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Inosine Complexes of Platinum(II) in Aqueous Solution

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Since the discovery that some platinum complexes were potent antitumor agents, there has been considerable interest in the study of nucleoside and nucleotideplatinum complexes [1–5]. Inosine (Ino) is the most soluble nucleoside in water and therefore the most suitable for a study of its reactions with platinum at high concentration. K_2PtCl_4 has four chlorine ligands which can be displaced by nucleophiles. In this paper we report a NMR study of the complexes formed when K_2PtCl_4 and inosine react in aqueous solution in different concentration ratios. We have already reported the synthesis of $K[Pt(Ino)Cl_3]$ [3].

Experimental

Inosine was purchased from Raylo Chemical Ltd and K_2PtCl_4 from Matthey Bishop Inc.

The NMR spectra were measured on a Perkin-Elmer R-12 spectrometer. Inosine was added in infinitely small amount to a K_2PtCl_4 D_2O solution. The NMR spectrum was measured when equilibrium was reached. All the solutions were stable for months.

$K[Pt(Ino)Cl_3]$ was prepared as already reported [3].

Results and Discussion

The NMR spectra of the solutions formed when K_2PtCl_4 and inosine were mixed in D_2O in different ratios, are shown in Fig. 1. The spectra were compared to the NMR spectra of free inosine and of $K[Pt(Ino)Cl_3]$ which give spectra showing no change with time in D_2O [3]. In Fig. 1, F_2, F_8, M_2 and M_8 represent the NMR signals of protons H(2) and H(8) for free inosine and complexed inosine in $K[Pt(Ino)Cl_3]$ respectively. In $K[Pt(Ino)Cl_3]$, M_8 becomes a triplet with a coupling constant $J(^{195}Pt–H(8)) = 25$ Hz and is much shifted downfield relative to free inosine, while M_2 remains a singlet and the shift is smaller. This indicates that H(8) is closer to the platinum atom and that therefore the binding site is N(7). In Fig. 1(a), Pt: Ino = 2:1, M_2 and M_8 (the latter with coupling C) can be assigned to the signals of H(2) and H(8) of complexed inosine in $K[Pt(Ino)Cl_3]$. Therefore when K_2PtCl_4 and inosine are mixed in D_2O in a 2:1 proportion, the main product is $K[Pt(Ino)Cl_3]$. Two weaker peaks B_2 and B_8 can be observed. The intensity of these two peaks increase as the concentration of inosine increase. In Fig. 1(b) Pt: Ino = 1:1, 1(c) Pt: Ino = 1:1.25 and 1(d) Pt: Ino = 1:1.5. B_2 and B_8 were assigned to the signals of H(2) and H(8) of inosine in $[Pt(Ino)_2Cl_2]$. Since B_2 appears at about the same position as F_2 but B_8 is much shifted downfield compared to F_8, the binding site of inosine in $[Pt(Ino)_2Cl_2]$ is again N(7).

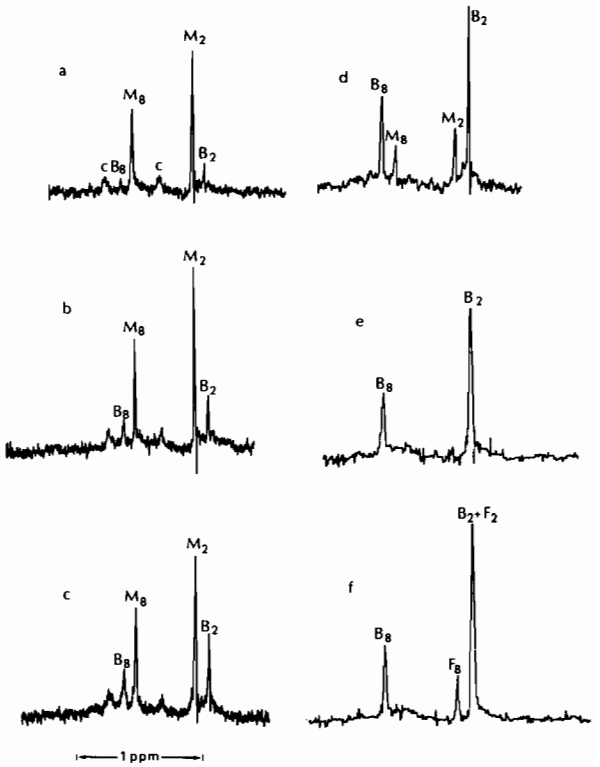

Fig. 1. NMR spectra of the solutions formed when K_2PtCl_4 and inosine were mixed in D_2O in different ratios.

When Pt: Ino = 1:2 a yellow oily paste appeared at the bottom of the tube. Since the uncharged complex $[Pt(Ino)_2Cl_2]$ is not very soluble in D_2O, it has a tendency to precipitate out. The addition of inosine to the mixture causes the paste to dissolve since inosine reacts with $[Pt(Ino)_2Cl_2]$ to produce charged species $[Pt(Ino)_3Cl]Cl$ and $[Pt(Ino)_4]Cl_2$ which are more soluble in D_2O. The intensity of B_2 and B_8 continue to increase with increasing inosine. No new bands can be assigned to $[Pt(Ino)_3Cl]Cl$ or $[Pt(Ino)_4]Cl_2$ even at ratios of Ino/Pt = 3 or 4. This is probably because the signals of H(2) and H(8) in these charged complexes are at the same positions as

the signals of H(2) and H(8) of $[Pt(Ino)_2Cl_2]$. In Fig. 1(e) (Pt: Ino = 1:4) $K[Pt(Ino)Cl_3]$ has almost disappeared and the coupling C′ of H(8) with ^{195}Pt can be observed. In Fig. 1(f) Ino/Pt is slightly greater than four. The signal F_8 of free inosine appeared while F_2 is covered by B_2.

It is worth mentioning that the signals of H(2) in inosine, $[Pt(Ino)_2Cl_2]$, $[Pt(Ino)_3Cl]Cl$ and $[Pt(Ino)_4]Cl_2$ in D_2O are at about the same position. But in $K[Pt(Ino)Cl_3]$, the signal is shifted downfield by ~0.1 ppm. Therefore the environment around H(2) in the latter complex seems slightly different than in the other complexes. This slight shift (0.1 ppm) of the H(2) proton has been observed in all other platinum monoinosine complexes [6] and seems a normal result of the Pt–N(7) binding. But it is surprising to observe that when a second molecule is bonded to Pt through N(7), this shift is not observed.

The possibility of a second interaction in solution between Pt and inosine closed to H(2) in the monoinosine complex has been examined. N(1) is not involved in any platinum binding since H(2) does not couple with ^{195}Pt. But inosine could act as a bidentate ligand leading to the following reaction

$$K[Pt(Ino)Cl_3] \longrightarrow [Pt(Ino)Cl_2] + KCl$$

where O(6) would be coordinated to Pt. However a few tests are not consistent with the above reaction. Addition of excess KCl or DCl (up to 2%) has not affected the position of the NMR signal of M_2 in Fig. 1(a). Furthermore when the reaction was repeated with 6-methylinosine (O(6) absent), the same NMR spectrum was obtained, showing that O(6) is not responsible for the small shift observed of the H(2) signal, thus eliminating the possibility of the above reaction.

We have at present no good explanation for the small difference observed in the H(2) position for monoinosine and polyinosine complexes. It could be caused by a difference in base stacking. It is well known that base stacking in inosine and some inosine complexe is quite important even in solution.

Acknowledgments

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