

Reactivity of Novel *cis*-Platinum(II) Complexes with Thymidine Derivatives

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The first example of a facile reaction of a *cis*-platinum(II) complex with thymidine and substituted thymidines in dimethyl sulphoxide and dimethylformamide is reported and the adducts $\{[1,1'\text{-bis(diphenylphosphino)-ferrocene-}P,P']\text{Pt(nucleoside)(solvent)}\}^+$ are characterized by ^{31}P and ^1H n.m.r. spectroscopy.

The understanding of the mechanism of the primary interaction of *cis*-platinum(II) complexes with DNA appears to be a coveted goal for bioinorganic chemists.¹ The range of approaches devoted to this target spans from the investigation on the interaction of DNA or polynucleotides with *cis*-platinum complexes² to the analysis of the reactivity of 'simple' nucleobases towards a variety of platinum complexes containing a *cis*-Pt(ligand)₂ moiety.³

Particular attention appears to have been paid to the behaviour of guanine-based nucleotides or oligonucleotides as the consequence of the widely diffused conviction that guanine-containing sequences are primarily involved in the selective lesions of DNA caused by *cis*-Pt^{II} drugs in the relevant chemotherapy of cancer. No particular attention has been devoted to thymine-based derivatives, possibly because of the known very low metal ion bonding ability of the N(3) site in thymine nucleosides.⁴

During our studies on the chemistry and electrochemistry of simple heteropolymetallic phosphino complexes,⁵ on chemical and biological models of metal toxicity,⁶ and on the structure of synthetic polynucleotides, we found that *cis*-[(dppf)PtCl₂] (**1**) [dppf = 1,1'-bis(diphenylphosphino)-ferrocene-*P,P'*; {Fe(η⁵-C₅H₄PPh₂)₂}] is the precursor of a bimetallic *cis*-platinum(II) species which is very reactive with 3',5'-diacetylthymidine [Ac₂(dT)] in dimethyl sulphoxide (DMSO) and dimethylformamide (DMF). A combination of ^{31}P n.m.r. and voltammetric techniques[†] demonstrates in fact that just one chloride ligand can be removed from (**1**) by AgBF₄ in acetonitrile, acetone, DMSO, and DMF to give AgCl and species (**2**) (Scheme 1).

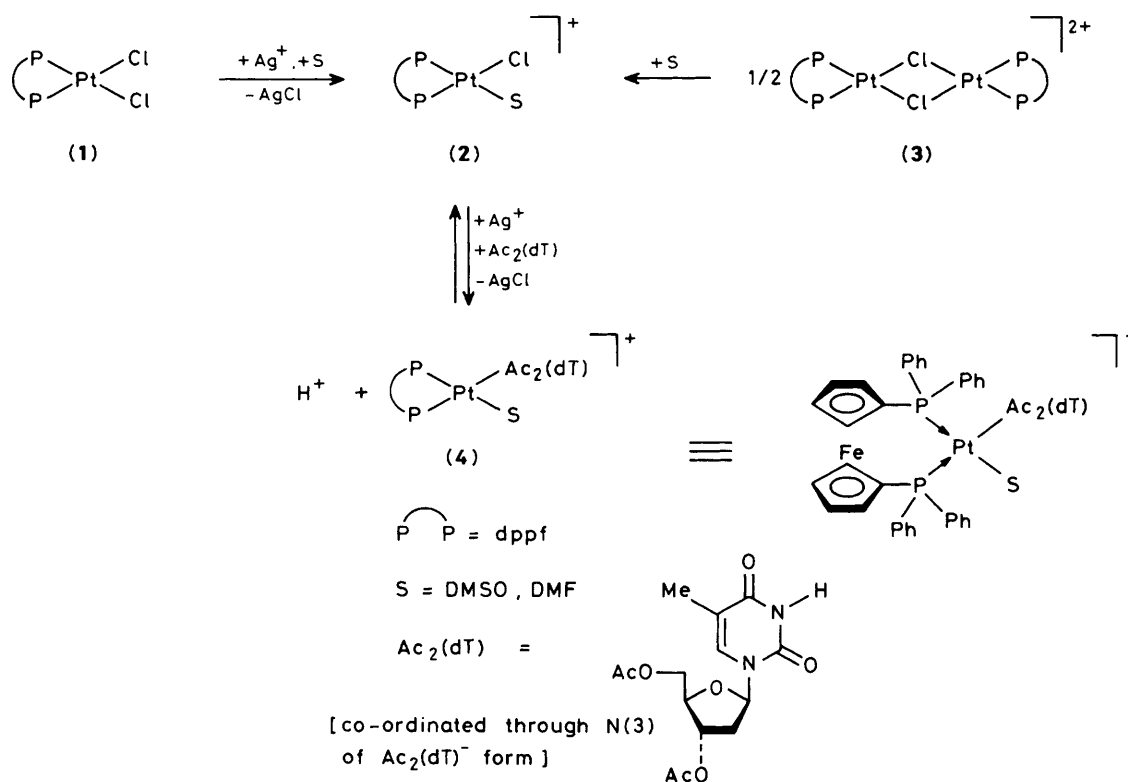
Complex (**3**),[‡] dissolved in DMSO, gives also quantitatively (**2**), whose $^{31}\text{P}\{^1\text{H}\}$ n.m.r. spectrum exhibits two doublets centred at δ 19.0 [$|J(^{195}\text{Pt}-^{31}\text{P})|$ 3913 Hz] and 5.2 p.p.m. [$|J(^{195}\text{Pt}-^{31}\text{P})|$ 4086 Hz] with $|^2J(\text{P}-\text{P})|$ 17.1 Hz, in agreement with the presence of two different ligands *trans* to the phosphorus atoms in dppf. Addition of one equivalent of Ag⁺ to solutions of (**2**) in DMSO does not cause any chemical change. However, if one equivalent of Ac₂(dT) is also present, AgCl precipitation occurs and an instantaneous change in the ^{31}P n.m.r. spectrum is observed with extensive formation of (**4**), *ca.* 70%. The generation of (**4**) is accompanied by the release of protons and potentiometric measurements indicate that the formation of (**4**) occurs with the release of an equimolar amount of H⁺.§ The lower field doublet is shifted to higher field to give an AB pattern, while the doublet previously centred at δ 5.2 p.p.m. moves slightly to lower field [$\delta(\text{P}_A)$ 8.4, $|J(^{195}\text{Pt}-^{31}\text{P})|$ 3452 Hz; $\delta(\text{P}_B)$ 6.5 p.p.m., $|J(^{195}\text{Pt}-^{31}\text{P})|$ 4394 Hz; $|J(\text{P}_A\text{P}_B)|$ 19 Hz] (data in DMSO). A quite similar behaviour is observed in DMF and the comparison of ^{31}P n.m.r. data allows us to attribute the higher field resonance to the phosphorus atom *trans* to Ac₂(dT).¶ The

[‡] The BF₄⁻ salt of (**3**) was obtained by addition of one equivalent of AgBF₄ to a suspension of (**1**) in acetone (potentiometric control by a silver electrode) followed by filtration of AgCl, partial solvent removal, and addition of ethanol (reddish-brown microcrystalline powder). Elemental analysis was satisfactory. ^{31}P N.m.r. (CH₂Cl₂): δ 18.2 p.p.m. (singlet) with $|J(^{195}\text{Pt}-^{31}\text{P})|$ 3988 Hz. Higher $\nu_{\text{Pt}-\text{Cl}}$ band in Nujol mull falls at 300 cm⁻¹ (expected range is 335–310 cm⁻¹) ('Infrared Spectra of Inorganic and Coordination Compounds,' ed. K. Nakamoto, Wiley-Interscience, 1970, p. 216).

§ The concentration of H⁺ in DMSO was determined potentiometrically by means of a combined glass electrode, which was calibrated with HBF₄ solutions at constant ionic strength (0.1 M NEt₄ClO₄).

¶ $\delta(\text{P}_A)$ 7.8, $|J(^{195}\text{Pt}-^{31}\text{P})|$ 3403 Hz; $\delta(\text{P}_B)$ 6.1 p.p.m., $|J(^{195}\text{Pt}-^{31}\text{P})|$ 4394 Hz; $|J(\text{P}_A\text{P}_B)|$ 19 Hz, in DMF at 27 °C.

[†] The reaction was monitored monoamperometrically by following the appearance of the polarographic wave of added Ag⁺ at the dropping mercury electrode polarized at -0.3 V vs. Ag/0.1M Ag⁺ (in acetonitrile) reference electrode.



Scheme 1

same co-ordination behaviour in DMSO is observed for 3'-Ac(dT) and by thymidine itself. Complex (1) is unreactive towards Ac₂(dT) in DMSO for at least five hours at 80°C. The structure of (4) (Scheme 1) is supported by the following findings: (i) the proton resonance due to the hydrogen atom bound to the heterocyclic nitrogen N(3) (δ 11.3, [2H₆]DMSO) shows a decrease in intensity quantitatively concomitant with the conversion of (2) into (4) as estimated from ³¹P n.m.r. data; moreover, the ¹H Me(5) resonance centred at δ 1.81 for free Ac₂(dT) in DMSO decreases concomitantly in intensity and the new Me(5) resonance develops at δ 1.50; further strong perturbations of phenyl and cyclopentadienyl rings as well as significant changes in the spectrum of the sugar are also observed; (ii) no reaction of (2) is observed when N(3)-methylthymidine is employed as potential ligand for at least 24 hours under the conditions used for the reactive thymidines; (iii) the change in the ³¹P n.m.r. spectrum caused by the addition of Ac₂(dT) and Ag⁺ to (2) is in accordance with the substitution of the second chloride ligand originally present in (1) by the nucleoside employed; (iv) the same reaction pattern is observed on starting from the BF₄⁻ salt of (3) in DMSO, upon addition of one equivalent of Ag⁺ and of Ac₂(dT); (v) Ac₂(dT) has to be co-ordinated to Pt^{II} in its deprotonated form, likely to be through N(3).⁷

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|| The results of *in vitro* experiments on the biological activity of (3) (A. Furlani and V. Scancia, Institute of Pharmacology and Pharmacognosy, University of Trieste, Trieste, Italy) and our results on the reactivity of (2) with other nucleosides and synthetic polynucleotides will be reported later.