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The Kinetics and Mechanism of the Reaction of 2′-Deoxy-5′-guanosinemonophosphoric acid and the Diaqua Form of *cis*-Platin

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Abstract

2′-Deoxy-5′-guanosinemonosphoric acid (B) reacts with *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ in two steps to form the *cis*-$[Pt(NH_3)_2B_2]^{y+}$ ion. In the first step 2′-d-5′-$GMPH_2$ reacts some ten times faster than 5′-$GMPH_2$ does. Rate constants, $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta V^{\#}$ are very similar for the two bases in the second reaction. It is proposed that the product in the first step contains no water and is *cis*-$[Pt(NH_3)_2B]^{x+}$ in which the nucleobase is bidentate bonding through both N(7) of guanine and an oxygen atom of the phosphate group.

In its roles as an anti-cancer drug, *cis*-platin, *cis*-$[Pt(NH_3)_2Cl_2]$, interacts specifically with DNA as opposed to RNA [1]. Of the four bases of which DNA is made up, *cis*-platin shows a preference for guanine [2]. This raises the question of whether *cis*-platin has a greater affinity for 2′-deoxy-5′-guanosine than for 5′-guanosine. In this work we have studied the rates of reaction of 2′-deoxy-5′-guanosinemonophosphoric and 5′-guanosinemonophosphoric acids, 2′-d-5′-$GMPH_2$ and 5′-$GMPH_2$, respectively.

In order to avoid competing reactions involving chloride ions, *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ was used. Solutions of *cis*-$[Pt(NH_3)_2(OH_2)_2](CF_3SO_3)_2$ [3] and the acids tend to be self-buffering having pH between 2.8 and 3.2, so that the reactants were present as *cis*-$[Pt(NH_3)_2(OH_2)_2]^{2+}$ [4] itself and 2′-d-5′-$GMPH^-$ or 5′-$GMPH^-$ [5]. (The bases will be designated B without any indication of the state of the protonation.) The kinetics at normal pressures were followed using UV spectroscopy (300 nm) under conditions similar to those we used earlier for investigating 5′-$GMPH_2$ [2]. The kinetics at elevated pressure were followed in a modified Zeiss PMQ II spectrophotometer equipped with a thermostated (±0.1 °C) high pressure cell [6] which holds the pill-box sample cell [7, 8].

Changes in UV spectra indicated two consecutive reactions, each first order in platinum and base, for 2′-d-5′-$GMPH_2$, just as was observed for 5′-$GMPH_2$ [2]. The first step was studied between 4.6 and 12.0 °C under second order conditions ($[Pt] = [2'\text{-d-}5'\text{-}GMPH_2] = 0.6–1.5 \times 10^{-3}$ M). Graphs of $(A_t - A_o)/(A_\infty - A_t)$ against time were linear [9]. The second step was followed between 15.0 and 33.8 °C under pseudo-first order conditions ($[Pt] = 1.5 \times 10^{-4}$ M, $[2'\text{-d-}5'\text{-}GMPH_2] = 1.5–2.5 \times 10^{-3}$ M) and plots of $\ln(A_t - A_\infty)$ against time were linear [9]. Unfortunately products could not be isolated. However changes in the NMR H(8) resonance of the guanine unit are compatible with the formation in sequence of two products, both bonded to platinum at N(7), see Table I. This information and the kinetics suggest that the two steps are reactions (1) and (2). (x and y could well be 1 and 0, respectively.)

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

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TABLE I. NMR δ-Values of H(8) in D_2O at *ca.* 25 °C

	2′-d-5′-$GMPH_2$	5′-$GMPH_2$
B	8.92	8.84
cis-$[Pt(NH_3)_2B(OH_2)]^{x+}$ or *cis*-$[Pt(NH_3)_2B]^{x+}$	8.62	8.64
cis-$[Pt(NH_3)_2B_2]^{y+}$	8.47	8.49

0020-1693/87/$3.50

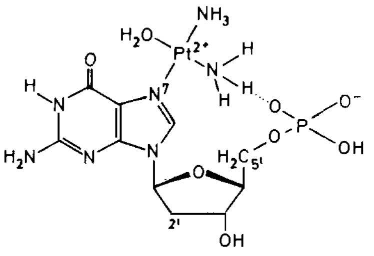
TABLE II. Kinetic Data

B	Reaction	k (25.0 °C) (M^{-1} s^{-1})	k (37.0 °C) (M^{-1} s^{-1})	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ J K^{-1} mol^{-1})	$\Delta V^{\#}$ (25.0 °C) (cm^3 mol^{-1})
5'-dGMPH$_2$	1	(16.4)	(27.8)	31.2 ± 4.3	−117 ± 15	
5'-GMPH$_2$	1	(1.44)[a]	(2.82)[a]	40.6 ± 4.4[a]	−106 ± 16[a]	
5'-dGMPH$_2$	2	0.170	0.456	60.8 ± 5.3	−55.7 ± 17.9	−4.7 ± 0.2
5'-GMPH$_2$	2	0.238[a]	0.650[a]	62.8 ± 1.5[a]	−46.3 ± 5.2[a]	−10.9 ± 0.7

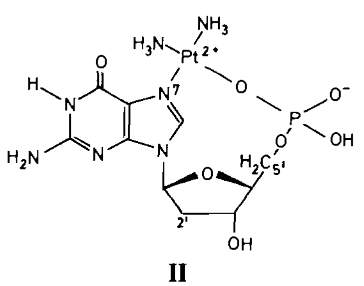
Values in parentheses are extrapolated values. [a]From ref. 2.

$$cis\text{-}[Pt(NH_3)_2B(OH_2)_{0,1}]^{x+} + B \longrightarrow cis\text{-}[Pt(NH_3)_2B_2]^{y+} + 0{,}1H_2O \quad (2)$$

Rate constants, $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta V^{\#}$ are given in Table II. Spectral changes were too small to allow an accurate determination of $\Delta V^{\#}$ for the first step of the reaction under pseudo-first order conditions. The entropies of activation for reaction (1) are notably more negative than those for (2) implying more ordering in the first case. Two possible explanations both involve cyclisation. It is known that the 5'-phosphate group in a nucleotide can hydrogen bond to an NH_3 ligand of the *cis*-$Pt(NH_3)_2$ unit [10]. Therefore it is feasible that the first product is cyclic by virtue of its hydrogen bonding as in **I**. However to account for the less negative values of $\Delta S_2^{\#}$ it is then necessary to postulate that such hydrogen bonding does not occur in the second product, but there seems to be no good reason for making this assumption. Therefore a preferable explanation is that in reaction (1) formation occurs of a cyclic complex of the type proposed by Sigel's group [11]. In this cyclic complex the phosphate group (as well as N(7) of the guanine unit) is coordinated to the platinum, so that no water ligand is present, see **II**.



I



II

The second curious feature is that the parameters for reaction (1), notably k_1 and $\Delta H_1^{\#}$, are much more different for the two bases than are those for step (2). The latter indicates that there is no particular kinetic selectivity between the deoxy- and the oxy-base, which is what one would expect on the basis of the argument that a change of the 2'-substituent from –H to –OH would not affect substitution at N(7) which is four bonds away. It therefore seems reasonable to propose that the *cis*-$Pt(NH_3)_2$ unit has no particular preference for 2'-d-5'-GMPH$_2$ over 5'-GMPH$_2$ and that reaction (1) is unusual.

The anomalous behaviour of reaction (1) can be explained on the basis that H is less bulky than OH, so that there is more flexibility in the 2'-deoxyribose than the ribose ring. This argument provides a second piece of evidence to support the formation of the cyclic first product postulated above as well as giving an explanation for reaction (1) going faster with 2'-d-5'-GMPH$_2$: the greater flexibility of the 2'-deoxy ring facilitates cyclisation.

The activation parameters $\Delta S^{\#}$ and $\Delta V^{\#}$ support an associative mechanism. The more negative $\Delta S^{\#}$ value for reaction (1) is in line with the formation of a cyclic complex as suggested above [11]. Rather surprising is the significant difference in $\Delta V^{\#}$ for reaction (2) notwithstanding the fact that k_2, $\Delta H_2^{\#}$ and $\Delta S_2^{\#}$ are so similar for the two nucleophiles. This may be related to specific solvational effects around the 2'-substituent during the formation of the final product. The order of magnitude of $\Delta V^{\#}$ is very typical for substitution reactions of square planar complexes [12].

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References

1 J. J. Roberts and A. J. Thomson, *Prog. Nucleic Acid Res., Mol. Biol., 22,* 71 (1979).

2 S. S. Eapen, M. Green and I. M. Ismail, *J. Inorg. Biochem., 23,* 233 (1985) and refs. therein.

3 G. Y. H. Chu and R. S. Tobias, *J. Am. Chem. Soc., 98,* 2641 (1976).

4 M. C. Lim and R. B. Martin, *J. Inorg. Nucl. Chem., 38,* 1911 (1976).

5 R. B. Martin, *Acc. Chem. Res., 18,* 32 (1985).

6 F. K. Fleischmann, E. G. Conze, D. R. Stranks and H. Kelm, *Rev. Sci. Instrum., 45,* 1427 (1974).

7 W. J. le Noble and R. Schlott, *Rev. Sci. Instrum., 47,* 770 (1976).

8 R. van Eldik, in R. van Eldik (ed.), 'Inorganic High Pressure Chemistry: Kinetics and Mechanisms', Elsevier, Amsterdam, 1986, Chap. 1.

9 J. H. Espenson, 'Chemical Kinetics and Reaction Mechanisms', McGraw-Hill, New York, 1981, p. 23.

10 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).

11 H. Sigel and K. H. Scheller, *Eur. J. Biochem., 138,* 291 (1984) and refs. therein.

12 M. Kotowski and R. van Eldik, in R. van Eldik (ed.), 'Inorganic High Pressure Chemistry: Kinetics and Mechanisms' Elsevier, Amsterdam, 1986, Chap. 4.