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Kinetic and Thermodynamic Selectivity in the Reactions of the Diaqua Form of *cis*-Platin with 3′- and 5′-Guanosinemonophosphoric Acid

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There are several unusual features in the reaction of *cis*$[\mathrm{Pt(NH_3)_2(OH_2)_2}]^{2+}$ with an equilibrium mixture of 2′-/3′-GMPH$_2$ compared with that of 5′-GMPH$_2$: the second step in the reaction is significantly faster than the first, the overall reaction is reversible and there is a *cis* kinetic effect.

Several pieces of work [1–3] suggest that *cis*-platin, *cis*-$[\mathrm{Pt(NH_3)_2Cl_2}]$, reacts more quickly with nucleotides containing a 5′- as opposed to a 3′-phosphate group. Therefore we have extended our earlier work [4] on the kinetics of the reaction of *cis*-$[\mathrm{Pt(NH_3)_2(OH_2)_2}]^{2+}$ and 5′-guanosinemonophosphoric acid, 5′-GMPH$_2$, to the isomeric 2′-/3′-system in order to obtain a quantitative measure of the selectivity.

The platinum salt used was *cis*-$[\mathrm{Pt(NH_3)_2(OH_2)_2}](\mathrm{CF_3SO_3})_2$ [5]. 3′-Monophosphates undergo acid catalysis forming an equilibrium with their 2′-isomers [6]. ^{1}H NMR indicated that the yeast guanylic acid used here, which was obtained from the Sigma Chemical Company, contains 2′- and 3′-GMPH$_2$ in the approximate ratio 60:40.

The rate of reaction of *cis*-$[\mathrm{Pt(NH_3)_2(OH_2)_2}]^{2+}$ and 2′-/3′-GMPH$_2$ in water was followed at λ 222 nm between temperatures of 6.2 and 46.6 °C, concentrations being *ca.* 1.67×10^{-5} and $1.67–6.67 \times 10^{-4}$ mol dm^{-3}, respectively. Initial pH lay between 4.00 and 3.30 so that *cis*-$[\mathrm{Pt(NH_3)_2(OH_2)_2}]^{2+}$ was present as itself since its pK_a is 5.5 [7]; in the 3′-GMPH$_2$ the G component was protonated at N(1) and the monophosphate group carried one proton [8]. (The earlier work [4] on 5′-GMPH$_2$ was also done at a pH at which there was the same state of protonation [8]. B will be used to denote nucleotide without implying any particular state of protonation.)

5′-GMPH$_2$ reacts with *cis*-$[\mathrm{Pt(NH_3)_2(OH_2)_2}]^{2+}$ in two steps [4]:

$$cis\text{-}[\mathrm{Pt(NH_3)_2(OH_2)_2}]^{2+} + \mathrm{B} \longrightarrow cis\text{-}[\mathrm{Pt(NH_3)_2B(OH_2)}]^{x+} + \mathrm{H_2O} \qquad (1)$$

$$cis\text{-}[\mathrm{Pt(NH_3)_2B(OH_2)}]^{x+} + \mathrm{B} \longrightarrow [\mathrm{Pt(NH_3)_2B_2}]^{y+} + \mathrm{H_2O} \qquad (2)$$

No sign of reversibility was detected in either reaction [4]. In contrast in the present system the traditional plots of $|\ln(A_\infty - A_t)|$ against t are strictly linear indicating only one rate determining step. (Since the spectra of the first and second products are very different in the 5′-GMPH$_2$ system, it seems impossible that they could be identical in the 2′-/3′-GMPH$_2$ case.) Secondly graphs of k_{obs} against [2′-/3′-GMPH$_2$] have finite intercepts showing that this step is reversible. The simplest explanation of these phenomena is that reaction (1) is reversible and that reaction (2) does not take place. However the kinetic data are also compatible with both reactions occurring reversibly, (1) being rate determining, and (2) very fast; (the intercept is then equal to $k_{-1}K_2$).

Unfortunately no product or products could be isolated from the reaction. Therefore in order to identify what was formed, changes in the H(8) NMR peak of the guanosine unit were investigated at varying ratios of B to Pt from 1:3 to 3:1 $[\mathrm{B}] \simeq 2 \times 10^{-2}$ M. Changes in the H(8) resonance from *ca.* 9.0 in 2′-/3′-GMPH$_2$ itself to *ca.* 8.57 and *ca.* 8.44 indicate that two types of N(7)-bonded products are formed. (The peaks are reasonably sharp, have a fine structure as would be expected from isomers and are slightly dependent in δ-value on concentration and composition.) Both sets of peaks are present in mixtures of composition 1:3 and 1:1, but that at *ca.* δ 8.57 is only present in trace quantity at a ratio of 2:1 and not at all at 3:1. Hence the resonances around δ 8.57 and around δ 8.44 are assigned to the *cis*-$[\mathrm{Pt(NH_3)_2B(OH_2)}]^{x+}$ and *cis*-$[\mathrm{Pt(NH_3)_2B_2}]^{y+}$ species, respectively.

Thus the NMR data support the second postulated mechanism, that of the two step process in which the second reaction is fast. (Using ^{1}H NMR Reedijk's group have observed that the analogous disodium salt, 3′-GMPNa$_2$, reacts with *cis*-$[\mathrm{Pt(NH_3)_2(OH_2)}]^{+}$ to give an insoluble mono-base then a bis-base complex [1].) The graphs of $\ln k_1$ and $\ln(k_{-1}/K_2)$ against $1/T$ were strictly linear with correlation coefficients of −0.995 and −0.999 respectively, from which we conclude that reaction (1) for 2′- and for 3′-GMPH$_2$ must have very similar activation parameters.

The possibility of the formation of phosphate, as opposed to an N(7)-bonded guanine, complex was considered, as species such as *cis*-$[\mathrm{Pt(NH_3)_2(OPO_3H_2)(OH_2)}]^{+}$ are known [9, 10]. Since there is very little change in UV spectrum when *cis*-$[\mathrm{Pt(NH_3)_2(OH_2)_2}]^{2+}$ is allowed to react with $\mathrm{Na_2HPO_4/H_3PO_4}$ buffer solutions at pH 3.0–4.0, the apparent unreacted starting material revealed by the kinetics (in the k_{-1}/K_2 term) could in fact be a phosphate complex. The ^{31}P NMR peak of *cis*-$[\mathrm{Pt(NH_3)_2(OPO_3H_2)(OH_2)}]^{+}$ lies at δ 5.8 (w.r.t. H$_3$PO$_4$) and shows ^{195}Pt satellites [9]. The difference in our

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TABLE I. ^{31}P NMR δ Values[a]

B	0.269	0.465
cis-$[Pt(NH_3)_2B(OH_2)]^{x+}$	0.272	0.492
cis-$[Pt(NH_3)_2B_2]^{y+}$	0.290	0.440

[a] Concentrations *ca.* 5 × 10^{-3} M, pD = 2.3 to 2.5.

δ-values (see Table I) from δ 5.8 together with the absence of satellites leads us to conclude that no phosphate complexes are formed here.

Kinetic data are given in Table II, k_1, $\Delta H_1^{\ddagger}$ and $\Delta S_1^{\ddagger}$ for 2′-/3′-$GMPH_2$ are very similar to the corresponding parameters for reaction (2) for 5′-$GMPH_2$, while the kinetic preference of the last base in reaction (1) is not strikingly larger. There is, however, a considerable kinetic preference by the 2′-/3′-system in reaction (2) since its k_2 is too large to measure. This observation is not only interesting in itself but also in a wider context of labilising effect. Here is an example of a *cis* as opposed to the common *trans* kinetic effect seen in platinum(II) systems.

The other notable difference between the 2′-/3′- and the 5′-systems is the reversibility of the former. In ^1H NMR and kinetics studies we observed no reversibility in the case of 5′-$GMPH_2$ and can estimate for it $K_2 \geqslant 3.5 \times 10^4$ dm^3 mol^{-1} at 25.0 °C [11]. In the 2′-/3′-system K_1K_2, that is $k_1/(k_{-1}/K_2)$, is 3450 dm^3 mol^{-1} at the same temperature [11]. This illustrates that there is a greater affinity towards the *cis*-$Pt^{II}(NH_3)_2$ moiety on the part of 5′-$GMPH_2$ compared with 2′-/3′-$GMPH_2$ and that it is thermodynamic rather than kinetic in character.

There remains the question of why two molecules of 5′-$GMPH_2$ react ‘completely’ with *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ while two of the 2′-/3′-$GMPH_2$ system do not. Lippard's group [12] have by both X-ray studies and molecular dynamics demonstrated that the phosphate group of a 5′-GMP unit can hydrogen-bond to an NH_3 ligand of *cis*-$Pt^{II}(NH_3)_2$ group. Models demonstrate that this is impossible in the 2′-GMP case and only just feasible for the 3′-GMP system. Therefore it is proposed that in the 5′-system the enhanced stability of *cis*-$[Pt(NH_3)_2B_2]^{y+}$ in solution w.r.t. reaction (2) arises in the same way, namely from hydrogen bonding.

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References

1 A. T. M. Marcelis, C. Erkelens and J. Reedijk, *Inorg. Chim. Acta, 91*, 129 (1984).
2 J.-P. Girault, G. Chottard, J.-Y. Lallemand and J.-C. Chottard, *Biochemistry, 21*, 1352 (1982).
3 A. B. Robbins, *Chem.-Biol. Interact., 6*, 35 (1973).
4 S. S. Eapen, M. Green and I. M. Ismail, *J. Inorg. Biochem., 23*, 233 (1985).
5 G. Y. H. Chu and R. S. Tobias, *J. Am. Chem. Soc., 98*, 2641 (1976).
6 D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 44 (1952).
7 M. C. Lim and R. B. Martin, *J. Inorg. Nucl. Chem., 38*, 1911 (1976).
8 R. B. Martin, *Acc. Chem. Res., 18*, 32 (1985).
9 T. G. Appleton, R. D. Berry, C. A. Davis, J. R. Hall and H. A. Kimlin, *Inorg. Chem., 23*, 3514 (1984).
10 R. N. Bose, R. E. Viola and R. D. Cornelius, *J. Am. Chem. Soc., 106*, 3336 (1984).
11 S. S. Eapen, *M. Sc. Thesis*, York, 1985.
12 S. E. Sherman, D. Gibson, A. J.-J. Wang and S. J. Lippard, *Science, 230*, 412 (1985); J. Kozelka, G. A. Petsko, S. J. Lippard and G. J. Quigley, *J. Am. Chem. Soc., 107*, 4079 (1985).

TABLE II. Activation Parameters for Reaction (1)

	k_1 (dm^3 mol^{-1} s^{-1})		k_{-1}/K_2 (10^4 s^{-1})		$\Delta H_1^{\ddagger}$ (kJ mol^{-1})	$\Delta H_{-1}^{\ddagger}$ (kJ mol^{-1})	$\Delta S_1^{\ddagger}$ (J K^{-1} mol^{-1})	$\Delta S_{-1}^{\ddagger}$ (J K^{-1} mol^{-1})
	25.0 °C	37.0 °C	25.0 °C	37.0 °C				
2′-/3′-$GMPH_2$	0.320	0.838	0.928	1.70	59.2 ± 3.8	36.4 ± 1.0	−56 ± 12	−200 ± 3
5′-$GMPH_2$	1.44	2.82	*ca.* 0	*ca.* 0	40.6 ± 4.4		−106 ± 16	
5′-$GMPH_2$ (reaction 2)	0.238	0.650	*ca.* 0	*ca.* 0	62.8 ± 1.5		−46.3 ± 5.2	