Mononucleoside Platinum Complexes

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Summary New platinum complexes with mononucleosides have been prepared by a new method which is also applicable to pyridine and amine analogues.

THE reaction of nitrogen bases with $K_2[PtCl_4]$ in aqueous solution generally gives uncharged complexes, *cis*-$[PtB_2Cl_2]$ (B = NH_3 and pyridine). Although the monobase complex $K[PtBCl_3]$ has been proposed as an intermediate in the reaction, it has not yet been isolated. The monobase complexes have been prepared by refluxing *cis*-$[Pt(NH_3)_2Cl_2]$ in concentrated hydrochloric acid,[1] by careful reduction of $K[PtBCl_5]$,[2,3] and by heating an aqueous solution of $K_2[PtCl_4]$ with a pyridine salt.[4] These methods cannot be used for the preparation of mononucleoside analogues, which have not yet been reported.

Continuing our studies on platinum nucleoside complexes,[5,6] we have found a method (yield 85%) to prepare mononucleoside complexes $K[Pt(Nuc)Cl_3]$ (Nuc = nucleoside, Guo = guanosine, Ino = inosine, and Xao = xanthosine) and the bridge complex $K_2[(PtCl_3)_2(Ado)]$ (Ado = adenosine) as follows. $K_2[PtCl_4]$ and the nucleoside (1 mmol each) were stirred overnight at 60—70 °C in 50 ml of $HCONMe_2$ or $MeCONMe_2$. The solution was concentrated to 5 ml by evaporation at 30—40 °C, cooled at 0 °C overnight, and

TABLE

N.m.r. spectra of the nucleosides and of the complexes.[a]

Compounds	2-H	8-H	1′-H	J(Pt–H-2)	J(Pt–H-8)	Solvent
Guanosine		4·95	2·70			Me_2SO
$K[Pt(Guo)Cl_3]$		5·25	2·80		27	D_2O
$K[Pt(Guo)Cl_3]$		5·25	2·80		27	2% DCl
Xanthosine		4·80	2·66			Me_2SO
$K[Pt(Xao)Cl_3]$		5·25	2·70		27	10% DCl
Inosine	5·15	5·27	2·88			D_2O
$K[Pt(Ino)Cl_3]$	5·25	5·77	3·04		25	D_2O
Adenosine[b]	5·14	5·26	2·90			D_2O
Adenosine	5·15	5·34	2·85			Me_2SO
$K_2[(PtCl_3)_2(Ado)]$	5·67	5·77	3·00	25	25	D_2O

[a] Chemical shifts in τ values; coupling constants in Hz; Me_4NCl as internal standard; concentration 0·2 M. [b] Concentration 0·02 M in D_2O.

filtered; the compound was precipitated by adding acetone–ether (1:1). The compound was washed with ether and recrystallized from a cold solution of 0·3N-HCl (5 ml) and propan-2-ol–ether (1:2; 50 ml). The equimolar ratio of $K_2[PtCl_4]$ and nucleoside is essential in the preparation of the adenosine complex but not for the synthesis of the Guo, Ino, and Xao complexes. The molar conductance of a fresh solution of $K[Pt(Ino)Cl_3]$ (0·001M) is 118 Ω^{-1} cm^2 mol^{-1}, which is characteristic of 1:1 electrolytes. The elemental analysis of the complexes are satisfactory. All the complexes are soluble in water and stable in acidic solution.

The n.m.r. spectra of the compounds were measured (Table). In the inosine complex, 8-H becomes a triplet and is much shifted downfield, while 2-H remains a singlet and the shift is smaller. This indicates that 8-H is closer to the platinum atom and couples with ^{195}Pt [J(Pt–H-8) 25 Hz] and that therefore N-7 is the binding site. In the guanosine and xanthosine complexes, the 8-H protons are also coupled with ^{195}Pt and are significantly shifted downfield, indicating that the binding sites are the same as in the inosine complex. In the adenosine complex, both 2-H and 8-H are coupled with ^{195}Pt and are shifted downfield by nearly the same magnitude. This phenomenon has already been observed when adenosine reacts with a large excess of [Pt(dien)Cl]Cl (dien = diethylenetriamine) in aqueous solution[6] and indicates that both N-1 and N-7 are the binding sites.

This method is also applicable to pyridine and amine complexes. $K[Pt(2,6\text{-lutidine})Cl_3]$ (yield 60%) and $K[Pt(NH_3)Cl_3]$ (yield 30%) have been synthesized and characterized.

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