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LETTER

Behaviour of the organometallic complex *cis*-dimethylbis[sulfinyl-bis[methane]-*S*]-platinum(II) in aqueous solution

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In recent years, there has been an intense interest in the synthesis and kinetic studies of platinum(II) complexes containing sulfoxide ligands [1]. More recently, *cis*-[Pt(OOCACOO)(Me_2SO)$_2$] (A = CH_2, cycloalkyl) complexes have been used as versatile synthons for a general synthesis of antitumor symmetrical and dissymmetrical (malonato)platinum(II) compounds [2], and the preparation and antitumor activity of complexes of formula [PtCl(R'R"SO)(diam)]$^+$ (diam = bidentate amine; R'R"SO = substituted sulfoxides), the first well-defined antitumor platinum compounds containing sulfur as ligand, have been reported [3]. We have been interested in the study of displacement of sulfur-bonded dimethyl sulfoxide and thioethers (L) from *cis*-[Pt(R)$_2$(L)$_2$] (R = Me or Ph) by chelating ligands in benzene and dichloromethane [4]. During these studies, we found that the complex *cis*-[$PtMe_2(Me_2SO)_2$] (**1**) is soluble in water. This fact and the increasing acceptance that antitumor activity is not strictly limited to complexes of the type *cis*-[$PtCl_2(NH_3)_2$], prompted us to check the antitumor activity of **1** and we found that it is active *in vivo* against the sarcoma ascites yoshida tumor [5]. Therefore, we have studied the behaviour of *cis*-[$PtMe_2(Me_2SO)_2$] in water and its reactions with bases, acids and anions through NMR spectroscopy. We report the results in this paper.

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Experimental

Synthesis of cis-[$PtMe_2(Me_2SO)_2$]

cis-Dimethylbis[sulfinyl-bis[methane]-*S*]platinum-(II) was prepared by reacting *cis*-[$PtCl_2(Me_2SO)_2$] with $SnMe_4$ in Me_2SO according to the method of Eaborn *et al.* [6].

NMR spectra

Proton NMR spectra were recorded in D_2O at 300 MHz by using a Varian Gemini 300 spectrometer. Proton chemical shifts are relative to the methyl resonance of 3-(trimethylsilyl)propanesulfonate (TSS).

NMR titrations

Proton NMR titrations were carried out on a freshly prepared solution (5 ml) of **1** (0.01 M) in D_2O. An Orion model SA 520 pH meter with a combination glass/reference electrode calibrated against phosphate (pH 6.87) and borate (pH 9.18) buffer solutions was used for measurement of pD, and the correction factor pD = pH + 0.4 was applied. The stock solution of **1** has a pD of 8.25, and carbonate-free NaOD (1 M) was added in small increments to raise the pD. A 1-ml aliquot was removed and placed in an NMR tube (5 mm diameter), which was then placed in the instrument. The glass electrode remained covered by the solution remaining in the sample vessel. After the pD measurement, the aliquot was recombined with the bulk sample, and more NaOD was added to change the pD to a new value. All NMR measurements were carried out at magnet temperature (22 °C) without regulation of the probe temperature; pD measurements were also done at room temperature, 22 ± 2 °C.

Results and discussion

Hydrolysis of cis-[$PtMe_2(Me_2SO)_2$]

The proton NMR spectrum of a solution of **1** (0.01 M) in D_2O shows clearly that two compounds and free Me_2SO are present (Fig. 1). The pattern of the main species is the same as that reported for *cis*-[$PtMe_2(Me_2SO)_2$] in $CDCl_3$ [6] and presents the expected resonances for the methyl protons at 0.674 ppm (J(Pt–H) = 78 Hz) and for the dimethyl sulfoxide protons at 3.236 ppm (J(Pt–H) = 13 Hz) with the correct ratio of intensities. The coupling of the methyl resonances of Me_2SO with ^{195}Pt confirmed the bonding through sulfur in the aqueous solution and the low coupling constant is consistent with the presence of a strong *trans* influence ligand in the *trans* position,

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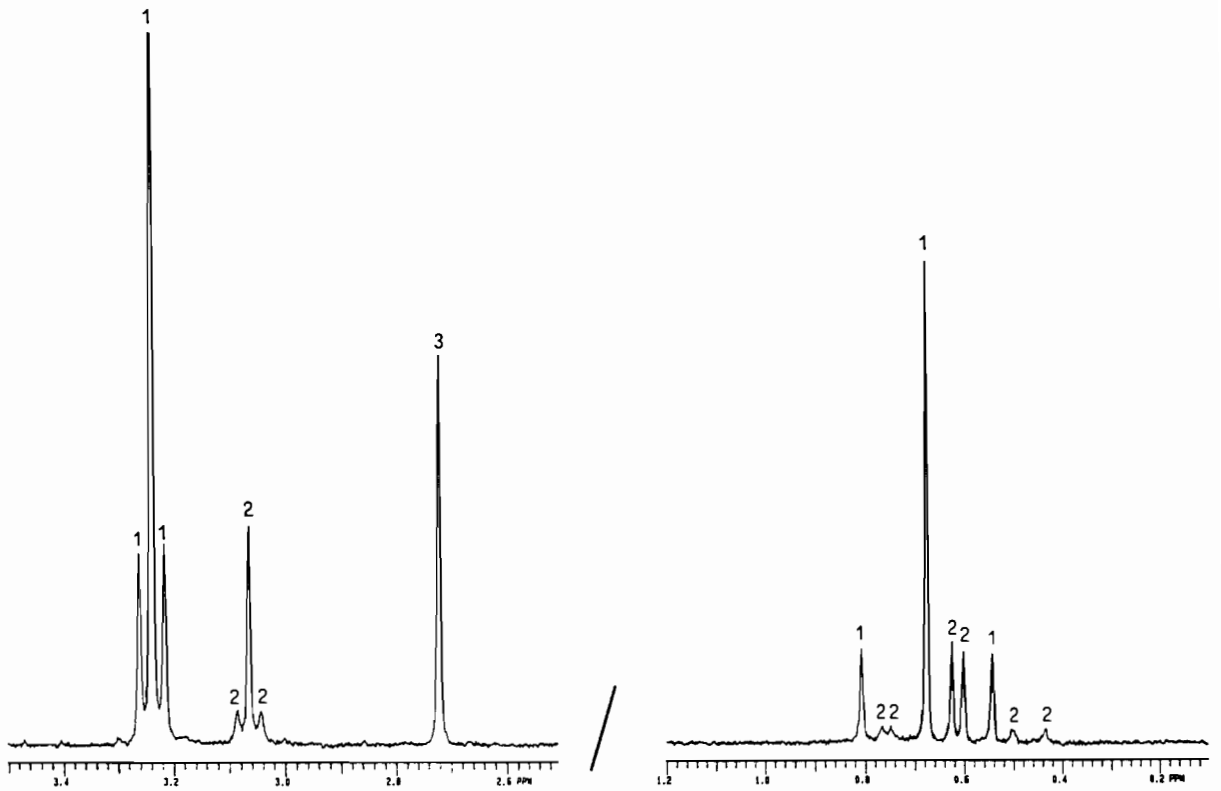

Fig. 1. ^{1}H NMR spectra (300 MHz) of equilibrium mixture of *cis*-[$PtMe_2(Me_2SO)_2$], *cis*-[$PtMe_2(Me_2SO)(D_2O)$] and free Me_2SO. Peaks labelled 1 are due to *cis*-[$PtMe_2(Me_2SO)_2$], 2 due to *cis*-[$PtMe_2(Me_2SO)D_2O$)] and 3 due to Me_2SO.

thereby indicating that the *cis* configuration is retained. The new species shows a single peak at 3.061 ppm (6 H) with ^{195}Pt satellites (J(Pt–H) = 12 Hz) due to the dimethyl sulfoxide protons and two singlets (6 H in all) of equal intensity, each with satellites from coupling to ^{195}Pt, corresponding to the methyl *trans* to Me_2SO (0.624 ppm, J(Pt–H) = 75 Hz) and to the methyl *trans* to water (0.601 ppm, J(Pt–H) = 100 Hz), respectively. These data are consistent with the formulation of the new species as *cis*-[$PtMe_2(Me_2SO)(D_2O)$] (**2**). The relative peak areas of the three species show that the hydrolysis of compound **1** can be represented by the equilibrium:

$$cis\text{-}[PtMe_2(Me_2SO)_2] + D_2O \overset{K_h}{\rightleftharpoons} cis\text{-}[PtMe_2(Me_2SO)(D_2O)] + Me_2SO$$

On the basis of the relative peak areas at equilibrium (established within the time required to record the NMR spectrum), the hydrolysis constant, K_h, is 1.3×10^{-3} M at $T = 295$ K (the average value obtained from five measurements in the concentration range 0.006–0.05 M is 1.1×10^{-3} M). Thus, about 70% of the starting complex **1** is present at equilibrium. The water-solubilising properties of dimethyl sulfoxide in its metal complexes is likely to be the factor promoting the good aqueous solubility of *cis*-[$PtMe_2(Me_2SO)_2$]. With the passing of time, the peak of free Me_2SO increases and decomposition occurs, leading to formation of a metallic mirror on the wall of the NMR tube. At the end of this process (about two days) only free dimethyl sulfoxide is present in solution. When [$^2H_6$]Me_2SO (0.02 mmol) was added to a freshly prepared solution of *cis*-[$PtMe_2(Me_2SO)_2$] (0.01 mmol) in D_2O, the signals in the Pt–CH_3 region due to the aquo complex suddenly vanished and only compound **1** and free Me_2SO were present. Therefore, the hydrolysis of **1** and the reverse reaction are fast, compared with the rate of hydrolysis of $[Pt(en)(Me_2SO)_2]^{2+}$ (rate constant 2.55×10^{-4} s^{-1}, $I = 0.1$; 30 °C) [7].

pK_a Determination

When the pD of a 0.01 M solution of **1** in D_2O was increased to 13.83, the aquo complex **2** deprotonated to $[PtMe_2(Me_2SO)(OD)]^-$ (**3**), and corresponding changes occurred in the proton NMR spectrum (methyl *trans* to dimethyl sulfoxide 0.528 ppm, J(Pt–H) = 76 Hz; methyl *trans* to hydroxide 0.297 ppm, J(Pt–H) = 88 Hz). The singlet of the coordinated Me_2SO was observed at 3.057 ppm

(J(Pt–H) = 13 Hz) and was in the ratio 1:1 with the free dimethyl sulfoxide. A very small amount of *cis*-[$PtMe_2(Me_2SO)_2$] was still present. No change was observed when this solution was allowed to stand overnight. On the other hand, **3** was the only product when the solution was prepared in $NaOD/D_2O$ 2.5 M. Because of the variety of the species in equilibrium present in solution, it would be difficult to determine the acid dissociation constant K_a for coordinated water in *cis*-[$PtMe_2(Me_2SO)(D_2O)$]. However, in this case, proton NMR spectroscopy provides a means for determining this constant. Aqua and hydroxo species are in fast exchange on the NMR time-scale, due to a fast protonation/deprotonation process, so that one singlet with satellites is expected for the methyl *trans* to aqua/hydroxo and one for the methyl *trans* to dimethyl sulfoxide. The shift of the methyl *trans* to aqua/hydroxo, which shows the largest chemical shift change during the titration, was chosen for measurement. The shift variation is given by eqn. (1) [8], where δ_A and δ_B are the chemical shifts for the protonated and deprotonated forms of the complex, respectively, and δ the chemical shift at measured pH.

$$pK_a = pH + \log[(\delta - \delta_B)/(\delta_A - \delta)] \quad (1)$$

The value of pK_a that gives the best (least-squares) fit of eqn. (1) to the experimental data (see 'Supplementary material') between pH 10.96 and 12.74 was calculated as 11.72. The experimental data are plotted in Fig. 2. This value of pK_a is very different from the value of 4.05 found by us [9] for the complex $[Pt(en)(Me_2SO)(H_2O)]^{2+}$ and from the values of pK_a typical of aqua complexes of Pt(II) containing sulfoxide ligands [10]. The difference could be in part due to the high *trans* influence of the methyl of *cis*-[$PtMe_2(Me_2SO)(D_2O)$], which would weaken the Pt–O bond and thereby decrease the acidity of the aqua ligand. However, the difference of ionic charge could also be important.

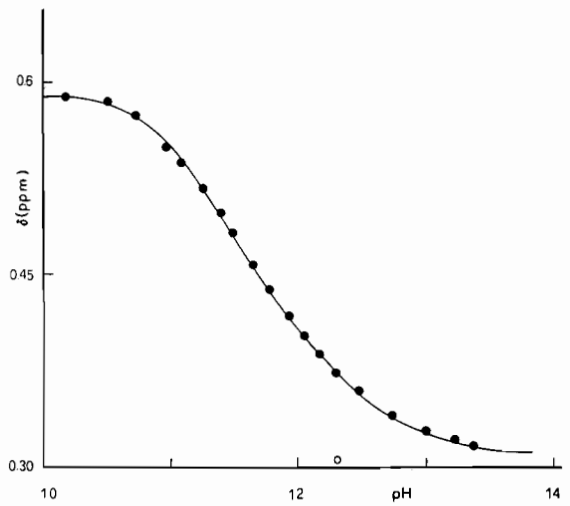

Fig. 2. pH dependence of the proton chemical shift of the methyl *trans* to D_2O/OD^- of *cis*-[$PtMe_2(Me_2SO)(D_2O)$].

Reaction with acids

When a known excess of D_2SO_4 (0.08 mmol) or $HClO_4$ (0.12 mmol) is added to 1 ml of a solution of *cis*-[$PtMe_2(Me_2SO)_2$] (0.01 M) in D_2O, the proton NMR spectrum changes suddenly, the CH_3–Pt signals disappear and a new species is formed with a singlet at 3.454 ppm (J(Pt–H) = 39 Hz) due to the coordinated Me_2SO. Free dimethyl sulfoxide is also present in the ratio 1:1 with the complex. This species is likely to be the compound $[Pt(Me_2SO)(H_2O)_3]^{2+}$, prepared *in situ* by Elding and Groning [11] by reacting $[Pt(Me_2SO)Cl_3]$ with a excess of $AgNO_3$. The protonolysis of an aqueous solution of *cis*-[$PtMe_2(Me_2SO)_2$] involves both the Pt–CH_3 bonds and occurs in a different way from the protonolysis of *cis*-[$PtMe_2(PEt_3)_2$] in methanol [12]. In the latter case, upon addition of a sufficient excess of an ethereal solution of HBF_4 (or aqueous $HClO_4$), *cis*-$[PtMe(PEt_3)_2(S)]^+$ (S = solvent) is formed, as evidenced by ^{31}P NMR.

Equilibrium data for anation reactions of 1

In investigating the antitumor activity, the complex *cis*-[$PtMe_2(Me_2SO)_2$] was dissolved in an aqueous solution of NaCl 0.154 M, used to approximate extracellular concentrations. When NaCl (0.154 mmol) is added to a solution (1 ml) of **1** (0.1 M) in D_2O, the proton NMR spectrum clearly shows that an equilibrium is established between the starting complex and a new species *cis*-$[PtMe_2(Me_2SO)(Cl)]^-$ (methyl *trans* to dimethyl sulfoxide 0.639 ppm, J(Pt–H) = 75 Hz; methyl *trans* to chloride 0.631 ppm, J(Pt–H) = 97 Hz; methyls of Me_2SO 3.114 ppm, J(Pt–H) = 11 Hz). On the basis of the relative peak heights, the equilibrium constant K_{Cl} is 0.07. When sodium azide is reacted in stoichiometric ratio with **1** in D_2O, the complex *cis*-$[PtMe_2(Me_2SO)(N_3)]^-$ is formed (methyl *trans* to Me_2SO 0.637 ppm, J(Pt–H) = 75 Hz; methyl *trans* to azide 0.544 ppm, J(Pt–H) = 91 Hz, methyls of dimethyl sulfoxide 3.041 ppm, J(Pt–H) = 12 Hz). The calculated equilibrium constant K_{N_3} is 7.9 and a ten times excess of azide is sufficient to completely form the product. The reaction does not proceed further. It is therefore clear that, in aqueous solution, the complex *cis*-[$PtMe_2(Me_2SO)_2$] readily loses one dimethyl sulfoxide for substitution by anionic nucleophiles. The second sulfoxide, however, remains bound to the platinum throughout. Usually both the dimethyl sulfoxides of **1** are substituted by neutral monodentate and bi-

dentate ligands [4, 6]. We suggest that, in our case, the π-acceptor properties [13] of the remaining Me_2SO may strengthen the Pt–S bond and prevent its substitution by anionic ligands.

Supplementary material

Table SI, giving the variation of NMR parameters with pH, is available on request from the authors.

Acknowledgement

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