

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

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(Received September 9, 1985; revised June 30, 1986)

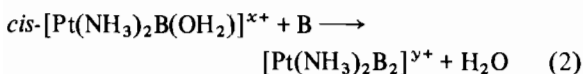
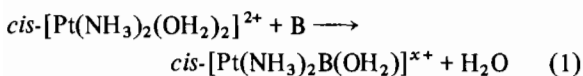
There are several unusual features in the reaction of *cis*-[Pt(NH₃)₂(OH₂)₂]²⁺ with an equilibrium mixture of 2'-/3'-GMPH₂ compared with that of 5'-GMPH₂: the second step in the reaction is significantly faster than the first, the overall reaction is reversible and there is a *cis* kinetic effect.

Several pieces of work [1–3] suggest that *cis*-platin, *cis*-[Pt(NH₃)₂Cl₂], 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*-[Pt(NH₃)₂(OH₂)₂]²⁺ and 5'-guanosinemonophosphoric acid, 5'-GMPH₂, to the isomeric 2'-/3'-system in order to obtain a quantitative measure of the selectivity.

The platinum salt used was *cis*-[Pt(NH₃)₂(OH₂)₂]- (CF₃SO₃)₂ [5]. 3'-Monophosphates undergo acid catalysis forming an equilibrium with their 2'-isomers [6]. ¹H NMR indicated that the yeast guanylic acid used here, which was obtained from the Sigma Chemical Company, contains 2'- and 3'-GMPH₂ in the approximate ratio 60:40.

The rate of reaction of *cis*-[Pt(NH₃)₂(OH₂)₂]²⁺ and 2'-/3'-GMPH₂ 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 × 10⁻⁴ mol dm⁻³, respectively. Initial pH lay between 4.00 and 3.30 so that *cis*-[Pt(NH₃)₂(OH₂)₂]²⁺ was present as itself since its pK_a is 5.5 [7]; in the 3'-GMPH₂ the G component was protonated at N(1) and the monophosphate group carried one proton [8]. (The earlier work [4] on 5'-GMPH₂ 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'-GMPH₂ reacts with *cis*-[Pt(NH₃)₂(OH₂)₂]²⁺ in two steps [4]:



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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'-GMPH₂ system, it seems impossible that they could be identical in the 2'-/3'-GMPH₂ case.) Secondly graphs of k_{obs} against $[2'-/3'-\text{GMPH}_2]$ 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 $[\text{B}] \approx 2 \times 10^{-2}$ M. Changes in the H(8) resonance from ca. 9.0 in 2'-/3'-GMPH₂ 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*-[Pt(NH₃)₂B(OH₂)]^{x+} and *cis*-[Pt(NH₃)₂B₂]^{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 ¹H NMR Reedijk's group have observed that the analogous disodium salt, 3'-GMPNa₂, reacts with *cis*-[Pt(NH₃)₂(OH₂)]⁺ 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'-GMPH₂ 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*-[Pt(NH₃)₂-(OPO₃H₂)(OH₂)]⁺ are known [9, 10]. Since there is very little change in UV spectrum when *cis*-[Pt(NH₃)₂(OH₂)₂]²⁺ is allowed to react with Na₂HPO₄/H₃PO₄ 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 ³¹P NMR peak of *cis*-[Pt(NH₃)₂-(OPO₃H₂)(OH₂)]⁺ lies at δ 5.8 (w.r.t. H₃PO₄) and shows ¹⁹⁵Pt satellites [9]. The difference in our

TABLE I. ^{31}P NMR δ Values^a

B	0.269	0.465
<i>cis</i> -[Pt(NH ₃) ₂ B(OH ₂)] ^{x+}	0.272	0.492
<i>cis</i> -[Pt(NH ₃) ₂ B ₂] ^{y+}	0.290	0.440

^aConcentrations *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 , ΔH_1^\ddagger and ΔS_1^\ddagger for 2'-/3'-GMPH₂ are very similar to the corresponding parameters for reaction (2) for 5'-GMPH₂, 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'-GMPH₂ and can estimate for it $K_2 \geq 3.5 \times 10^4$ dm³ 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 dm³ mol⁻¹ at the same temperature [11]. This illustrates that there is a greater affinity towards the *cis*-Pt^{II}(NH₃)₂ moiety on the part of 5'-GMPH₂ compared with 2'-/3'-GMPH₂ and that it is thermodynamic rather than kinetic in character.

There remains the question of why two molecules of 5'-GMPH₂ react 'completely' with *cis*-[Pt(NH₃)₂(OH₂)₂]²⁺ while two of the 2'-/3'-GMPH₂ 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 NH₃ ligand of *cis*-Pt^{II}(NH₃)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(NH₃)₂B₂]^{y+} in solution w.r.t. reaction (2) arises in the same way, namely from hydrogen bonding.

Acknowledgements

Our thanks to Johnson Matthey plc for the loan of K₂PtCl₄ and to the Science and Engineering Research Council of the U.K. for a research grant and the use of their high field NMR services at the University of Warwick.

References

- 1 A. T. M. Marcellis, 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)		ΔH_1^\ddagger (kJ mol ⁻¹)	ΔH_{-1}^\ddagger (kJ mol ⁻¹)	ΔS_1^\ddagger (J K ⁻¹ mol ⁻¹)	ΔS_{-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	<i>ca.</i> 0	<i>ca.</i> 0	40.6 ± 4.4		-106 ± 16	
5'-GMPH ₂ (reaction 2)	0.238	0.650	<i>ca.</i> 0	<i>ca.</i> 0	62.8 ± 1.5		-46.3 ± 5.2	