Platinum Blues. Experimental Support for the Occurrence of Platinum(III) in a Blue Compound Involving 1-Methylnicotinamide and Guanosine as Ligands

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A blue platinum complex involving guanosine and 1-methylnicotinamide has been obtained in a two-step reaction. The coordination sites on both ligands have been deduced from a spectrometric (^1H and ^{13}C NMR, visible and infrared) study. Analysis of the EPR hyperfine pattern strongly suggests that the actual paramagnetic centers are platinum(III) ions and the complex has to be considered as a localized mixed-valence species.

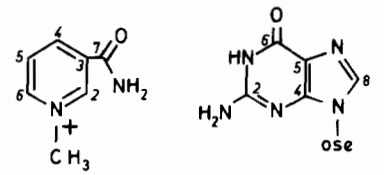

Fig. 1. Methylnicotinamide and guanosine. numbering schemes of the ^1H and ^{13}C nuclei.

Introduction

Blue platinum complexes have been known since the beginning of this century, when a blue species was reported to have formed in the reaction of $Pt(CH_3CN)_2Cl_2$ with a silver salt in aqueous solution [1]. Two main factors account for the current upsurge of interest in these species. Firstly, their composition and structure often remain uncertain; up to now only one crystalline blue has been obtained and its structure determined by X-ray diffraction [2–5]. Secondly, some of these species, and more particularly the so-called 'pyrimidine-blues', have been shown to be antitumour agents [6, 7]. These compounds are obtained through the reaction of aquated form of *cis*-dichlorodiammino platinum(II) with pyrimidine bases of DNA or RNA or other substituted 2,4-dihydroxypyrimidines [6, 8]. Various studies [8–12] showed these species to be oligomeric, probably through the formation of chains of amidate-bridge platinum atoms displaying a formal non-integral oxidation state (in order to account for their paramagnetism).

The examples of blue complexes in which a purine base would be bonded to the platinum are very rare [5, 13] and, to our knowledge, there is no mention of a guanosine blue. We now report on the possibility of preparing a blue species involving guanosine as ligand together with 1-methylnicotinamide (*cf.* Fig. 1). However it cannot be truly considered as a 'purine blue' since the color is not related to a specific effect of guanosine. Although the failure to obtain a crystalline sample prevents crystallographic determinations, this species, which appears as a definite compound, has been characterized in the solid state (IR, ESR) and in solution (^1H and ^{13}C NMR, ESR). The data enable some conclusions to be drawn regarding the nature of this new platinum blue.

Experimental

Microanalyses were performed by the Laboratoire Central de Microanalyse du CNRS. NMR spectra (^1H, ^{13}C) were obtained in D_2O (pH ~ 5) and DMSO-d_6 solutions on a Bruker WH90 spectrometer using DSS or TMS as internal references. The concentration range of these solutions was 0.05–0.1 mol. Electronic spectra were recorded on a Cary 14 spectrophotometer. Infrared spectra were obtained as Nujol mulls or CsBr pellets on a Perkin-Elmer 557 spectrometer calibrated with polystyrene film. ESR spectra were recorded on a Bruker ER 200 D spectrometer, the microwave frequency being calibrated with diphenylpicrylhydrazyl. Oxidative titration was monitored by spectrophotometry and carried out in dilute sulphuric acid solution with standard ceric sulphate solution [12].

Preparation of the Complexes

The blue complex (A) involving guanosine as ligand is prepared in a two-step reaction. Firstly 1-methylnicotinamide is reacted with K_2PtCl_4 to

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TABLE I. ^{1}H Chemical Shifts (ppm, internal DDS) of the Ligands (Nic and Guo) and the (A) and (B) Complexes in D_2O (pH 6) For the numbering of the ^{1}H nuclei, see Fig. 1.

	Nic.				Guo.	
	H-2	H-4,5	H-6	CH_3	H-8	H-1
Free ligand	9.22	8.11	8.89	4.33	8.00	5.94
(A)	9.5	8.2	9.0	4 3	8.7	5 9
(B)	9.6	8.2	9.1	4 3	–	–

TABLE II. ^{13}C Chemical Shifts (ppm, internal DDS) of the Ligands (Nic and Guo) and the (A) and (B) Complexes in D_2o (pH 6). For the numbering of the ^{13}C nuclei, see Fig. 1.

	Nic							Guo				
	C-2	C-3	C-4	C-5	C-6	C-7	CH_3	C-2	C-4	C-5	C-6	C-8
Free ligand	148.0	133.4	145.8	128.9	150.5	166.1	52.3	154.6	152.4	117.6	157.8	137.0
(A)	147	137	≅146*	131	≅151*	169	52	155	151	120	157	143
(B)	148	137	≅146*	130	≅151*	169	52	–	–	–	–	–

*See text.

yield a blue species (B) which is then reacted with guanosine to afford (A).

The synthesis and analytical data for the (B) species have been described previously [14]. To a dry mixture of 1 mmol (expressed as mole of total platinum present in the sample) of (B) and 2.2 mol of guanosine, 55 ml of water were added. A gradual dissolution of the two components was observed even at room temperature, while the pH dropped from 5.5 to 4.7. The mixture was incubated overnight at 50 °C in the dark and then filtered to remove any unreacted (B) compound. The filtrate was evaporated to half-volume at ~50 °C and then left at 4 °C to precipitate out the excess of guanosine, which was filtered off. This procedure was repeated twice, yielding ~10 ml of a blue solution which was treated by acetone. A blue-grey precipitate was obtained which was washed with acetone and ether and then dried under vacuum (5 mm Hg, 30 °C) overnight. Analyses yielded the following data. C, 31.7; H, 4.04; N, 16.1; Cl, 7.6; Pt, 18.6, which leads to a crude formulation such as $PtC_{27}H_{42}N_{12}O_{15}Cl_{2.2}$ (*Anal.* calcd.: C, 31.0; H, 4.00; N, 16.0; Cl, 7.4; Pt, 18.6) or, in an abbreviated form, $Pt(Nic\text{-}H)Guo_2Cl_{2.2}\cdot 4H_2O$.

Results and Discussion

The new platinum blue (A), which involves ligands 1-methylnicotinamide (abbreviated as Nic) and guanosine (Guo), is obtained through the reaction of guanosine with a precursor (B), As previously reported [14], this (B) species is a blue amorphous solid, scarcely soluble in all common solvents and, therefore, not fully characterized. From analytical and infrared data it was inferred that one mol of the deprotonated ligand (Nic–H) is actually involved per platinum atom and that chloride anion(s) are bonded to the metal. A possible formulation would be $Pt_4(Nic\text{–}H)_4Cl_9(H_2O)_n$. However, this species displays the main characteristics of the blue compounds, *i.e.* the blue color which is removed by oxidizing and reducing agents and the production of an ESR signal. It is noteworthy that (B) is obtained in the presence of chloride ions, the ligand being used in the hydrochloride form, while several authors [6, 8, 9] have reported that platinum blues cannot be prepared in the presence of Cl^- or CH_3COO^- ions.

(B) reacts with guanosine even under very mild conditions, since a complete dissolution of these products and a drop in pH occur within one hour at room temperature.

Although (A) is stable in the solid state, the blue color of the aqueous solution is altered more or less rapidly according to pH values: the addition of base increases the rate of decay of the color. Similarly, reducing and oxidizing agents also decolourize solutions, providing a method of estimating the formal oxidation state of the platinum ions [5, 12].

An oxidation titration was carried out in dilute sulphuric acid with standard ceric sulphate solution

and monitored spectrophotometrically by the percent decrease in the absorption band at 590 nm (*vide infra*). $1.7_5 \pm 0.08$ equivalent of cerium per platinum atom was necessary for complete oxidation. Assuming that the resulting product is platinum(IV), the average platinum oxidation state would be 2.2–2.3 in (A). Values ranging from 2.1 to 3.7_5 have been previously assigned to various blue species [5, 12].

Spectroscopic Properties

Electronic spectra

In aqueous solutions, the UV spectrum displays a broad and intense absorption centered at 257 nm, which is attributable to guanosine [15]. The visible part is characterized by a much less intense transition at 590 nm. Reflectance spectroscopy on a solid (powder) sample leads to a very similar pattern ($\lambda_{max} \cong 600$ nm).

^1H, ^{13}C NMR

Owing to the presence of two types of ligands, the ^1H and ^{13}C NMR spectra are complex. Furthermore, the signals are somewhat broadened. This effect may be due to the paramagnetism of the sample (*vide infra*) and/or to its oligomeric nature. In each case, the inspection of the electronic spectra taken immediately before and after the NMR experiments has shown that the 590 nm absorption has not been altered. Nevertheless, comparisons of the (A) and (B) species and the free ligands enable attribution of the main absorptions (Tables I and II). Among the guanosine ^1H resonances, the H-8 doublet occurs downfield (0.7 ppm) relative to the free ligand while the H-1′ singlet remains almost unperturbed. This behaviour strongly suggests that guanosine coordinates to the platinum through N-7 [16–19]. The data relating to the nicotinamide moiety are less conclusive. The (A) and (B) spectra (D_2O solutions) are almost identical. Among the set of downfield shifts observed after complexation (0.3 to 0.1 ppm) the major effects seem to be related to the *H*-2 nucleus. However, DMSO-d_6 solutions afford an interesting observation. In free nicotinamide a broad signal at 6.28 ppm is attributed to the N*H*$_2$ protons. This signal is no longer present in the (A) spectrum, which instead dipslays resonance at 4.7 ppm. Such a high field signal may be assigned to a N*H* nucleus. The broadness of the resonance peaks prevents us from seeing any Pt–H coupling, as observed in other studies [16, 20–23].

The ^{13}C chemical shift changes in the proton-decoupled spectra of (A) enable us to confirm that the bonding sites are as suggested above. The shifts of the C-8 and C-5 resonances in the guanosine moiety are consistent with coordination at N-7 since these two nuclei are adjacent to the nitrogen [17, 24]. The C-6 resonance of nicotinamide (and to a lesser extent the C-4 one) is partially obscured by the guanosine C-4 and C-8 absorptions, but the feature of the spectrum indicates that they are not removed from their previous positions in the free ligand by more than 0.5 ppm. In this instance, the most affected nuclei are C-3 and C-7, locating the interaction site with the metal at the amido group.

Infra-red

The infra-red spectrum of the (A) species displays six distinct absorptions in the 1550–1700 cm^{-1} region. By comparison with known platinum–guanosine complexes, the three strong absorptions at 1685, 1620 and 1580 cm^{-1} may be considered as characteristic features of guanosine (N-7)–platinum coordination [16, 17]. The remaining bands (1635, 1595 and 1565 cm^{-1}) which also appear in the (B) spectrum have to be attributed to the nicotinamide moiety. In fact all the characteristic absorptions found in the (B) spectrum may be observed in the (A) spectrum and lead to the same conclusions. The disappearance of the NH_2 deformation modes (situated at 1180, 770 and 630 cm^{-1} in the free ligand), and the concomitant appearance in (A) and (B) spectra of new bands at 1285 and 820 cm^{-1} (which may be attributed to deformation modes of NH and NCO groups), supports the involvement of the deprotonated NH_2 group in bonding of the metal. However, the behaviour of the so-called 'amide bands' suggests that the oxygen and the nitrogen of the amido group are both bonded to the platinum. From a consideration of their own characters, the amide I band (mainly ν_{CO}) on the one hand, and the amide II and III bands (mainly δ_{NH} and ν_{CN}), on the other, are expected to undergo opposite shifts upon complexation via one amide site (oxygen or nitrogen) [25, 26]. These three bands actually suffer similar shifts to lower frequencies: from 1675 to 1620 (amide I), from 1615 to 1560 (amide II) and from 1380 to 1290 cm^{-1} (amide III). In the (B) spectrum a rather broad band is observed at 315 cm^{-1}, attributed to ν_{PtCl}. This absorption is lacking in the (A) spectrum.

ESR

The (A) and (B) complexes are paramagnetic, judging from magnetic susceptibility measurements (B) [14] and electron-spin resonance spectroscopy (A) and (B). ESR signals are detected when (A) is studied in the solid state (powder) and in aqueous solution. Both sets of measurements yield practically identical g-values. Hyperfine interactions (only perceptible in the solid state) become reasonably well resolved in solution, and are not drastically affected by lowering the temperature from 200 to 70 K. These spectra may be interpreted in terms of an axially symmetrical ion. A strong absorption at about 2850 G is attributed to the perpendicular

component ($g_\perp = 2.41_8$) and a weaker one at ~3480 G to the parallel ($g_\parallel = 1.97_9$). The large g-shift (≅0.44) characterizing the main absorption suggests considerable spin–orbit coupling of the odd-electron, which is a typical behaviour of paramagnetic heavier transition metal ions. Very similar data have been gained from ESR spectra of the one-dimensional chain compound $K_2Pt(CN)_4Br_{1/3}\cdot 3H_2O$ ($g_\parallel = 1.946$, $g_\perp = 2.336$) [27]. of Pt(IV) doped Magnus' green salt ($g_\parallel = 1.932$; $g_\perp = 2.504$) [28]. of various Pt(III) complexes produced by γ-irradiation [29, 30], such as $[Pt(C_5H_5)_4]^{3+}$ ($g_\parallel \cong 2$; $g_\perp = 2.377$) [30] or of the *cis*-diamine platinum α-pyridone blue ($g_\parallel = 1.976$; $g_\perp = 2.376$) [4]. These results have been interpreted in terms of d_{z^2}-like hole state with an admixture of the degenerate $d_{xy,yz}$ state due to spin–orbit interaction. Keeping into consideration second-order perturbation terms, the following g-values are calculated [31, 32]

$$g_\parallel = 2N^2 - 3N^2(\xi/\Delta E)^2;$$

$$g_\perp = 2N^2 + 6N(\xi/\Delta E) - 6N^2(\xi/\Delta E)^2$$

where N is the normalization coefficient for the zero-order wave functions arising from the spin–orbit interaction, ΔE is the average energy separation between the d_{z^2} and $d_{xz,yz}$ states and ξ is the parameter of the spin coupling. Substitution of the experimental g-values in these two expressions yields N = 0.998 and ξ/ΔE = 0.076 which may be compared with the values of N = 0.977 and ϵ/ΔE = 0.071 in the *cis*-diammineplatinum α-pyridone blue [4].

Another interesting feature of the (A) spectrum is the appearance of a hyperfine pattern which is particularly well-resolved in the perpendicular component (Fig. 2). The two main singlet lines corresponding to $g_\parallel$ and $g_\perp$ are accompanied by weaker doublet satellite lines separated by 205 and 297 × 10^{-4} cm^{-1} respectively. These splittings may be assigned to the hyperfine interaction of the unpaired electron with a ^{195}Pt nucleus, the only stable isotope with a ½ spin. Since its natural abundance is 33.7%, the relative absorption strength of one of the doublet components to the main singlet should be 0.25, in good agreement with the experimental intensity distribution. This simple pattern contrasts with the extensive coupling observed in the spectrum of α-pyridone blue in solution [5]. Bearing in mind that this extensive hyperfine coupling has been related to the delocalization of the unpaired electron over several platinum centers, the three-line pattern strongly suggests the occurrence of localized unpaired spin in (A). Moreover, the hyperfine interaction parameters deduced from the experimental hyperfine coupling constants are consistent with such a hypothesis.

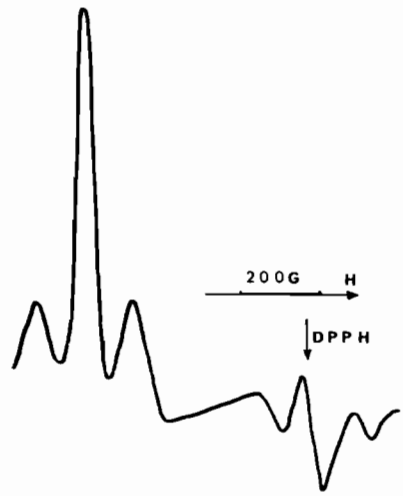

Fig 2. EPR spectrum of the (A) complex in D_2O (9 623 MHz, 100 K)

These parameters may be obtained from a crystal-field treatment which, according to Krigas and Rogers [29], leads to the following equations:

$$A_\parallel = -K + P[4N^2\beta^2 + 12(\xi/\Delta E)^2 - 6(\xi/\Delta E)N]/7$$

$$A_\perp = -K + P[-2N^2\beta^2 - 9(\xi/\Delta E)^2 + 45(\xi/\Delta E)N]/7$$

where N, ξ and ΔE are as above (N = 0.998; ξ/ΔE = 0.076), K is the isotropic hyperfine interaction, β^2 the total spin density in the d_{z^2} orbital and $P = g_e g_N \beta_e \beta_N \langle r^{-3}\rangle_{5d}$. Assuming that the covalency is negligible ($\beta^2 = 1$) and the experimental values, $|A_\parallel| = 205 \times 10^{-4}$ cm^{-1} and $|A_\perp| = 297 \times 10^{-4}$ cm^{-1} are both negative, gives:

$P = 317 \times 10^{-4}$ cm^{-1}, $\langle r^{-3}\rangle_{5d} = 8.2$ a.u.

$K = 367 \times 10^{-4}$ cm^{-1} and $\chi = -14.4$ a.u.,

χ (the core polarization hyperfine field per unit spin) being obtained from K by the equation [29, 33]:

$$\chi = -3/2\ (h\ ca_o^3/g_e g_N \beta_e \beta_N)K$$

The relatively close agreement (in both sign and order of magnitude) between these values and the data relating to the free ion Pt^{3+}, i.e. [29]: P = 509 × 10^{-4} cm^{-1}, $\langle r^{-3}\rangle_{5d} = 8.4$ a.u., $\chi = -20.5$ a.u., supports our hypothesis concerning the origin of the hyperfine structure in the (A) spectrum. The agreement is even better if one considers the $[PtCl_5]^{2-}$ species which is characterized by the following values [29]:

$P = 321.10^{-4}$ cm^{-1}; $\langle r^{-3}\rangle_{5d} = 8.4$ a.u.;

$X = -22.6$ a.u.

The quantity $\langle r^{-3} \rangle_{5d}$ displays the same value in (A) and in the mononuclear ion $[PtCl_5]^{2-}$, where the delocalization of the unpaired spin over a number of platinum centers is doubtful.

Conclusions

From the afore-mentioned results it is clear that the (A) species displays the main features observed with other blue compounds. However, a striking difference is found in the ESR spectra which show a simple pattern suggesting that coupling of the free electron would occur with one ^{195}Pt nucleus. Furthermore, these ESR spectra remain practically identical whether the substance is studied in the solid state (powder) or in fresh aqueous solution and, in this instance, they are not widely affected by temperature variations. Therefore it is likely that (A) maintains an oligomeric structure upon initially dissolving in water [34] and that NMR data (solution) may be used in conjunction with EPR and IR results (solid) to gain structural information.

The analytical data may be accommodated by assuming a formulation such as $[Pt_n(NiC-H, Cl)_n\text{-}Guo_{2n}]Cl_{4,2n}$. From NMR and IR data, it is very likely that on the one hand, guanosine is acting as a unidentate ligand through N-7 and 1-methylnicotinamide as a bidentate through the oxygen and the nitrogen of the deprotonated amido group and, on the other, no Pt–Cl bond remains in the structure of (A).

The suggested formulation implies that the n platinum atoms are responsible for a (2n + 1) charge and, therefore, that each of them displays a formal oxidation state equal to 2 + 1/n, *i.e.* 2.25 if n = 4 or 2.20 if n = 5. This conclusion is supported by oxidation titration measurements. This was not quite unexpected, since the hypothesis of platinum in a non-integral formal oxidation state has previously been put forward and experimentaly established in a few instances. Nevertheless the 2.25 and 2.20 values cannot be explained in a four (or five) platinum unit by the simultaneous occurrence of Pt(II) and Pt(IV), but may be described in terms of one Pt(III) associated with (n – 1) Pt(II). This arrangement would be consistent with the ESR data which strongly suggest that the actual paramagnetic species, in solution and in the solid state, is a Pt(III) ion. However the description of (A) in the usual terms of delocalized mixed-valent species does not seem fully appropriate and this compound would be better considered as a localized mixed-valent species, involving Pt(II) and Pt(III) in an oligomeric unit. On the basis of ESR spectra, this feature, which may be extended to the (B) species, is not likely shared by all other known platinum blues.

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