The Synthesis and Characterisation of some Xanthine Complexes: Evidence for the Existence of Oxygen Involvement using O(6) and O(2)

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Abstract

Complexes containing the methylxanthine ligands, 1-methyl, 3-methyl, 7-methyl, 8-methyl and 9-methylxanthine have been prepared, with the platinum metals platinum(II), rhodium(III) and palladium(II). The resulting complexes are characterised using infrared spectroscopy, ESCA and thermal analysis. Coordination through the ring nitrogen and the exocyclic oxygens, O(2) and O(6), is demonstrated.

Introduction

The interaction of nucleic acids and their constituents has been widely reported in recent years [1–5] since the discovery that certain platinum complexes exhibited anticancer activity [6]. Complexes containing the pyrimidine bases uracil and their thioderivatives [7], thymine [8] and cytosine [9], have been the subject of several studies in an attempt to determine their mode of binding to metal ions. In the purine bases attention has been focused on adenine (Ad) and guanine (Gu) [10–12] as these are major constituents of DNA and RNA, and because guanine has been shown to be one of the most reactive sites of DNA and interacts selectively with platinum antitumor drugs [13, 14]. Complexes of the type $[PtCl_2L(H_2O)_n]$ where L = Ad, Gu, were prepared recently and shown to react through the heterocyclic nitrogen atoms [15]. Other complexes involving guanine have lead to some controversy over whether the actual binding atom was N-7 [16] or whether it was bidentate through N-7, O-6 [17], or bound by other atoms entirely [18]. NMR studies using the model nucleobase 9-ethylguanine [19] showed that platinum is coordinated to N-7 and this reduces base specificity, by affecting hydrogen bonding between the base pairs.

Xanthine is a purine base which occurs as a minor constituent in tRNA. The crystal structure of neutral xanthine has not been reported [3] but methyl-substituted derivatives of these bases can be used as models for other bases. Theophylline (1,3-dimethylxanthine) has been used as a model for guanosine [20]. Alkylation of the xanthine ring limits the number of possible binding sites and increases the solubility of the ligand. Complexes of a series of alkylated xanthine derivatives in which ruthenium(II) and ruthenium(III) are bound to N-7 or C-8 were prepared [21] while the cobalt complex bis(dimethylglyoximate)xanthinato(tri-n-butylphosphine)-cobalt(III) possessed an N-9 coordinated xanthine with protonated N-1 and N-3 nitrogens [22]. The presence of an alkyl group at N-3 presents considerable steric hindrance to coordination at N-9 by large metal ions such as those in the second and third row transition metal block [23, 24]. Consequently, in caffeine, (1,3,9-trimethylxanthine) where the N-7 is also blocked, the ruthenium coordinates through the C-8 position [24] as expected by analogy to the ruthenium–imidazole complexes [25]. Mixed ligand complexes of xanthosine of the composition $[Pt(N)_2L_2]$ where L is xanthosine or other nucleoside, and N is a nitrogen donor ligand, have been reported and shown to be bound at N-7 [26, 27]. Other xanthine complexes with rhodium and iridium [28], and palladium [29] were reported, together with their infrared spectra. There has recently been a study of some N-methyl substituted xanthines with copper(II) [30], and of some xanthine, hypoxanthine and guanine complexes with the same metal [31]. The most likely binding sites in caffeine and theophylline were thought to be the N-9 and N-7 imidazole nitrogens, while theobromine possessed N-1 and N-9

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binding sites. Bidentate bridging involving the N-9 and N-7 or N-3 nitrogens was reported as likely for xanthine and hypoxanthine [31] based on spectral and magnetic measurements. No evidence was found to suggest that the O-6 was also used in binding in these latter cases, although previously chelation through N-7, O-6 in a theophyllinato complex of copper [32], and tridentate coordination with Pt(IV) through O-6, N-7 and N-9 was suggested [33]. With Pt(II) and Rh(II) however, the complexes were terminal unidentate type with a neutral theophylline ligand bound through the imidazole N-9 position [34, 35]. Palladium complexes involving solely nitrogen coordination have also been reported recently [36].

We previously reported a platinum(II)-(9-methylxanthine) complex utilizing the N(7), O(6) positions [37], and in this paper we wish to report the formation and characterisation of a series of N-methyl substituted xanthines and present data to suggest that the O-6 position and the O-2 positions can both be used in coordination.

Experimental

Chemicals and Reagents

Samples of 1-methylxanthine, 7-methylxanthine and 9-methylxanthine were obtained from Fluka AG Chem Fabrik CH-9470 Buchs. 3-methylxanthine was obtained from Aldrich Chemical Company Inc. *Cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ were obtained from Johnson-Matthey Chemicals. All the chemicals were used without further purification. $[Pd(NO_2)_2(NH_3)_2]$ was synthesized following the procedure used by Cull and Johassen [38].

Analytical Studies

(i) Infrared Spectroscopy–Infrared analysis spectra were recorded on a Perkin-Elmer 567 spectrometer by preparing CsI discs (4000–200 cm^{-1}), or using a nujol mull with KBr disc (4000–400 cm^{-1}).

(ii) Microanalyses of C, H and N were performed by the Microanalytical Laboratory of the National University of Singapore, using the PE 240 Auto Analyser. Cl was determined using Cheng's method where the absorbing medium was first passed through a zerolite 236 ion exchange column to remove the metal and then titrated with $Ba(ClO_4)_2$ using thorin as the indicator.

(iii) Thermogravimetric studies were performed using a Perkin Elmer (TGS-1) thermobalance and a Perkin-Elmer temperature programmer (UU-1). The complex, $[Pd(NH_3)_2(9mxa)_2]$, was analysed at four different heating rates, in static air.

Synthesis of Complexes

The complexes prepared, their colours and their binding sites are listed in Table I. Probable deprotonation sites, based on the pK_a values of the methylxanthine bases, are also given.

Preparation from cis-[Pt(NH$_3$)$_2$Cl$_2$]

0.072 g (0.23 mmol) of *cis*-$[Pt(NH_3)_2Cl_2]$ was reacted with 9.6 ml of 0.05 M $AgNO_3$ solution. The white AgCl precipitated was filtered using a sintered glass funnel previously coated with $BaSO_4$. 0.16 g (0.96 mmol) of 9-methylxanthine and 9.6 ml of 0.05 M NaOH solution were then added to the clear filtrate. The mixture was kept in a stoppered flask for 2 days at 65 °C. The solution was then heated to 95 °C to complete the reaction. The white precipitate obtained was filtered off and dried in a desiccator, and analysed as $[Pt(NH_3)_2(9mxa)]Cl$.

Preparation of complexes from trans-[Pt(NH$_3$)$_2$Cl$_2$]

(a) The above procedure was repeated using *trans*-$[Pt(NH_3)_2Cl_2]$ instead of *cis*-diamminedichloro-

TABLE I. Prepared Complexes, their Binding Sites and Colours.

Complex Formulae	Binding Site	Deprotonation	Colour
$[Pd(NH_3)_2(1mxa)_2]$	N(9)	N(9)	orange
$[Rh(1mxa)_3Cl_3]$	N(9) or (7)		pink orange
$[Pd(3mxa)_2Cl_2]$	N, O(2)		yellow
$[Pt(NH_3)_2(3mxa)_2]$	O(2)	N(9)	yellow
$[Pd(NH_3)_2(7mxa)_2]$	N(9)	N(1) or (3)	yellow
$[Pd(NH_3)_2(7mxa)]_2$	N(1), O(6)	N(1), N(3)	yellow
$[Pd(7mxa)_2]Cl_2 \cdot H_2O$	N(1 or 3) and O(2)		fawn
$[Pd(NH_3)_2(8mxa)_2]$	N, O(6)		yellow
$[Pd(NH_3)_2(8mxa)]_2$	O(6), N(7)	N(1), N(9)	yellow
$[Pd(NH_3)_2(9mxa)_2]$	N(7)	N(1) or N(3)	yellow
$[Pd(NH_3)_2(9mxa)]_2$	O(6), N(7)	N(1) or (3)	brown yellow
$[Pt(NH_3)_2(9mxa)_2]$	N(7)	N(1), N(3)	yellow
$[Pt(NH_3)_2(9mxa)]Cl$	O(6), N(7)	N(1) or (3)	yellow

platinum(II). The product obtained was filtered off and left to dry in a desiccator. It was analysed as $[Pt(NH_3)_2(9mxa)_2]$.

(b) 0.149 g (0.897 mol) of 3-methylxanthine and 0.27 g (0.897 mmol) of *trans*-$[Pt(NH_3)_2Cl_2]$ were put into a 50 ml round-bottomed flask. 36 ml of water and 9 ml of ethanol were transferred into the flask. The mixture was refluxed with stirring for about 1 day. It was then distilled to remove excess solvent. The concentrated solution in the flask was left to cool. The substance that was precipitated out was filtered off as white, flaky solid. It was left to dry in a desiccator, and analysed as $[Pt(NH_3)_2(3mxa)_2]$.

Preparation of $[Pd(NH_3)_2(mxa\text{-}H)_2]$

0.05 g (0.30 mmol) of either 1-, 3-, 7-, 8- or 9-methylxanthine was added to 5 ml of ethanol and a slurry was obtained. 0.035 g (0.15 mmol) of $[Pd(NO_2)_2(NH_3)_2]$ was dissolved in 5 ml of ethanol and added to the slurry. The mixture was heated at 50 °C for 40 min, and on cooling a precipitate was obtained which was dried in a desiccator.

Preparation of $[Pd(NH_3)_2(mxa\text{-}2H)_2]_2$

0.05 g (0.30 mmol) of either 7-, 8- or 9-methylxanthine was added to 5 ml of ethanol. To this slurry an excess (>0.07 g) of $[Pd(NO_2)_2(NH_3)_2]$ was added and the mixture refluxed at 50 °C for 40 min. Again the mixture was cooled and filtered by suction, and dried in a desiccator.

Preparation of $[Pd(mxa)_2Cl_2]$

0.05 g (0.30 mmol) of either 3- or 7-methylxanthine was added to acidified ethanol and stirred for about 5 min before adding 0.05 g (0.28 mmol) of $PdCl_2$ previously dissolved in an hot water/ethanol solution. Heating the 3-methylxanthine and the $PdCl_2$ at 40 °C for about an h was necessary before a precipitate was formed on cooling, but in the case of 7-methylxantine a yellow precipitate formed immediately. In both cases the yellow precipitate was filtered and dried.

Preparation of $[Rh(1mxa)_3Cl_3]$

0.197 g (0.75 mmol) of hydrated rhodium trichloride was dissolved in ethanol and stirred for 5 min and then an excess of 1-methylxantine was added and the solution was heated for about one h. On cooling a red precipitate was formed which was filtered and dried.

Results and Discussion

Infrared Studies

The assignments in the infrared were obtained from a comparison of the previous data available and from our own studies on the methyl-substituted xanthines. Deuteration of 1-methylxanthine and 9-methylxanthine helped to elucidate the positions of the N–H peaks. The problem of the individual assignments for the carbonyl stretching frequencies proved more difficult. The identification of the ν(C(6)=O) and ν(C(2)=O) has largely been ignored in the literature [29, 30, 31, 36, 39]. From a comparison with the analogous dioxopyrimidine base, uracil [40], the assignments would give the ν(C(6)=O) at lower wavenumber, at about 1675 cm^{-1}. However, other authors have suggested the band at about 1720 cm^{-1} is responsible for this particular carbonyl stretching frequency [41], from a comparison with the guanine spectrum where a single carbonyl at the C(6) position gives a single peak at about 1715 cm^{-1}. It has been conceded that the addition of methyl groups to the ring structure of uracil will give rise to complications and the assignment of the carbonyl positions in thymine was not so easily resolved [42, 43], and the reverse assignments were thought to be possible [42]. The comparison of 1-methyl, 3-methyl, 7-methyl, 9-methyl and 1,3,9-trimethyl-xanthine and their deutero-analogues has led us to the conclusion that ν(C(6)=O) and ν(C(2)=O) occur at 1720 cm^{-1} and 1675 cm^{-1} respectively. This is in agreement with the assignments for guanine and the only other assignment we have found in the literature [41]. Our assignments in the 1800–1500 cm^{-1} range are given in Table II.

The assignments for the other regions in the spectra follow closely those used recently [30, 31] although additional assignments of N–H peaks are possible resulting from our deuteration studies. The infrared spectra of 1-methylxanthine and its deutero-analogue are shown in Fig. 1. The major regions of change are:

For 1-methylxanthine:

(i) 2898 cm^{-1}: this strong band is probably due to ν(N–H) and appears at 2370 cm^{-1} in the deuterosample.

(ii) 1560 cm^{-1}: this strong band is absent in the deuterosample and is likely to be due to [ν(C=C), ν(C=N) and mainly δ(N–H)] composite bands.

(iii) 1485 cm^{-1}: this strong band which is due to ν(C=C), ν(C=N) and δ(N–H) is shifted to a strong band at 1192 cm^{-1} in the deuterosample.

(iv) 1448 cm^{-1}: this strong band which may be due to δ(N–H) shows up at 1100 cm^{-1} in the deuterosample.

(v) 1390 cm^{-1}: this strong band appears at 1055 cm^{-1} as a strong band in the deuterosample. It is probably due to $\delta(N^3–H)$.

(vi) 1148 cm^{-1}: this strong band is assigned to ω-[Im(N–H)] and appears in the deuterosample at 862 cm^{-1}.

TABLE II. Major Infrared Assignments for N-Methylxanthines.

Assignment	1-MeXa	3-MeXa	7-MeXa	8-MeXa	9-MeXa	1,3,9-TriMeXa	Caf.[a]
$\nu(C^6{=}O)$	1725s(sp)	1720sh	1715m		1720vs		
	1720m						
		1705s			**1705s(sp)**	1700s	1702s
$\nu(C^2{=}O)$ and	1675sh	1690sh	1680s	1690sh	1695w(sp)		
ν(C=C) and	1640sh(b)			1675w(sp)		1663s	1667s
ν(C=N)	1625s						
	1650sh				**1665s(sp)**		
	1615s						
ν(C=C) and		1600s	1600m	1605m	1600m	1592s	1605s
ν(C=N) and	1560s(sp)	1560s	1570s(sp)		1570s(sp)		
$\delta(N^3{-}H)$						1548s	1548s
	(absent)				**1600m**		
					1560s(sp)		
			1508s(sp)				
	1485s	1472m	1475w	1470s(sp)	1460m(sp)	1470s(sp)	1477m
							1460s
	1460m				**1465s(sp)**		
$\delta(N^{1,3}{-}H)$	1448s	1445m	1445s(sp)		1435m	1445m	1445m
and ν(C–N)		1425m(sp)	1425w	1425s(sp)		1430m	
and ring	**1425m**				**1435sh**		
vibrations							
						1405s	
$\delta(N^3{-}H)$ and	1390s			1392m(sp)	1385m	1390s	1380s
ring	(absent)		1375s	1360s	1372m		1368m
vibrations	**1342m**		1350s		**1385w**	1350m	
			1320s	1335s	1338m	1335s	1335w
	1310m	1310s			1324m	1310s	
					1305s		
ω(N–H)	1275s	1285s	1270s	1270s	1260s		1283w
	1267sh				(absent)		
	1252s				**1240s**		
	1250s			1240m		1245s	1236m
	1220sh						
	1209s	1218s	1210s(sp)		1216w		1210w
		1200s					
	1192s				**1190w**		
					1190s		
		1168s	1175w		1185s	1185w(sp)	1183w
	1172sh				**1172w**		
ω[Im(N–H)]	1148s(sp)		1138s(sp)	1150s			1140w
and ring	(absent)						
vibrations						1115s(sp)	
	1100s						
					1070w		
		1056w	1080s		1070s	1065s	1070w
	1055s				**1055s**		
					1052s	1050s	
	1030m				**1018m**		
	1023s				1010s		1011w
	1010m		1005s				
		980s			998s	980s	

[a] Figures for caffeine are taken from ref. 30. Deuterated samples are shown in **boldface**.

Similarly for 9-methylxanthine:

(i) 1435 cm^{-1}: this band of medium intensity is probably due to δ(N–H) and appears in the deuterosample at 1070 cm^{-1}.

(ii) 1260 cm^{-1}: this strong band is likely to be due to ω(N–H). It appears at 960 cm^{-1} in the deuterosample as a weak band.

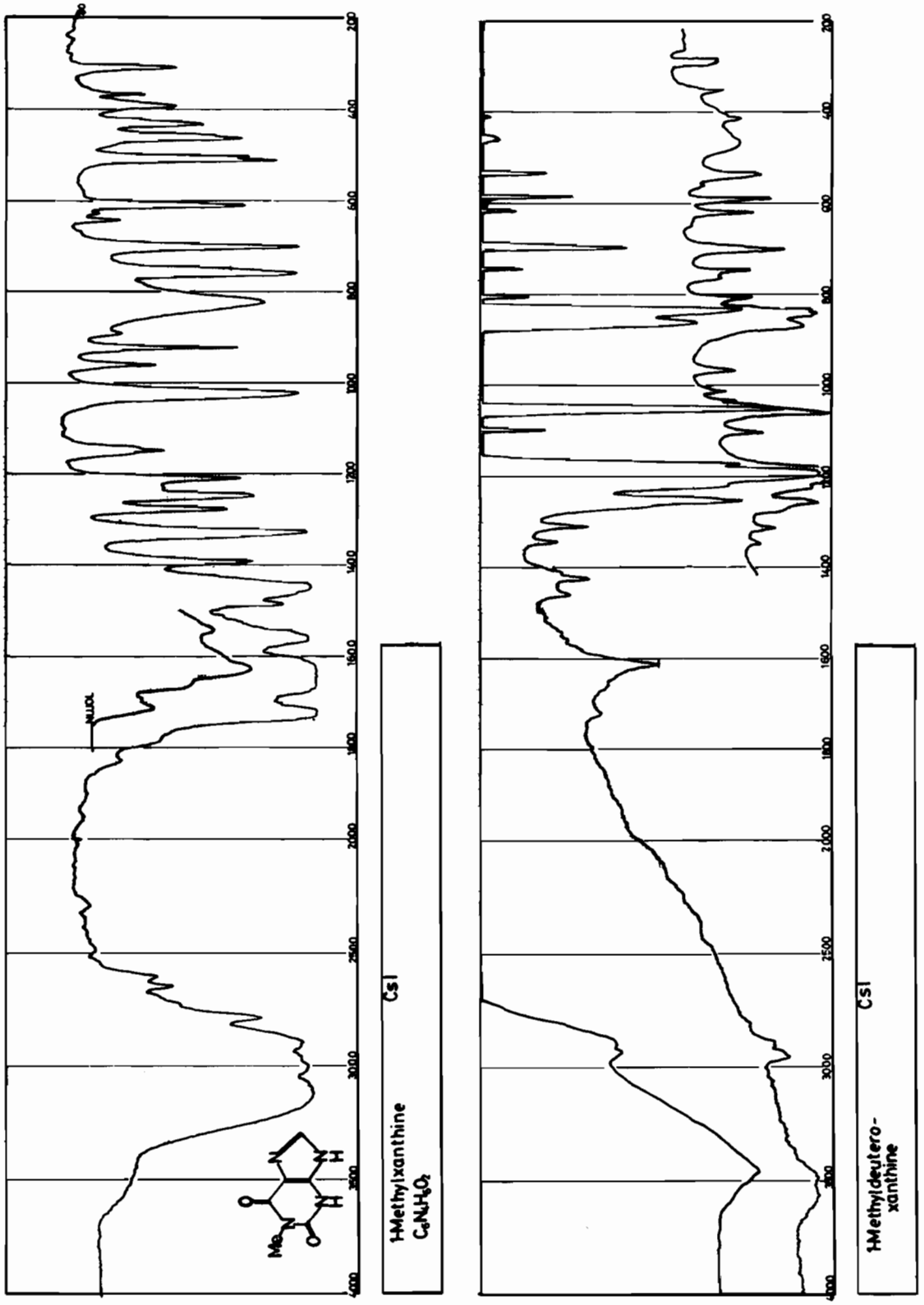

Fig. 1. Infrared spectra of 1-methylxanthine and its deuterated analogue.

(iii) 1190 cm^{-1} and 1185 cm^{-1}: these strong bands are very much reduced in intensity and they appear as a weak split band at about 885 cm^{-1}. They are likely to be due to ω(N–H).

(iv) 998 cm^{-1}: this is found at 760 cm^{-1} in the deuterosample and is assigned to ω[Im(N–H)].

Complexes of 1-methylxanthine

The complexes prepared were $[Rh(1mxa)_3Cl_3]$ and $[Pd(NH_3)_2(1mxa)_2]$. The infrared spectrum of the rhodium complex showed very little change in the carbonyl region but the reduction in intensity of the bands at 1560 cm^{-1} and 1148 cm^{-1} indicates the involvement of an imidazole nitrogen. Additional bands at 320 cm^{-1} and 292 cm^{-1} suggest the *mer*-tris(-1-methylxanthine)trichlororhodium(III) complex. A similar spectrum is observed in the palladium complex and nitrogen coordination seems most likely, although the actual nitrogen involved is not certain. It would be reasonable to assume an imidazole nitrogen is involved, as in the rhodium complex. In this case deprotonation at N(9) would be followed by coordination at this site.

Complexes of 3-methylxanthine

The complexes prepared were $[Pd(3mxa)_2Cl_2]$ and $[Pt(NH_3)_2(3mxa)_2]$. In both complexes the lower carbonyl band is reduced by about 30 cm^{-1}. This implies some involvement of the O(2) position in coordination, which is surprising in view of the close proximity of the methyl group. Rearrangement in the palladium complex is necessary to accommodate coordination and this is apparent from the shifts in the ring frequencies that occur at about 1600 cm^{-1}, 1565 cm^{-1}, 1472 cm^{-1}, 1425 cm^{-1}, 1320 cm^{-1}, 1285 cm^{-1}, 1218 cm^{-1}, 1200 cm^{-1} and 1165 cm^{-1} [30]. The possibility of N-coordination is another alternative, and in this case there is the additional possibility of hydrogen bonding between the ammine group and the O(6) atom.

Complexes of 7-methylxanthine

Two of the palladium complexes prepared were the monomeric $[Pd(NH_3)_2(7mxa)_2]$ and the dimeric $[Pd(NH_3)_2(7mxa)]_2$. Diamminebis(-7-methylxanthinato)palladium(II) (Fig. 2) shows very little difference in the carbonyl region, with a broad absorption extending over the complete range of 1715–1685 cm^{-1}. By contrast bis(diammine-μ-7-methylxanthinatopalladium(II)) shows a marked shift to lower wavenumber in this region, indicating the involvement of C(6)=O. One of the nitrogens is involved in the bonding as well since there are shifts in the ring frequencies. The peak at 1575 cm^{-1} due to the composite [ν(C=N) and ν(C=C) and δ(N–H)] is very much reduced, indicating the considerable rearrangement that takes place on double-deprotonation. The two bands at 1475 cm^{-1} and 1445 cm^{-1} in the ligand were greatly reduced in intensity, and shifted by over 40 cm^{-1}. Several additional bands occurring between 450 cm^{-1} and 200 cm^{-1} have been assigned as ν(M–L) bands, Table III. The bis(-7-methylxanthine)-

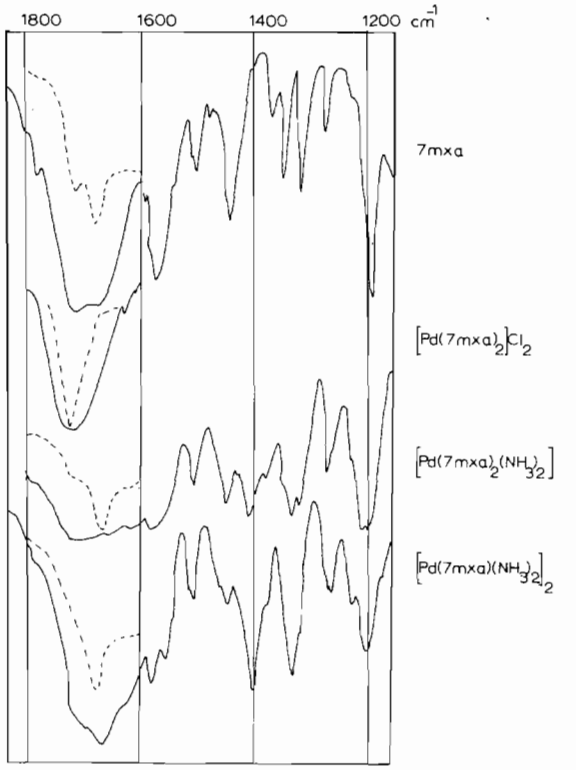

Fig. 2. Infrared spectra in the 1800 cm^{-1} to 1200 cm^{-1} region for 7-methylxanthine and its palladium complexes.

TABLE III. Far Infrared Frequencies for the Metal Complexes.

Complex Formulae	(cm^{-1})
$[Pd(NH_3)_2(1mxa)_2]$	309(s)
$[Rh(1mxa)_3Cl_3]$	355(sh), 340(m), 330(m), 320(sh), 309(s), 292(s), 282(s)
$[Pt(NH_3)_2(3mxa)_2]$	300(s)
$[Pd(NH_3)_2(7mxa)_2]$	343(sh), 323(m), 292(w), 270(s)
$[Pd(NH_3)_2(7mxa)]_2$	355(w), 320(s), 295(w), 255(s)
$[Pd(7mxa)_2]Cl_2 \cdot H_2O$	350(s), 308(w), 292(w), 270(s), 248(s)
$[Pd(NH_3)_2(8mxa)_2]$	382(s), 305(s)
$[Pd(NH_3)_2(8mxa)]_2$	382(s), 305(s, split)
$[Pd(NH_3)_2(9mxa)_2]$	423(w), 340(w), 330(w), 305(s), 255(w), 246(w), 232(w)
$[Pd(NH_3)_2(9mxa)]_2$	305(s)
$[Pt(NH_3)_2(9mxa)_2]$	305(w), 245(w), 205(w)
$[Pt(NH_3)_2(9mxa)]Cl$	285(w), 220(w)

palladium(II) chloride complex prepared from palladium dichloride, shows further evidence of the ambidentate behaviour of the xanthines as ligands. The carbonyl stretching frequency at 1680 cm^{-1}, due to C(2)=O, disappears, the only peak remaining is at 1715 cm^{-1}, due to the C(6)=O group. The ligand also utilises one of the nitrogen atoms since the ESCA clearly shows considerable nitrogen involvement, and we have therefore suggested the pyrimidine nitrogen as the most likely site of coordination (Fig. 3). Peaks at 270 cm^{-1} and 350 cm^{-1} have been assigned to metal–ligand interactions.

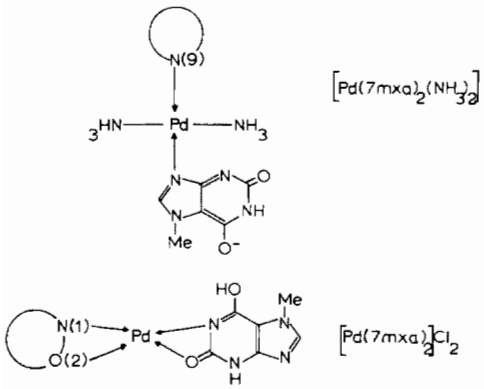

Fig. 3. Proposed structures for diamminebis(-7-methylxanthinato)palladium(II) and bis(-7-methylxanthine)palladium(II) chloride.

Complexes of 9-methylxanthine

Four complexes were prepared involving this ligand. Of the two platinum complexes, $[Pt(NH_3)_2(9mxa)_2]$ and $[Pt(NH_3)_2(9mxa)]Cl$, the latter complex has been discussed previously as a good example of the involvement of the carbonyl group in coordination [37]. The main regions of change in the spectrum of 9-methylxanthine are 1750–1640 cm^{-1}, 1590 cm^{-1} and 1300–1100 cm^{-1}. The ν(C(6)=O) band to which the band at 1710 cm^{-1} in the spectrum is assigned, undergoes a very large shift. This is a clear indication of carbonyl interaction at the C(6)=O position. Small shifts in the pyrimidine ring δ(N–H) bands at 1460 cm^{-1} and 1435 cm^{-1} are apparent. The bands at 1605 cm^{-1} and 1570 cm^{-1} which contain the ν(C=C) and ν(C=N) components show a shift to higher wavenumbers and are split. This has been used to indicate that one of the ring nitrogens is being used in coordination to the metal [30, 44–46]. In addition, the ring vibrations at 1305 cm^{-1}, 1070 cm^{-1} and 1052 cm^{-1} show changes in their positions and are reduced in their intensities, while the N–H bands at 1260 cm^{-1}, 1190 cm^{-1} and 1180 cm^{-1} are also reduced. The existence of N(7)–O(6) coordination has been suggested previously on the basis of the occurrence of carbonyl stretching frequencies in the region of 1630 cm^{-1}, [18, 29, 43] and the split band in this region is probably due to both coordinated carbonyl and the (C=C) and (C=N) stretching modes. In the other complex, $[Pt(NH_3)_2(9mxa)_2]$, there is a lack of change in the carbonyl bands. The bands at 1600 cm^{-1} and 1570 cm^{-1} however are shifted to higher wavenumbers, 1620 cm^{-1} and 1595 cm^{-1} respectively and very much reduced in intensity. Since these bands contain the ν(C=C) and ν(C=N) components, the shift and reduction in intensity indicate that one of the ring nitrogens is being coordinated to the metal [30, 44–46]. The bands at 1460 cm^{-1} and 1435 cm^{-1} are very much reduced in intensity in the spectrum of the complex, suggesting deprotonation at N(1) or N(3). Since the carbonyl groups are not involved in coordination, N(7) involvement is probable. The palladium complexes are similar to those of 7-methylxanthine where both monomeric and dimeric complexes are formed, with the dimeric complex involving bridging xanthine. Diamminebis(-9-methylxanthinato)palladium(II) shows little change in the C(6)=O and C(2)=O bands. Reduction in the bands at 1460 cm^{-1} and 1435 cm^{-1} leaves them just visible and nitrogen interaction at N(7) is the most likely type of coordination. In the spectrum of the dimeric complex the broad band at 1720 cm^{-1} is reduced to a very sharp band at 1700 cm^{-1}. This indicates some interaction once again involving the carbonyl group(s). A near total collapse of the N–H bands and the reduction of the peak at 1600 cm^{-1} and shift to lower wavenumber are good indications of the rearrangement within the ring and further coordination involving one of the nitrogens, presumably N(7).

Complexes of 8-methylxanthine

As with 7-methylxanthine a monomeric monodeprotonated complex, $[Pd(NH_3)_2(8mxa)_2]$ and a dimeric double-deprotonated complex, $[Pd(NH_3)_2(8mxa)]_2$ were prepared. In the dimeric species, at least, carbonyl involvement is evident from the infrared spectra. The band is much broader in the complex, extending to 1620 cm^{-1} and this has been used previously to indicate the involvement of carbonyl coordination [18, 29, 43]. There are considerable changes in the nitrogen peaks also and a bridging complex involving O(6) and nitrogen seems most likely. The monomeric complex has a simpler carbonyl band, quite similar to the original ligand. Changes in the ring nitrogen indicate that coordination has occurred through one of the nitrogen atoms. However, as the carbonyl band is somewhat broader than in the original, carbonyl coordination and the existence of isomers cannot be discounted.

Thermogravimetry Studies

Previously we have shown the usefulness of thermal analysis in the determination of complex structures [7]. In the present study data from TG

studies were used to extract the activation energy of a decomposition reaction. Many methods are available in the literature for analysing such data. Only methods involving different heating rates (*e.g.* Ozawa [47] and Friedman [48]) can give the correct activation energy for cases of 'varying order'. However, the Friedman method requires first the determination of the rates of fractional conversion at each degree of conversion, while Ozawa's method makes direct use of the data from the thermogram. Hence, in our study of $[Pd(NH_3)_2(9mxa)_2]$, the Ozawa method was used [49].

$$\log F(C) = \log \frac{AE}{R} - \log \beta - 2.315 - 0.4567 \frac{E}{RT}$$

where T is the temperature in degrees absolute (K), A is the pre-exponential factor, R is the gas constant (8.314J mol^{-1} K^{-1}), C is the degree of decomposition, β is the heating rate and E is the activation energy.

The complex was subjected to heating rates of 5 °C min^{-1}, 10 °C min^{-1}, 20 °C min^{-1} and 40 °C min^{-1}. For each of these runs, a percentage weight loss versus temperature graph was plotted. The temperature for 40%, 50% and 60% decomposition was obtained from each of these graphs (Fig. 4).

In order to determine the activation energy, a plot of the logarithm of the heating rates (log β) against the reciprocal of the temperatures ($1/T$) for a fixed degree of conversion was made; the slope of the resulting straight line is $-0.4567\ E/R$ (Fig. 5). The results are as follows:

for 40% decomposition (line A), E = 1285 kJ mol^{-1}
for 50% decomposition (line B), E = 525.0 kJ mol^{-1}
for 60% decomposition (line C), E = 516.7 kJ mol^{-1}

Thus the activation energy for 40% decomposition (1285 kJ mol^{-1}) is much higher than for 50% and 60% decomposition (525.0 and 516.7 kJ mol^{-1} respectively). One explanation for the exceptionally high activation energy is the decomposition of the ligand prior to the decomposition of the complex. It is possible that it is the pyrimidine ring of the purine system that is ejected, and is followed immediately by the breaking away of the imidazole ring since the complex is unstable after the decomposition of the ligand. In fact, the loss of the pyrimidine ring will result in a percentage weight loss of 36.4%, (very close to the observed weight loss of 35.4%) and the energy required for this reaction is the sum of the energies for breaking a C–C bond and C–N bond. Since there are 2 ligands per molecule of the complex, this energy is about 1222 kJ mol^{-1} which is close to the activation energy determined for the 40% decomposition.

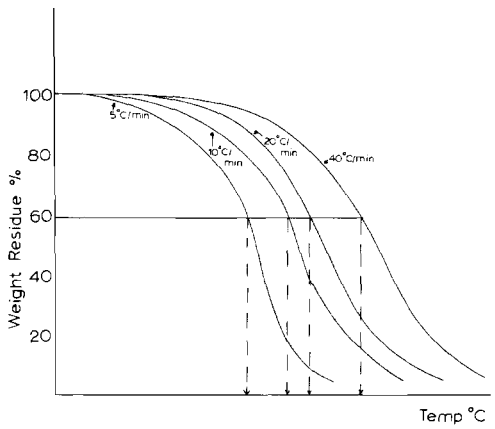

Fig. 4. The determination of the 40% decomposition temperatures for the complex $[Pd(NH_3)_2(9mxa)_2]$ at four heating rates.

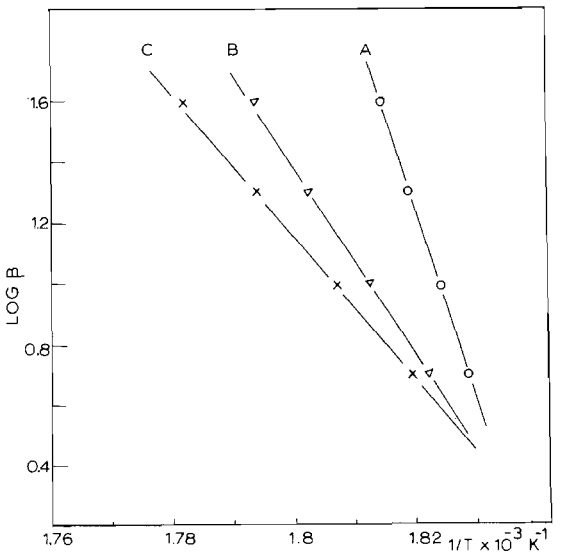

Fig. 5. Plot of log β (heating rate) against $1/T$ for the determination of activation energy based on Osawa's method.

The activation energies for 50% and 60% decomposition are very similar and would correspond to the energy required to break a Pd–N bond. The average of the 2 values is (525.0 + 516.7)/2 = 520.9 kJ mol^{-1}.

ESCA Studies

We have previously shown that coordination through the heterocyclic nitrogen atom in pyrimidine bases can be detected by the shift in binding energy and changes in the band widths [7]. The full study of the ESCA results will be published elsewhere, but using a similar procedure of measuring the change in binding energy on coordination, will indicate the extent of involvement of the nitrogen atom. The results for the N_{1s} binding energies measured are given in Table IV.

The spectra were referenced internally, to the C_{1s} peak at 285.0 eV. The apparent binding energies were measured from the spectra, and corrected by the dif-

TABLE IV. Differences Observed in the N_{1s} Binding Energies of the Complexes on Coordination (±0.2 eV).

Complex Formulae	N_{1s} Binding energy (eV)	Difference on coordination
1-methylxanthine	399.7	
$[Pd(NH_3)_2(1mxa)_2]$	400.4	0.7
$[Rh(1mxa)_3Cl_3]$	400.8	1.1
7-methylxanthine	399.8	
$[Pd(NH_3)_2(7mxa)_2]$	399.9	0.1
$[Pd(NH_3)_2(7mxa)]_2$	399.8	0.0
$[Pd(7mxa)_2]Cl_2 \cdot H_2O$	400.9	1.1
8-methylxanthine	400.0	
$[Pd(NH_3)_2(8mxa)_2]$	400.1	0.1
$[Pd(NH_3)_2(8mxa)]_2$	400.7	0.7
9-methylxanthine	400.0	
$[Pd(NH_3)_2(9mxa)_2]$	400.3	0.3
$[Pd(NH_3)_2(9mxa)]_2$	400.4	0.4

ference observed in the measured C_{1s} peak, and the standard value for the C_{1s} peak at 285.0 eV.

Those complexes without ammonia ligands show the clearest N_{1s} spectra. The best example is shown in Fig. 6, that of $[Pd(7mxa)_2]Cl_2$. On coordination, the change in N_{1s} binding energy of the ligand nitrogen is 1.1 eV. A similar change is also observed in the O_{1s} binding energy (531.0 eV to 531.9 eV), and neither this peak, nor the Cl_{2p} chlorine doublet at 199.8 eV and 198.4 eV shows any evidence of broadening. It is interesting to note that although the changes of the N_{1s} peaks in the complexes are often quite small, they are all to higher binding energy, and imply that nitrogen is involved in bonding. We are proceeding with the deconvolution of the spectra in order to isolate the component peaks. At the present time it is not possible to distinguish between the imidazole and the pyrimidine nitrogens as their binding energies are very close together.

In conclusion we have demonstrated that the methylxanthine ligand can coordinate using the O(6) and O(2) oxygens, as well as the already established ring nitrogen atoms. We also present evidence for the clear existence for N(7), O(6) bidentate coordination, as suggested by other authors for the mechanism of interaction of purine bases with platinum anti-cancer drugs.

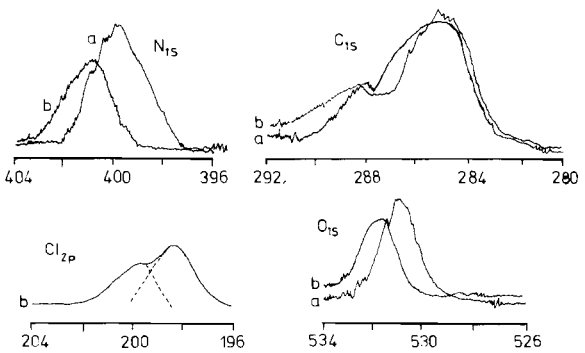

Fig. 6. The ESCA spectra of (a) 7-methylxanthine and (b) $[Pd(7mxa)_2]Cl_2$.

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