Acidity Constants and Rates of Reaction for Guanosine Complexes derived from Cisplatin

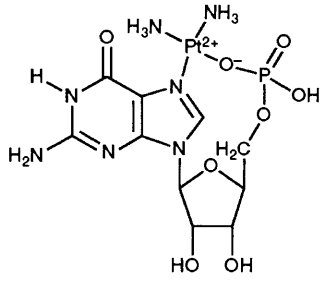
David M. Orton and Michael Green*

Department of Chemistry, University of York, Heslington, York Y01 5DD, UK

The p*K*a values and rate constants relating to *cis*-$[Pt(NH_3)_2X(OH)]^{n+}$ have been measured for X = guanosine and its 3′- and 5′-monophosphates (G, 3′-GMP and 5′-GMP); the hydroxo ligand in *cis*-$[Pt(NH_3)_2(5'\text{-GMP})(OH)]$ is surprisingly labile.

This communication dwells on three themes: (*i*) pK_a values for equilibria (1) lie between 5.2 and 5.8, see Table 1, so that in neutral solution the platinum complex is present largely in its hydroxo form $n = a - 1$, (*ii*) hydroxo ligands in platinum(II) complexes are inert to substitution,[4,5] so that the OH^- ligand in equilibrium (1) will be replaced very slowly, (*iii*) within the cell one of the active forms of cisplatin, the anticancer drug, is[6] *cis*-$[Pt(NH_3)_2(OH_2)(OH)]^+$. How, therefore, does this complex carry out its chemotherapeutic role of loosing its OH^- ligand (as well as the OH_2 group) when reacting with two guanosine units of DNA?[7]

cis-$[Pt(NH_3)_2X(OH_2)]^{a+} \rightleftharpoons$ *cis*-$[Pt(NH_3)_2X(OH)]^{n+} + H^+$ (1)



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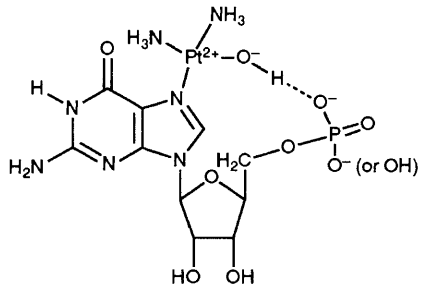

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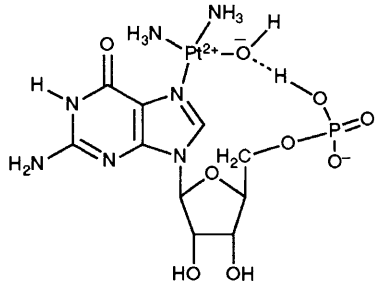

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Table 1 pK_a Values for equilibria (1) at 25 °C

X	pK_a	Ref.
H_2O	5.2–5.5	1
Cl	6.85	2
$(NH_3)_2X$ = dien	6.13	3[a]
G	5.68	[b]
3′-GMP	5.26 (6.44)[c]	[b]
5′-GMP	5.22 (7.50)[c]	[b]

[a] dien = $H_2NCH_2CH_2NHCH_2CH_2NH_2$. [b] This work, values ± 0.10. [c] pK_a for phosphate group: $-COPO_3H^- \rightleftharpoons -COPO_3^{2-} + H^+$.

Theme (*i*): pK_a values have been measured for equilibrium (1) for X = guanosine (G), 3′-guanosinemonophosphate (3′-GMP) and 5′-guanosinemonophosphate (5′-GMP). The *cis*-$[Pt(NH_3)_2X(OH)]^{n+}$ was prepared *in situ* by making a solution of *cis*-$[Pt(NH_3)_2(OH_2)_2](CF_3SO_3)_2$ alkaline, adding an equimolar quantity of X and allowing the mixture to stand for 5, 5 and 2 h for X = G, 3′-GMP and 5′-GMP, respectively. (The sodium salts of the last two were used.) The formation of *cis*-$[Pt(NH_3)_2X(OH)]^{n+}$ was confirmed by ^1H NMR [H(8) of X: δ *ca.* 8.9]. The pK_a values were obtained from pH titrations using trifluoromethanesulfonic acid at 25.0 °C with solutions with a concentration of 3×10^{-3} mol dm^{-3} using a Ross semimicro combination of pH electrode connected to a Phillips PW 9420 pH meter. The pK_a values, listed in Table 1, are not abnormal and show that in neutral solution the predominant species relating to equilibrium (1) are the hydroxo complexes, *cis*-$[Pt(NH_3)_2G(OH)]^+$ and *cis*-$[Pt(NH_3)_2$(3′-GMP or 5′-GMP)(OH)]. (pK_a for the phosphate groups of the GMP ligands are also listed.) At pH 7, the phosphate of the 3′-GMP complex is deprotonated, while that of 5′-GMP still carries a hydrogen atom.

Theme (*ii*): it follows that if the OH ligand in *cis*-$[Pt(NH_3)_2G(OH)]^+$ is inert, then this complex will react with G to give *cis*-$[Pt(NH_3)_2G_2]^{2+}$ only very slowly. The rate of reaction (2) has been measured at 25.0 °C by following changes in absorbance at λ 298 nm; (complex] = [G] = 5×10^{-4} mol dm^{-3}, under conditions pH 6.5.

$$cis\text{-}[Pt(NH_3)_2G(OH)]^+ + G \rightarrow cis\text{-}[Pt(NH_3)_2G_2]^{2+} + OH^- \quad (2)$$

$$cis\text{-}[Pt(NH_3)_2G(OH_2)]^{2+} + G \rightarrow cis\text{-}[Pt(NH_3)_2G_2]^{2+} + H_2O \quad (3)$$

Data for reaction (2) [and for (3) which involves the corresponding aqua species] are given in Table 2. Reaction (2) is clearly slow, the OH^- ligand being inert as is normal for a Pt^{II} system.

Theme (*iii*): this last observation raises the question of whether a 3′- or 5′-phosphate group can activate the replacement of the hydroxo ligand. Therefore, the rates of reaction (4) were measured for X = 3′- and 5′-GMP under the same conditions used for reaction (2), relative pH now being 6.6 and 7.2, respectively. [At these values both protonated and deprotonated phosphate groups will be present so charges are omitted in eqn. (4).] The k_4 values are listed in Table 2 and compared with data for reaction (5) which involves the corresponding aqua complexes.

Table 2 Rates constants/dm^3 mol^{-1} s^{-1} for reactions (2) to (5) at 25.0 °C

X, base involved	$k_{2,4}$	$k_{3,5}$
G	<0.01[a]	0.085[b], 0.085[c], 0.158[d]
3′-GMP	<0.01[a]	0.32[e]
5′-GMP	0.12[a]	0.24[b]

[a] This work. [b] Ref. 8. [c] Ref. 9. [d] Ref. 10. [e] Ref. 11.

$$cis\text{-}[Pt(NH_3)_2X(OH)] + X \rightarrow cis\text{-}[Pt(NH_3)_2X_2] + OH^- \quad (4)$$

$$cis\text{-}[Pt(NH_3)_2X(OH_2)]^+ + X^- \rightarrow cis\text{-}[Pt(NH_3)_2X_2] + H_2O \quad (5)$$

The 3′-GMP hydroxo complex is like that of G: the Pt–OH bond is inert. In contrast the 5′-GMP hydroxo complex contains a labile hydroxo group (and the pH rises from 7.2 to about 8 as it is released). When X = 5′-GMP, reaction (4) is only 2 times slower than (5).

How, then, is the OH^- ligand activated? The *cis*-$Pt(NH_3)_2$ unit coordinates to the N(7) of guanosine and its monophosphates. After such coordination, modelling experiments show that the 5′-phosphate group can approach the *cis*-$Pt(NH_3)_2$ moiety closely with ease, while the 3′-phosphate unit cannot. Moreover macrocyclic complexes such as **1** have been observed.[12,13] It is proposed that in *cis*-$[Pt(NH_3)_2$(5′-GMP)(OH)] there is hydrogen bonding between the phosphate group and the hydroxo ligand as in **2** or **3**. The fact that the pK_a value for loss of a proton from the phosphate group in *cis*-$[Pt(NH_3)_2$(5′-GMP)(OH)] is one unit higher than that for the 3′-GMP system supports this suggestion. We propose that in addition the hydrogen bonding activates the hydroxo group to substitution.

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