Coordination Modes of 9-Methyladenine in *cis*-Platinum(II) Complexes with Dimethyl(phenyl)phosphanes as Ancillary Ligands − Synthesis and Characterization of *cis*-$[PtL_2(9\text{-MeAd})_2](NO_3)_2$, *cis*-$[PtL_2\{9\text{-MeAd}(-H)\}]_3(NO_3)_3$, and *cis*-$[L_2Pt\{9\text{-MeAd}(-H)\}PtL_2](NO_3)_3$

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Treatment of 9-methyladenine (9-MeAd) with *cis*-$[PtL_2(NO_3)_2]$ (**1**) (L = PMe_2Ph) in a 2:1 molar ratio generated the bis(adduct) *cis*-$[PtL_2(9\text{-MeAd})_2](NO_3)_2$ (**2**), which was isolated and fully characterized by multinuclear (^1H, ^{31}P, ^{13}C, ^{195}Pt and ^{15}N) NMR analysis, which showed that the two nucleobases are selectively coordinated through the N1 atom. Small amounts of a mono(adduct) *cis*-$[PtL_2(S)(9\text{-MeAd})]^{2+}$ (**3**) (S = solvent) and of a diplatinated species *cis*-$[L_2Pt(S)\{9\text{-MeAd}(-H)\}PtL_2]^{3+}$ (**4**) are formed in DMSO solution when 9-MeAd is present in smaller quantities than **1**. Complex **3** is platinated at N1, with a solvent molecule representing the fourth ligand around the metal center. Complex **4** contains an adenine molecule deprotonated and platinated at N1,N6,N7, with two *cis*-L_2Pt units bonded to nitrogen atom N1 and to nitrogen atoms N6 and N7, respectively. With increasing relative concentration of the nucleobase, both complexes **3** and **4** progressively convert into the bis(adduct) **2**, the only species detectable in solution when the Ad/Pt molar ratio is 2:1. The trinuclear compound *cis*-$[L_2Pt\{9\text{-MeAd}(-H)\}]_3(NO_3)_3$ (**5**) (L = PMe_2Ph), containing an NH_2-deprotonated nucleobase bridging the metal centers through the N1 and N6 atoms, is quantitatively formed when the dinuclear hydroxo complex *cis*-$[Pt(\mu\text{-OH})L_2]_2(NO_3)_2$ (**6**) reacts with 9-MeAd in CH_3CN solution. The isolated complex was fully characterized by multinuclear NMR spectroscopy and mass spectrometry. It appears to be stable in solution in CH_3CN and chlorinated solvents, whereas in DMSO it partially converts into a new species, probably the dinuclear analog *cis*-$[PtL_2\{9\text{-MeAd}(-H)\}]_2(NO_3)_2$, in which the adenine maintains its coordination mode. At equilibrium the trinuclear/dinuclear species molar ratio is 20:1. Through the addition of a stoichiometric amount of nitrate **1** to a DMSO solution of **5** we were able to generate the diplatinated compound **4** in high yield. Complex **4** displays a new coordination mode for the adeninate ion, with N1 bonded to one platinum atom whereas N6 and N7 are chelated to a second one.

Introduction

Among the model nucleobases, 9-substituted adenine exhibits the most versatile coordination properties.[1] As a neutral molecule it generally binds a metal atom at the N7 position, less frequently at the N1 atom, and only rarely through both these donor atoms (Scheme 1).[2,3]

Deprotonation of the exocyclic NH_2 group affords an additional site for metal coordination, and adducts of the adeninate ligand in which N1 and N6 bridge two metal atoms have been characterized.[4] More recently, chelation of a metal atom with the involvement of the adeninate N1 and N6 atoms, followed by conversion into the more stable N6/N7 isomer, has also been described.[5]

As part of a study dealing with the role of the ancillary ligands in the reactivity of platinum complexes toward model nucleobases, we have found that coordination of the neutral 9-methyladenine (9-MeAd) at the metal center of the water-soluble *cis*-$[Pt(NO_3)_2(PMe_3)_2]$ complex occurs selectively at the N1 atom, as indicated by a comprehensive multinuclear NMR analysis of the isolated bis(adduct) *cis*-$[Pt(PMe_3)_2(9\text{-MeAd})_2]^{2+}$.[6] We have also shown that the dinuclear hydroxo complex *cis*-$[Pt(\mu\text{-OH})(PMe_3)_2]_2^{2+}$ is able to deprotonate the NH_2 group of the adenine, as shown in Equation (1).

$$cis\text{-}[Pt(\mu\text{-OH})L_2]_2^{2+} + 2\,(9\text{-MeAd}) \rightarrow cis\text{-}[PtL_2\{9\text{-MeAd}(-H)\}]_2^{2+} + 2\,H_2O \quad (1)$$

The resulting cation, *cis*-$[Pt(PMe_3)_2\{9\text{-MeAd}(-H)\}]_2^{2+}$, contains adeninate ions bridging two *cis*-L_2Pt^{2+} units through the N1 and N6 atoms, a coordination mode previously established for the 9-ethyladenine (9-EtAd) analog

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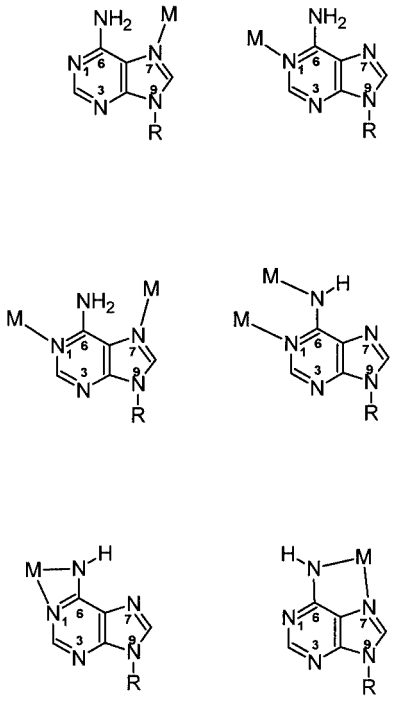
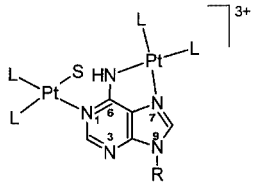


Scheme 1. Coordination modes of neutral and deprotonated 9-substituted adenines

cis-$[Pt(PMe_3)_2\{9\text{-EtAd}(-H)\}]_2(NO_3)_2$ by X-ray diffraction.[7]

In this paper we present the synthesis and characterization of three new (adenine)platinum(II) complexes with dimethyl(phenyl)phosphanes (L= PMe_2Ph) as ancillary ligands. The addition of a stoichiometric amount of nucleobase to *cis*-$[PtL_2(NO_3)_2]$ (**1**) in DMSO solution quantitatively forms the complex *cis*-$[PtL_2(9\text{-MeAd})_2](NO_3)_2$ (**2**). Similarly to the trimethylphosphane analog,[6] the bis(adduct) **2** contains the neutral 9-MeAd ligands coordinated at the N1 site. In order to investigate the possible involvement of the N7 site, we also examined mixtures of 9-MeAd and nitrate **1**, by ^{31}P NMR spectroscopy, at Ad/Pt molar ratios lower than 2. Under these conditions we noticed, concomitantly with the formation of the mono(adduct) *cis*-$[PtL_2(S)(9\text{-MeAd})]^{2+}$ (**3**, S = solvent), the presence of significant amounts of the diplatinated complex *cis*-$[L_2Pt(S)\{9\text{-MeAd}(-H)\}PtL_2]^{3+}$ (**4**), containing a deprotonated adenine molecule binding two *cis*-L_2Pt^{2+} units through the N1 and the N6/N7 atoms, as shown in Scheme 2.



Scheme 2. Proposed structure for complex **4**; S represents a solvent molecule

The deprotonation of the nucleobase induced by simultaneous platination at the N1 and the N7 sites is a reversible process, since the bis(adduct) **2** is the only product obtained when the Ad/Pt ratio is adjusted to 2. Together with the details of the spectroscopic characterization of this diplatinated species **4**, we report here on the synthesis of *cis*-$[PtL_2\{9\text{-MeAd}(-H)\}]_3(NO_3)_3$ (**5**), a cyclic trinuclear complex formed by condensation of the dinuclear hydroxo complex *cis*-$[Pt(\mu\text{-OH})L_2]_2(NO_3)_2$ (**6**) with adenine. The trinuclear complex **5**, in which the NH_2-deprotonated adenines bridge the metal centers through the N1 and N6 atoms, converts easily, although not quantitatively, into the diplatinated species **4** upon treatment with the nitrate **1** in DMSO solution. A detailed multinuclear (^1H, ^{13}C, ^{31}P, ^{195}Pt and ^{15}N at natural abundance) NMR study of the reaction mixture allowed the complete characterization of the complex **4**, in which the adenine exhibits an unprecedented coordination mode.

Results and Discussion

Treatment of 9-Methyladenine with *cis*-$[PtL_2(NO_3)_2$ (1) − Characterization of *cis*-$[PtL_2(9\text{-MeAd})_2](NO_3)_2$ (2) and *cis*-$[PtL_2(S)(9\text{-MeAd})](NO_3)_2$ (3)

In spite of the low solubility of *cis*-PtL_2Cl_2 (L = PMe_2Ph) in water, substitution of the chloride ligands occurs easily when a suspension of the compound is treated with $AgNO_3$. The resulting dinitrato complex **1** dissolves in coordinating solvents such as DMSO, CH_3CN, H_2O and DMF to form the ionic complexes *cis*-$[PtL_2S_2]^{2+}$ (S represents a solvent molecule). As would be expected,[8] solutions of **1** in water are acidic as a result of an acid/base equilibrium [Equation (2)] and the dinuclear hydroxo complex **6** is obtained in good yield when the solutions are neutralized with a strong base.[8,9]

$$2\ cis\text{-}[PtL_2(H_2O)_2]^{2+} \rightleftarrows cis\text{-}[Pt(\mu\text{-OH})L_2]_2^{2+} + 2\ H_3O^+ \quad (2)$$

Both the nitrato complex **1** and the hydroxo complex **6** appear to be very reactive towards the model nucleobase 9-MeAd. Thus, addition of 2 equiv. of 9-MeAd to a DMSO solution of **1** causes the dissolution of the nucleobase within a few minutes, with the quantitative formation of the bis(adduct) **2**. This complex was isolated and fully characterized by multinuclear NMR spectroscopy and the pertinent data are reported in Tables 1−4.

All the NMR spectra display two sets of resonances, attributed to two species (in a 48:52 ratio) containing two N1-coordinated adenine units. The correct assignment of the coordination sites requires the use of suitable two-dimensional inverse detection NMR techniques, as underlined in a previous report.[6] The first step is the contextual assignment of all protons and carbon atoms of the adenine moiety through ^1H,^{13}C correlation experiments. In particular, 2-H and 8-H are distinguishable by their $^1J_{H,C}$ coupling constants [^1J(2-H,C2) = 200 Hz; ^1J(8-H,C8) = 212 Hz] and their cross-peaks with C6 (detected through 2-H and NH_2) and C5 (detected through 8-H and NH_2) which are the

Table 1. ^{1}H NMR spectroscopic data (δ in ppm) for 9-MeAd and complexes **2**−**5** (L = PMe_2Ph)

Compound	2-H	8-H	NH_2/NH	NMe	PMe_2
9-MeAd	8.13	8.06	7.13	3.69	–
$[PtL_2(9\text{-MeAd})_2]^{2+}$ [a]	8.84	8.22	8.6	3.66	1.86; 1.64
2	8.73	8.20	8.6	3.64	1.81; 1.73
$[PtL_2(S)(9\text{-MeAd})]^{2+}$	8.74	8.34	8.75	3.76	1.74, 1.74
3					1.63, 1.54
$[L_2Pt(S)\{9\text{-MeAd}(-H)\}PtL_2]^{3+}$	8.46	8.44	6.5[b]	3.79	1.55; 1.61
4					1.77; 1.78
					1.92; 1.99
					2.01; 2.11
$[PtL_2\{9\text{-MeAd}(-H)\}]_3^{3+}$	8.12	8.38	7.17	3.58	1.08; 1.14
5					1.78; 1.84

[a] The first row refers to the 48% abundant conformer. [b] The NH proton of complex **4** displays $^2J_{H,Pt}$ = 89 Hz and $^3J_{H,P}$ = 6.5 Hz.

Table 2. ^{13}C NMR spectroscopic data (δ in ppm) for 9-MeAd and complexes **2**−**5** (L = PMe_2Ph)

Compound	C2	C4	C5	C6	C8	NMe	PMe_2
9-MeAd	152.4	149.8	118.3	155.8	141.3	29.3	–
$[PtL_2(9\text{-MeAd})_2]^{2+}$ [a]	150.8	147.6	118.9	153.8	143.7	29.7	12.3/11.9
2	151.5	147.3	119.3	153.2	143.5	29.7	12.2/11.9
$[PtL_2(S)(9\text{-MeAd})]^{2+}$	152.3	147.9	119.1	153.2	143.7	29.8	11.9/11.9
3							12.7/13.2
$[L_2Pt(S)\{9\text{-MeAd}(-H)\}PtL_2]^{3+}$	156.1	145.5	126.2	161.6	144.0	31.1	12.8/12.5
4							11.5/11.3
							14.9/15.3
							13.9/13.7
$[PtL_2\{9\text{-MeAd}(-H)\}]_3^{3+}$	154.3	146.4	120.2	157.8	141.0	29.5	12.7/13.0
5							14.0/11.4

[a] The first row refers to the 48% abundance conformer.

Table 3. ^{31}P and ^{195}Pt NMR spectroscopic data (δ in ppm; *J* in Hz) for complexes **2**−**5** (L = PMe_2Ph); the chemical shift values of the protons correlating with ^{31}P and ^{195}Pt are given in parentheses

Complex	^{31}P	$^1J_{P,Pt}$	^{195}Pt
$[PtL_2(9\text{-MeAd})_2]^{2+}$ [a]	−19.61	3225	−4350
	(8.84, 1.64, 1.86)	3230	(8.84, 1.64, 1.86)
2	−19.73		−4325
	(8.73, 1.73, 1.81)		(8.73, 1.73, 1.81)
$[PtL_2(S)(9\text{-MeAd})]^{2+}$	−12.07	3360	−4280
3	(8.74, 1.74)	3750	(8.74, 1.54, 1.63, 1.74)
	−20.14		
	(1.54, 1.63)		
$[L_2Pt(S)\{9\text{-MeAd}(-H)\}PtL_2]^{3+}$	−11.98	3320	−4272
4	(8.46, 1.77, 1.78)	3660	(8.46, 1.55, 1.61, 1.77, 1.78)
	−20.96	3650	−4378
	(1.55, 1.61)	3170	(6.5, 1.92, 1.99, 2.01, 2.11)
	−15.12		
	(8.44, 2.01, 2.11)		
	−16.19		
	(6.5, 1.92, 1.99)		
$[PtL_2\{9\text{-MeAd}(-H)\}]_3^{3+}$	−16.15	3170	−4277
5	(7.17, 1.08, 1.14)	3325	(7.17, 8.12, 1.08, 1.14, 1.78, 1.84)
	−18.94		
	(8.12, 1.78, 1.84)		

[a] The first row refers to the 48% abundance conformer.

Table 4. ^{15}N NMR spectroscopic data (δ in ppm; *J* in Hz) for 9-MeAd and complexes **2**−**5** (L = PMe_2Ph)

Compound	N1	N3	N6	N7	N9
9-MeAd	−141.1	−151.0	−296.9	−137.1	−225.9
$[PtL_2(9\text{-MeAd})_2]^{2+}$ [a]	−200.3	−142.2	−284.5	−132.8	−218.2
2	$^2J_{N,P}$ = 60	−144.3	−284.5	−132.8	−218.2
	−202.5				
	$^2J_{N,P}$ = 60				
$[PtL_2(S)(9\text{-MeAd})]^{2+}$	−195.5	−144.0	−284.0	−131.5	−218.5
3	$^2J_{N,P}$ = 60				
$[L_2Pt(S)\{9\text{-MeAd}(-H)\}PtL_2]^{3+}$	−190.0	−149.1	−243.6	−187.5	−214.0
4	$^2J_{N,P}$ = 50		$^2J_{N,P}$ = 45	$^2J_{N,P}$ = 50	
$[PtL_2\{9\text{-MeAd}(-H)\}]_3^{3+}$	−199.2	−157.2	−270.8	−127.4	−219.7
5	$^2J_{N,P}$ = 50		$^2J_{N,P}$ = 50		

[a] The first row refers to the 48% conformer.

most deshielded and shielded adenine carbon atoms, respectively (Table 2). The second step is represented by $^1H,^{15}N$ inverse detection experiments, which show that only the 2-H protons correlate with platinated nitrogen atoms (recognisable by the presence of a $^2J_{N,P}$ coupling constant of about 50 Hz), enabling the presence of an isomeric mixture of N1- and N7-coordinated bases to be definitely ruled out. The presence of two species must be due to the hindered rotation of the nucleobases around the platinum−nitrogen bond, resulting in a *head-to-head* and *head-to-tail* arrangement of the adenines. This finding is in agreement with results previously reported for the complex with L = PMe_3,[6] showing that it is the phenyl group in the ancillary ligand − and not the adenine coordination site − that influences the conformer ratio. It should be noted that each conformer displays a couple of diastereotopic methyl signals readily attributable to the corresponding phosphorus atom through $^1H,^{31}P$ correlation experiments. The methyl proton signals allow the ^{195}Pt resonances to be detected in inverse detection mode. The same ^{31}P and ^{195}Pt signals are detectable, even though more weakly, through the 2-H protons, confirming the platination of atom N1.

The coordination of the adenine is a reversible process. In fact, addition of nitrate **1** to a solution of bis(adduct) **2** causes the immediate appearance of an AB multiplet at δ = −12.07 and −20.14 ppm in the ^{31}P NMR spectrum (Table 3), in addition to the resonances of **2**. It is reasonable to attribute the AB multiplet to the mono(adduct) **3**, in which the fourth ligand should be a solvent molecule, as suggested by the large difference between the $^1J_{P,Pt}$ values for the two ^{31}P resonances. The multinuclear NMR characterization of this species (Table 1−4) supports the hypothesis of the formation of a mono(adduct). In fact, almost all the adenine signals are very similar to those of the bis(adduct) **2**, and only 8-H, NMe and N1, which in this case is also the only platinated nitrogen atom, are slightly deshielded with respect to **2**. The highest chemical shift difference is that observed above for one phosphorus resonance, found at δ = −12.07 ppm, relative to δ ≈ −19.7 ppm in the bis(adduct) **2** and attributable with confidence to the substitution of an adenine moiety by a solvent molecule to form the mono(adduct) **3**. The presence of a cross-peak between the adenine 2-H and the deshielded P at δ = −12.07 ppm in the inverse detection correlation experiment indicates that this signal is due to the phosphane group *trans* to N1, and hence *cis* to the entering solvent molecule.

In addition to the mono- and bis(adducts), solutions of 9-MeAd and nitrate **1** contain a third species (complex **4**), readily detectable when the Ad/Pt molar ratio is about 1:3. This minor component (ca. 8%) features two AB multiplets, with the same relative intensities, in the ^{31}P NMR spectrum (Figure 1).

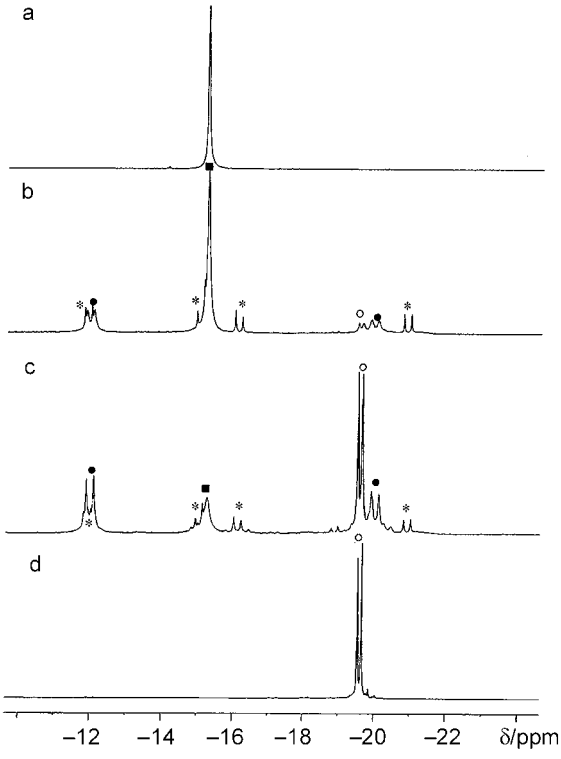


Figure 1. ^{31}P NMR spectra (central part, at 121.5 MHz in $[D_6]$DMSO) of: a) approximately 0.1 M solution of nitrate **1**; b) after addition of nucleobase (molar ratio Ad/Pt = 1:2.85); c) molar ratio Ad/Pt = 1:1; d) molar ratio Ad/Pt = 2:1; ■ denotes nitrate **1**, ○ denotes bis(adduct) **2**, • denotes mono(adduct) **3**, * denotes complex **4**

The resonances labelled by stars in Figure 1 (part b and c) disappear when the Ad/Pt molar ratio is increased to 2, leaving the singlets of the bis adduct **2** at δ = −19.61 and −19.73 ppm as the only detectable signals (Figure 1, part d). The characterization of the adenine complex **4** is discussed later.

Treatment of 9-Methyladenine with *cis*-[Pt(μ-OH)L_2]$_2$(NO_3)$_2$ (6) − Characterization of the Trinuclear Complex *cis*-[PtL_2{9-MeAd(−H)}]$_3$(NO_3)$_3$ (5)

We have shown that the dinuclear hydroxo complex *cis*-[Pt(μ-OH)L_2]$_2^{2+}$ (L = PMe_3) reacts with 9-MeAd (or 9-EtAd) in water as shown in Equation (1), to give the dinuclear complex *cis*-[PtL_2{9-MeAd(−H)}]$_2^{2+}$ containing the NH_2-deprotonated nucleobase, bridging two metal centers through atoms N1 and N6.[6,7] Under the same conditions, the dinuclear hydroxo complex **6** gives a very complex mixture of products, as indicated by the plethora of resonances in the ^{31}P NMR spectrum of the resulting solution, whereas in aprotic solvents a much simpler pattern is obtained. Thus, a suspension of **6** and 9-MeAd (molar ratio 1:2) in [D_6]DMSO becomes clear in ca. 30 min and the ^{31}P NMR spectrum of the resulting solution shows the presence of two AB systems at δ = −18.94/−16.15 and −21.69/−20.95 ppm, the relative intensities of which (20:1) have not changed significantly after several days, indicating that an equilibrium has already been reached. Moreover, in CD_3CN only one AB system is obtained, at δ = −20.03/−17.58 ppm, with well-resolved ^{195}Pt satellites. This spectrum also remains unchanged after several days. The elemental analysis of the product formed in acetonitrile is consistent with the formulation [PtL_2{9-MeAd(−H)}]$_n$(NO_3)$_n$, whereas the ESI-MS spectrum shows the highest *m*/*z* value at 1982, with the expected isotopic distribution, due to the cation {[PtL_2{9-MeAd(−H)}]$_3$(NO_3)$_2$}$^+$, strongly supporting the trinuclear nature of **5**. The stability of isolated **5** is confirmed by the presence of a single set of resonances in the ^{1}H and ^{31}P NMR spectra in $CDCl_3$ or CD_3CN solutions. In contrast, partial conversion into a new species occurs after a few hours at room temperature in [D_6]DMSO, since the ^{31}P NMR spectrum exhibits the same pattern as found when the condensation reaction [Equation (1)] was performed in this solvent. The NMR spectroscopic data obtained through multinuclear experiments are collected in Tables 1−4. ^{1}H,^{15}N NMR correlation spectra (Figure 2) clearly show that platination involves atoms N1 and N6.

The nitrogen signals at δ = −199.2 ppm (detected through the 2-H proton at δ = 8.12 ppm) and δ = −270.8 ppm (detected through the NH proton at δ = 7.17 ppm) are clearly attributable to atoms N1 and N6, respectively. These two resonances in fact display the typical *f*1 modulation due to $^2J_{N,P}$ couplings, in addition to the *f*2 modulation due to $J_{H,N}$ coupling constants. The ^{15}N chemical shift changes of the platinated nitrogen atoms, a shielding of δ = 58 ppm for N1 and a deshielding of δ = 26 ppm for N6, are similar to those found for the dinuclear analog *cis*-[$Pt(PMe_3)_2${9-MeAd(−H)}]$_2$(NO_3)$_2$.[7] In the current case, however, the ^{31}P NMR spectrum obtained for **5** at a low field (36.23 MHz) does not exhibit the long-range platinum-phosphorus couplings found in structurally authentic-

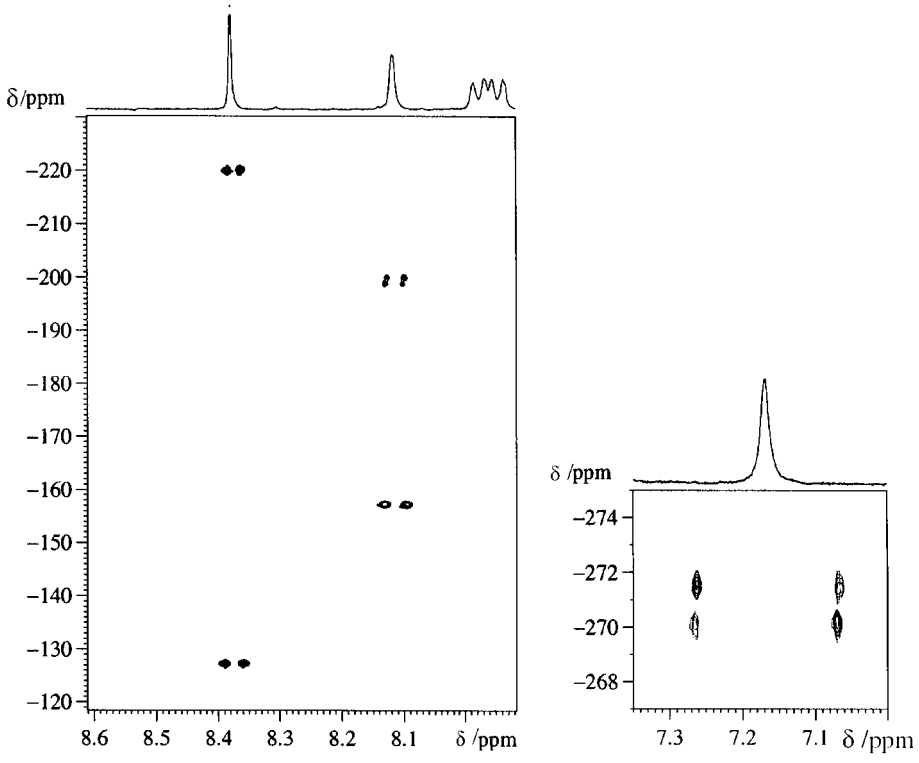


Figure 2. ^{1}H,^{15}N inverse detected spectra of complex **5**; left: HMBC experiment (aromatic region, evolution time 50 ms); right: HMQC experiment (NH region, evolution time 5.6 ms)

ated dinuclear species,[7] in agreement with the higher nuclearity of the complex **5** evidenced by mass spectrometry. The minor component found in the [D_6]DMSO solution of **5** is tentatively attributable to the dinuclear cation *cis*-[PtL_2{9-MeAd(−H)}]$_2^{2+}$ in equilibrium with the predominant trinuclear one. The ^{31}P NMR parameters of the dinuclear species (δ = −21.69/−20.95 ppm) indicate more shielded and less differentiated ^{31}P nuclei than in the trinuclear analog. These spectroscopic features have also been observed with other di- and trinuclear cyclic oligomers containing bridging nucleobases.[10]

Spectroscopic Characterization of the Diplatinated Complex *cis*-[L_2Pt(S){9-MeAd(−H)}PtL_2](NO_3)$_3$ (4)

Solutions of nitrate **1** and 9-MeAd at low Ad/Pt molar ratios contain, in addition to the mono- and bis(adducts), a third species, labelled above as complex **4**, characterized by two AB systems in the ^{31}P NMR spectrum (Figure 1, part b). Its characterization was accomplished by the same multinuclear approach as used for the bis and mono(adducts) on a sample containing Ad/Pt in a 1:3.4 ratio and the results are reported in Tables 1−4. The inverse detection ^{1}H,^{13}C, ^{1}H,^{31}P and ^{1}H,^{195}Pt correlation experiments clearly show that this species contains a single adeninate unit coordinated to two different metal centers, as shown in Scheme 2. The three signals at δ = 8.46, 8.44 and 6.5 ppm (with the same relative intensities) are readily attributable to the 2-H, 8-H and NH protons and belong to the same deprotonated adenine molecule, as inferred from the ^{1}H,^{13}C heteronuclear multiple bond correlation spectrum (Figure 3).

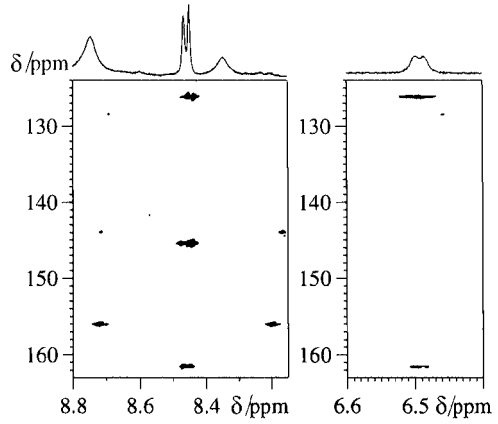


Figure 3. ^{1}H,^{13}C inverse detected spectrum of complex **4** acquired, with a 42 ms evolution delay, on the sample containing Ad/Pt in a 1:3.4 ratio; the spectrum displays, besides the long-range correlations, residual one-bond correlations at δ = 156.1 and 144.0 ppm

In fact, we observe that the 2-H and 8-H protons both detect C4 at δ = 145.5 ppm, the 8-H and NH protons C5 at δ = 126.2 ppm, and the 2-H and NH protons C6 at δ = 161.6 ppm. Furthermore, in the ^{1}H,^{31}P spectrum (Figure 4), 2-H correlates with ^{31}P at δ = −11.98 ppm, 8-H with ^{31}P at δ = −15.12 ppm, and NH with ^{31}P at δ = −16.19 ppm. This is a behavior typical of protons close to or bonded to platinated nitrogen atoms, suggesting three-site (N1, N6 and N7) platination of the deprotonated nucleobase.

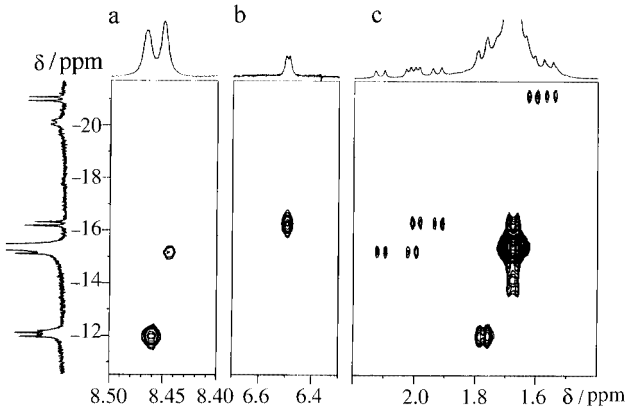


Figure 4. ^{1}H,^{31}P inverse detected spectrum of complex **4** acquired, with a 42 ms evolution delay, on a sample containing Ad/Pt in a 1:3.4 ratio: a) aromatic region, b) NH region, c) aliphatic region; the highest correlation in the aliphatic region is due to unchanged nitrate **1** (methylphosphane signals are found at δ = 1.67 ppm in the ^{1}H NMR spectrum, whereas the ^{31}P NMR signal is at δ = −15.3 ppm)

In addition, the ^{1}H,^{195}Pt spectrum confirms that NH metalation occurs with a ^{195}Pt signal that resonates at δ = −4378 ppm, even though the cross peaks are of low intensity under these conditions. The same experiment performed at low field (200 MHz) allows a second correlation to be detected between 2-H and a ^{195}Pt at δ = −4272 ppm. The low concentration of the diplatinated species did not allow us to detect these two signals in the directly acquired ^{195}Pt spectrum and all ^{15}N signals in the ^{1}H,^{15}N inverse detection mode.

The presence of a deprotonated adenine moiety in this intriguing species prompted us to investigate the involvement of the N7 sites of the trinuclear complex **5** in the platination process when the nitrate **1** is added. The ^{31}P NMR spectrum of a [D_6]DMSO solution of **5** and **1** in 1:3 molar ratio, measured immediately after the mixing of the reactants, is reported in Figure 5.

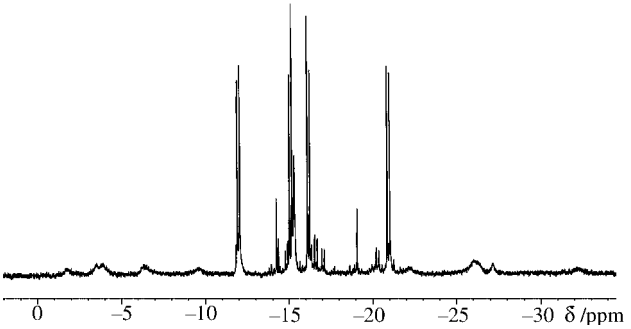


Figure 5. ^{31}P NMR spectrum of a [D_6]DMSO solution of **5** and **1** in 1:3 molar ratio

Figure 5 shows that we were able to obtain a solution containing a major product (80%) displaying the spectroscopic characteristics already found for the diplatinated spe-

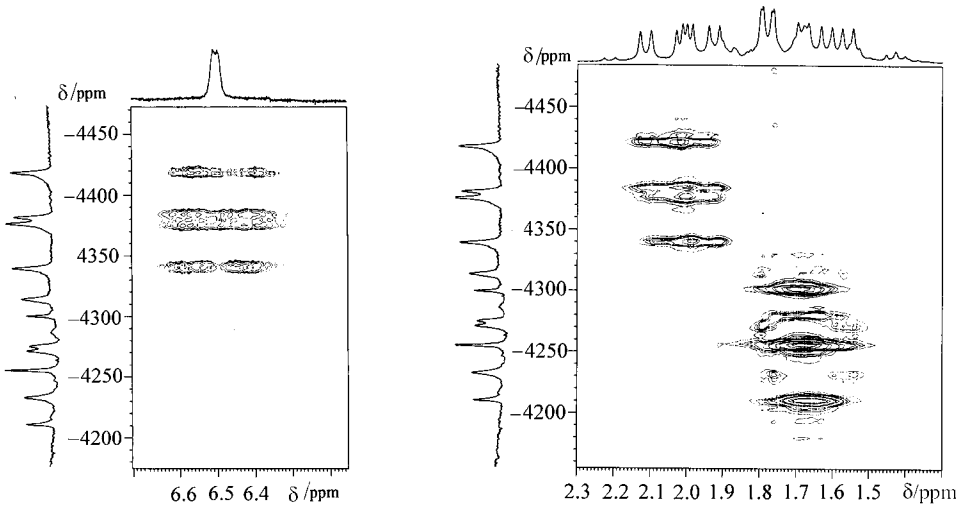


Figure 6. $^{1}H,^{195}Pt$ inverse detected spectra of complex **4** obtained from **5** and **1** in 1:3 molar ratio; left: HMBC experiment (NH region, evolution time 6.2 ms); right: HMBC experiment (aliphatic region, evolution time 12.5 ms); a high correlation in the aliphatic region due to unchanged nitrate **1** ($\delta^{195}Pt = -4254$ ppm) is also present

cies **4**, the unchanged nitrate **1** and other minor species. The directly acquired ^{195}Pt spectrum (displayed as *f*1 trace in Figure 6) reveals the presence of two well-resolved double doublets at the expected chemical shifts, together with the triplet due to the unchanged nitrate **1**. The $^{1}H,^{195}Pt$ spectrum (Figure 6) shows the correlations already found for the diplatinated complex **4** in the sample with Ad/Pt in a 1:3.4 ratio. Furthermore, the signals of the methyl groups bonded to the phosphorus nuclei at $\delta = -15.12$ and -16.19 ppm (see Figure 4) detect ^{195}Pt at $\delta = -4378$ ppm, whereas the signals of the methyl groups bonded to the phosphorus nuclei at $\delta = -11.98$ and -20.96 ppm detect ^{195}Pt at $\delta = -4272$ ppm. Overall, the H,Pt and H,P correlations strongly suggest that nitrogen atoms N6 and N7 chelate or bridge a platinum atom at $\delta = -4378$ ppm, whereas N1 of the same adeninate unit is bonded to a platinum atom at $\delta = -4272$ ppm.

The high concentration of the diplatinated complex **4** allowed us to determine all $^{1}H,^{15}N$ correlations and $^{2}J_{N,P}$ couplings (Figure 7 and Table 4) and to confirm the three-site platination of adenine.

It is evident from Figure 7 that NH and the two aromatic adenine protons detect platinated nitrogen atoms: NH detects N6 at $\delta = -243.6$ ppm, whereas 2-H and 8-H detect N1 at $\delta = -190.0$ ppm and N7 at $\delta = -187.5$ ppm, respectively. These three signals, in addition to a *f*2 modulation due to $J_{H,N}$ couplings, display the *f*1 modulation due to $^{2}J_{N,P}$ typical of metalation, definitely establishing that the adenine unit has three platinated sites. The N1 and N7 coordination shifts ($\delta \approx -50$ ppm) are very similar to those previously observed for platinated N1 sites, while a more marked shift ($\delta = -53$ ppm) is observed for N6 in the diplatinated complex **4** with respect to N6 in the trinuclear complex **5** ($\delta = -26$ ppm). It is also worth mentioning that the NH proton of **4** shows (in ^{1}H NMR spectra recorded at low field or in coupled $^{1}H,^{195}Pt$ correlation spectra) a

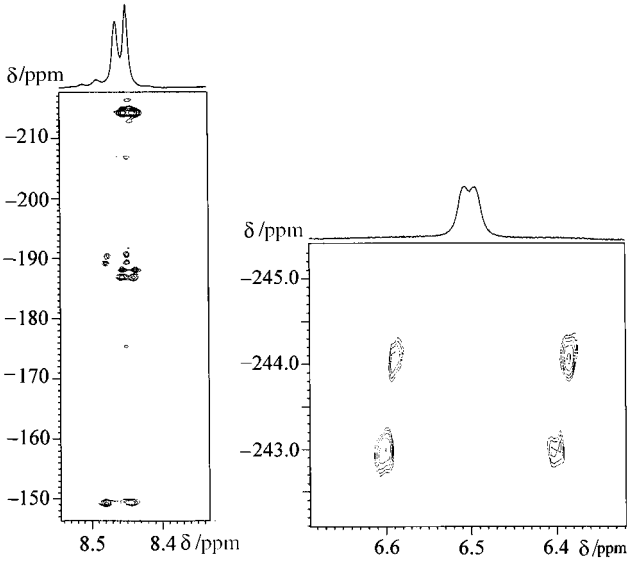
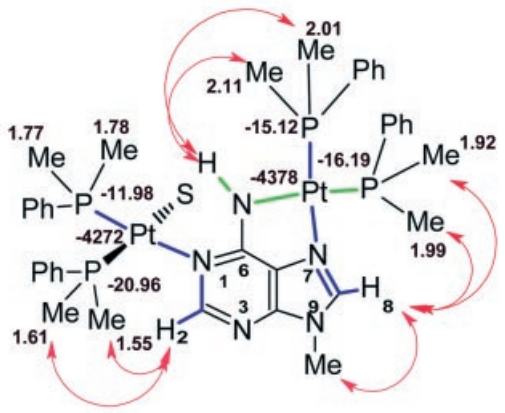


Figure 7. $^{1}H,^{15}N$ inverse detected spectra of complex **4** obtained from **5** and **1** in 1:3 molar ratio; left: HMBC experiment (aromatic region, evolution time 50 ms); right: HMQC experiment (NH region, evolution time 5.6 ms)

$^{2}J_{H,Pt}$ value of 89 Hz, while the corresponding coupling is unresolved in the trinuclear complex **5**. Both these observations suggest probable chelation in the case of **4**.

To gain further insight into the structure of this interesting complex, a nuclear Overhauser effect[11] study was undertaken, in order to find protons spatially close together. The results validate all the attributions previously derived on the bases of heteronuclear correlations and are graphically summarized in Scheme 3.

Both NOESY (nuclear Overhauser enhancement spectroscopy) and ROESY (rotating-frame Overhauser enhancement spectroscopy) experiments[10] were performed, but the



Scheme 3. The most significant NOE correlations (red arrows) and heteronuclear H,P correlations (blue and green paths) for complex **4**

best results were achieved through the second type of experiment. In the NOESY spectra, indeed, not all the cross peaks were detected and those present were of both signs. This means that the correlation time of complex **4** is $\omega_0\tau_c \approx 1.1$ (at 400 MHz), as is the case for molecules of molecular weight around 1200 Da at this field value,[10] confirming that the diplatinated species **4** has the nuclearity depicted in Scheme 2. The same experiment carried out on the trinuclear complex **5** shows, in fact, only negative cross-peaks, as to be expected for species of higher molecular weight. The nuclear Overhauser study confirms that, in this class of platinum complexes, the higher long-range coupling constants are those between a phosphorus atom and the nuclei of the ligand in a *trans* relationship to it (see Scheme 3). In the case of **4**, for instance, 2-H − which correlates with ^{31}P at δ = −11.98 ppm − is spatially closer to the methyl groups (δ = 1.55 and 1.61 ppm) bonded to ^{31}P at δ = −20.96 ppm, the NH proton that correlates with ^{31}P at δ = −16.19 ppm is spatially closer to the methyl groups (δ = 2.01 and 2.11 ppm) bonded to ^{31}P at δ = −15.12 ppm, and 8-H − which correlates with ^{31}P at δ = −15.12 ppm − is spatially closer to the methyl groups (δ = 1.92 and 1.99 ppm) bonded to ^{31}P at δ = −16.19 ppm. In addition, a weak Overhauser effect is detected between the NH proton and the methyl groups at δ = 1.55 and 1.61 ppm, but is higher than that with the methyl groups at δ = 1.77 and 1.78 ppm. This strongly suggests a distortion of the coordination plane of the platinum atom bonded to N1 (δ = −4272 ppm) with respect to the adenine plane, in agreement with previous findings.[3] Additional evidence is provided by the significant deshielding experienced by the methyl groups of the two phosphane ligands bonded to the chelated ^{195}Pt atom at δ = −4378 ppm, consistent with their proximity to the aromatic plane. The chemical shifts of the phosphane ligands bonded to ^{195}Pt at δ = −4272 ppm are very similar to those found for the mono(adduct) **3** and indicate the presence of a solvent molecule in the fourth coordination platinum site. Finally, we observe that the N6/N7 complexation could hardly be deduced from trends in ^{13}C or ^{1}H chemical shifts. More significant are the changes observed in the ^{15}N chemical shifts upon coordination and the value of the coupling constant (89 Hz) between the NH proton and the chelated ^{195}Pt at δ = −4378 ppm.

The formation of the diplatinated complex **4** under the two different sets of conditions described deserves further comment. Concomitant platination at the N1 and N7 sites of neutral adenines is known when the donor atoms in ancillary ligands are nitrogen or chlorine atoms.[3,12] As observed above, N1 is the preferred metalation site of neutral adenine when phosphanes are used as ancillary ligands, but N6/N7 platination also occurs in the presence of a large excess of platinum. The formation of complex **4** could be explained in terms of the initial formation of an N1- and N7-diplatinated intermediate in which the pK_a of NH_2 is lowered by the phosphane ligands, with the consequent formation of an adeninate ion that eventually chelates one platinum atom through N6 and N7. This hypothesis requires the presence of a base in the reaction medium, a role that can be played by the solvent and/or by residual water molecules. The participation of water molecules in the deprotonation is indicated by the observed changes to the signal of a trace of water in [D_6]DMSO solution. This signal is shifted significantly downfield when platinum is in large excess, and progressively moves upfield to its normal δ value (δ = 3.3 ppm) when the Ad/Pt ratio is enhanced. Nevertheless, a direct contribute of the solvent as a base cannot be ruled out.

The disruption of the original N1/N6-bridged trinuclear complex **5** is required when it is treated with the nitrate **1** to form **4**; metalation at N7 probably occurs, forming highly charged, sterically crowded and unstable species that rearrange to less charged and crowded complexes. This process could, in the simplest case, produce two isomeric diplatinated and chelated N1/N6 or N6/N7 complexes. The latter of these is the more stable form found in DMSO solution, in agreement with the higher stability of five-membered rings with respect to four-membered rings, as already reported for mononuclear molybdenum adeninate complexes.[5]

Conclusion

We have reported here on the different coordination modes of 9-MeAd in platinum complexes with phosphanes as ancillary ligands. The results can be summarized as follows:

i) 9-MeAd in its neutral form binds selectively at the N1 site to the metal center of the *cis*-L_2Pt^{2+} units. The role of the different substituents on the phosphane ligands (L = PMe_3, PMe_2Ph) is merely to change slightly the relative stability of the conformers in the bis (adduct) **2**.

ii) The deprotonation of the nucleobase at the NH_2 amino group, promoted by the hydroxo ligand present in the reacting platinum complex **6**, results in the formation of cyclic adducts *cis*-$[PtL_2\{9\text{-MeAd}(-H)\}]_n^{n+}$, in which the

adeninate ions selectively bind the metal atom at the N1 and N6 positions. The relative stability of the oligomers is dependent on the ancillary ligands and on the solvent. The dinuclear complex ($_n$ = 2) is the more stable species when L is PMe_3, whereas the trinuclear **5** appears to be the more stable form with the more sterically demanding PMe_2Ph ligand.

iii) The involvement of the N7 adenine atom in the platination process occurs concomitantly with the N6 chelation, which in turn requires NH_2 deprotonation. The three-site platination of the same adenine unit observed in complex **4** represents an unprecedented coordination mode of 9-MeAd in platinum(II) complexes.

Experimental Section

Materials and Methods: The nucleobase 9-MeAd[13] and the platinum complexes *cis*-[$PtCl_2(PMe_2Ph)_2$][14] were synthesized as previously reported. ^{1}H, ^{13}C, ^{31}P, ^{195}Pt and ^{15}N NMR spectra were obtained in [D_6]DMSO solutions at 300 K in 5-mm sample tubes with Bruker 400AMX WB (operating at 400.13, 100.61, 161.98, 85.88 and 40.56 MHz, respectively) or Bruker AVANCE 300 MHz (operating at 121.5 MHz for ^{31}P) spectrometers, unless otherwise stated. The ^{1}H and ^{13}C chemical shifts were referenced by assigning ^{1}H impurity in the solvent at δ = 2.49 ppm and the ^{13}C multiplet at δ = 39.5 ppm, respectively. The external references were H_3PO_4 (85% w/w in D_2O) for ^{31}P, Na_2PtCl_4 in D_2O (adjusted to δ = −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-quantum or multiple-bond correlation (HMQC or HMBC) experiments,[15,16] using parameters similar to those previously reported.[6] The conditions for NOESY and ROESY phase-sensitive spectra[11] by time-proportional phase incrementation (TPPI) were: mixing time 200 ms, spectral width 8.7 ppm with 4096 complex points in *f*2; 512 *t*1 values and 128 scans for *t*1 value. A squared sine function (SSB 2) in *f*2 and in *f*1 was applied prior to Fourier transformation. For the ROESY experiment the spin-lock field was 4000 Hz.

Synthesis of *cis*-[$Pt(NO_3)_2(PMe_2Ph)_2$] (1): A solution of $AgNO_3$ (1.26 g, 7.44 mmol) in H_2O (15 mL) was added to a water (100 mL) suspension of *cis*-[$PtCl_2(PMe_2Ph)_2$] (2.02 g, 3.72 mmol). The AgCl precipitate was eliminated by filtration and the filtrate was concentrated under vacuum to provide **1** as a white solid (1.43 g, 65%). ^{1}H NMR (400.13 MHz, [D_6]DMSO): δ = 1.67 (d, $^2J_{H,P}$ = 11.9 Hz, 6 H, PMe_2), 7.48 (m, 2 H, *m*-H), 7.56 (m, 1 H, *p*-H), 7.70 (m, 2 H, *o*-H) ppm. ^{13}C NMR (100.61 MHz, [D_6]DMSO): δ = 11.8 (m, $^1J_{C,P}$ = 45 Hz, PMe), 128.9 (d, $^1J_{C,P}$ = 67.2 Hz, C1), 128.9 (t, $^2J_{C,P}$ = 5.7 Hz, C_{ortho}), 131.4 (t, $^3J_{C,P}$ = 5.5 Hz, C_{meta}), 138.0 (s, C_{para}). ^{195}Pt NMR (85.88 MHz, [D_6]DMSO): δ = −4254 (t, $^1J_{Pt,P}$ = 3840 Hz) ppm. ^{31}P NMR (161.98 MHz, [D_6]DMSO): δ = −15.32 (s, $^1J_{P,Pt}$ = 3842 Hz) ppm. ^{31}P NMR (121 MHz, CD_3CN): δ = −18.3 (br. s, $^1J_{P,Pt}$ approximately 3800 Hz), in D_2O: δ = −17.2 (s, $^1J_{P,Pt}$ 3824 Hz). $C_{16}H_{22}N_2O_6P_2Pt$ (595.4): calcd. C 32.28, H 3.72, N 4.70; found C 32.22, H 3.65, N 4.72.

Synthesis of *cis*-[$Pt(PMe_2Ph)_2$(9-MeAd)$_2$]$(NO_3)_2$ (2): A suspension of *cis*-[$Pt(NO_3)_2(PMe_2Ph)_2$] (250 mg, 0.41 mmol) and 9-MeAd (125 mg, 0.84 mmol) in water (50 mL) was stirred at room temperature for approximately 1 h. The resulting solution was concentrated under vacuum and the residue was dissolved in MeOH (20 mL). The solution was filtered to eliminate traces of platinum, and addition of Et_2O afforded a white, microcrystalline precipitate, which was further purified from MeOH/Et_2O, filtered and dried under vacuum. The yield of pure product was 222 mg (61%). $C_{28}H_{36}N_{12}O_6P_2Pt$ (893.7): calcd. C 37.63, H 4.06, N 18.80; found C 37.53, H 4.15, N 18.68. ^{1}H NMR (400.13 MHz, [D_6]DMSO): major conformer: δ = 1.73 (d, $^2J_{H,P}$ = 11.2 Hz, 3 H, PMe), 1.80 (d, $^2J_{H,P}$ = 11.2 Hz, 3 H, PMe), 3.64 (s, 3 H, NMe), 7.3−7.7 (m, 5 H, Ph), 8.20 (s, 1 H, 8-H), 8.73 (s, 1 H, 2-H); minor conformer: δ = 1.64 (d, $^2J_{H,P}$ = 11.2 Hz, 3 H, PMe), 1.86 (d, $^2J_{H,P}$ = 11.2 Hz, 3 H, PMe), 3.66 (s, 3 H, NMe), 7.3−7.7 (m, 5 H, Ph), 8.22 (s, 1 H, 8-H), 8.84 (s, 1 H, 2-H) ppm. ^{31}P NMR (161.98 MHz, [D_6]DMSO): major conformer: δ = −19.73 (s, $^1J_{P,Pt}$ = 3231 Hz); minor conformer: δ = −19.61 (s, $^1J_{P,Pt}$ = 3225 Hz) ppm. ^{31}P NMR (36.23 MHz, D_2O): δ = −22.14 (s, $^1J_{P,Pt}$ = 3140 Hz) and −22.45 (s, $^1J_{P,Pt}$ = 3142 Hz) ppm.

Preparation of *cis*-[{$Pt(\mu$-OH)$(PMe_2Ph)_2$}$_2$]$(NO_3)_2$ (6): A solution of $AgNO_3$ (0.98 g, 5.78 mmol) in H_2O (12 mL) was added to a suspension of *cis*-[$PtCl_2(PMe_2Ph)_2$] (1.57 g, 2.89 mmol) in water (67 mL). The immediately formed precipitate of AgCl was filtered and the resulting solution was neutralized with a solution (31.0 mL) of NaOH (0.092 M). After the mixture had been stirred at room temperature for 0.5 h, the white precipitate that separated was recovered by filtration, washed twice with H_2O (10 mL), recrystallized from EtOH/Et_2O and dried under vacuum to give **6** (0.72 g, 45%). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.54 (d, $^2J_{P,H}$ = 11.7 Hz, 6 H, PMe), 4.09 (s broad, 1 H, OH), 7.74−7.49 (m, 5 H, Ph) ppm. ^{31}P NMR (161.98 MHz, [D_6]DMSO): δ = −14.50 (s, $^1J_{P,Pt}$ = 3456 Hz) ppm. $C_{32}H_{46}N_2O_8P_4Pt_2$ (1100.8): calcd. C 34.98, H 4.03, N 2.54; found C 35.02, H 3.98, N 2.61.

Synthesis of *cis*-[$Pt(PMe_2Ph)_2${9-MeAd(−H)}$]_3(NO_3)_3$ (5): A suspension of *cis*-[$Pt(\mu$-OH$)_2(PMe_2Ph)_2$]$(NO_3)_2$ (210 mg, 0.19 mmol) and 9-MeAd (57 mg, 0.38 mmol) in CH_3CN (3 mL) was stirred at room temperature for approximately 1 h. Addition of Et_2O to the resulting solution afforded a white, microcrystalline precipitate, which was filtered off, washed with Et_2O and dried under vacuum to give **5** (184 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (s, 1 H, 8-H), 8.15 (s, 1 H, 2-H), 7.85−7.37 (m, 10 H, Ph), 7.22 (s, 1 H, NH), 3.71 (s, 3 H, NMe), 1.89 (d, $^2J_{H,P}$ = 11.5 Hz, 3 H, PMe), 1.71 (d, $^2J_{H,P}$ = 11.6 Hz, 3 H, PMe), 1.13 (d, $^2J_{H,P}$ = 10.0 Hz, 3 H, PMe), 1.11 (d, $^2J_{H,P}$ = 10.3 Hz, 3 H, PMe) ppm. ^{31}P NMR (161.98 MHz, $CDCl_3$): δ = −21.88 (d, $^2J_{P,P}$ = 23.9, $^1J_{P,Pt}$ = 3842 Hz), −18.06 (d, $^2J_{P,P}$ = 23.9, $^1J_{P,Pt}$ = 3163 Hz) ppm. ^{1}H NMR (300 MHz, CD_3CN): δ = 8.175 (s, 1 H, 8-H), 8.06 (s, 1 H, 2-H), 7.85−7.37 (m, 10 H, Ph), 7.24 (s, 1 H, NH), 3.71 (s, 3 H, NMe), 1.82 (d, $^2J_{H,P}$ = 11.5 Hz, 3 H, PMe), 1.73 (d, $^2J_{H,P}$ = 11.6 Hz, 3 H, PMe), 1.09 (d, $^2J_{H,P}$ = 10.0 Hz, 3 H, PMe), 1.078 (d, $^2J_{H,P}$ = 10.3 Hz, 3 H, PMe) ppm. ^{31}P NMR (161.98 MHz, CD_3CN): δ = −20.69 (d, $^2J_{P,P}$ = 24.3, $^1J_{P,Pt}$ = 3340 Hz), −18.06 (d, $^2J_{P,P}$ = 24.3, $^1J_{P,Pt}$ = 3190 Hz) ppm. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.08/1.14 (d, $^2J_{H,P}$ = 10.7 Hz, 18 H, PMe), 1.78/1.84 (d, $^2J_{H,P}$ = 11.7 Hz, 18 H, PMe), 3.58 (s, 9 H, NMe), 7.17 (d, $J_{H,P}$ = 6.5 Hz, NH), 7.3−7.6 (m, 18 H, $H_{meta,para}$), 7.84 (m, 6 H, H_{ortho}), 7.96 (m, 6 H, H_{ortho}), 8.12 (s, 3 H, 2-H), 8.38 (s, 3 H, 8-H) ppm. ^{31}P NMR (161.98 MHz, [D_6]DMSO): δ = −16.15 (d, $^2J_{P,P}$ = 24.4, $^1J_{P,Pt}$ = 3170 Hz), −18.94 (d, $^2J_{P,P}$ = 24.4, $^1J_{P,Pt}$ = 3320 Hz). $C_{66}H_{84}N_{18}O_9P_6Pt_3$ (2044.6): calcd. C 38.77, H 4.14, N 12.33; found C 38.85, H 4.24, N 11.88.

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