Platinum(II) Complex involving 9-Methylxanthine: Evidence for N(7), O(6) Interaction

JAMES R. LUSTY* and PUI FUN LEE

Department of Chemistry, National University of Singapore, Kent Ridge, Singapore 0511

Received November 17, 1983

The interaction of bases derived from nucleic acids, with transition metals has been widely reported in recent years [1–4]. In particular the purine bases adenine and guanine have received much attention [5–8]. Guanine has been shown to be one of the most reactive sites of DNA and interacts selectively with platinum antitumour drugs [9]. The xanthine bases occur as minor constituents in tRNA and methyl-substituted derivatives of this base have been utilised as model compounds for nucleosides [10]. Alkylation of the heteroatoms in the ring reduces the number of binding sites available. A recent report [11] has shown that in copper perchlorate complexes involving N-methylxanthines, caffeine (1,3,7-trimethylxanthine) coordinates through the N(9) while theophylline (1,3-dimethylxanthine) coordinates through the N(7) atom. Similarly for theobromine (3,7-dimethylxanthine) it was the N(9) or N(1) positions that were thought to be likely coordinating sites. Xanthine and hypoxanthine complexes of copper(II) were found to contain dimeric or polymeric species and involve purely nitrogen coordination [12]. Methylxanthine palladium complexes were reported to give N(9) coordination, deduced mainly from nmr evidence [13]. We wish to report here a platinum complex of 9-methylxanthine where the N(7) and O(6) positions are used to form a chelating monomeric complex.

Experimental

9-Methylxanthine was obtained from Fluka Chemicals and cis-diamminedichloroplatinum(II) was obtained from Johnson–Matthey Chemicals. Both were used without further purification.

0.072 g (0.23 mmol) of *cis*-diplatin was reacted with 9.6 ml of 0.05 *M* $AgNO_3$ solution. The white AgCl precipitated was filtered and 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 two 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. This method is adapted from the method described by Lippert [14]. The resulting white complex was impure and needed several recrystallisations to obtain a product that gave satisfactory analysis for $[Pt(NH_3)_2(9MXa)]Cl$. From the thermogravimetric analysis, run for both the impure and recrystallised samples, the impurity was identified as excess ligand.

Results and Discussion

9-Methylxanthine has available several sites for coordination. The ligand infrared is shown in Fig. 1. On coordination there are considerable differences in the spectrum, especially in the carbonyl stretching frequencies. The identification of the individual carbonyl peaks for C(2)=O and C(6)=O has been largely ignored in the literature [5, 11–13]. Some xanthosine complexes of copper were prepared and the ν(C(2)=O) and ν(C(6)=O) positions were assigned at 1690 cm^{-1} and 1712 cm^{-1} respectively [15]. We have been investigating the infrared spectra of several N-methylxanthine derivatives and their complexes, and have carried out deuteration studies on the ligands and we are in agreement with these assignments. This agrees with the single carbonyl frequency observed in guanine, which has ν(C(6)=O) at about 1715 cm^{-1}, although it is not entirely compatible with the order observed in the spectrum of uracil [17]. However, even the addition of methyl groups causes complications to the spectrum of uracil which are not easily resolved [17, 18], irrespective of the addition of the imidazole entity.

The major regions of change in the spectrum of the ligand are 1750–1640 cm^{-1}, about 1590 cm^{-1}, and 1300–1100 cm^{-1}. We have assigned the bands at 1710 cm^{-1} and at 1690 cm^{-1} (a shoulder on the main absorption) to ν(C(6)=O) and ν(C(2)=O) and it is the former band that undergoes the most dramatic change. It is reduced to a weak band in the complex. This is a clear indication of the existence of carbonyl interaction at the C(6)=O position. With the deprotonation of the ligand a single N–H remains, and we observe differences in this region of the spectrum. Small shifts are apparent in the pyrimidine ring δ(N–H) bands at 1460 cm^{-1} and 1435 cm^{-1} while the bands that contain the ν(C=C) and ν(C=N) components at 1605 cm^{-1} and 1570 cm^{-1} show a considerable shift to higher wavenumber, and are split. This has been used to indicate that one of the ring nitrogens is being utilised in the coordination to the metal [11, 19, 20, 21]. Other ring vibrations also undergo shifts and are often reduced in intensity. In particular the ring vibrations at 1305 cm^{-1}, 1260

---

*Author to whom correspondence should be addressed.

0020-1693/84/$3.00

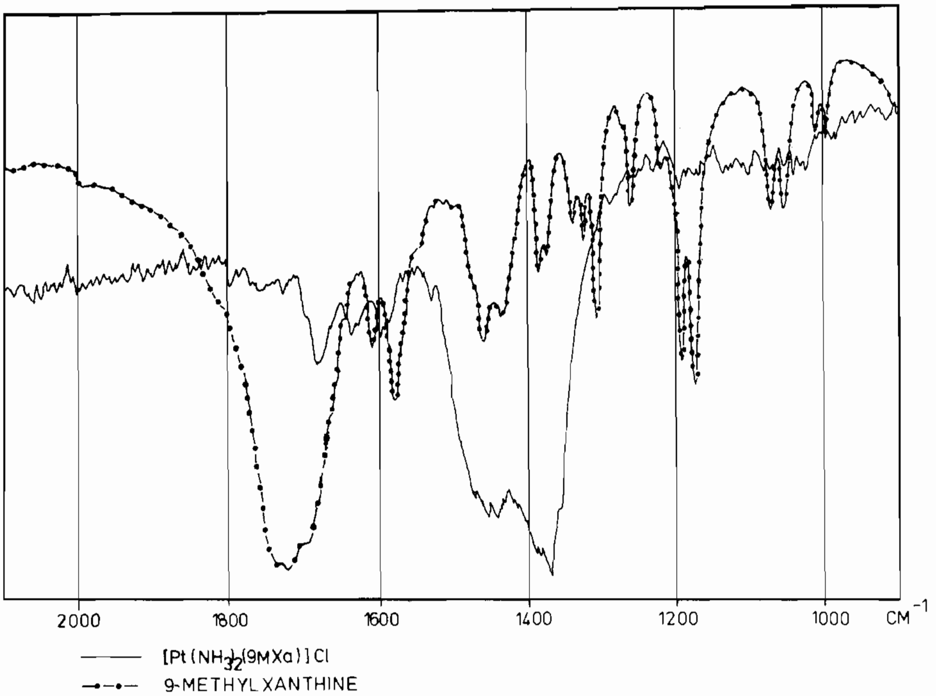

Fig. 1. Infrared spectra of 9-methylxanthine and the complex, [Pt(NH$_3$)$_2$(9MXa)]Cl.

cm^{-1}, 1190 cm^{-1}, 1180 cm^{-1}, 1070 cm^{-1} and at 1052 cm^{-1} show the greatest change in intensity and position. The existence of O(6), N(7) chelation has been suggested previously on the basis of the occurrence of carbonyl stretching frequencies in the region of 1630 cm^{-1} [5, 22, 23], and the split band in this region is probably due to both coordinated carbonyl and the (C=C) and (C=N) stretching modes. We have not assigned the ν(M–L) bands at present but additional complex bands at 600 cm^{-1}, 460 cm^{-1}, 430 cm^{-1} and 320 cm^{-1} could be due to metal–ligand stretching. The resulting complex would have the structure shown in Fig. 2. The N(3) proton is the more acidic of the two protons but the coordination of O(6) would be likely to influence the acidity of the neighbouring proton on N(1) and either of these sites is a possibility for deprotonation. The interaction of N(7) is expected since the N(9) site is blocked but chelation using the O(6) position as well was not apparent in the recently prepared copper complexes.

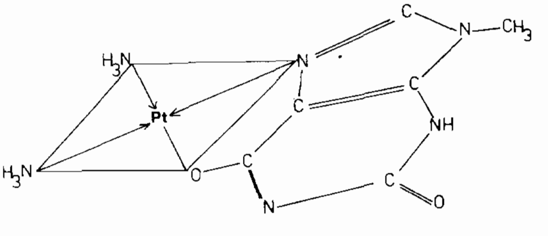

Fig. 2. Probable structure for [Pt(NH$_3$)$_2$(9MXa)]Cl.

References

1 L. G. Marzilli, *Prog. Inorg. Chem., 23,* 255 (1976).
2 D. J. Hodgson, *Prog. Inorg. Chem., 23,* 211 (1976).
3 G. L. Eichorn, 'Inorganic Biochemistry', Vol. 1 (1973), Vol. 2 (1980), Vol. 3 , Elsevier, N.Y., (1981).
4 A. W. Prestayako, S. T. Crooke and S. W. Carter, 'Cisplatin, Current Status and New Developments', Academic Press, New York, N.Y., 1980.
5 N. Hadjiliadis and G. Pneumatikakis, *J. Chem. Soc. Dalton Trans.*, 1691 (1978).
6 C. M. Mikulski, R. De Prince, T. B. Tran, F. J. Iaconianni, L. L. Pytlewski, A. N. Speca and N. M. Karayannis, *Inorg. Chim. Acta, 56,* 163 (1981).
7 A. N. Speca, L. L. Pytlewski, C. M. Mikulski, N. M. Karayannis, *Inorg. Chim. Acta, 66,* L53 (1982).
8 A. N. Speca, C. M. Mikulski, F. J. Iaconianni, L. L. Pytlewski and N. M. Karayannis, *Inorg. Chim. Acta, 37,* L551 (1979).
9 P. J. Stone, A. D. Kelman and F. M. Sinex, *Nature (London), 251,* 736 (1974).
10 L. G. Marzilli, T. J. Kistenmaker and C. H. Chang, *J. Am. Chem. Soc., 95,* 7505 (1973).
11 C. M. Mikulski, T. B. Tran, L. Mattucci and N. M. Karayannis, *Inorg. Chim. Acta, 78,* 269 (1983).
12 C. M. Mikulski, T. B. Tran, L. Mattucci and N. M. Karayannis, *Inorg. Chim. Acta, 78,* 211 (1983).
13 E. Calacio, J. M. Salas, M. A. Romero, A. Sanchez and M. Nogueras, *Inorg. Chim. Acta, 79,* 250 (1983).
14 B. Lippert and D. Neugebauer, *Inorg. Chim. Acta, 46,* 171 (1980).
15 H. C. Nelson and J. F. Villa, *J. Inorg. Nucl. Chem., 41,* 1643 (1979).
16 H. Susi and J. S. Ard, *Spectrochim. Acta, 27A,* 1549 (1971).
17 M. Goodgame and K. W. Johns, *J. Chem. Soc. Dalton Trans.*, 1680 (1977).

18 H. Susi and J. S. Ard, *Spectrochim. Acta, 30A*, 1843 (1974).
19 C. M. Mikulski, L. Mattucci, Y. Smith, T. B. Tran and N. M. Karayannis, *Inorg. Chim. Acta, 66*, L71 (1982).
20 S. Shirotake and T. Sakaguchi, *Chem. Pharm. Bull., 26*, 2941 (1978).
21 R. Savoir, J.-J. Jutier, L. Prizant and A. L. Beauchamp, *Spectrochim. Acta, 38A*, 561 (1982).
22 G. Pneumatikakis, N. Hadjiliadis and T. Theophanides, *Inorg. Chim. Acta, 17*, 915 (1978).
23 G. Pneumatikakis, N. Hadjiliadis and T. Theophanides, *Inorg. Chim. Acta, 22*, 915 (1977).