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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-[L₂Pt(μ -OH)]₂(NO₃)₂ (L = PPh₃) with 1-methylthymine (1-MeTy), in DMF, leads to the formation of the mononuclear *neutral* adduct cis-L₂Pt{1-MeTy(-H)}(ONO₂) (**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-[L₂Pt{1-MeTy(-H)}(1-MeCy,N³)]NO₃ (**2**) in which both the nucleobases are N(3)-platinated. In CD₂Cl₂ 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-[L₂Pt{1-MeTy (-H)}(1-MeCy, N^4)]NO₃ (**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 PMe₃, *cis*-[(PMe₃)₂Pt{1-MeTy(-H)}(1-MeCy,N³)]NO₃ (**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*-[(PMe₃)₂Pt{1-MeCy(-H),N³N⁴}]₂(NO₃)₂, previously characterised by us.

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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 NH₂ protons to the N(3) site of the cytosine ligand, occurs selectively in the cationic complex *cis*-[(PPh₃)₂Pt{1-MeTy(-H)}(1-MeCy)]⁺ (**2**), containing the deprotonated 1-methylthymine (1-MeTy) and the neutral cytosine ligand, 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-L₂Pt{1-MeTy(-H)}(ONO₂) (L = PPh₃, **1**) characterised by X-ray single crystal analysis. The isolated complex cis-[(PPh₃)₂Pt{1-MeTy(-H)}(1-MeCy,N⁴)]NO₃ (**3**), was characterised by multinuclear and 2D-NMR spectroscopy.

In order to evaluate the role of the PPh₃ ligands in the stabilisation of the cytosine in its tautomeric form, we have prepared the complex *cis*- $[L_2Pt{1-MeTy(-H)}(1-MeCy)]^+$ (L = PM₃, **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*- $[(PMe_3)_2Pt{1-MeCy(-H),N^3N^4}]_2(NO_3)_2$, 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*- $[(dppf)Pt{1-MeTy(-H)}(1-MeCy,N^3)]BF_4$, where dppf is 1,1'-bis(diphenylphosphino)ferrocene [4].

2. Experimental

2.1. Synthesis and materials

cis-[L₂Pt(μ -OH)]₂(NO₃)₂ (L = PPh₃[5], PMe₃[2]) and 1-MeCy [6] were prepared as previously reported. 1-MeTy and all the solvents





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(CH₂Cl₂, DMF, DMSO-*d*₆, CDCl₃, CD₂Cl₂, CD₃CN, Et₂O) were Aldrich products.

2.1.1. Synthesis of cis-(PPh₃)₂Pt{1-MeTy(-H)}(ONO₂) (1)

To a solution of $cis-[(PPh_3)_2Pt(\mu-OH)]_2(NO_3)_2$ (72.6 mg, $4.5 \times 10^{-2} \text{ mmol}$) 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 Et₂O (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 CHCl₃, by vapour diffusion of Et₂O at room temperature, afforded crystals having the composition cis-(PPh₃)₂Pt{1-MeTy (-H)}(NO₃) · 3H₂O. Elem. Anal. Calc. for C₄₂H₄₃N₃O₈P₂Pt (974.8): C, 51.75; H, 4.45; N, 4.31. Found: C, 51.58; H, 4.26; N, 4.20%. ¹H NMR in CDCl₃ (δ): 7.78–6.91 cm (30H, PPh₃); 6.32 s (1H, H(6)), 2.95 s (3H, NCH₃), 1.65 s (3H, CH₃); ¹H NMR in DMSO- d_6 (δ) 7.72-7.09 cm (30H, PPh₃), 6.88 s (1H, H(6)), 2.96 s, (3H, NCH₃), 1.49 s (3H, CH₃). The ³¹P{¹H} NMR data are collected in Table 1.

2.1.2. Synthesis of cis-[(PPh₃)₂Pt{1-MeTy(-H)} (1-MeCy,N³)]NO₃ (**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

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

Solvent	$P_A (^1 J_{PPt})$	$P_B (^1 J_{PPt})$	$^{2}J_{\rm PP}$
CH ₂ Cl ₂	7.41 (3294)	4.85 (4230)	21.9
CDCl₃	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
CH₃CN ^a	7.62 (4174)	3.73 (3050)	21.9

^a Fresh solution.

I	a	bl	e	2
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 $^{31}P{^1H}$ 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

a white solid that was recovered by filtration, washed with Et₂O and dried under vacuum. (71.8 mg, yield 66%). Elem. Anal. Calc. for C₄₇H₄₄N₆O₆P₂Pt (1045.92): C, 53.97; H, 4.25; N, 8.03. Found: C, 52.86; H, 4.14; N, 7.97%. ¹H NMR in CD₂Cl₂ at 25 °C (δ): 7.65– 7.16 cm (30H, PPh₃); 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, NCH₃), 2.93 s (3H, NCH₃) 1.50 s (3H, CH₃); ¹H NMR in CD_2Cl_2 at $-40 \circ C$ (δ): 7.92–6.36 cm (30H, PPh₃); 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, NCH₃), 2.91 s (3H, NCH₃), 1.34 s (3H, CH₃); 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, NCH₃), 2.84 s (3H, NCH₃), 1.55 s (3H, CH₃). ¹H NMR in DMSO-d₆ at 25 °C (δ): 7.55–7.23 cm (31H, PPh₃ 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, NCH₃), 2.80 s (3H, NCH₃), 1.40 s (3H, CH₃). The ³¹P{¹H} NMR data are collected in Table 2.

2.1.3. Synthesis of cis-[(PPh₃)₂Pt{1-MeTy(-H)} (1-MeCy,N⁴)]NO₃ (**3**)

Twenty-one milligrams of **1** (2.28 \times 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 Et₂O afforded a white solid that was recovered by filtration, washed with Et₂O and dried under vacuum. The yield of **3** was 15.7 mg, 65%. Elem. Anal. Calc. for C₄₇H₄₄N₆O₆P₂Pt (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, PPh₃); 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, ³*J*_{HH} 7.0 Hz), 3.11 (s, 3H, NCH₃), 2.49 (s, 3H, NCH₃), 1.42 (s, 3H, CCH₃); 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, NCH₃), 2.71 (s, 3H, NCH₃), 1.49 (s, 3H, CCH₃). ¹H NMR in CD₂Cl₂: 10.99 s (1H, N3H), 7.65–7.18 (30H, PPh₃), 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, NCH₃), 6.40 s (1H, H6), 3.00 (s, 3H, NCH₃), 1.53 (s, 3H, CCH₃). The ³¹P{¹H} NMR data are collected in Table 2.

2.1.4. Synthesis of cis-[(PMe₃)₂Pt{1-MeTy(-H)}(1-MeCy, N^3)]NO₃ (**4**)

A mixture of cis-[(PMe₃)₂Pt(μ -OH)]₂(NO₃)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 CH₂Cl₂/DMSO

Compound	Solvent (temp., K)	$P_A(^1J_{PPt})$	$P_{B}(^{1}J_{PPt})$	$^{2}J_{PP}$
2	CD ₂ Cl ₂ (298)	0.98 br s (ca. 3443)	-1.88 d (3630)	20.0
2	CD ₂ Cl 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- <i>d</i> 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 ₂ Cl 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- <i>d</i> 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 Et₂O. The white solid, collected by filtration, washed with Et₂O and dried under vacuum was 43 mg (yield 19%). The elemental analysis and NMR data are consistent with the composition *cis*-[(PMe₃)₂Pt{1-MeTy(-H)}(1-MeCy,N³)]-NO₃ · DMSO · H₂O. Elem. *Anal.* Calc. for C₁₇H₃₂N₆O₆P₂Pt · DM-SO · H₂O (769.6): C, 29.57; H, 5.50; N, 10.89. Found: C, 29.31; H, 5.64; N, 10.87%. ¹H NMR in DMSO-d₆: 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, PMe₃, ²J_{HP} 10 Hz). ³¹P{¹H} in DMSO-d₆, δ (ppm): two AX multiplets at -28.3 (¹J_{PPt} 3424 Hz), -29.3 (¹J_{PPt} 3424 Hz), -29.4 (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 ¹H and ³¹P (operating at 300.13 and 121.5 MHz, respectively); with a Bruker 400 AMX-WB spectrometer for ¹⁵N (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 ³¹P NMR spectra in CH₂Cl₂, DMF and CH₃CN were obtained using a capillary containing D₂O for lock signal.

The ¹H 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 ³¹P, and CH_3NO_2 (in CDCl₃ at 50% w/w) for ¹⁵N. 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 K α radiation ($\lambda = 0.71073$ 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** · 0.5(H₂O): C₄₂H₃₈N₃O_{5.50}P₂Pt, *M* = 929.78, monoclinic, space group *P*2₁/*c*, *a* = 12.184(3), *b* = 13.796(3), *c* = 24.926(4) Å, *β* = 93.27(2)°, *V* = 4183.0(15) Å³, *Z* = 4, *D*_{calc} = 1.476 g/cm³, 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*σ*(*I*), max positive and negative peaks in Δ*F* map 0.669, -0.577 e Å⁻³.

3. Results and discussion

3.1. Characterisation of cis-(PPh₃)₂Pt{1-MeTy(-H)}(ONO₂) (1)

The reaction of cis-[(PPh₃)₂Pt(µ-OH)]₂(NO₃)₂ with 1-MeTy, carried out in different solvents (CH₂Cl₂, DMF, CH₃CN), affords the neutral complex cis-(PPh₃)₂Pt{1-MeTy(-H)}(ONO₂) (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 man-

Fig. 1. Molecular structure of complex **1**, *cis*-(PPh₃)₂Pt{1-MeTy(-H)}(ONO₂) (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).

ifests 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–ONO₂ bond distance is 2.117(4) Å, with Pt–O–N bond angle of 120.2(4)°.

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, $87.14(19)^\circ$, is narrower in comparison to the P(1)–Pt–P(2) one, $98.28(7)^\circ$, 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*–[(PPh₃)₂Pt{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*-[(PMe₃)₂Pt-{1-MeTy(–H)}(CH₃CN)]⁺ and *cis*-[(PMe₃)₂Pt-{1-MeTy(–H)}(CH₃CN)]⁺ and *cis*-[(PMe₃)₂Pt-{1-MeTy(–H)}(CH₃CN)]⁺, [12] respectively, where the base is trans to PMe₃.

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 $78.0(1)^\circ$, while the nitro group is more bent, and the mean plane figures out a dihedral angle of $64.6(2)^\circ$. 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*-[(PPh₃)₂Pt(1-MeCy)(ONO₂)]-NO₃ and *cis*-[(PPh₃)₂Pt(9-MeGu)(ONO₂)]NO₃ [13].



The unit cell of **1** shows a void accessible to solvent of 309.0 Å³ (ca. 7.4% of the volume). We also obtained another crystal form of *cis*-(PPh₃)₂Pt{1-MeTy(-H)}(ONO₂), monoclinic, space group *P*2₁/*c*, unit cell *a* = 11.899(2), *b* = 21.878(3), *c* = 15.985(3) Å, β = 90.63(2)° 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 ¹H 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 ³¹P 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 CH₃CN.

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

Similar trends on the ³¹P NMR parameters were noticed for related complexes formed in the reactions of *cis*-[(PMe₃)₂Pt(μ -OH)]₂X₂ (X⁻ = ClO₄, NO₃) [12] and *cis*-[(dppf)Pt(μ -OH)]₂X₂ (dppf = 1,1'-bis(diphenylphosphino)ferrocene; X⁻ = BF₄) [4] with 1-MeTy. In those cases the complexes *cis*-[(PMe₃)₂Pt{1-MeTy</sub> (-H)}(CH₃CN)]ClO₄ and *cis*-[(dppf)Pt{1-MeTy(-H)}(DMF)]BF₄ were structurally characterised. In the present case, attempts to isolate similar solvento complexes led invariably to **1**.

3.2. Characterisation of cis-[(PPh₃)₂Pt{1-MeTy(-H)}(1-MeCy,N³)]NO₃ (**2**)

The addition of 1 equiv. of 1-MeCy to a DMF solution of 1 affords immediately the mixed complex cis-[(PPh₃)₂Pt{1-MeTy (-H)}(1-MeCy, N^3)]NO₃ (2) resulting in the fast replacement of the nitrato ligand by the added nucleobase. The reaction occurs quantitatively in DMF and CH₂Cl₂ 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.

The presence of two conformers in solutions of **2** was clearly evidenced in the ¹H and ³¹P NMR spectra. As shown in Fig. 2a, at room temperature, the ³¹P NMR spectrum of a freshly prepared solution of **2** in CD₂Cl₂ is characterised by two resonances having the same relative intensities: a very broad singlet at δ 0.98 ppm (flanked by ¹⁹⁵Pt 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 ¹H NMR spectrum at room temperature, each nucleobase shows a single set of resonances. The assignments of the cytosine NH₂ protons were obtained through inverse detected



¹H, ¹⁵N heteronuclear multiple bond coherence experiments (HMBC). In CD₂Cl₂, the two NH resonances at δ 8.61 and 8.38 ppm correlate with the same ¹⁵N resonance at δ = –270.5 (¹*J*_{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*-[(PPh₃)₂Pt{1-MeTy(-H)}(1-MeCy,N⁴)]NO₃, **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 ³¹P NMR spectra by the appearance of a sharp AB system at lower field, as shown in Fig. 2d for a solution of **2** in CD₂Cl₂. After 8 days the residual concentration of **2** is about 6% in CD₂Cl₂ as well as in DMF.

3.3. Characterisation of cis-[(PPh₃)₂Pt{1-MeTy(-H)}(1-MeCy,N⁴)]NO₃ (**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 ¹H and ¹⁵N nuclei through HMBC experiments.

The ¹H NMR spectrum of **3** in CD₂Cl₂ 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 δ = -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 ³¹P nuclei (²J_{NP} = 118 Hz).



ppm 10 9 8 7 6

Fig. 3. ^{15}N , ¹H HMBC spectrum of *cis*-[(PPh₃)₂Pt{1-MeTy(-H)}(1-MeCy,N⁴)]NO₃ (3) in CD₂Cl₂ (evolution time 5.5 ms).



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–CH₃ group (thymine) lie on the same side of the P₂Pt 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 ¹⁹⁵Pt 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 PPh₃ 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 CD₂Cl₂ 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. 5. ${}^{31}P{}^{1}H$ NMR spectra (central part) of **3**: (a) in CD₂Cl₂ at 25 °C; (b) in CD₂Cl₂ 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 ³¹P 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 PPh₃ 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 PMe₃, *cis*-[(PMe₃)₂Pt{1-MeTy(-H)}(1-Me-Cy,N³)]NO₃ (**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*-[(PMe₃)₂Pt{1-MeCy (-H)}]_n(NO₃)_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*-[(PMe₃)₂Pt(μ -OH)]₂(NO₃)₂ and 1-MeTy in DMF, followed by addition of 1 equiv. of 1-MeCy, is scarcely soluble in DMF and CH₂Cl₂. 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 ³¹P (Fig. 6a) and ¹H NMR spectra (see Section 2). The binding of the cytosine at the N(3) site is documented by the presence of the NH₂ resonances in the range δ 7.9–7.7 in the ¹H NMR.

As shown in Fig. 6b, after 20 h at room temperature, two new sets of sharp multiplets ($\delta = -25.9$ 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*-[(PMe₃)₂Pt{1-MeCy(-H), N^3N^4 }]₂(NO₃)₂, the dinuclear species formed when *cis*-[(PMe₃)₂Pt(μ -OH)]₂(NO₃)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 ¹H NMR spectrum. In several

weeks at room temperature about 50% of *cis*-[(PMe₃)₂ Pt{1-MeCy(-H)}]₂²⁺ appears to have converted into the thermodynamically stable trinuclear derivative *cis*-[(PMe₃)₂Pt{1-MeCy (-H)}]₃³⁺, 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-[(PMe₃)₂Pt {1-MeCy(-H)}]₂²⁺ 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 ¹H 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-[(PPh₃)₂Pt{1-MeTy(-H)}(1-MeCy,N³)]⁺, formed by the facile substitution of the nitrato ligand in the thyminato complex cis-(PPh₃)₂Pt{1-MeTy(-H)}(ONO₂). 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,N³)]BF₄ (dppf = 1,1'-bis(diphenylphosphino)ferrocene) [4]. In that case, however, the isomer cis-[(dppf)Pt{1-MeTy(-H)}(1-MeCy,N⁴)]⁺ was stable only in solution.



Fig. 6. ${}^{31}P{}^{1}H$ NMR spectra (central part) of *cis*-[(PMe₃)₂Pt{1-MeTy(-H)}(1-MeCy,N³)]NO₃ (**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 PPh₃ ligands in the stabilisation of the cytosine ligand in its iminooxo form stems on the comparison with the reactivity of **4**, the PMe₃ 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 $cis-[(PMe_3)_2Pt\{1-MeCy(-H)\}]_2^{2+}$ and to the trinuclear analogue $cis-[(PMe_3)_2Pt\{1-MeCy(-H)\}]_3^{3+}$.

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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