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

Bruno Longato,[a]* Giuseppe Pilloni,[b] Gian Maria Bonora,[c] and Benedetto Corain[a]

[a] *Centro di Studio sulla Stabilita' e Reattivita' dei Composti di Coordinazione, C.N.R., c/o Dipartimento di Chimica Inorganica Metallorganica ed Analitica, Via Marzolo 1,35100, Padova, Italy*

[b] *Dipartimento di Chimica Inorganica Metallorganica ed Analitica, Via Marzolo 1,35100, Padova, Italy*

[c] *Centro di Studio sui Biopolimeri, C.N.R, c/o Dipartimento di Chimica Organica, Via Marzolo 1,35100, Padova, Italy*

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'-bis(diphenylphosphino)-ferrocene-*P*,*P'*}Pt(nucleoside)(solvent)]$^+$ are characterized by ^{31}P and ^{1}H 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 complexes[2] 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)PtCl$_2$] (**1**) [dppf = 1,1'-bis(diphenylphosphino)-ferrocene-*P*,*P'*; {Fe(η^5-C$_5$H$_4$PPh$_2$)$_2$}] is the precursor of a bimetallic *cis*-platinum(II) species which is very reactive with 3',5'-diacetylthymidine [Ac$_2$(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 AgBF$_4$ in acetonitrile, acetone, DMSO, and DMF to give AgCl and species (**2**) (Scheme 1).

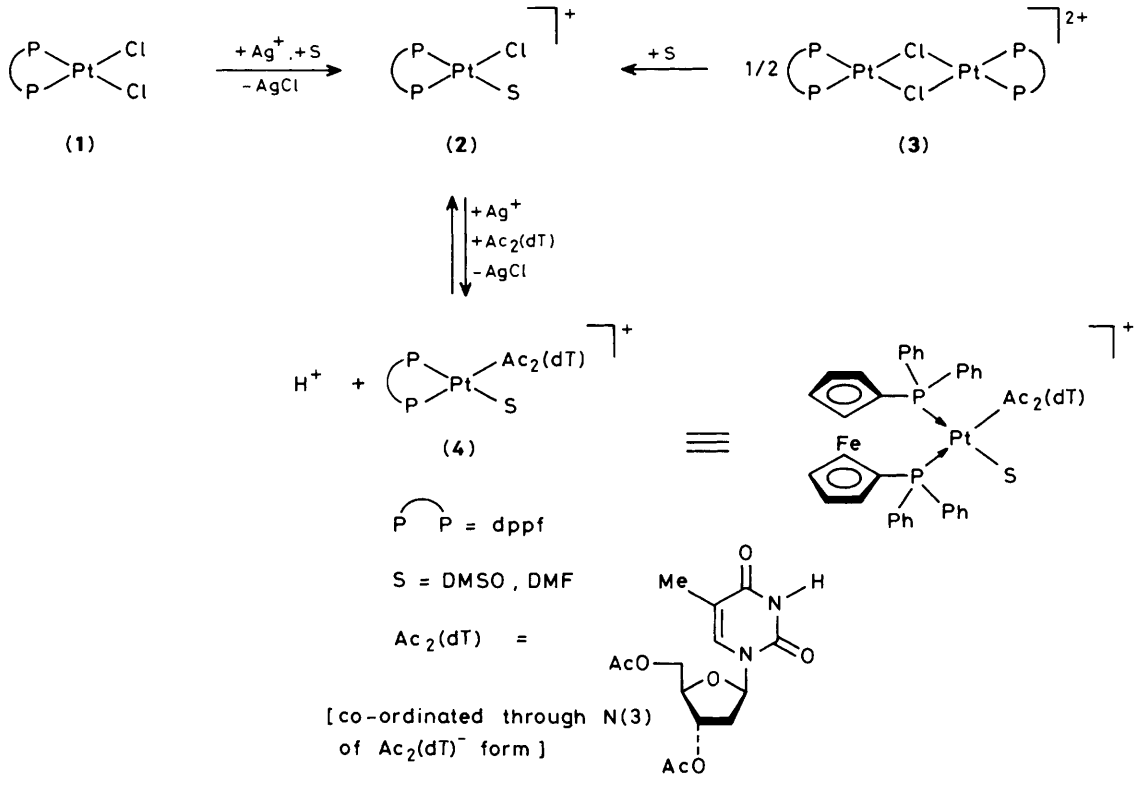
† The reaction was monitored monoamperometrically by following the appearance of the polarographic wave of added Ag$^+$ at the dropping mercury electrode polarized at −0.3 V *vs.* Ag/0.1M Ag$^+$ (in acetonitrile) reference electrode.

Complex (**3**),‡ dissolved in DMSO, gives also quantitatively (**2**), whose ^{31}P{^{1}H} n.m.r. spectrum exhibits two doublets centred at δ 19.0 [$|J(^{195}Pt–^{31}P)|$ 3913 Hz] and 5.2 p.p.m. [$|J(^{195}Pt–^{31}P)|$ 4086 Hz] with $|^2J(P–P)|$ 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 Ac$_2$(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 [δ(P$_A$) 8.4, $|J(^{195}Pt–^{31}P)|$3452 Hz; δ(P$_B$) 6.5 p.p.m., $|J(^{195}Pt–^{31}P)|$4394 Hz; $|J(P_AP_B)|$ 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 Ac$_2$(dT).¶ The

‡ The BF$_4^-$ salt of (**3**) was obtained by addition of one equivalent of AgBF$_4$ 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. (CH_2Cl_2): δ 18.2 p.p.m. (singlet) with $|J(^{195}Pt–^{31}P)|$ 3988 Hz. Higher ν_{Pt-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 HBF$_4$ solutions at constant ionic strength (0.1 M NEt$_4$ClO$_4$).

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



Scheme 1

same co-ordination behaviour in DMSO is observed for 3′-Ac(dT) and by thymidine itself. Complex (**1**) is unreactive towards $Ac_2(dT)$ 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, [$^2H_6$]DMSO) shows a decrease in intensity quantitatively concomitant with the conversion of (**2**) into (**4**) as estimated from ^{31}P n.m.r. data; moreover, the ^1H Me(5) resonance centred at δ 1.81 for free $Ac_2(dT)$ 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 ^{31}P n.m.r. spectrum caused by the addition of $Ac_2(dT)$ 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 BF_4^- salt of (**3**) in DMSO, upon addition of one equivalent of Ag^+ and of $Ac_2(dT)$; (v) $Ac_2(dT)$ has to be co-ordinated to Pt^{II} in its deprotonated form, likely to be through N(3).[7]‖

‖ 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.

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