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Synthesis and characterization of *cis*-[$(PPh_3)_2$Pt{9-MeAd(-H),N^6N^7}]X ($X^- = NO_3$, PF_6): The first example of a platinum(II) complex containing the N^6,N^7-chelated 9-methyladenine anion

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Dedicated to Prof. Piero Zanello.

Abstract

Reaction between the binuclear hydroxo complex *cis*-[$(PPh_3)_2$Pt(μ-OH)]$_2X_2$ ($X^- = NO_3$, **1a**; PF_6^-, **1b**) and the model DNA base 9-methyladenine (9-MeAd) leads to the formation of the mononuclear species *cis*-[$(PPh_3)_2$Pt{9-MeAd(-H),N^6N^7}]X ($X^- = NO_3$, **2a**; PF_6, **2b**), in which the nucleobase chelates the Pt(II) ion with the N6 and N7 atoms. The coordination mode of the nucleobase has been determinated through a multinuclear (^{1}H, ^{31}P, ^{13}C, ^{15}N and ^{195}Pt) NMR analysis and the nuclearity of the complex has been obtained by E.S.I. mass spectrometry. **2** represents the first example of an isolated platinum complex in which the NH_2-deprotonated adenine exhibits this binding mode.

Keywords: Platinum(II) complexes; 9-Methyladenine; Multinuclear NMR; Phosphine

1. Introduction

Although the coordination modes of the DNA nucleobases in particular toward platinum (II and IV) centres [1–3] have been investigated in great detail over the years, some aspects dealing with the role of the ancillary ligands on the site of metallation of these model biomolecules are still unexplored. In this contest, we have shown that the reaction of the hydroxo complexes *cis*-[L_2Pt(μ-OH)]$_2$-$(NO_3)_2$ (L = tertiary phosphine) with 9-substituted adenines affords the polynuclear cyclic species *cis*-[L_2Pt{adenine(-H),N^1N^6}]$_n(NO_3)_n$ in which the NH_2-deprotonated nucleobases bridge selectively the metal centres through the N(1) and N(6) atoms. The nuclearity of the adeninate complexes appears to be dependent on the nature of the neutral ligands L. PMe_3 stabilizes the dinuclear species ($n = 2$ [4,5]), while the trinuclear analogues ($n = 3$) are formed when L are PMe_2Ph [6] and $PMePh_2$ [7]. With the latter phosphine the cation *cis*-[$(PMePh_2)_2$Pt{9-MeAd(−H),N^1N^6}]$_3^{3+}$ is stable only in chlorinated solvents. In fact, when dissolved in DMSO or DMF, it immediately converts into a complex mixture of products, among them the mononuclear derivative *cis*-[$(PMePh_2)_2$Pt{9-MeAd(-H),N^6N^7}]$^+$ in which the nucleobase acts as a chelating ligand through the N(6) and N(7) atoms [7].

More recently, we reported the structural characterization of the azametallacycle *cis*-[L_2PtNH=C(Me){9-MeAd(-2H)}]$^+$ (L = PPh_3) depicted in Chart 1 [8].

This acetamidine complex releases in chlorinated solvents the inserted CH_3CN molecule to give quantitatively the new adeninato species *cis*-[L_2Pt{9-MeAd(-H),N^6N^7}]$^+$ (L = PPh_3, **2**), which has been now obtained by reacting *cis*-[$(PPh_3)_2$Pt(μ-OH)]$_2X_2$ ($X^- = NO_3$, **1a**; PF_6, **1b**) with 9-MeAd. In this paper, we report the synthesis and the

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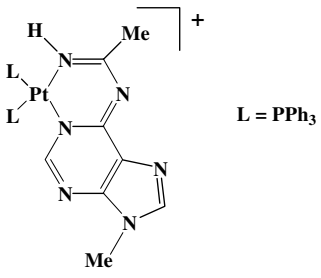

Chart 1.

characterization of this complex, isolated as nitrate (**2a**) and hexafluorophosphate (**2b**) salts. The N^6,N^7-chelation of the nucleobase in **2** has been established through a complete multinuclear NMR analysis and the nuclearity of the complex has been proved by E.S.I. mass spectrometry. This binding mode of the adeninate ion has been previously described only for Mo(IV) [9], Rh(III) [10,11], Ir(III) [12] and Ru(II) [13,14] complexes.

2. Experimental

2.1. Materials

cis-$[(PPh_3)_2Pt(\mu\text{-}OH)]_2(NO_3)_2$ (**1a**) [8] and 9-MeAd [15] has been prepared as previously reported. $(NBu_4)PF_6$ and all the solvents (CH_2Cl_2, DMF, DMSO-d_6, $CDCl_3$, CD_3CN, Et_2O) were used as supplied (Aldrich products).

2.2. 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, ^{31}P and ^{195}Pt (operating at 300.13, 121.5 and 64.2 MHz, respectively) and with a Bruker 400 AMX-WB spectrometer for ^{13}C and ^{15}N (operating at 100.6 and 40.6 MHz, respectively). The ^1H and ^{13}C 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, Na_2PtCl_4 in D_2O (adjusted to $\delta = -1628$ ppm from Na_2PtCl_6) for ^{195}Pt 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 [6]. ESI-MS spectra were performed with a MSD SL Trap mass spectrometer (Agilent Technologies, Palo Alto, CA, USA) operating in positive ion mode from m/z 100–2200. A 5×10^{-6} M solution of compound **2a** dissolved in dichloromethane was directly infused into the ion source at a flow rate of 10 μL min^{-1} by a syringe pump.

2.3. Preparation of the complexes

2.3.1. Synthesis of cis-[(PPh$_3$)$_2$Pt{9-MeAd(-H),N^6,N^7}](NO$_3$) (**2a**)

300 mg of 1a (0.188 mmol) were dissolved in 5 mL of CH_2Cl_2 (in ca 30 min. at room temp.) and 9-MeAd (56 mg, 0.376 mmol) was then added. After 2 h under stirring a yellow solution was obtained. Addition of Et_2O (15 mL) afforded a pale yellow solid that was recovered by filtration, washed with two different amounts of Et_2O (3 mL) and dried under vacuum to give 250 mg of 2a (yield: 71 %). Elem. *Anal.* Calc. for $C_{42}H_{36}N_6O_3P_2Pt$ (929.81): C, 54.25; H, 3.91; N, 9.03. Found: C, 53.90; H, 3.84; N, 8.74%. ^1H NMR in $CDCl_3$: 8.202 s (1H, H(2)), 6.442 s (1H, H(8)), 3.775 s (3H, NCH_3), 4.507 dd (1H, NH, $^3J_{HP}$ 6 and 3 Hz ca.), 7.57–7.06 (15H, PPh_3); ^1H NMR in DMSO-d_6: 8.035 s (1H, H(2)), 6.616 s (1H, H(8)), 3.559 s (3H, NCH_3), 4.240 dd (1H, NH, $^3J_{HP}$ 6.8 and 2.9 Hz), 7.66–7.24 (15H, PPh_3); ^{13}C HMBC inverse detected NMR (100.61 MHz, evolution time 50 ms) in $CDCl_3$: $\delta = 30.7$ NCH_3 ($^1J_{CH} = 143$ Hz); 125.9 C5; 140.0 C8 ($^1J_{CH} = 215$ Hz); 147.6 C4; 158.2 C2 ($^1J_{CH} = 202$ Hz); 164.9 C6.

2.3.2. Synthesis of cis-[(PPh$_3$)$_2$Pt(μ-OH)]$_2$(PF$_6$)$_2$ (**1b**)

A solution of $(NBu_4)PF_6$ (47.7 mg, 0.123 mmol) in dichloromethane (3 mL) was dropwise added to a solution of 1a (97.5 mg, 0.061 mmol) in CH_2Cl_2 (4 mL). The white solid formed was recovered by filtration, washed with several aliquots of CH_2Cl_2 and dried under vacuum. The yield of **1b** was 88 mg (80%). Elem. *Anal.* Calc. for $C_{72}H_{62}F_{12}O_2P_6Pt_2$ (1763.27): C, 49.04; H, 3.55. Found: C, 49.11; H, 3.32%. ^1H NMR in DMSO-d_6: 3.36 br s (1H, OH), 7.66–7.09 cm (30H, PPh_3); $^{31}P\{^1H\}$ NMR in DMSO-d_6: $\delta = 6.67$ PPh_3(s, $^1J_{PPt} = 3705$ Hz); $\delta = -143.88$ PF_6 ($^1J_{PF} = 710.7$ Hz).

2.3.3. Synthesis of cis-[(PPh$_3$)$_2$Pt{9-MeAd(-H),N^6N^7}](PF$_6$) (**2b**)

9-MeAd (10.5 mg, 0.070 mmol) was added to a solution of 1b (61.3 mg, 0.035 mmol) dissolved in hot DMF (4 mL) and the solution was stirred for 3 h at room temperature. Addition of Et_2O (12 mL) to the resulting yellow solution afforded a pale yellow solid of 2b, which was recovered by filtration, washed with Et_2O (10 mL) and dried under vacuum (55 mg, yield 77%). Elem. *Anal.* Calc. for $C_{42}H_{36}F_6N_5P_3Pt$ (1012.77): C, 49.81; H, 3.59; N, 6.91. Found: C, 49.97; H, 3.53; N, 6.78%. ^1H NMR in DMSO-d_6: 8.047 s (1H, H(2)), 6.675 s (1H, H(8)), 3.667 s (3H, NCH_3), 4.350 dd (1H, NH, $^3J_{HP}$ 6.9 and 2.8 Hz), 7.80–7.08 (15H, PPh_3); $^{31}P\{^1H\}$ NMR in DMSO-d_6: AB multiplet, $\delta = 9.95$ (d, $^1J_{PPt} = 3896$ Hz; $^2J_{PP} = 19.76$ Hz); $\delta = 6.16$ (d, $^1J_{PPt} = 3091$ Hz; $^2J_{PP} = 19.76$ Hz); $\delta = -143.45$ PF_6 ($^1J_{PF} = 709.5$ Hz).

2.3.4. Synthesis of cis-(PPh$_3$)$_2$Pt(ONO$_2$)$_2$

850 mg of *cis*-$(PPh_3)_2PtCl_2$ (1.07 mmol) was dissolved in 10 mL of CH_2Cl_2; 365 mg of $AgNO_3$ (2.15 mmol) was dissolved in 5 mL of hot ethanol and the solution was added dropwise to that of *cis*-$(PPh_3)_2PtCl_2$. The suspension has been stirred for 24 h in the dark and then was filtered to remove AgCl. Addition of 30 mL of diethyl ether to the solution afforded a white solid which was recovered by filtration, washed with Et_2O and dried under vacuum

(659 mg, yield 73%). Elem. *Anal.* Calc. for $C_{36}H_{30}N_2O_6P_2Pt$ (843.67): C, 51.25; H, 3.59; N, 3.32. Found: C, 51.64; H, 3.42; N, 3.55%. $^{31}P\{^1H\}$ NMR in $CDCl_3$: $\delta = 3.35$ (s, $^1J_{PPt} = 4018$ Hz). The X-ray structure of this complex [16] will be reported elsewhere.

3. Results and discussion

The reaction between the hydroxo complexes *cis*-$[L_2Pt(\mu\text{-}OH)]_2X_2$ ($L = PPh_3$; $X^- = NO_3$, **1a**; PF_6, **1b**) and 9-MeAd, in various solvents, leads to the quantitative formation of the mononuclear species *cis*-$[L_2Pt\{9\text{-}MeAd\text{-}(-H),N^6N^7\}]X$, which has been isolated with good yield from CH_2Cl_2 ($X^- = NO_3$, **2a**) and DMF ($X^- = PF_6$, **2b**) solutions, respectively (Chart 2).

The coordination mode of the NH_2-deprotonated adenine has been studied through a multinuclear (^1H, ^{13}C; ^{31}P; ^{15}N and ^{195}Pt) NMR analysis in $CDCl_3$ and DMSO-d_6. A single set of resonances for the nucleobase protons were detectable in the ^1H NMR spectrum of **2** and their attribution was performed through $^{15}N,^1H$ HMBC experiments. The pertinent ^{15}N NMR data are collected in Table 1.

As seen in Fig. 1, the adenine methyl protons at δ 3.775 correlate with the nitrogen resonance at −218.1 ppm, attributed to N(9) atom, which is also in resonance with the singlet at δ 6.442, which is therefore attributed to the H(8) proton. This proton shows correlation with the N(7) resonance at −191.9 ppm. As a consequence, the singlet at 8.202 is attributable to the H(2) proton which, in fact, shows correlations with the nitrogen resonances at δ −135.5 and −157.5 ppm, due to N(1) and N(3) atoms, respectively.

In the ^1H NMR spectrum the resonance of the exocyclic H(6) proton appears as a poorly resolved doublet of doublets at δ 4.507, as a result of the coupling with the ^{31}P nuclei ($^3J_{HP}$ ca. 6 and 3 Hz), flanked by very broad ^{195}Pt satellites ($^2J_{HPt}$ ca. 100 Hz). A better resolution of this resonance was found in DMSO-d_6, as shown in Fig. 2, in which the $^{15}N,^1H$ HMQC spectrum is shown. The N(6) resonance, centered at δ − 242.7, exhibits $^1J_{NH}$ and $^2J_{NP}$ values of ca. 80 and 59 Hz, respectively.

The $^{31}P\{^1H\}$ NMR spectra in various solvents of **2a** are characterized by a sharp AB multiplet flanked by ^{195}Pt satellites and these data are collected as shown in Table 2. A

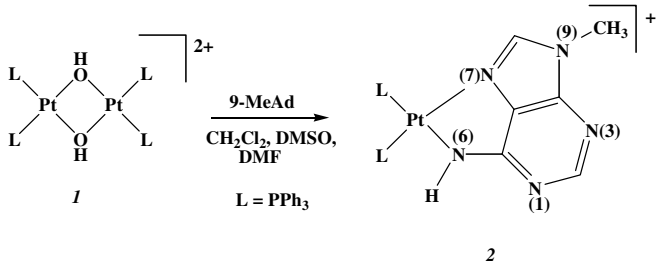

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Chart 2.

Table 1
^{15}N NMR inverse detected data for complex **2a** in various solvents (δ in ppm, J in Hz) at 25 °C

Solvent	N(1)	N(3)	N(6)	N(7)	N(9)
DMSO-d_6	−131.5	−153.2	−243.1 ($^1J_{NH}$ 80 Hz)	−191.5	−216.8
$CDCl_3$	−135.5	−157.5	−242.7 ($^1J_{NH}$ 85 Hz)	−191.9	−218.1

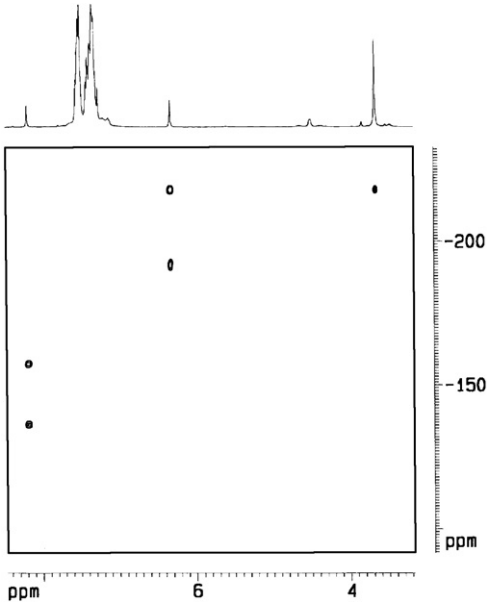

Fig. 1. $^{15}N,^1H$ HMBC spectrum of **2a** in $CDCl_3$ (evolution time 50 ms).

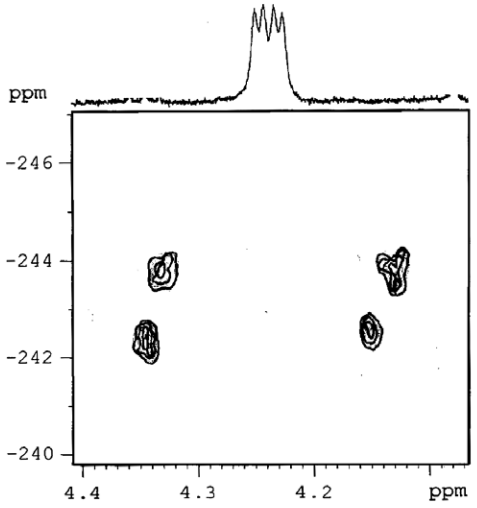

Fig. 2. $^{15}N,^1H$ HMQC spectrum of **2a** in DMSO-d_6 (evolution time 5.5 ms).

^{31}P, ^1H HMBC NMR experiment confirms the N^6,N^7-chelation of the nucleobase. As shown in Fig. 3, both the AB doublets of the two chemically different ^{31}P nuclei correlate with the H(6) resonance at δ 4.507 ppm, but only one of these (at δ 9.00 ppm) correlates with the H(8) resonance, at 6.442 ppm.

Table 2
$^{31}P\{^{1}H\}$ NMR data for complex **2a** in various solvents (δ in ppm and J in Hz) at 25°C

Solvent	P(A); $^{1}J_{PPt}$	P(B); $^{1}J_{PPt}$	$^{2}J_{PP}$
CH_2Cl_2[a]	8.82 (3863)	6.12 (3108)	19.8
$CDCl_3$	9.00 (3811)	6.19 (3136)	19.9
DMF [a]	9.80 (3879)	6.08 (3125)	20.0
DMSO-d_6	9.20 (3850)	5.57 (3162)	19.9
CD_3CN[b]	9.29 (3894)	5.93 (3109)	19.9

[a] D_2O capillary for lock signal.
[b] Fresh solution.

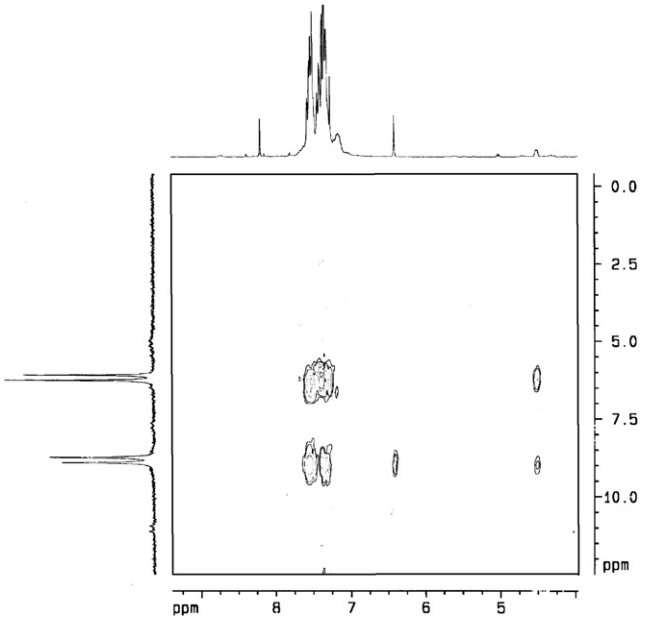

Fig. 3. $^{31}P,^{1}H$ HMBC spectrum of **2a** in $CDCl_3$.

This last correlation allows the attribution of the ^{31}P resonance with the higher $^{1}J_{PP}$ value to the phosphine in trans to the N(7) atom.

As anticipated, in the 300 MHz ^{1}H NMR spectrum of **2a** in $CDCl_3$, the H(6) resonance exhibits very broad ^{195}Pt satellites. A better evidence of this two-bond ^{1}H–^{195}Pt interaction comes from a ^{195}Pt, ^{1}H HMBC experiment (shown in Fig. 1 of the Supplementary Material). The ^{195}Pt resonance, at δ −4948, in addition to the coupling with the ^{31}P nuclei, appears in resonance with the proton at δ 4.507, with $^{2}J_{PtH} = 105$ Hz.

The coordination mode of the 9-substituted adenine found in **2**, structurally authenticated in Ru, Mo, Ir and Rh complexes [9–14], has only a few precedents in the Pt chemistry [7]. We have monitored the condensation reaction between the hydroxo complex **1** and 9-MaAd in a variety of solvents. In all the cases, the ^{31}P NMR spectrum of the reaction mixture exhibits only the resonances due to chelated complex **2** (Table 2), indicating the relatively high thermodynamic stability of this species. When the reaction is carried out in CH_3CN, the azametallacycle *cis*-$[(PPh_3)_2$-PtNH=C(Me){9-MeAd(-2H)}$]^+$ (Chart 1) is formed, as a result of the formal addition of the exocyclic N(6)H bond of the adeninate ion into a metal-coordinated solvent molecule [8]. However complex **2**, dissolved in acetonitrile, is stable enough to be characterized also in this solvent, since the insertion reaction of CH_3CN occurs in ca. 2 h at room temperature.

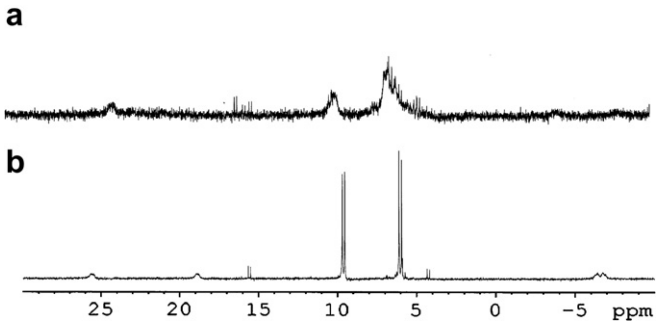

Fig. 4. $^{31}P\{^{1}H\}$ NMR spectra of the mixture of (a) *cis*-$(PPh_3)_2Pt(ONO_2)_2$ and 9-MeAd (molar ratio 1:1) in DMSO-d_6; (b) after addition of proton sponge.

The stability of species **2a** is further suggested by the observation that a solution of *cis*-$(PPh_3)_2Pt(ONO_2)_2$ containing 1 equiv. of 9-MeAd, in the presence of proton sponge, is almost quantitatively converted into **2a**. As shown in Fig. 4a, the ^{31}P NMR spectrum of a DMSO-d_6 solution of *cis*-$(PPh_3)_2Pt(ONO_2)_2$ and 9-MeAd exhibits a broad signal at 6 and 10 ppm ca. likely due to a mixture of isomers resulting on the platination of the nucleobase at the N(1)- and/or N(7) sites. Deprotonation of the nucleobase, obtained by addition of proton sponge, causes the appearance of the sharp multiplet typical of **2a** (Fig. 4b).

Since we were unable to grow crystals of **2a** and **2b** suitable for X-ray analyses, the nuclearity of the complex has been confirmed by E.S.I. mass spectrometry. The spectrum of **2a** (shown in Fig. 2 of the Supplementary Material), recorded in CH_2Cl_2, shows only the peak at 867.1 m/z, with the correct isotopic pattern, corresponding to the monocation $[(PPh_3)_2Pt\{9\text{-MeAd(-H)}\}]^+$.

4. Conclusions

The deprotonation of the exocyclic amino group in the model nucleobase 9-MeAd leads to the formation of the adeninate anion that behaves *selectively* as N^6,N^7-chelating ligand toward the cation *cis*-$\{L_2Pt\}^{2+}$ when L is PPh_3. In contrast, the less hindered phosphines PMe_3 [4,5] and PMe_2Ph [6] stabilize polynuclear adducts in which the same anion acts as a bridging ligand through the N1, N6 atoms. Both of the binding modes of the adenine are observed with $L = PMePh_2$ [7]: the trinuclear cyclic cation *cis*-$[(PMePh_2)_2Pt\{9\text{-MeAd}(-H),N^1N^6\}]_3^{3+}$ is stable in the solid state, whereas in DMSO solution the main species appears to be the chelated species *cis*-$[(PMePh_2)_2Pt\{9$-MeAd(-H),$N^6N^7\}]^+$, analogous to complex **2**.

Similar effects of the ancillary ligands on the coordination modes of the NH_2-deprotonated 1-methylcytosine

toward the same *cis*-$\{L_2Pt\}^{2+}$ units have been recently documented by our group [17]. Also in this case the presence of the steric demanding PPh_3 ligands favors the formation of mononuclear adducts.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2007.02.025.

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