Short Communication

Oxidation of the complex *cis*-$[(NH_3)_2Pt(N(3)\text{-}1\text{-}MeC)(N\text{-}gly)](NO_3)\cdot 2H_2O$. An unusual rearrangement of the initial N(3) coordination of 1-MeC with Pt(II) to a final amino coordination with Pt(IV)

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Abstract

The oxidation of the (1-methylcytosine)–Pt(II)–(glycine) ternary complex *cis*-$[(NH_3)_2Pt(N(3)\text{-}1\text{-}MeC)(N\text{-}gly)](NO_3)$ with $S_2O_8^{2-}$, to its Pt(IV) analog was carried out in aqueous solution. The reaction was accompanied by chelation of the amino acid and rearrangement of the N(3)-coordinated nucleobase, producing a final product of the formula *cis*-$[(NH_3)_2Pt(H_2N(4)\text{-}1\text{-}MeC)(N,O\text{-}gly)(H_2O)]_2(SO_4)_3$. The structure of this complex was examined by means of ^1H NMR spectroscopy and a reaction path involving a bischelated intermediate is proposed to account for its formation.

Introduction

It is known that Pt(II) complexes of amino acids can readily be oxidized to the corresponding Pt(IV) with Cl_2 or H_2O_2 [1–6]. If the amino acid is ($-NH_2$) coordinated in a monodentate fashion, oxidation is followed by N,O chelation.

It is also known that complexes of $(NH_3)_2Pt^{2+}$ with nucleobases like 1-methyluracil [7] or 1 methylcytosine [8] may be oxidized by Cl_2 or H_2O_2 to the corresponding Pt(IV) complexes. Oxidation replaces a hydrogen by a chlorine at the C(5) or adds to the C(5)=C(6) double bond in the case of 1-methyluracil [7], while in the case of 1-methylcytosine an N(3),N(4) chelate (involving the N(4) amino group) is formed in the final product [8].

In the case of the ternary complex *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(gly)]^+$ [9], with the nucleobase coordinated through N(3) and the aminoacid through ($-NH_2$), two optical isomers are expected to be formed after oxidation to Pt(IV) and subsequent N,O chelation of glycine [1–5]. This well characterized complex was selected for oxidation not only for its simple and very well known structure but also for its stability towards *cis* to *trans* isomerization found to occur with other similar ternary complexes [9]. The possible isolation of the two expected enantiomers was among the aims of our study.

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Experimental

0.15 g *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(gly)](NO_3)\cdot 2H_2O$, prepared according to the literature [9], was dissolved in 4 ml H_2O and to this solution a solution of 0.08 g $K_2S_2O_8$ dissolved in 6 ml H_2O was added slowly under stirring. After stirring the mixture for 2 h at room temperature the pH of 1.5 was raised to 5.0 by the addition of 0.1 N KOH. The mixture was evaporated to a small volume under vacuum, loaded onto a Sephadex G-10 column and eluted with water. The product was eluted in the early fractions and isolated as a yellow powder after freeze drying (yield 22% based on the metal).

Results and discussion

Attempts to oxidize the ternary complex with Cl_2 or H_2O_2 were unsuccessful, leading to the decomposition of the starting complex. The best results were obtained using a stoichiometric amount of $K_2S_2O_8$ or $(NH_4)_2S_2O_8$. These caused a drop in the pH of the reaction mixture from 5.5 to a value of 1.5 and to the appearance of a yellow color. The oxidation reaction can be represented as follows:

$$2cis\text{-}[(NH_3)_2Pt(N(3)\text{-}1\text{-}MeC)(N\text{-}gly)](NO_3) + 2S_2O_8^{2-} + 2H_2O \xrightarrow{2\,h} cis\text{-}[(NH_3)_2Pt(H_2N(4)\text{-}1\text{-}MeC)(N,O\text{-}gly)(H_2O)]_2(SO_4)_3 + SO_4^{2-} + 2NO_3^- \quad (1)$$

The product of reaction (1) was only 60–70% pure as observed by ^1H NMR spectroscopy, while methods of further purification did not improve it. The ^1H NMR

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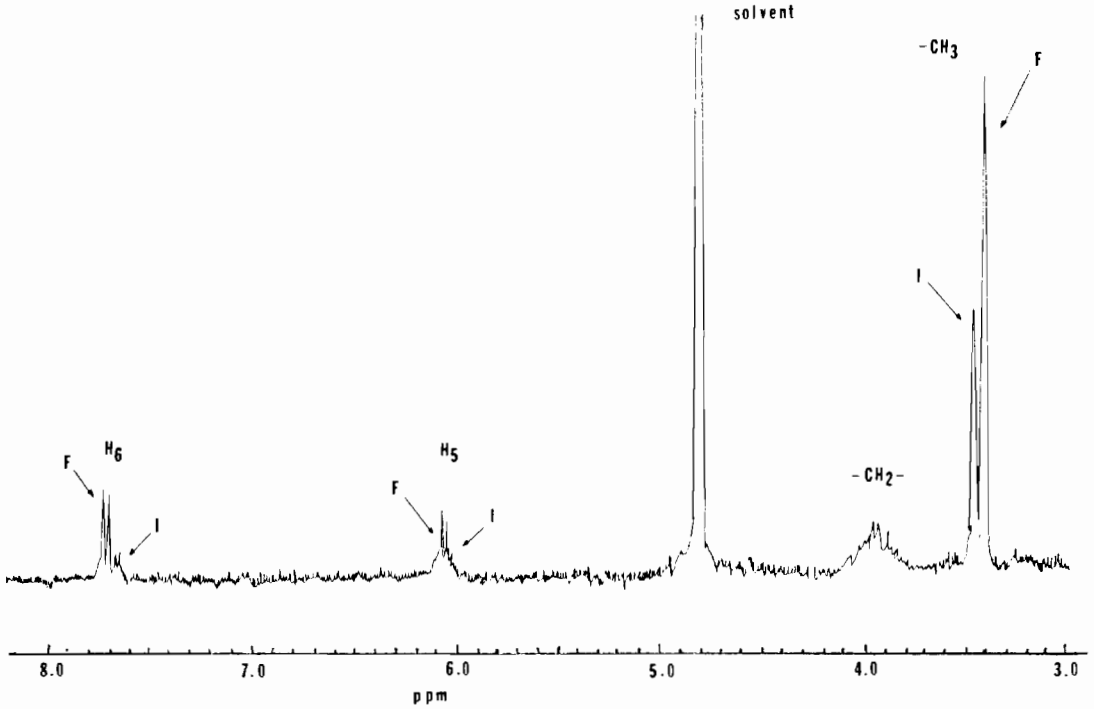


Fig. 1. ^{1}H NMR spectrum (300 MHz) of the reaction mixture of *cis*-$[(NH_3)_2Pt(N(3)\text{-}1\text{-}MeC)(N\text{-}gly)]^+$ by $S_2O_8^{2-}$. Crude product, *cis*-$[(NH_3)_2Pt(H_2N(4)\text{-}1\text{-}MeC)(N,O,\text{-}gly)(OH_2)]^{3+}$, pD = 4.3, F = Final product, I = Intermediate product.

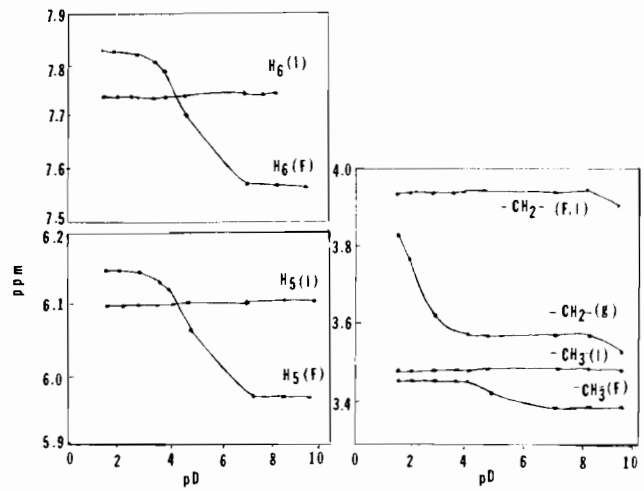
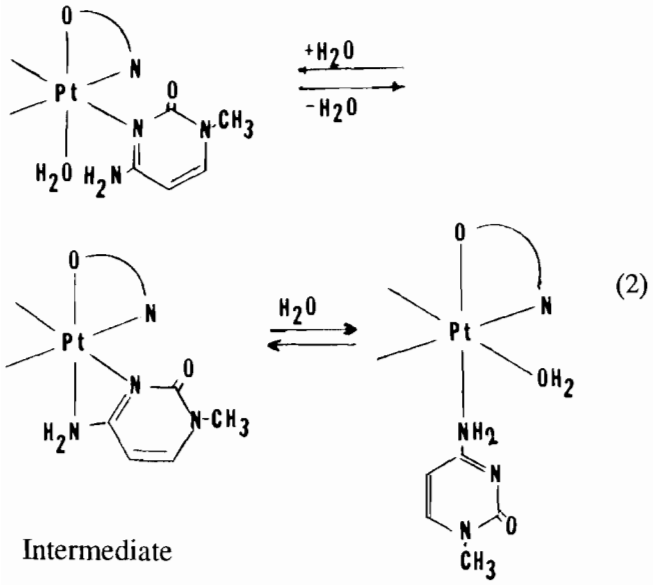


Fig. 2. Chemical shifts of the protons of free gly (g), the oxidation product $[(NH_3)_2Pt(H_2N(4)\text{-}1\text{-}MeC)(N,O\text{-}gly)(OH_2)]^{3+}$ (F) and the intermediate $[(NH_3)_2Pt(N(3),H_2N(4)\text{-}1\text{-}MeC)(N,O\text{-}gly)]$ (I) as a function of pD.

spectrum of the product obtained at the end of the reaction is shown in Fig. 1.

The initial doublet at 7.5 ppm assigned to the H(6) proton of the coordinated 1-MeC of the starting complex, is changed to two doublets at 7.8 and 7.7 ppm in about 2:1 proportion, as the integration shows, pD = 4.7. The band at 7.7 ppm is due to an intermediate product, since it is diminished gradually during the reaction. Similar changes are also observed in the bands at 6.0 and 3.4 ppm, corresponding to H(5) and the 1-methyl group of 1-MeC of the starting complex. The initial resonance at 3.25 ppm of N-coordinated glycine is replaced by a multiplet at about 4.0 ppm in the final product. The two methylene protons of gly, being equivalent to the N-monocoordinated gly [9] or the N,O chelated gly in *cis*-$[(NH_3)_2Pt(gly)]^+$ [10], where the coordination plane of Pt(II) is also a symmetry plane of the molecule, show only one singlet in the ^{1}H NMR spectra. However, in the reaction product, *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(N,O\text{-}gly)(H_2O)]_2(SO_4)_3$, N,O-chelation of gly [1–6] causes inequivalency of the two methylene protons (since the carboxylate oxygen can occupy only an axial position) and separated signals are expected [11]. As a consequence, a multiplet centered at about 4.0 ppm is observed, being the result of two separate signals for each of the final and intermediate products of the reaction and possibly of the two expected enantiomers for each, coupled with ^{195}Pt.

The pD dependence of the various protons H(5), H(6), CH_3(1) or 1-MeC and $-CH_2-$ of gly are given in Fig. 2. The gly $-CH_2-$ protons do not show pD dependence, indicating the N,O chelated coordination of the amino acid. The pD dependence of the three protons H(5), H(6) and CH_3(1) of 1-MeC in the final product, however, show the breaking of the initial Pt–N(3) bond of the starting complex. The nucleobase is still coordinated to Pt(IV), since all the proton



Intermediate

Final

(2)

resonances are shown downfield compared to the free 1-MeC. In the intermediate product there is no pD dependence of the above protons, showing the retention of the Pt–N(3) bond in it. These results may be interpreted with the reaction taking place in eqn. (2). This implies an N(3),NH_2(4) chelated structure of 1-MeC in the intermediate oxidation product and an NH_2(4) monocoordinated ligand in the final product.

From Fig. 2. the pK_a of the reaction

$$[(NH_3)_2Pt(N(3)H\text{-}1\text{-}MeC)(N,O\text{-}gly)(OH_2)]^{2+} \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} [(NH_3)_2Pt(N(3)\text{-}1\text{-}MeC)(N,O\text{-}gly)(OH_2)]^{3+} \quad (3)$$

can be estimated to be $pK_a = 4.8$.

The larger downfield shifts of the H(5) and H(6) protons of 1-MeC of the final oxidation product, compared to the ones of the starting complex, are expected as a consequence of protonation at N(3) of the base in the former versus metallation in the latter.

A similar result was also found in the case of the oxidation of other Pt(II)–1-MeC complexes [12].

Two enantiomers are naturally expected for both proposed structures of the intermediate and final products above. Attempts to separate the two products by conventional chromatographic techniques (e.g. gel filtration) have so far been unsuccessful. Attempts to separate the expected enantiomers of both complexes were also unsuccessful. An extension of the oxidation studies to other similar ternary complexes [9] is in progress.

Acknowledgement

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