A Possible I_d Process in the Reaction of 5′-Guanosinemonophosphoric Acid and *cis*-$[Pt(NH_2Pr^i)_2(OH_2)_2]^{2+}$, a Reduced Form of CHIP or Iproplatin, the Anti-cancer Drug

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Rate data are presented for the reaction of *cis*-$[Pt(NH_2Pr^i)_2(OH_2)_2]^{2+}$ with 5′-guanosinemonophosphoric acid which occurs in two steps, the second of which has a large positive entropy of activation.

CHIP, *cis,cis,trans*-$[Pt^{IV}(NH_2Pr^i)_2Cl_2(OH)_2]$, is one of the second generation of platinum-containing anti-cancer drugs. However compared with cisplatin, *cis*-$[Pt^{II}(NH_3)_2Cl_2]$, the original drug, it reacts very slowly with nucleotides; (we[1] have estimated that the rate constant at 37 °C for the reaction of CHIP and 5′-guanosinemosphoric acid, 5′-$GMPH_2$ or B, is less than 10 $dm^3\ mol^{-1}\ h^{-1}$†). Therefore it has been suggested that in order to be active, CHIP must be modified to a

† At 37.0 °C, if [Pt] = [B] = 10^{-5} mol dm^{-3}, $t_{\frac{1}{2}} > 10^4$ h.

Table 1. Rate constants, activation parameters, and changes in δ-value of H(8) of the guaninine unit (G) in reactions (1) and (2).[a]

am	Reaction	k(25.0 °C) /dm^3 mol^{-1} s^{-1}	k(37.0 °C) /dm^3 mol^{-1} s^{-1}	$\Delta H^{\ddagger}$ /kJ mol^{-1}	$\Delta S^{\ddagger}$ /J K^{-1} mol^{-1}	Change in δ H(8) of G
NH_2Pr^i	(1)	1.69	2.96	33.4 ± 2.8	−128.5 ± 9.5	8.84 to 8.66
NH_3	(1)	1.44	2.82	40.6 ± 4.4	−106 ± 16	8.84 to 8.64
NH_2Pr^i	(2)	0.162	0.848	103.7 ± 3.2	87.8 ± 11	8.66 to 8.49
NH_3	(2)	0.238	0.650	62.8 ± 1.7	−46.6 ± 5.1	8.64 to 8.49

[a] Kinetic data for am = NH_3 from ref. 5; ^{1}H n.m.r. data remeasured.

platinum(II) form and is, in fact, reduced by iron(II) or by ascorbic acid.[2] The rate constant for the latter process is 0.58 dm^3 mol^{-1} s^{-1} at 37.0 °C.[3]‡ In this communication we present rate data for the reaction of the platinum(II) species, *cis*-$[Pt(NH_2Pr^i)_2(OH_2)_2]^{2+}$, and 5′-GMPH$_2$.

Cis-$[Pt(NH_2Pr^i)_2I_2]$ was converted into *cis*-$[Pt(NH_2Pr^i)_2(OH_2)_2](CF_3SO_3)_2$ using the method of Tobias's group.[4] The reaction of *cis*-$[Pt(NH_2Pr^i)_2(OH_2)_2]^{2+}$ and 5′-GMPH$_2$ was observed to proceed in two steps, and was studied quantitatively at λ 222 nm under similar conditions used to investigate the corresponding reaction of *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ and 5′-GMPH$_2$.[5] Each step is first order in platinum and in 5′-GMPH$_2$, or B, and ^{1}H n.m.r. demonstrates the formation of two products in sequence. This behaviour and the similarity with the reaction of *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ and 5′-GMPH$_2$[5] lead us to propose the same processes in each case, [see equations (1) and (2), am = NH_2Pr^i or NH_3], the guanine unit(s) G being bonded through N(7). Rate data, activation parameters, and δ-values for H(8) of G are given in Table 1.

$$cis\text{-}[Pt(am)_2(OH_2)_2]^{2+} + B \rightarrow cis\text{-}[Pt(am)_2B(OH_2)]^{x+} + H_2O \quad (1)$$

$$cis\text{-}[Pt(am)_2B(OH_2]^{x+} + B \rightarrow cis\text{-}[Pt(am)_2B_2]^{y+} + H_2O \quad (2)$$

Usually entropies of activation for ligand exchange reactions of platinum(II) are negative, as normally expected for an I_a or A process, and those involving *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ and nucleobases are unexceptional[5] (see Table 1, am = NH_3). Thus the large positive value observed here for $\Delta S^{\ddagger}_2$ (am = NH_2Pr^i) is remarkable. However proposals have been made that various reactions involving platinum(II) are dissociative, though some have been disproved.[6] Fairly recently, positive $\Delta S^{\ddagger}$ values have been observed in substitution reactions involving a platinum(II) system,[7] while in another, a D mechanism has been established.[8] In the present system changing am from NH_3 to NH_2Pr^i in *cis*-$[Pt(am)_2B(OH_2)]^{x+}$ introduces three bulky groups around the platinum centre. It is suggested, therefore, that this replacement causes reaction (2) to change from being associative to dissociative in character.

Added in proof. An article on the testing of Iproplatin has recently appeared.[9]

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‡ At 37.0 °C, if [Pt] = [ascorbic acid] = 10^{-5} mol dm^{-3}, $t_{\frac{1}{2}}$ = 5 h.

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