A Platinum Blue Complex of a Sugar Molecule bearing an Amidoxime group

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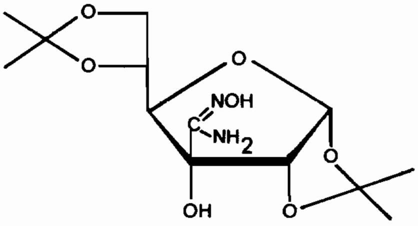
The family of organometallic compounds known as Platinum Blues has been intensively investigated [1] since the discovery of their antitumor activity associated with low toxicity [2]. Furthermore they show peculiar physico-chemical properties (blue color, paramagnetism) which allow them to be considered as unusual platinum complexes. They are generally obtained from amide or lactam ligands reacting with aquo species of cis-diammine platinum (II) [3] or K_2PtCl_4 [4].

Taking the potential biological effect of these compounds into account, it is desirable to find ligands which facilite the transport and increase the solubility of these complexes. With this in view, a preliminary essay was made using a carbohydrate molecule bearing an amidoxime group (I) and here we report the evidence of a novel Platinum Blue formed in this reaction. We also show the importance of oxidizing agents (atmospheric oxygen, Ce(IV) ions) for the preparation of this Platinum Blue complex.



(I)

Experimental

The preparation procedure and the crystal structure of (I) will be described in detail elsewhere [5]. *cis*-Diamminedichloro platinum(II) (*cis*-DDP) was purchased at Johnson Matthey and used without further purification.

Preparations

A solution of the *cis*-diammine platinum(II) hydrolysis product was prepared by mixing 1 g of *cis*-DDP and 1.13 g of $AgNO_3$ in 5 ml of water. After a night in the dark, under stirring, at room temperature, the solution was centrifuged to remove the AgCl precipitate.

a) Reaction in the Presence of Oxygen (Air)

120 mg (3.7×10^{-4} mol) of ligand (I) were dissolved under vigorous stirring in 2.5 ml of D_2O. The resulting limpid solution was added to 555 μl (3.7×10^{-4} mol) of the *cis*-diamminediaquo platinum(II) aqueous solution finally giving a colourless solution. A. This reactive mixture was kept at 273 ± 5 K for a day. The solution slowly turned blue.

b) Reaction in the Absence of Oxygen

120 mg (3.7×10^{-4} mol) of ligand were dissolved in 2.5 ml of D_2O previously deoxygenated by bubbling argon. Then 555 μl of the *cis*-diamminediaquo platinum(II) aqueous solution were added, under an argon atmosphere, and the bubbling was continued for 1 h. The resulting solution (solution B) was allowed to react at 273 ± 5 K in a tightly closed NMR tube.

Measurements

Electronic spectra were recorded on a PYE UNICAM SP 1800 spectrophotometer in the 800–300 nm range. NMR spectra were recorded on a BRUCKER WH 360 operating in the Fourier transform mode. ^{13}C-NMR spectra were obtained directly at 274 ± 2 K, with the reaction mixture prepared in D_2O.

ESR spectra were recorded at 77 K on a BRUCKER ER 200 D spectrometer (X-band, 100 KHz field modulation) The klystron frequency for each spectrum was measured using a transfer oscillator and a RACAL frequency meter.

Results

Solution B, from which oxygen had been excluded, was studied 24 h after its preparation by electronic spectrophotometry, ^{13}C-NMR and ESR. It remained colorless and no ESR signal was detected. The ^{13}C-NMR spectrum was only slightly different from the free ligand spectrum with a small shift ($\simeq$ +4 ppm) of the transition at 156.9 ppm attributed

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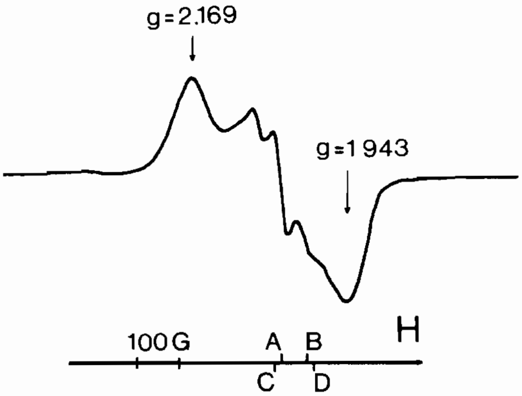

Fig. 1. ESR spectrum obtained at 77 K with an aqueous solution of compound (I) after reaction with *cis* DDP (blue solution). The field values marked A and B correspond to the 'parallel' (M_I = 1, −1) transitions for a nitroxide radical [6]. C and D correspond to the 'parallel' transitions for an iminoxy radical [7]

to the amidoxime C′(3) carbon. The colourless solution A, freshly prepared (1 h) and kept in contact with air at 273 K gave rise to a ^{13}C-NMR spectrum similar to that obtained with the pure ligand. 24 h later, the solution colour had turned pale green but no ESR spectrum could be observed. After two days it had acquired a blue coloration and a broadening of the NMR lines was observed; the C′(3) signal had decreased and a new transition was observed at around 215.5 ppm. The other peaks were only slightly shifted but they showed a complicated shape compatible with the existence of several oligomeric species. ESR signals appeared simultaneously with the blue coloration. An example of an ESR spectrum obtained with a frozen blue solution (77 K) is shown in Fig. 1. The intensity of the ESR transitions initially increased with the reaction time, passing through a maximum, and then decreased. This behaviour parallels the variation of the optical density at 735 nm.

Discussion

The experimental results show that, in the presence of oxygen, *cis*-DDP and an allofuranose derivative bearing an amidoxime group in the C(3) position can give rise to a blue paramagnetic species whose ESR spectrum ranges over 200 G. Such a spectrum does not seem to be consistent with a simple organic free radical (*e.g.*: $R_2C{=}N{-}O$ (iminoxy) or $R_2N{-}O$ (nitroxide)) (Fig. 1) and leads us to identify this species as a paramagnetic platinum complex of (**I**). The modification of the C′(3) NMR transition shows that a 'Pt(II)L' complex – involving a coordination with the oxime nitrogen atom – is probably produced during the formation process of the paramagnetic blue complex. This hypothesis has been checked by adding 20 mg of $Ce(SO_4)_2$ to the colourless solution B, 24 h after its preparation. This solution immediately became paramagnetic and turned blue. Such behaviour is in good accord with the following scheme:

$$\text{'Pt(II)L'} + \text{Ce(IV)} \xrightarrow{\text{fast}} \text{Platinum Blue}$$

$$\text{'Pt(II)L'} + \text{O}_2\text{(air)} \xrightarrow{\text{slow}} \text{Platinum Blue}$$

It is worth emphasizing the pattern of the ESR spectrum. The simplest spectrum is obtained immediately after addition of Ce(IV) ions to solution B. A further oxidation of the solution leads to some slight modifications in the spectrum which probably indicate that several neighbouring species contribute to the final spectrum – this is in good accordance with the ^{13}C-NMR spectrum which shows the sample's complex nature (*vide supra*). Although platinum(II) or (IV) complexes are generally diamagnetic, some mixed valence monodimensional complexes and 'Platinum Blues complexes' exhibit ESR spectra which are characterized by an axial g tensor: $g_\perp \simeq 2.4$ and $g_\parallel \simeq 1.9$ [1]. These spectra are generally interpreted in terms of a d_{z^2} hole state. The ESR spectrum shown in Fig. 1 is clearly different from those obtained with the 'usual' Platinum Blues. Its g anisotropy is smaller than that observed with amide or lactam ligands and does not have an axial symmetry.

In conclusion, we have shown that a blue paramagnetic species is produced when *cis*-diamminediaquo platinum(II) is allowed to react with an amidoxime function in the presence of an oxidizing agent. Moreover, the investigated ligand is particularly suitable for biological application and corresponds to the first example of an Amidoxime–Platinum Blue complex. Studies are presently in progress to investigate further the reactions occurring between *cis*-DDP and a $C(NH_2)NOH$ moiety.

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