Synthesis, Structure, and Facile Oxidation of a Novel 1,1′-Bis(*N,N*-dimethylaminomethyl)ferrocene Bridged Diplatinum Complex

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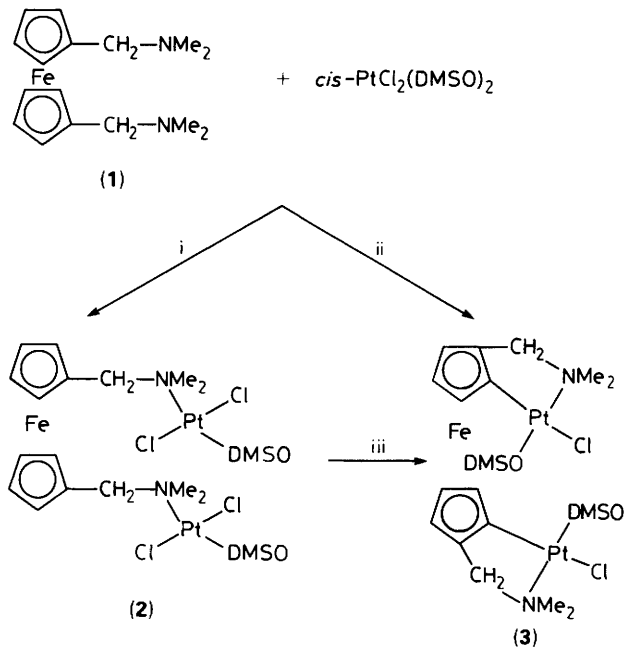
The reaction of *cis*-$PtCl_2(dmso)_2$ (dmso = dimethylsulphoxide) with the ferrocenyl amine $(\eta^5\text{-}Me_2NCH_2C_5H_4)_2Fe$ yields the readily oxidised, cyclometallated derivative $[\eta^5\text{-}PtCl(dmso)Me_2NCH_2C_5H_3]_2Fe$ through the intermediacy of the complex $[\eta^5\text{-}trans\text{-}PtCl_2(dmso)Me_2NCH_2C_5H_4]_2Fe$; an *X*-ray study of the cyclometallated species shows that the ferrocenyl bridged Pt atoms are located one above the other at a separation of 4.285(5)Å.

Interest in the role of inorganic and organometallic compounds as antitumour chemotherapeutic reagents has quickened in recent years with the discovery that numerous metallocene complexes display antitumour properties[1,2] which complement the activity of the well known cytostatic platinum complexes.[3,4] As part of our program of investigation into the antitumour potential of Pt^{II} complexes with ferrocenyl ligands,[5] we have examined the reactions of *cis*-$PtCl_2(dmso)_2$ (dmso = dimethyl sulphoxide) with the bidentate ligand 1,1′-bis(dimethylaminomethyl)ferrocene (**1**), Scheme 1. In acetone at 333—343 K, simple substitution of dmso produced the diplatinum complex $[\eta^5\text{-}trans\text{-}PtCl_2(dmso)Me_2CH_2C_5H_4]_2Fe$ (**2**)† as yellow crystals in 45% yield. In refluxing methanol, the same reagents gave the novel cyclometallated diplatinum complex $[\eta^5\text{-}PtCl(dmso)Me_2NCH_2C_5H_3]_2Fe$ (**3**)† as orange crystals in 40% yield. Metathetical reactions of (**3**) with the appropriate lithium salt gave the corresponding bromo, iodo, and acetato derivatives. The intermediacy of (**2**) in the cyclometallation process is confirmed by refluxing (**2**) in methanol for 0.5 h which gave (**3**) in high yield.

Crystals of (**3**) were examined by *X*-ray diffraction‡ and the solid-state structure is shown in Figure 1. The compound has two Pt^{II} atoms bridged by the diamine ligand. Cyclometallation results in the chelation of each Pt atom through the *ortho* carbon atoms of the cyclopentadienyl rings. The remaining co-ordination positions on each Pt are occupied by a chloride and an S-bound dmso ligand. The amine nitrogen atom co-ordinates *trans* to the dmso on each Pt. Chelation to the individual *N,N*-dimethylaminomethyl-cyclopentadienyl moi-

† Satisfactory elemental analyses were obtained. *Selected spectroscopic data* for (**2**): ^1H NMR ($CDCl_3$) δ 2.68 (s, 12H, $^3J_{Pt-H}$ 24.3 Hz, NCH_3), 3.37 (s, 12H, $^3J_{Pt-H}$ 18.0 Hz, SCH_3), 4.03 (s, 4H, CH_2N), 4.56—4.26 (m, 8H, C_5H_4); ^{195}Pt NMR ($CDCl_3$) δ −3060 p.p.m. (reference Na_2PtCl_6); $\nu_{S=O}$ 1146 cm^{-1}, ν_{Pt-S} 380 cm^{-1}, ν_{Pt-Cl} 340 cm^{-1}. For (**3**): ^1H NMR ($CDCl_3$) δ 2.60 (s, 3H, $^3J_{Pt-H}$ 34.0 Hz, NCH_3), 2.86 (s, 3H, $^3J_{Pt-H}$ 31.7 Hz, NCH_3), 3.06 (s, 3H, $^3J_{Pt-H}$ 30.2, NCH_3), 3.18 (s, 3H, $^3J_{Pt-H}$ 30.0 Hz, NCH_3), 3.52 (s, 3H, SCH_3), 3.53 (s, 3H, SCH_3), 3.60 (s, 3H, SCH_3), 4.10 (s, 3H, SCH_3), 3.98—4.62 (m, 6H, C_5H_3), NCH_3 and SCH_3 resonances differentiated by comparison with the spectrum of the $[^2H_6]$dmso derivative; ^{195}Pt NMR ($CDCl_3$) δ −3770, −3780 p.p.m.; $\nu_{S=O}$ 1130 cm^{-1}, ν_{Pt-S} 353 cm^{-1}, ν_{Pt-Cl} 273 cm^{-1}; FAB MS M^+ 915.

‡ *Crystal data* for $[\eta^5\text{-}Cl(dmso)PtMe_2NCH_2C_5H_3]_2Fe$; orange plates from CH_2Cl_2/methanol, monoclinic; a = 9.910(4), b = 10.331(4), c = 25.532(11) Å, β = 91.99(3)°, space group: $P2_1/c$, M = 915.57, D_c = 2.33 g cm^{-3}, Z = 4, μ(Mo-K_α) = 121.77 cm^{-1}. For the 2890 reflections collected (Nicolet P3 diffractometer at 138 ± 5 K with $I > 2\sigma I$), R is 0.0298, and R_w 0.0275. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 1. *Reagents and conditions*: i, 1 : 1, 333—343 K in dry, oxygen free acetone until the Pt complex dissolved; ii, 1 : 1, reflux < 353 K, 1 h, dry, oxygen free methanol; iii, reflux <353 K, 0.5 h, dry oxygen free methanol.

eties holds the Pt atoms one above the other at a separation of 4.285(5) Å, although there are no strong inter- or intra-molecular H-bonding interactions to impose this 'head-to-head'[6] arrangment of the Pt co-ordination planes. Indeed in the related compound (**2**), preliminary *X*-ray data[7] confirm that the platinum atoms adopt the alternative 'head-to-tail' configuration and are related by a crystallographic centre which accommodates the Fe atom of the ferrocenyl moiety. Head-to-head arrangements, however, are found in the μ-α-pyridone and μ-1-methylthyminato platinum blues and related compounds,[6] but in these molecules the smaller bite of the bridging ligands generally holds the Pt atoms within bonding distance of one another. In (**3**) the ring C atoms, the Pt–C σ bonds, and the Pt–Cl bonds are approximately eclipsed. However, the methylamine ring substituents are oriented transversely, allowing the Pt–N and Pt–S bonds to adopt roughly staggered conformations when viewed down the Pt····Pt vector. In order to minimise steric interactions between the chloro ligands and the methyl groups of the amine and sulphoxide ligands on the opposed Pt atoms, the Pt co-ordination planes are skewed away from each other [interplanar angle 27.1(1)°]. The angle between the ring planes of the ferrocene moiety is unexceptional at 4.9(4)°.

The solution behaviour of (**3**) is consistent with a facile equilibrium between two distinct forms. The ^{1}H NMR shows two sets of resonances with similar intensities for the amine protons (δ 2.604, 3.059 and 2.864, 3.184). However, the relative intensities of these sets of resonances vary with both temperature and solvent. Further, the ^{195}Pt NMR of (**3**) shows two distinct Pt resonances, which exhibit a similar intensity variation. Work is in progress to identify the species giving rise to this solution equilibrium.

Unexpectedly, (**3**) was found to be soluble in water and this feature together with interest in ferrocenium species, both as antitumour agents[1,2] and as drugs for sensitization in radiation therapy of hypoxic cell systems,[8,9] prompted an examination of the redox properties of (**2**) and (**3**). The chemically reversible one-electron oxidation of (**3**) is extremely facile,

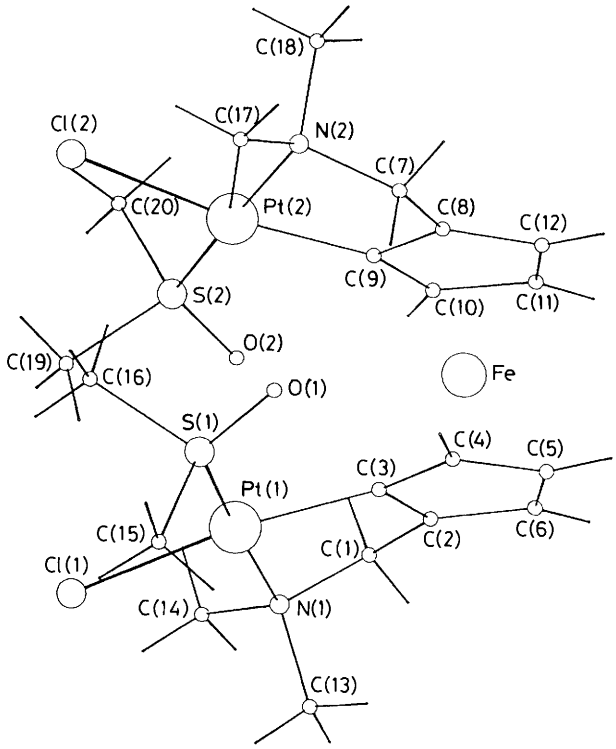


Figure 1. A view of the η^5-[PtCl(dmso)Me$_2$NCH$_2$C$_5$H$_3$]$_2$Fe molecule showing the atom numbering scheme. Relevant bond lengths Pt(1)–Cl(1) 2.412(2), Pt(1)–S(1) 2.204(2), Pt(1)–N(1) 2.142(7), Pt(1)–C(3) 2.010(10), Pt(2)–Cl(2) 2.422(2), Pt(2)–S(2) 2.191(2), Pt(2)–N(2) 2.130(7), Pt(2)–C(9) 2.001(9), Pt(1)·····Pt(2) 4.285(5) Å. Bond angles Cl(1)–Pt(1)–S(1) 90.9(1), Cl(1)–Pt(1)–N(1) 91.8(2), Cl(1)–Pt(1)–C(3) 172.0(3), S(1)–Pt(1)–N(1) 176.0(2), S(1)–Pt(1)–C(3) 95.8(3), N(1)–Pt(1)–C(3) 81.3(4), Cl(2)–Pt(2)–S(2) 90.9(1), Cl(2)–Pt(2)–N(2) 91.7(2), Cl(2)–Pt(2)–C(9) 172.7(3), S(2)–Pt(2)–N(2) 176.5(2), S(2)–Pt(2)–C(9) 94.9(3), N(2)–Pt(2)–C(9) 82.3(3)°.

[$E^{+/\circ}$ = 0.05 V *vs.* Ag/AgCl§ in acetone, 0.07 V *vs.* standard calomel electrode (SCE) in water] and contrasts sharply with the oxidation of (**2**) for which $E^{+/\circ}$ is 0.58 V *vs.* Ag/AgCl in acetone and in the range 0.38—0.51 V for a series of orthometallated ferrocenyl amine complexes containing a single platinum centre.[5] In water, (**3**) is spontaneously oxidised by oxygen to the green cation of (**3**), the rate of oxidation increasing markedly as the pH of the solution was lowered. Chemical oxidation ($AgBF_4$/acetone) also gave the cation of (**3**) as a green, air stable powder,¶ readily soluble in water. The ease of aerial oxidation of (**3**) opens up exciting possibilities for the *in vivo* production of ferrocenium species from platinum–ferrocene complexes. It is encouraging to note that (**3**) is one of a number of ferrocenyl amine complexes shown to exhibit low toxicity and to have significant activity against P388 tumours in mice.‖

§ Electrochemical solutions in acetone were 1.0 × 10^{-3} M in (**2**) and (**3**) and 0.1 M in tetraethylammonium perchlorate as the supporting electrolyte. Under identical conditions $E^{+/\circ}$ for the one-electron oxidation of ferrocene is 0.63 V *vs.* Ag/AgCl. Aqueous solutions of (**3**) (1.0 × 10^{-3} M) had KCl (0.5 M) as supporting electrolyte.

¶ Isolated as (**3**)$^+PF_6^-$; satisfactory analysis obtained; $\nu_{S=O}$ 1134 cm^{-1}.

‖ At the maximum dose administered, 32 mg kg^{-1} in peanut oil, the mean survival time was 15 days (control 10 days). Compound (**3**) also showed maximum activity at the highest dose level, suggesting that greater activity is possible.

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