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

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Abstract

The complexes *cis*-$[L_2PtS_2]^{2+}$ (L_2 = 1,1′-bis(diphenylphosphino)ferrocene and 1,2-bis(diphenylphosphino)ethane; S = dimethylformamide, dimethylsulfoxide) react in DMF or DMSO with diacetylthymidine and diacetyluridine, at room temperature, to give *cis*-$[L_2PtS(\text{nucleoside}(-H))]$ adducts. The conversion into the nucleoside derivatives depends on the nature of the diphosphine, the conversion being much higher (90 *versus* 10%, under initially equimolar conditions) for the ferrocenyl ligand. On the contrary, the same adducts are quantitatively obtained, under identical conditions, on starting from the *cis*-$[L_2(Pt(\mu\text{-}OH)]_2^{2+}$ complexes. All reacting complexes and related derivatives have been fully characterized by ^{31}P NMR. The biomolecules are present in their deprotonated form (nucleoside(–H)) and are probably N(3) bonded. The solvent ligand can be easily displaced by the chloride ion to give the neutral species *cis*-$[L_2Pt(\text{nucleoside}(-H))Cl]$ (L_2 = 1,1′-bis(diphenylphosphino)ferrocene), which have also been fully characterized by ^{31}P NMR.

Introduction

A preliminary communcation has been published on the high reactivity of *cis*-$[(dppf)PtS_2]^{2+}$ (**1**) (dppf) = 1,1′-bis(diphenylphosphino)ferrocene; S = dimethylformamide, dimethylsulfoxide) with diacetylthymidine ($Ac_2(dT)$) in coordinating solvents [1] (eqn. 1).

$$cis\text{-}[(dppf)PtS_2]^{2+} + Ac_2(dT) \rightleftharpoons cis\text{-}[(dppf)PtS(Ac_2(dT))]^{+} + H^{+} \quad (1)$$

It can be seen that as a consequence of the high Lewis acidity of the $\{(dppf)Pt\}^{2+}$ moiety, the employed biomolecule undergoes extensive metal coordination with concomitant deprotonation. Moreover, we have also reported that the complex $[(dppf)Pt(\mu\text{-}Cl)]_2^{2+}$ (**2**) exhibits a solvolytic behavior which is strongly dependent on the polarity and ligating ability of the solvents used [2]. Particularly interesting is the behavior of **1** in wet coordinating solvents, in which media it is extensively converted into the very stable complex $[(dppf)Pt(\mu\text{-}OH)]_2^{2+}$ (**3**), which has been characterized by X-ray single crystal analysis [2].

We report here on the reactivity of complexes **1**–**3** with diacetyldeoxythymidine ($Ac_2(dT)$) and diacetyldeoxyuridine ($Ac_2(dU)$) as well as on the behavior of the related species *cis*-$[(dppe)PtS_2]^{2+}$ with both nucleosides. Our results confirm the high reactivity of the moiety *cis*-$\{(dppf)Pt\}^{2+}$ towards nucleosides, in contrast with the behaviour of the related entity *cis*-$\{(dppe)Pt^{2+}\}$. Moreover, we report here on the isolation of the adducts *cis*-$[(dppf)PtCl(\text{nucleoside}(-H))]$ and *cis*-$[L_2PtS(\text{nucleoside}(-H))](BF_4)$ (L_2 = dppf, dppe).

Results and Discussion

The Systems [(dppf)PtS$_2$]$^{2+}$ and [(dppf)Pt(μ-OH)]$_2^{2+}$/Thymidines, Uridines (S = Dimethylformamide, DMF; Dimethylsulfoxide, DMSO)

The first aim of this work was the approximate determination of the equilibrium constant at 27 °C of eqn. (1), by means of ^{31}P NMR. $Ac_2(dU)$ and dT were also considered. For all nucleosides used, the reaction is instantaneous and the disappearance of the singlet due to the two equivalent phosphorus atoms of **1** is paralleled by the development of an AB multiplet due to the products $[(dppf)PtS(\text{nucleoside}(-H))]^{+}$ (**4**: **a**, $Ac_2(dT)$; **b**, dT, **c**, $Ac_2(dU)$) (Fig. 1 and Table I).

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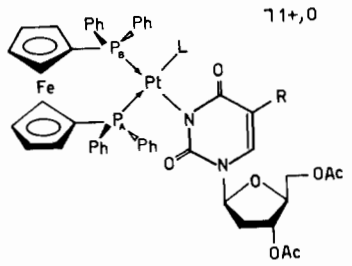

Fig. 1. The structure of complexes **4a–c** (L = S) and **5a–b** (L = Cl^-).

TABLE I. ^{31}P NMR Data for Complexes **4** in DMSO and DMF at 27 °C

Species	DMSO-d_6		DMF		K^c (27 °C)
	δ^a	J^b	δ^a	J^b	
4a	8.4	3452, 19	7.8	3403, 19	90
	6.5	4394, 19	6.1	4394, 19	
4b	8.3	3439, 19	7.7	3389, 19	90
	6.4	4408, 19	5.7	4413, 19	
4c	8.2	3460, 19	7.7	3406, 19	90
	6.3	4387, 19	5.7	4390, 19	

[a]Chemical shifts are in ppm from external H_3PO_4. [b]Coupling constants (Hz) of $^{195}Pt-^{31}P$ and $^{31}P-^{31}P$, respectively. [c]The figures are obtained upon reacting initially equimolar solutions of reagents (0.06 M) and after estimate of the conversion by integration intensities.

It can be seen that the approximate K values for the different nucleosides are practically identical in accordance with the similarity of the pK_a values of thymidine (9.8) and uridine (9.3) [3]. Complexes **4a** and **4c** can be prepared in good yield on starting from the corresponding complex **3**, according to eqn. (2).

$$\underset{\mathbf{3}}{\tfrac{1}{2}[(dppf)Pt(\mu\text{-}OH)]_2^{2+}} + \text{nucleoside} \xrightarrow[-H_2O]{S} \underset{\mathbf{4}}{[(dppf)PtS(\text{nucleoside}(-H))]^+} \quad (2)$$

The reaction required several hours to go to completion at room temperature (^{31}P NMR control) and the products were isolated simply by solvent removal under vacuum. They were characterized by IR (in the solid state) and by ^{31}P NMR in $CDCl_3$.

The most interesting feature of the IR spectra of **4a, c** is the presence of a band at 1580 cm^{-1} which can be attributed to one of the ν(CO) bands of the coordinated nucleosides. In the related *cis*-[$(NH_3)_2$-PtCl(thyminate)] complex, a band at 1550 cm^{-1} has been considered diagnostic for the N(3) metal-coordinated thymine ion [4]. The ^{31}P NMR spectra are quite consistent with the proposed structure (Table I) and the ^1H NMR spectra exhibit the expected pattern due to the organic residue. In particular, for **4a** the CH_3 resonance is shifted 0.31 ppm upfield as expected for the N(3) coordinated nucleobase [4].

Preparation and Isolation of [(dppf)Pt(nucleoside(–H))Cl] (Nucleoside = Ac_2(dT) 5a; Ac_2(dU), 5c)

The synthesis is quantitatively accomplished according to reaction (3) by using tetraethylammonium chloride.

$$[(dppf)PtS(\text{nucleoside}(-H))]^+ + Cl^- \xrightarrow[\text{or DMF}]{\text{DMSO}} [(dppf)Pt(\text{nucleoside}(-H))Cl] \quad (3)$$

Complexes **5** can be alternatively generated in DMSO or DMF upon addition of the nucleoside to complex **2**, but the reaction is very slow and non-quantitative (NMR control).

The IR spectra in the solid state are in accordance with the presence of both the nucleoside (ν(CO) = 1750, 1640 and 1575 cm^{-1}) and chloride (ν(Pt–Cl) = 310 cm^{-1}) bound to platinum(II). The ^{31}P NMR spectrum of **5a, c** dissolved in DMSO reveals the presence of two isomeric species (in *ca.* 1:1 ratio) in which one phosphorus atom experiences two slightly different magnetic environments (Fig. 2). It is seen that one line of the expected doublet (A) is, in fact, a pair of doublets as a consequence of the slightly different chemical environment of P_A caused by the two possible orientations (*syn* or *anti*) [5] of the sugar residue with respect to P_A (Fig. 1). The relevant spectral data are collected in Table II. The attribution of the pattern A to the phosphorus atom P_A, *trans* to the chloride ligand, is based on the expected higher $^{195}Pt-^{31}P$ coupling constant [6].

The data in $CDCl_3$ for **5a** indicate that the solvent also makes atoms P_B non-equivalent in the two isomers; moreover, for **5c**, the small magnetic non-equivalence is observed only for atoms P_B.

Reactivity of [(dppe)PtS_2]$^{2+}$ (S = DMF) (6) and of [(dppe)Pt(μ-OH)]$_2^{2+}$ (7)

Complexes **6**, **7** can be prepared by the same procedure used for the corresponding dppf analogs **1** and **3**. They are found to react rapidly with Ac_2(dT) and Ac_2(dU) (eqns. 1, 2) in DMSO but the reaction of **6** with both nucleosides (eqn. 1) is much less extended and only 10% of the product is formed under initial equimolar conditions. On the contrary, complex **7** reacts in DMSO and DMF more slowly (a few hours) but quantitatively with both nucleosides to to give adducts **8**: *cis*-[(dppe)PtS(Ac_2(dT)(–H))]$^+$ (**8a**) and *cis*-[(dppe)PtS(Ac_2(dU)(–H))]$^+$ (**8b**). Complexes **8** (S = DMSO or DMF) could be isolated as BF_4^- salts.

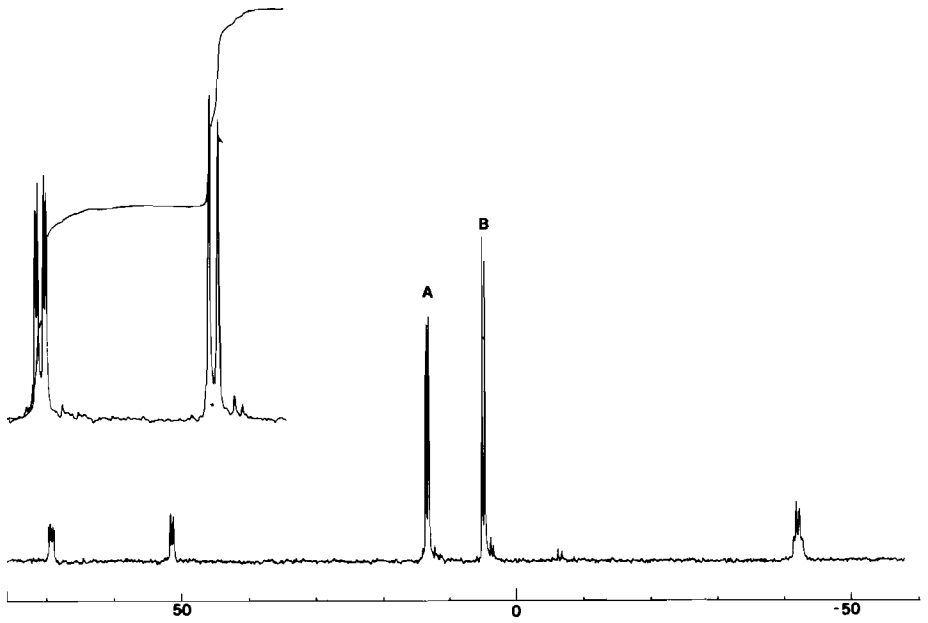

Fig. 2. $^{31}P\{^{1}H\}$ NMR spectrum of [(dppf)PtCl(Ac_2(dT)(−H))] (**5a**), in DMSO-d_6.

TABLE II. ^{31}P NMR Data of Complexes [(dppf)Pt(nucleoside(−H))Cl] in DMSO and DMF at 27 °C

Nucleoside	DMSO-d_6		$CDCl_3$	
	δ^a	J^b	δ^a	J^b
Ac_2(dT) isomer I	13.6	4036, 17.1	14.03	4040, 14.6
	4.9	3373, 17.1	5.35	3406, 14.6
isomer II	13.4	4036, 17.1	13.95	4032, 15.9
	4.9	3373, 17.1	5.13	3398, 15.9
Ac_2(dU) isomer I	13.3	4043, 14.6	13.81	4025, 14.6
	4.8	3385, 14.6	5.39	3397, 14.6
isomer II	13.2	4043, 15.8	13.81	4025, 15.9
	4.8	3385, 15.8	5.13	3396, 15.9

[a]Chemical shifts are in ppm from external H_3PO_4. [b]Coupling constants (Hz) of $^{195}Pt-^{31}P$ and $^{31}P-^{31}P$, respectively.

Their IR spectra (Nujol mulls) are quite similar to those exhibited by the related species **4**. Upon dissolution in DMF, they display AB ^{31}P NMR patterns, which are consistent with the presence of a single species, quite analogous to the related complexes **4** (Table III). In DMSO solutions, two species (probably isomers) can be observed, one of which (the more abundant one) corresponds to that seen in DMF. Both species exhibit rather broad resonances and this observation suggests that they may give rise to a relatively fast configurational equilibrium. It is possible that the second complex contains *S*-bonded DMSO [7].

Conclusions

The *cis*-$\{L_2Pt\}^{2+}$ moiety appears to be an effective Lewis acid towards moderately weak Lewis bases

TABLE III. ^{31}P NMR Data for Complexes [(dppe)PtS(nucleoside(−H))]$^+$ in DMSO and DMF at 27 °C

Species	DMSO-d_6		DMF		Remarks
	δ^a	J^b	δ^a	J^b	
8a	34.9	3292, n.d.[c]	36.4	3364, 7.9	more abundant in DMSO
	33.5	4063, n.d.	32.9	4095, 7.9	
	41.2	3052, n.d.			less abundant in DMSO
	35.4	3190, n.d.			
8b	35.3	3300, n.d.	36.3	3272, 7.3	more abundant in DMSO
	33.3	4054, n.d.	32.7	4084, 7.3	
	41.8	3049, n.d.			less abundant in DMSO
	36.2	3160, n.d.			

[a]Chemical shifts are in ppm from external H_3PO_4. [b]Coupling constants (in Hz) of $^{195}Pt-^{31}P$ and $^{31}P-^{31}P$, respectively. [c]Not determined, owing to the broadness of the relevant peaks.

such as thymidines and uridines. The *cis*-[L_2PtS-(nucleoside(–H))]BF_4 and *cis*-[L_2Pt(nucleoside-(–H))Cl] derivatives turn out to be stable species both in the solid state and in solution in polar coordinating solvents. In weakly coordinating media, they appear to be sensitive to traces of water and they slowly hydrolyse to give complex **3** eventually. As to the effect of the nature of the diphosphine, a comparison between the reactivity of complexes **1** and **6** in the same reaction (eqn. 1) clearly indicates that dppf makes platinum(II) a stronger (*ca.* 10-fold) Lewis acid, and hence more reactive, than dppe. It should be concluded that dppf is a poorer σ-donor ligand than dppe. The apparently identical high reactivity exhibited by complexes **3** and **7** is evidently due to the presence in the substrate of the hydroxo ligand, which removes the liberated protons and drives reaction (2) to completion.

Experimental

All chemicals used were reagent grade. The solvents were dried over molecular sieves. The nucleosides thymidine (dT) and deoxyuridine (dU) (Fluka) were acetylated according to the procedure previously reported [8]. Literature methods were used for the preparation of complexes (dppf)$PtCl_2$ [9], (dppe)$PtCl_2$ [10], and [(dppf)Pt(μ-X)]$_2(BF_4)_2$ (X = Cl^-, OH^-) [2]. Infrared spectra were recorded on a Perkin-Elmer 599B spectrometer. NMR spectra were obtained with a Jeol FX 90Q spectrometer at 27 °C with the residual solvent peak as an internal reference for the proton spectra. The $^{31}P\{^1H\}$ NMR spectra in DMF were obtained by using a coaxial capillary containing D_2O for deuterium lock. All chemical shifts are reported positive to lower shielding.

Synthesis of Compounds 4

A solution of **3** (0.200 g, 0.117 mmol) and Ac_2-(dT) (77 mg, 0.234 mmol) in DMF (5 ml) was stirred at room temperature for 24 h. Solvent removal under vacuum gave a solid which was washed with Et_2O, collected by filtration and dried under vacuum. The yield of yellow microcystalline **4a** was 270 mg, 93%. *Anal.* Calc. for $C_{51}H_{52}N_3P_2FePtO_8BF_4$: C, 49.61; H, 4.24; N, 3.40. Found: C, 48.23; H, 4.21; N, 3.45%. ^{31}P NMR in $CDCl_3$: AB pattern with δ 8.5 (J(PtP) 3416 Hz), 6.5 (J(PtP) 4393 Hz) and J(PP) 18.5 Hz. IR (Nujol mull), ν(CO) region: 1740, 1640 with a shoulder at *ca.* 1670, 1580 cm^{-1}. With a quite similar procedure compound **4c** was obtained in 96% yield. *Anal.* Calc. for $C_{50}H_{50}N_3P_2FePtO_8$-$BF_4$: C, 49.20; H, 4.12; N, 3.44. Found: C, 47.03; H, 4.08; N, 3.30%. ^{31}P NMR in $CDCl_3$: AB pattern with δ 8.3 (J(PtP) 3390 Hz), 6.4 (J(PtP) 4390 Hz), J(PP) 18.5 Hz. IR (Nujol mull), ν(CO) region: 1740, 1640 with shoulder at 1660, 1580 cm^{-1}.

Synthesis of Compounds 5

To a solution of complex **4a** (190 mg, 0.154 mmol) in DMF (3 ml) was added NEt_4Cl (28 mg, 0.153 mmol). The resulting reaction mixture was vacuum evaporated, and the residue dissolved in $CHCl_3$ (3 ml). After filtration, the addition of Et_2O determined the precipitation of a yellow–orange solid which was collected by filtration and purified by dissolution in $CHCl_3$ and precipitation with Et_2O. The yield of **5a** was 120 mg (70%). *Anal.* Calc. for $C_{48}H_{45}N_2O_7FeP_2ClPt$: C, 51.93; H, 4.09; N, 2.52. Found: C, 50.97; H, 4.07; N, 2.14%. With the same procedure complex **5c** was prepared with a yield of 83%. IR (Nujol mull): 1740, 1640, 1575 cm^{-1} (strong, ν(CO)); 310 cm^{-1} (weak, ν(PtCl)).

Synthesis of Compound 6

A solution of (dppe)$PtCl_2$ (0.300 g, 0.45 mmol) in DMF (3 ml) was stirred with a solution of $AgBF_4$ (0.179 g, 0.903 mmol) in DMF (2 ml) for 2 h at room temperature. The solvent was vacuum evaporated and the residue taken up with Et_2O (30 ml). After vigorous stirring, a white powder was formed and collected by filtration. The yield of pure **6** was 0.37 g (90%). *Anal.* Calc. for $C_{32}H_{38}N_2O_2P_2$-PtB_2F_8: C, 42.08; H, 4.19; N, 3.07. Found: C, 42.77; H, 4.30; N, 2.97%. ^1H NMR in DMSO-d_6: 8.0 (s, 2H, $(CH_3)_2NCOH$); 7.7 (cm, 20H, C_6H_5), 2.88 (s, 3H, $(CH_3)_2NCOH$); 2.72 (s, 3H), $(CH_3)_2NCOH$), 2.6 (cm, 4H, $(CH_2)_2$). ^{31}P NMR in DMSO-d_6: 36.8 (s, J(PtP) 3902 Hz).

Synthesis of Compound 7

A solution of $AgBF_4$ (0.293 g, 1.50 mmol) in methanol (5 ml) was added dropwise to a solution of (dppe)$PtCl_2$ (0.500 g, 0.75 mmol) in CH_3OH (25 ml). The resulting reaction mixture was stirred for 2 h and filtered. The filtrate was concentrated under vacuum to *ca.* 10 ml. Addition of Et_2O determined the precipitation of a white microcrystalline solid which was filtered and purified by recrystallization from CH_3OH/Et_2O. The yield of pure 7 was 0.367 g (70%). *Anal.* Calc. for $C_{26}H_{25}P_2PtOBF_4$: C, 44.78; H, 3.61. Found: C, 43.59; H, 3.53%. ^1H NMR in DMSO-d_6: δ 7.7 (complex multiplet, 20H, C_6H_5), 5.5 (broad singlet, 1H, OH), 2.6 (cm, 4H, $(CH_2)_2$; ^{31}P NMR in DMSO-d_6: δ 34.0 (singlet flanked by ^{195}Pt satellites with J(PPt) 3557 Hz). IR (Nujol mull): 3560 cm^{-1} (weak, ν(OH)).

Synthesis of Compounds 8

A solution of [(dppe)Pt(μ-OH)]$_2(BF_4)_2$ (0.200 g, 0.143 mmol) and Ac_2(dU) (90 mg, 0.286 mmol) in DMSO (2 ml) was stirred at room temperature for 2 h. The solvent was vacuum evaporated and the resulting oily residue treated with Et_2O. Upon freezing at 77 K and warming to room temperature the oil formed a powdered white product, which was collected by filtration, washed with ether and dried

under vacuum. The yield of **8b** was 0.21 g (70%). *Anal.* Calc. for $C_{41}H_{45}N_2O_8SP_2PtBF_4$: C, 46.03; H, 4.24; N, 2.62. Found: C, 43.98, H, 4.29; N, 2.56%. IR (Nujol mull, ν(CO) bands): 1740 (vs), 1630 with shoulder at *ca.* 1650 (s, br), 1580 (m) cm^{-1}. With the same procedure, operating in DMF, complex **8a** was obtained in 85% yield. *Anal.* Calc. for $C_{43}H_{48}O_8N_3P_2PtBF_4$: C, 47.83; H, 4.57; N, 3.89. Found: C, 47.63; H, 4.42; N, 3.55%. IR Nujol mull, ν(CO) region): 1740, 1640 with shoulder at *ca.* 1660, 1580 cm^{-1}.

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