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Stabilisation of the iminooxo tautomer of 1-methylcytosine in Pt^{II} complexes: Role of the ancillary ligands

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ABSTRACT

Reaction of *cis*-$[L_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ (L = PPh_3) with 1-methylthymine (1-MeTy), in DMF, leads to the formation of the mononuclear *neutral* adduct *cis*-$L_2Pt\{1\text{-}MeTy(-H)\}(ONO_2)$ (**1**) whose structure in the solid state has been obtained by single crystal X-ray diffraction. The deprotonated nucleobase is bounded at the N(3) site, with the pyrimidinic ring almost perpendicular (78.0(1)°) to the metal coordination plane. The fourth ligand is a monodentate nitrate group. Addition of 1 equiv. of 1-methylcytosine (1-MeCy) causes the immediate replacement of the nitrato ligand to form the cationic complex *cis*-$[L_2Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy,N^3)]NO_3$ (**2**) in which both the nucleobases are N(3)-platinated. In CD_2Cl_2 at −40 °C **2** exists as a mixture of two conformers (2:1 molar ratio) arising from the different orientation of the nucleobases with respect to the metal coordination plane.
In solution of DMSO, DMF or chlorinated solvents, **2** slowly converts into the isomer *cis*-$[L_2Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy,N^4)]NO_3$ (**3**), containing the tautomeric form of the cytosine stabilised through the coordination at the N(4) atom, as a mixture of conformers whose relative abundance is dependent on the solvent and the temperature.
In contrast, the analogous complex of **2** containing the phosphine PMe_3, *cis*-$[(PMe_3)_2Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy,N^3)]NO_3$ (**4**), also isolated as pure compound, in DMSO solution slowly rearranges leading to the elimination of the neutral 1-MeTy, with the formation of the dinuclear cytosinate complex *cis*-$[(PMe_3)_2Pt\{1\text{-}MeCy(-H),N^3N^4\}]_2(NO_3)_2$, previously characterised by us.

1. Introduction

Much is known on the binding modes of the model nucleobase N(3)-substituted 1-methylcytosine (1-MeCy) to a metal centre, as neutral and as N(4)-deprotonated (1-MeCy(–H)) ligand [1]. The usual site of metallation of the neutral base is the N(3)-endocyclic atom. However, the cases in which the iminooxo tautomer of the cytosine is stabilised through the coordination at the exocyclic N(4) have been also described [2] (Scheme 1).

In this paper we present an example of platinum(II) complex in which the initially N(3)-bonded cytosine (mode a) rearranges into its more stable tautomeric derivative (mode b). Such isomerisation, which requires the shift of one of NH_2 protons to the N(3) site of the cytosine ligand, occurs selectively in the cationic complex *cis*-$[(PPh_3)_2Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy)]^+$ (**2**), containing the deprotonated 1-methylthymine (1-MeTy) and the neutral cytosine ligands, both coordinated at the N(3)-atom. The mixed complex **2** was prepared by the replacement of the nitrate group by a cytosine ligand in the precursor *cis*-$L_2Pt\{1\text{-}MeTy(-H)\}(ONO_2)$ (L = PPh_3, **1**) characterised by X-ray single crystal analysis. The isolated complex *cis*-$[(PPh_3)_2Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy,N^4)]NO_3$ (**3**), was characterised by multinuclear and 2D-NMR spectroscopy.

In order to evaluate the role of the PPh_3 ligands in the stabilisation of the cytosine in its tautomeric form, we have prepared the complex *cis*-$[L_2Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy)]^+$ (L = PM_3, **4**), containing the less hindered and more basic trimethyl phosphine. **4** in DMSO slowly rearranges leading to the elimination of the neutral 1-MeTy and the formation of the dinuclear cytosinate complex *cis*-$[(PMe_3)_2Pt\{1\text{-}MeCy(-H),N^3N^4\}]_2(NO_3)_2$, previously characterised [3]. The formal migration of the metal from the N3 to N4 site of the cytosine molecule in Pt(II) complex was previously observed in the related species *cis*-$[(dppf)Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy,N^3)]BF_4$, where dppf is 1,1′-bis(diphenylphosphino)ferrocene [4].

2. Experimental

2.1. Synthesis and materials

cis-$[L_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ (L = PPh_3[5], PMe_3[2]) and 1-MeCy [6] were prepared as previously reported. 1-MeTy and all the solvents

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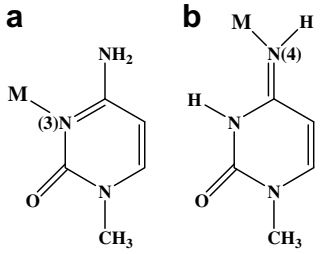


Scheme 1.

(CH_2Cl_2, DMF, DMSO-d_6, $CDCl_3$, CD_2Cl_2, CD_3CN, Et_2O) were Aldrich products.

*2.1.1. Synthesis of cis-$(PPh_3)_2Pt\{1\text{-}MeTy(-H)\}(ONO_2)$ (**1**)*

To a solution of *cis*-$[(PPh_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ (72.6 mg, 4.5×10^{-2} mmol) in CH_2Cl_2 (5 mL) 1-MeTy (12.7 mg, 9.0×10^{-2} mmol) was added, and the suspension stirred at room temperature for ca. 24 h. The resulting mixture was filtered to eliminate trace amounts of a solid. Addition of Et_2O (35 mL) to the filtrate afforded a white solid which was isolated and dried under vacuum. The yield of **1** was 64 mg (77%). Purification of the solid from $CHCl_3$, by vapour diffusion of Et_2O at room temperature, afforded crystals having the composition *cis*-$(PPh_3)_2Pt\{1\text{-}MeTy(-H)\}(NO_3)\cdot 3H_2O$. Elem. *Anal.* Calc. for $C_{42}H_{43}N_3O_8P_2Pt$ (974.8): C, 51.75; H, 4.45; N, 4.31. Found: C, 51.58; H, 4.26; N, 4.20%. ^1H NMR in $CDCl_3$ (δ): 7.78–6.91 cm (30H, PPh_3); 6.32 s (1H, H(6)), 2.95 s (3H, NCH_3), 1.65 s (3H, CH_3); ^1H NMR in DMSO-d_6 (δ) 7.72–7.09 cm (30H, PPh_3), 6.88 s (1H, H(6)), 2.96 s, (3H, NCH_3), 1.49 s (3H, CH_3). The $^{31}P\{^1H\}$ NMR data are collected in Table 1.

*2.1.2. Synthesis of cis-$[(PPh_3)_2Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy,N^3)]NO_3$ (**2**)*

To a solution of **1** (95.9 mg, 0.10 mmol) in 5 mL of CH_2Cl_2 was added 1-MeCy (12.6 mg, 0.10 mmol) which dissolved in a few minutes, under stirring at room temperature. Addition of Et_2O afforded a white solid that was recovered by filtration, washed with Et_2O and dried under vacuum. (71.8 mg, yield 66%). Elem. *Anal.* Calc. for $C_{47}H_{44}N_6O_6P_2Pt$ (1045.92): C, 53.97; H, 4.25; N, 8.03. Found: C, 52.86; H, 4.14; N, 7.97%. ^1H NMR in CD_2Cl_2 at 25 °C (δ): 7.65–7.16 cm (30H, PPh_3); 8.61 s (1H, N4H), 8.38 s (1H, N4H), 6.36 s (1H, H6), 6.78 d (1H, H6, $^3J_{HH}$ 6 Hz), 6.08 d (1H, H5, $^3J_{HH}$ 6 Hz), 2.86 s (3H, NCH_3), 2.93 s (3H, NCH_3) 1.50 s (3H, CH_3); ^1H NMR in CD_2Cl_2 at −40 °C (δ): 7.92–6.36 cm (30H, PPh_3); more abundant conformer, 8.60 s (1H, N4H), 8.32 s (1H, N4H), 6.39 s (1H, H6), 6.78 d (1H, H6, $^3J_{HH}$ 6 Hz), 6.20 d (1H, H5, $^3J_{HH}$ 6 Hz), 2.99 s (3H, NCH_3), 2.91 s (3H, NCH_3), 1.34 s (3H, CH_3); less abundant conformer, 8.71 s (1H, N4H), 8.31 s (1H, N4H), 6.39 s (1H, H6), 6.80 d (1H, H6, $^3J_{HH}$ 6 Hz), 6.14 d (1H, H5, $^3J_{HH}$ 6 Hz), 3.15 s (3H, NCH_3), 2.84 s (3H, NCH_3), 1.55 s (3H, CH_3). ^1H NMR in DMSO-d_6 at 25 °C (δ): 7.55–7.23 cm (31H, PPh_3 and H6); 8.50 s (1H, N4H), 8.25 s (1H, N4H), 6.78 s (1H, H6), 5.59 d (1H, H5, $^3J_{HH}$ 6 Hz), 2.89 s (3H, NCH_3), 2.80 s (3H, NCH_3), 1.40 s (3H, CH_3). The $^{31}P\{^1H\}$ NMR data are collected in Table 2.

*2.1.3. Synthesis of cis-$[(PPh_3)_2Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy,N^4)]NO_3$ (**3**)*

Twenty-one milligrams of **1** (2.28×10^{-5} mol) were dissolved in 3 mL of DMF and then 1-MeCy (2.9 mg, 2.32×10^{-5} mol) was added. After 0.5 h a solution was obtained which was subsequently stirred for one week at room temperature. Addition of Et_2O afforded a white solid that was recovered by filtration, washed with Et_2O and dried under vacuum. The yield of **3** was 15.7 mg, 65%. Elem. *Anal.* Calc. for $C_{47}H_{44}N_6O_6P_2Pt$ (1045.92): C, 53.97; H, 4.25; N, 8.03. Found: C, 52.86; H, 4.14; N, 7.97%. ^1H NMR in DMSO-d_6: 7.60–7.26 (30H, PPh_3); more abundant conformer: 10.69 s (1H, N3H), 6.95 d (1H, H6, $^3J_{HH}$ 7.0 Hz), 6.83 s (1H, H6), 6.11 s (1H, N4H), 5.43 d (1H, H5, $^3J_{HH}$ 7.0 Hz), 3.11 (s, 3H, NCH_3), 2.49 (s, 3H, NCH_3), 1.42 (s, 3H, CCH_3); less abundant conformer: 10.96 s (1H, N3H), 6.92 d (1H, H6, $^3J_{HH}$ 7.0 Hz), 6.86 s (1H, H6), 6.20 s (1H, N4H), 5.61 d (1H, H5, $^3J_{HH}$ 7.0 Hz), 3.23 (s, 3H, NCH_3), 2.71 (s, 3H, NCH_3), 1.49 (s, 3H, CCH_3). ^1H NMR in CD_2Cl_2: 10.99 s (1H, N3H), 7.65–7.18 (30H, PPh_3), 6.71 d (1H, H6, $^3J_{HH}$ 7.0 Hz), 5.87 s (1H, N4H), 5.39 d (1H, H5, $^3J_{HH}$ 7.0 Hz), 3.18 (s, 3H, NCH_3), 6.40 s (1H, H6), 3.00 (s, 3H, NCH_3), 1.53 (s, 3H, CCH_3). The $^{31}P\{^1H\}$ NMR data are collected in Table 2.

*2.1.4. Synthesis of cis-$[(PMe_3)_2Pt\{1\text{-}MeTy(-H)\}(1\text{-}MeCy,N^3)]NO_3$ (**4**)*

A mixture of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ (146 mg, 0.17 mmol) and 1-MeTy (47.6 mg, 0.34 mmol) in DMF (5 mL) was stirred at room temperature for 48 h, during which most of the solid dissolved. Addition of 1-MeCy (42.5 mg, 0.34 mmol) to the resulting mixture caused the immediate precipitation of a solid, which was collected by filtration and purified by dissolution in CH_2Cl_2/DMSO

Table 1
$^{31}P\{^1H\}$NMR data of complex **1** in various solvents (δ in ppm and J in Hz) at 25 °C

Solvent	P_A ($^1J_{PPt}$)	P_B ($^1J_{PPt}$)	$^2J_{PP}$
CH_2Cl_2	7.41 (3294)	4.85 (4230)	21.9
$CDCl_3$	7.66 (3290)	5.07 (4240)	21.9
DMF	8.57 (3257)	5.55 (4320)	22.2
DMSO-d_6	9.30 (3309)	5.72 (4287)	22.3
CH_3CN[a]	7.62 (4174)	3.73 (3050)	21.9

[a] Fresh solution.

Table 2
$^{31}P\{^1H\}$ NMR data of **2** and **3** in different solvents and temperatures (δ in ppm and J in Hz). In square brackets the relative abundance of the conformers

Compound	Solvent (temp., K)	$P_A(^1J_{PPt})$	$P_B(^1J_{PPt})$	$^2J_{PP}$
2	CD_2Cl_2 (298)	0.98 br s (ca. 3443)	−1.88 d (3630)	20.0
2	CD_2Cl_2 (233)	1.82 d (3432)	−1.87 d (3596)	19.7 [35%]
		0.08 d (3434)	−1.83 d (3596)	19.5 [65%]
2	DMSO-d_6 (298)	0.40 br s (ca. 3478)	−2.38 d (3597)	19.9
2	DMF (298)	1.29 br s (ca. 3430)	−2.03 d (3637)	20.2
3	CD_2Cl_2 (298)	10.01 d (3524)	3.67 d (3194)	20.9 [94%]
		9.65 d[a]	2.87 d[a]	20.8 [6%]
3	CD_2Cl_2 (183)	10.51 d (ca.3449)	3.51 d (ca.3163)	20.5 [69%]
		10.03 d (ca.3449)	3.25 d (ca.3163)	21.0 [27%]
		9.48 d[a]	4.55 d[a]	20.2 [4%]
3	DMF (298)	10.79 d (3476)	3.55 d (3195)	21.0 [93%]
		9.96 d[a]	4.11 d[a]	20.4 [7%]
3	DMSO-d_6 (298)	10.31 d (3529)	2.87 d (3202)	20.9 [74%]
		9.38 d (3595)	3.54 d (3240)	20.6 [26%]

[a] $^1J_{PPt}$ not detected.

(10:1 vol/vol) and precipitated with Et_2O. The white solid, collected by filtration, washed with Et_2O and dried under vacuum was 43 mg (yield 19%). The elemental analysis and NMR data are consistent with the composition *cis*-[$(PMe_3)_2$Pt{1-MeTy(–H)}(1-MeCy,N^3)]-$NO_3 \cdot DMSO \cdot H_2O$. Elem. *Anal.* Calc. for $C_{17}H_{32}N_6O_6P_2Pt \cdot DMSO \cdot H_2O$ (769.6): C, 29.57; H, 5.50; N, 10.89. Found: C, 29.31; H, 5.64; N, 10.87%. ^{1}H NMR in DMSO-d_6: 8.38 s (1H), 8.03 s (1H), 7.76 d (1H, $^3J_{HH}$ 7.2 Hz), 7.37 s (1H), 5.78 d (1H, $^3J_{HH}$ 7.2 Hz), 3.18 s (3H), 3.10 s (3H), 1.71 s (3H), 1.43 d (9H, PMe_3, $^2J_{HP}$ 10 Hz). ^{31}P{^{1}H} in DMSO-d_6, δ (ppm): two AX multiplets at −28.3 ($^1J_{PPt}$ 3424 Hz), −29.3 ($^1J_{PPt}$ 3185 Hz) with $^2J_{PP}$ = 25.4 Hz (relative abundance 65%) and −28.4 ($^1J_{PPt}$ 3424 Hz), −29.4 ($^1J_{PPt}$ 3185 Hz) with $^2J_{PP}$ = 25.4 Hz (relative abundance 35%).

2.2. NMR measurements

NMR spectra were obtained in solution of various solvents at 300 K, in 5-mm sample tubes, with: a Bruker Avance 300 MHz for ^{1}H and ^{31}P (operating at 300.13 and 121.5 MHz, respectively); with a Bruker 400 AMX-WB spectrometer for ^{15}N (operating at 40.6 MHz); with a Bruker Avance DMX 600 (5 mm TXI probe with gradients) using gradients during the mixing time period (0.45 s) for the NOESY experiment. The ^{31}P NMR spectra in CH_2Cl_2, DMF and CH_3CN were obtained using a capillary containing D_2O for lock signal.

The ^{1}H chemical shifts were referenced to the residual impurity of the solvent. The external references were H_3PO_4 (85 w/w in D_2O) for ^{31}P, and CH_3NO_2 (in $CDCl_3$ at 50% w/w) for ^{15}N. Inverse detected spectra were obtained through heteronuclear multiple bond correlation (HMBC) experiments, using parameters similar to those previously reported [7].

2.3. X-ray structure determination

Diffraction data for compound **1** were collected at room temperature on a Nonius DIP-1030H system with Mo Kα radiation (λ = 0.71073 Å). Cell refinement, indexing and scaling of the data set were carried out using programs DENZO [8] and SCALEPACK [8]. The structure was solved by direct method and subsequent Fourier analyses [9] and refined by the full-matrix least-squares method based on F^2 with all observed reflections [9]. A residual in the ΔF map was interpreted as lattice water oxygen at half occupancy (hydrogen atoms not located). All the calculations were performed using the WINGX System, Ver 1.70.01 [10].

Crystal data of **1** $\cdot$ 0.5(H_2O): $C_{42}H_{38}N_3O_{5.50}P_2Pt$, M = 929.78, monoclinic, space group $P2_1/c$, a = 12.184(3), b = 13.796(3), c = 24.926(4) Å, β = 93.27(2)°, V = 4183.0(15) Å^3, Z = 4, D_{calc} = 1.476 g/cm^3, μ(Mo Kα) = 3.477 mm^{-1}, F(000) = 1852, θ range = 2.20–26.02°. Final R_1 = 0.0390, wR_2 = 0.0903, S = 0.834 for 484 parameters and 53637 reflections, 7948 unique [R_{int} = 0.0759], of which 4214 with $I > 2\sigma(I)$, max positive and negative peaks in ΔF map 0.669, −0.577 e Å^{-3}.

3. Results and discussion

3.1. Characterisation of *cis*-$(PPh_3)_2$Pt{1-MeTy(–H)}(ONO_2) (**1**)

The reaction of *cis*-[$(PPh_3)_2$Pt(μ-OH)]$_2(NO_3)_2$ with 1-MeTy, carried out in different solvents (CH_2Cl_2, DMF, CH_3CN), affords the neutral complex *cis*-$(PPh_3)_2$Pt{1-MeTy(–H)}(ONO_2) (**1**) as the only product that can be isolated.

The X-ray structural determination of **1**, reported in Fig. 1, shows the Pt ion in a square planar coordination geometry achieved through the phosphorous atoms, the nitrogen donor of the thymine and the nitrate oxygen. The coordination plane manifests a slight tetrahedral distortion with atom donors displaced by ca. ±0.06 Å. The nucleobase is bound to the metal through the deprotonated N(3) donor (Pt–N(3) 2.050(6) Å), which represents the preferentially binding site for this pyrimidine base, while the Pt–ONO_2 bond distance is 2.117(4) Å, with Pt–O–N bond angle of 120.2(4)°.

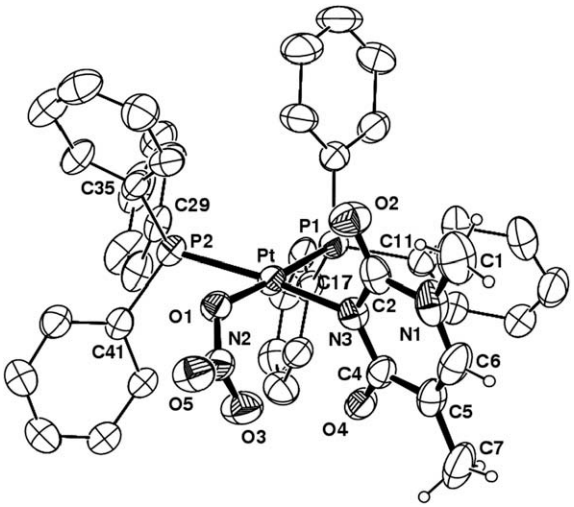


Fig. 1. Molecular structure of complex **1**, *cis*-$(PPh_3)_2$Pt{1-MeTy(–H)}(ONO_2) (labelling scheme of phenyl C atoms not indicated for sake of clarity). Coordination bond lengths (Å) and angles (°): Pt–N(3) 2.050(6), Pt–O(1) 2.117(4), Pt–P(1) 2.227(2), Pt–P(2) 2.270(2), N(3)–Pt–O(1) 87.14(19), N(3)–Pt–P(1) 91.39(16), O(1)–Pt–P(1) 174.60(13), N(3)–Pt–P(2) 170.32(15), O(1)–Pt–P(2) 83.28(13), P(1)–Pt–P(2) 98.28(7).

As far as Pt–P bond lengths, it is worth noting the shorter value measured for the phosphine trans to the nitrate, (2.227(2) Å) with respect to that *trans* to the nucleobase of 2.270(2) Å. The N(3)–Pt–O(1) angle, 87.14(19)°, is narrower in comparison to the P(1)–Pt–P(2) one, 98.28(7)°, likely induced by steric requirements.

The Pt–N(3) and Pt–P(2) bond distances, *trans* to each other, of length 2.050(6) and 2.270(2) Å, respectively, are comparable within their e.s.d.'s with the values of 2.072(5) and 2.268(2) Å found in the chlorine derivative, *cis*-[$(PPh_3)_2$Pt{1-MeTy(–H)}Cl] [11], but the former distance is significantly shorter with respect to the values of 2.12(1) and 2.097(9) Å measured in the less accurate monocationic species *cis*-[$(PMe_3)_2$Pt-{1-MeTy(–H)}(CH_3CN)]$^+$ and *cis*-[$(PMe_3)_2$Pt-{1-MeTy(–H)}{$CH_3C(NH)NH_2$}]$^+$, [12] respectively, where the base is trans to PMe_3.

The coordination bond angles C(2)–N(3)–Pt and C(4)–N(3)–Pt (116.3(6)° and 119.4(5)°, respectively) in **1** are only slightly different since the base presents a pseudo twofold axis. This feature contrasts with the unsymmetrical connection observed for cytosine and guanine bases where the exocyclic N donor angles differ in the range 7–12° [13].

The thymine base is oriented almost normal to the coordination mean plane forming a dihedral angle of 78.0(1)°, while the nitro group is more bent, and the mean plane figures out a dihedral angle of 64.6(2)°. The phenyl ring C(11) is oriented in such a way to favour an intramolecular π–π interaction with the model nucleobase (see Fig. 1, centroid-to-centroid distance 3.677(5) Å, the dihedral angle formed by the rings 28.0°), and also indicated by the eclipsed conformation for the torsion angle C(11)–P(1)–Pt–N(3) (1.5°). Another intramolecular weaker π–π interaction is manifested by phenyl rings C(17) and C(29) that form an angle of 2.7° and their centroids are 3.795(5) Å far apart. The present structure confirms an arrangement of the ligands analogous to that found in the monocationic derivatives *cis*-[$(PPh_3)_2$Pt(1-MeCy)(ONO_2)]-NO_3 and *cis*-[$(PPh_3)_2$Pt(9-MeGu)(ONO_2)]NO_3 [13].

The unit cell of **1** shows a void accessible to solvent of 309.0 Å^3 (ca. 7.4% of the volume). We also obtained another crystal form of *cis*-$(PPh_3)_2Pt\{1\text{-MeTy}(-H)\}(ONO_2)$, monoclinic, space group $P2_1/c$, unit cell $a = 11.899(2)$, $b = 21.878(3)$, $c = 15.985(3)$ Å, $\beta = 90.63(2)^\circ$ and containing 4.5 water molecules of crystallisation. These crystal data are slightly less accurate and reveal a complex conformation almost superimposable to that of **1**; thus their report is worthless.

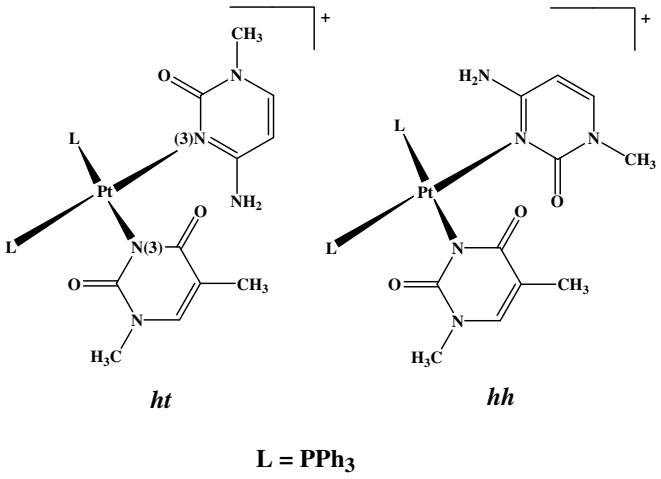
The ^{1}H NMR spectra of **1** in various solvents (see Section 2) exhibit a single set of resonances of the nucleobase protons indicative of the presence of a single species in solution. Similarly, the ^{31}P NMR spectra are characterised by a single AB pattern in which the values of chemical shift and $^1J_{PPt}$ are clearly dependent on the solvent, as shown in Table 1. The doublet at higher field exhibits the larger value of $^1J_{PPt}$ coupling (in the range 4230–4320 Hz) in chlorinated solvents, DMSO-d_6 and DMF but the opposite holds in CH_3CN.

The resonance with the higher value of $^1J_{PPt}$ is attributable to the phosphine *trans* to the nitrate ligand or to a solvent molecule.

Similar trends on the ^{31}P NMR parameters were noticed for related complexes formed in the reactions of *cis*-$[(PMe_3)_2Pt(\mu\text{-}OH)]_2X_2$ ($X^- = ClO_4$, NO_3) [12] and *cis*-$[(dppf)Pt(\mu\text{-}OH)]_2X_2$ (dppf = 1,1′-bis(diphenylphosphino)ferrocene; $X^- = BF_4$) [4] with 1-MeTy. In those cases the complexes *cis*-$[(PMe_3)_2Pt\{1\text{-MeTy}(-H)\}(CH_3CN)]ClO_4$ and *cis*-$[(dppf)Pt\{1\text{-MeTy}(-H)\}(DMF)]BF_4$ were structurally characterised. In the present case, attempts to isolate similar solvento complexes led invariably to **1**.

3.2. Characterisation of *cis*-$[(PPh_3)_2Pt\{1\text{-MeTy}(-H)\}(1\text{-MeCy},N^3)]NO_3$ (**2**)

The addition of 1 equiv. of 1-MeCy to a DMF solution of **1** affords immediately the mixed complex *cis*-$[(PPh_3)_2Pt\{1\text{-MeTy}(-H)\}(1\text{-MeCy},N^3)]NO_3$ (**2**) resulting in the fast replacement of the nitrato ligand by the added nucleobase. The reaction occurs quantitatively in DMF and CH_2Cl_2 whereas in DMSO an equilibrium between the species **1** and **2** is observed. The spectroscopic analysis of the isolated product is consistent with the presence of the deprotonated 1-MeTy and the neutral 1-MeCy, both platinated at the N(3) atom. Due to the different orientations of the nucleobases with respect to the metal coordination plane (Scheme 2), two conformers are expected for complex **2**. In the Scheme, the *ht* conformer is such to exhibit the methyl group, bound to the N1 atom in 1-MeCy and 1-MeTy, oriented in opposite directions.



Scheme 2.

The presence of two conformers in solutions of **2** was clearly evidenced in the ^{1}H and ^{31}P NMR spectra. As shown in Fig. 2a, at room temperature, the ^{31}P NMR spectrum of a freshly prepared solution of **2** in CD_2Cl_2 is characterised by two resonances having the same relative intensities: a very broad singlet at δ 0.98 ppm (flanked by ^{195}Pt satellites, $^1J_{PPt}$ ca. 3445 Hz) and a sharp doublet at δ −2.04 ($^1J_{PPt} = 3631$ Hz, $^2J_{PP} = 20.0$ Hz). Lowering the temperature at −40 °C, two AB multiplets, having relative intensities of ca 2:1, whose parameters are collected in Table 2, are detectable (Fig. 2b and c).

Similarly, in the ^{1}H NMR spectrum at room temperature, each nucleobase shows a single set of resonances. The assignments of the cytosine NH_2 protons were obtained through inverse detected

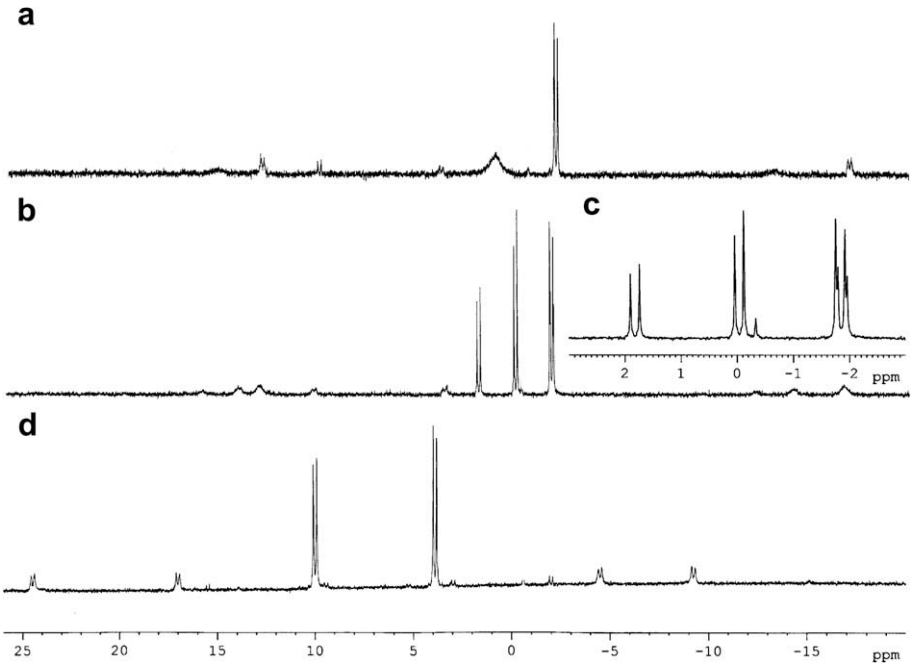


Fig. 2. $^{31}P\{^1H\}$ NMR spectra of *cis*-$[(PPh_3)_2Pt\{1\text{-MeTy}(-H)\}(1\text{-MeCy},N^3)]NO_3$ (**2**) in CD_2Cl_2 (ca. 0.1 M): (a) fresh solution, at 25 °C; (b,c) at −40 °C; (d) after 8 days, at 25 °C.

^{1}H, ^{15}N heteronuclear multiple bond coherence experiments (HMBC). In CD_2Cl_2, the two NH resonances at δ 8.61 and 8.38 ppm correlate with the same ^{15}N resonance at $\delta = -270.5$ ($^1J_{NH}$ = 69 and 89 Hz, respectively). The pertinent spectrum is reported in Fig. 1S of the Supplementary material. At low temperature (−40 °C) each nucleobase resonance appears doubled with a relative intensities of the signals of ca. 2:1 (see Section 2), in agreement with the presence of two head-to-tail and head-to-head conformers. The dynamic process leading to the broadening of one of the phosphine resonance, observed at room temperature (Fig. 2a), was not investigated in details.

In solution of chlorinated solvents, DMF or DMSO complex **2** is only moderately stable. In a few days at room temperature it converts in large extent into the isomer *cis*-[$(PPh_3)_2$Pt{1-MeTy(−H)}(1-MeCy,N^4)]NO_3, **3**, in which the cytosine is coordinated to the metal through the N4 atom. The migration of the metal from the N(3) to N(4) site of the cytosine is evidenced in the ^{31}P NMR spectra by the appearance of a sharp AB system at lower field, as shown in Fig. 2d for a solution of **2** in CD_2Cl_2. After 8 days the residual concentration of **2** is about 6% in CD_2Cl_2 as well as in DMF.

3.3. Characterisation of *cis*-[$(PPh_3)_2$Pt{1-MeTy(−H)}(1-MeCy,N^4)]NO_3 (**3**)

Complex **3** was isolated as a pure compound from a solution of DMF by slow diffusion of Et_2O but we were unable to obtain suitable crystals for X-ray structure analysis. Its characterisation, therefore, stems from NMR studies in solution. The presence of the cytosine in its iminooxo tautomeric form, platinated at the exocyclic N(4) atom, has been established by inverse detection of ^{1}H and ^{15}N nuclei through HMBC experiments.

The ^{1}H NMR spectrum of **3** in CD_2Cl_2 exhibits two NH resonances, at δ 10.99 and 5.87 ppm, having the same relative intensities, that correlate with two different nitrogen atoms at $\delta = -229.6$ ($^1J_{NH}$ = 89 Hz) and −252.1 ($^1J_{NH}$ = 78 Hz), attributable to the N3 and N4, respectively (Fig. 3). This latter signal appears further split due to the coupling with one of the ^{31}P nuclei ($^2J_{NP}$ = 118 Hz).

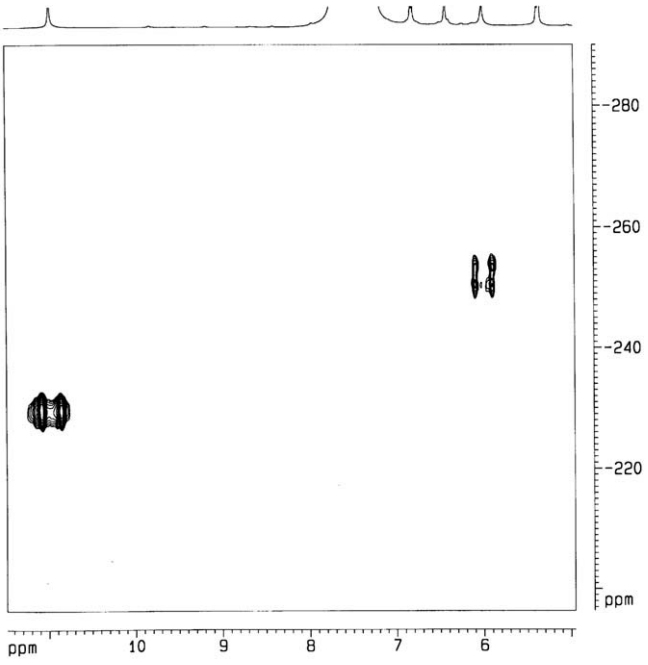
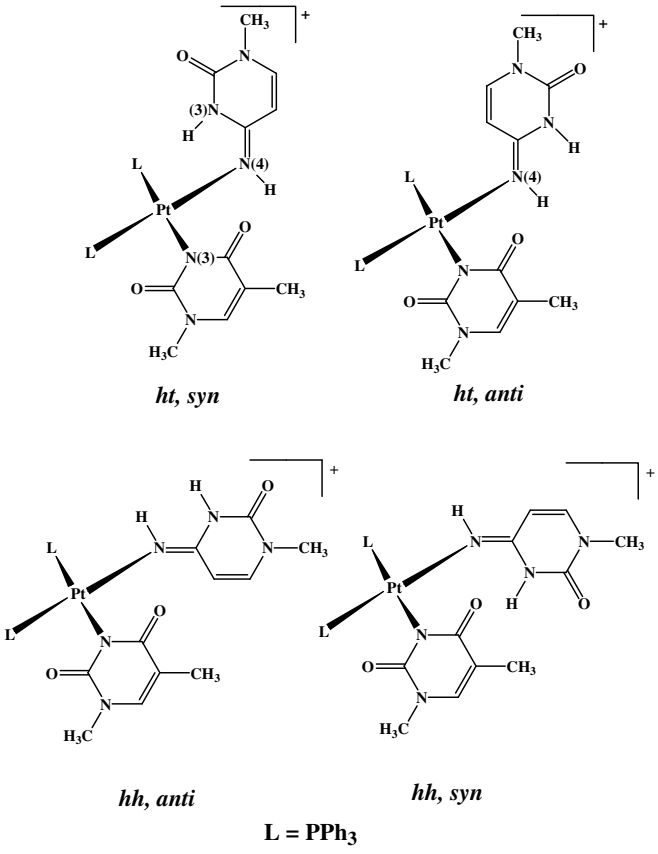


Fig. 3. ^{15}N,^{1}H HMBC spectrum of *cis*-[$(PPh_3)_2$Pt{1-MeTy(−H)}(1-MeCy,N^4)]NO_3 (**3**) in CD_2Cl_2 (evolution time 5.5 ms).



Scheme 3.

A simple inspection of the molecular models, allowing an orthogonal arrangement of the two nucleobases with respect to the Pt coordination plane, [2c] leads to draw eight possible conformers for complex **3**, four of them shown in Scheme 3.

In the *head-to-tail* conformation the hydrogen on the N4 atom (of cytosine) and the N1–CH_3 group (thymine) lie on the same side of the P_2Pt plane, whereas in the *head-to-head* arrangement they are on the opposite sides. Moreover, owing to the double bond character of the C4–N4 bond, the hydrogen atom bound at the N3 position can be near (*syn*) or far (*anti*) with respect to the metal.

Fig. 2d and 5a indicates that in CD_2Cl_2 **3** is present as a mixture of two conformers, one of which is largely predominant (ca. 20:1), both characterised by AB patterns (see Table 2). The major resonances, at δ 10.01 and 3.67 ppm, exhibit well resolved ^{195}Pt satellites. It is worth to note that the migration of the metal from the N3 to the N4 site of the cytosine determines a remarkable shift at lower field of both the PPh_3 resonances and significant changes of the $^1J_{PPt}$ values.

The *cis–trans* isomerism about the N4=C4 double bond was investigated through NOESY experiments that allow the evaluation of the relative distances between the protons [14]. In our case the cross peak between H5 and N4H is considerably more intensive than the N3H–N4H cross peak, and it appears in the contour plot at a relatively larger intensity level (as shown in Fig. 4).

These results allow us to say that the conformer having a *trans* arrangement of H3 and H4 around the cytosine N4=C4 double bond is the predominant species, although we cannot discriminate between the *ht*,*syn* and the *hh*,*syn* conformers.

The number of conformers depends on the solvent and the temperature. Fig. 5a and b shows the ^{31}P NMR spectra of **3** in CD_2Cl_2 at 25 and −90 °C, respectively. Each doublet of the main system AB observed at room temperature, appears to be replaced by a couple

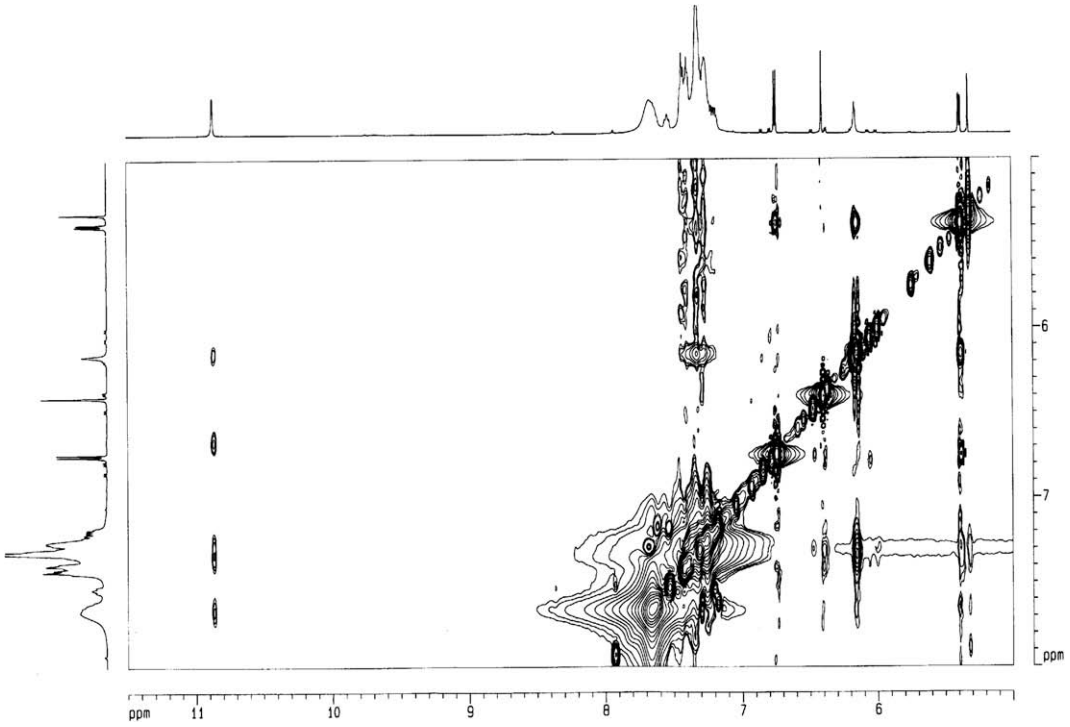


Fig. 4. NOESY spectrum of **3** in CD_2Cl_2.

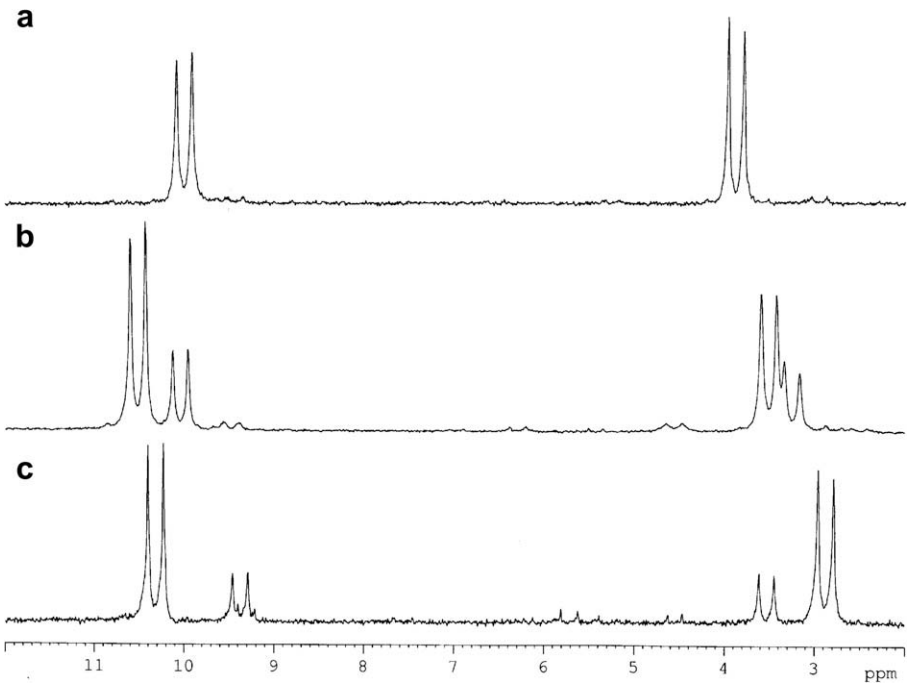


Fig. 5. $^{31}P\{^1H\}$ NMR spectra (central part) of **3**: (a) in CD_2Cl_2 at 25 °C; (b) in CD_2Cl_2 at −90 °C; (c) in DMSO-d_6, at 25 °C.

of signals having a relative intensity of 2.5:1 (Table 2) at low temperature. Moreover, in addition to a third relatively broad AB system (at δ 9.48 and 4.55 ppm), others very weak doublets are detectable in Fig. 5b. The ^{31}P NMR spectral changes with temperature find a correspondence on the ^1H NMR spectra (see Section 2). As expected, two set of signals (relative intensities 2.5:1) for each nucleobase were observed at −90 °C. These are likely to arise from a slow rotation of the cytosine ligand around the Pt–N4 bond, at low temperature.

In agreement with the observations carried out in related cytosine complexes [2c], the relative stability of the conformers depends on the nature of the solvent. As shown in Fig. 5c and Table 2, significant changes on the relative intensities of the NMR signal occur when **3** is dissolved (or prepared) in DMSO or DMF.

3.4. Role of the phosphine on the stabilisation of the cytosine in its iminooxo tautomeric form

The presence of the PPh_3 ligands in **3** appears to be important for the stabilisation of the cytosine ligand in its iminooxo form. Preliminary results obtained with the analogous complex of **2** containing the phosphine PMe_3, *cis*-[$(PMe_3)_2$Pt{1-MeTy(–H)}(1-MeCy,N^3)]NO_3 (**4**), in DMSO solution undergoes a different rearrangement that implies an interligand proton exchange, with elimination of the neutral 1-MeTy molecule. The final product is a mixture of polynuclear cyclic species *cis*-[$(PMe_3)_2$Pt{1-MeCy(–H)}]$_n(NO_3)_n$ (n = 2, 3), previously characterised by us [3], containing the N4-deprotonated cytosine bridging the metal centres through the N3 and N4 atoms.

Compound **4**, formed in quantitative yield (by NMR) by reacting stoichiometric amounts of *cis*-[$(PMe_3)_2$Pt(μ-OH)]$_2(NO_3)_2$ and 1-MeTy in DMF, followed by addition of 1 equiv. of 1-MeCy, is scarcely soluble in DMF and CH_2Cl_2. In DMSO-d_6, a fresh solution of **4** contains a mixture of two conformers (relative abundance 3:1), as indicated by the presence of two sets of signals in the ^{31}P (Fig. 6a) and ^{1}H NMR spectra (see Section 2). The binding of the cytosine at the N(3) site is documented by the presence of the NH_2 resonances in the range δ 7.9–7.7 in the ^{1}H NMR.

As shown in Fig. 6b, after 20 h at room temperature, two new sets of sharp multiplets (δ = −25.9 to −26.7 ppm and −31.0 to −31.9 ppm) develop along with a very broad system, partially overlapped with the signals of **4**. The AB pattern at higher field is attributable to *cis*-[$(PMe_3)_2$Pt{1-MeCy(–H),N^3N^4}]$_2(NO_3)_2$, the dinuclear species formed when *cis*-[$(PMe_3)_2$Pt(μ-OH)]$_2(NO_3)_2$ reacts with 1-MeCy [3]. The formation of this N4-deprotonated cytosine complex was confirmed by the appearance of the signals of the neutral 1-MeTy in the corresponding ^{1}H NMR spectrum. In several weeks at room temperature about 50% of *cis*-[$(PMe_3)_2$Pt{1-MeCy(—H)}]$_2^{2+}$ appears to have converted into the thermodynamically stable trinuclear derivative *cis*-[$(PMe_3)_2$Pt{1-MeCy(—H)}]$_3^{3+}$, shown in Fig. 6c as a sharp AB system at lower field. The same figure indicates that a small amount of the complex **4** is still present in the reaction mixture, along with other unknown species, not observed initially, responsible of the new singlets at δ −31.50 and −31.61 ppm.

The nature of the intermediate(s) leading to *cis*-[$(PMe_3)_2$Pt{1-MeCy(—H)}]$_2^{2+}$ remains undefined. The presence of an iminooxo species, analogue of **3**, seems to be ruled out, since the only detectable resonance in the low field region of the ^{1}H NMR spectrum was that of free 1-MeTy (at δ 11.18). A better insight in this system is strongly limited by the low solubility of **4** in chlorinated solvents or DMF.

4. Conclusion

In this paper we have presented the characterisation of a rare example of cytosine complex in which the tautomeric form of the nucleobase is stabilised through the metal coordination at the exocyclic nitrogen. The precursor of this species is the isomer *cis*-[$(PPh_3)_2$Pt{1-MeTy(–H)}(1-MeCy,N^3)]$^+$, formed by the facile substitution of the nitrato ligand in the thyminato complex *cis*-$(PPh_3)_2$Pt{1-MeTy(–H)}(ONO_2). The formal migration of the metal from the N3 to N4 site of the cytosine molecule, likely due to steric effects of ancillary ligands, was previously observed in the related phosphine complex *cis*-[(dppf)Pt{1-MeTy(–H)}(1-MeCy,N^3)]BF_4 (dppf = 1,1′-bis(diphenylphosphino)ferrocene) [4]. In that case, however, the isomer *cis*-[(dppf)Pt{1-MeTy(–H)}(1-MeCy,N^4)]$^+$ was stable only in solution.

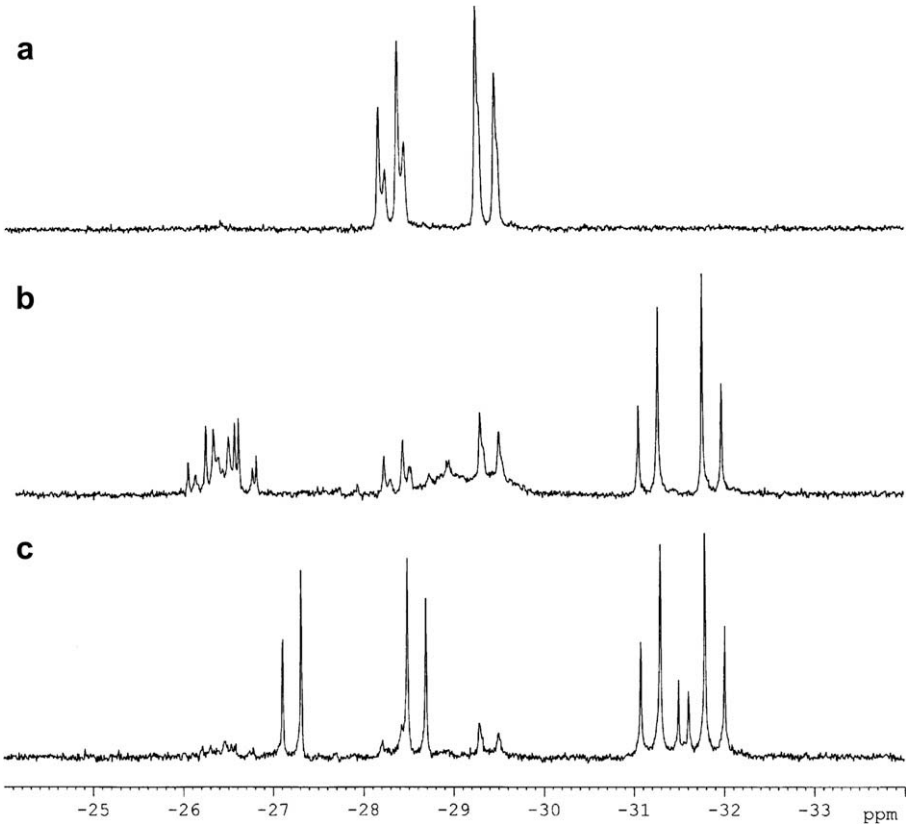


Fig. 6. ^{31}P{^{1}H} NMR spectra (central part) of *cis*-[$(PMe_3)_2$Pt{1-MeTy(–H)}(1-MeCy,N^3)]NO_3 (**4**) in DMSO-d_6, at 25 °C: (a) fresh solution; (b) after 20 h (at room temperature); (c) after 2 months (at room temperature).

Finally, the peculiar properties of the PPh_3 ligands in the stabilisation of the cytosine ligand in its iminooxo form stems on the comparison with the reactivity of **4**, the PMe_3 analogue of **2**. In this case a proton exchange from the cytosine to the thyminate ligand occurs, leading to the elimination of the thymine molecule, to the stabilisation of the cytosinate anion into the cyclic species *cis*-$[(PMe_3)_2Pt\{1\text{-}MeCy(-H)\}]_2^{2+}$ and to the trinuclear analogue *cis*-$[(PMe_3)_2Pt\{1\text{-}MeCy(-H)\}]_3^{3+}$.

Appendix A. Supplementary material

CCDC 678476 contains the supplementary crystallographic data for **1**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2008.04.030.

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