (6.2×10^{-4} mol) of K_2PtCl_4 in 30 ml of water were added. After 24 hours the color of the solution was yellow and there appeared a yellow solid compound, which was filtered and washed with water and acetone and then with small quantities of ether. The filtrate was evaporated in the fume hood to dryness and the residue was partially soluble in acetone. This was added to the initial precipitate. The procedure was repeated, until no residue insoluble in acetone was left. It was dried at 110° C under vacuum. Yield 25–40%. The deuterated complex $Pt(TAA\text{-}d_8)_2Cl_2$ was prepared in the same manner using TAA-d_8.

Bis(triacetyladenosine)dibromoplatinum(II), $Pt(TAA)_2Br_2$

1 g (2.5×10^{-3} mol) of the ligand and 0.377 g (6.2×10^{-4} mol) of K_2PtBr_4 were stirred in a solution of $CH_3CN:H_2O = 7:3$ (100 ml). The previous procedure was then followed. Yield 30–40%.

(Adenosinato-1-oxide)chloroplatinum(II), $[Pt(A\text{-}1\text{-}O\text{-}H^+)Cl]_n$

In this preparation, 0.250 g (8.7×10^{-4} mol) of the base and 0.366 g (8.7×10^{-4} mol) of K_2PtCl_4 were mixed for 6 to 8 hours in 100 ml of water at 50° C. The initial pH was 5.5 and the final pH was about 2.6. The light green colored product was filtered off by suction, washed with water, alcohol and ether and dried at 110° C under vacuum in the presence of NaOH. Yield: quantitative. When the reaction was carried out at room temperature it took longer time and gave lower yields.

(Adenosinato-1-oxide)bromoplatinum(II), $[Pt(A\text{-}1\text{-}O\text{-}H^+)Br]_n$

0.250 g (8.7×10^{-4} mol) of the base were dissolved in 100 ml of water at 50° C with 0.523 g (8.7×10^{-4} mol) of K_2PtBr_4 or 0.26 ml of a 20% solution of the salt in water, 1:1, were added. Following the same procedure as above the final product was isolated in quantitative yield.

(9-methyladenine)trichloroplatinum(II), $[Pt(9\text{-}methyladenineH)Cl_3]$

In a typical preparation, 0.05 g (3.3×10^{-4} mol) of the base and 0.139 g (3.3×10^{-4} mol) of K_2PtCl_4 were mixed for 5–7 hours in 10 ml of 3*N* HCl. Yellow crystals were separated from the solution. The reaction was complete in a week. The crystals were separated by filtration and washed with small quantities of water, alcohol and ether. Then they were dried at room temperature under vacuum in the presence of $CaCl_2$. *Yield* ≃90%. Single crystals were picked-up from this batch for X-ray crystal determination.

Using molar proportions of base : metal (2:1) in 0.1*N* HCl a yellow complex was obtained, the platinum content of which corresponded to the formula, $[PtCl_2$ (9-methyladenine)$]_n$ (Calculated = 47.00%; found = 47.56%).

Deuterated Products

Adenosine-d_8, triacetyladenosine-d_8 and 9-methyladenine (D_8-, $-ND_2$, $-CD_3$)

These derivatives were prepared by treating 0.1–0.2*M* of the base with D_2O (adenosine-d_8 and deuterated 9-methyladenine). Triacetyladenosine-d_8 was treated with $CD_3CN:D_2O = 2:8$ for 2 to 4 days at 70–80° C under vacuum in a sealed tube. The end of the reaction was determined by taking nmr spectra until the peak due to the H_8 proton completely disappeared.

Nmr Spectra

Nmr spectra of mixtures of adenosine and adenosine-d_8 and K_2PtCl_4, in molar proportions (2:1, 1:1, 1:2), were obtained.

0.1 g (3.8×10^{-4} mol) of adenosine or adenosine-d_8 were dissolved in 1 ml of 0.3*N* DCl and to this the corresponding amounts of K_2PtCl_4 for molar proportions (2:1, 1:1, 1:2) were added. The reactions were followed by taking the nmr spectra of the reaction mixtures in intervals of 30 minutes to 1 hour each time. All the reactions were complete in 4 to 5 hours.

Microanalyses

a) SCHWARZKOPF Micro-analytical Laboratory (U.S.A.); b) CHEMALYTICS, Inc. (U.S.A.).

Conductivity Measurements

The conductivity of the compounds was obtained by using an E365B conductoscope, Metrohm Ltd., Herisau, Switzerland.

Melting Points

The melting points were determined on a Fisher John's melting point apparatus and are uncorrected.

Nmr Spectra

The nmr spectra were taken with a Varian T60 high resolution spectrometer. TMS was used as internal reference.

Ir Spectra

The ir spectra were recorded using a Perkin–Elmer 621 spectrophotometer calibrated with polystyrene. The spectra were recorded in KBr disks. The positions of the absorptions are given within ± 2 cm^{-1}.

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