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Spontaneous Reduction of Mixed 2,2′-Bipyridine/Methylamine/Chloro Complexes of Pt^{IV} in Water in the Presence of Light Is Accompanied by Complex Isomerization, Loss of Methylamine, and Formation of a Strong Oxidant, Presumably HOCl

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Abstract: Three 2,2′-bipyridine (2,2′-bpy) complexes of Pt^{IV} have been synthesized, characterized by X-ray crystallography, and their solution behavior in D_2O studied by ^1H NMR spectroscopic analysis: *mer*-$[PtCl_3(2,2'\text{-bpy})(MeNH_2)]Cl\cdot H_2O$ (**4**), *trans*-$[PtCl_2(2,2'\text{-bpy})(MeNH_2)_2]Cl_2$ (**5**), and *trans*-$[Pt(2,2'\text{-bpy})(MeNH_2)_2(OH)_2]Cl_2$ (**6**; $MeNH_2$ = methylamine). Complexes **4** and **5** undergo hydrolysis of the Cl^- ions, both in the dark and daylight, as evident from a drop in the pH value. Two solvolysis products were detected in the case of **4**, which is indicative of species with equatorial and axial OH^- groups. The hydrolysis reaction of **5** implies that an axial Cl^- group is replaced by an OH^- moiety; in contrast, **6** remains virtually unaffected. Ordinary daylight, in particular irradiation with a 50-W halogen lamp, initially causes ligand-isomerization processes, which are followed by the reduction of **4** and **5** to Pt^{II} species. This reduction of **4** and **5** is accompanied by the formation of hypochlorous acid, as demonstrated qualitatively in the decoloration test of indigo, and loss of $MeNH_2$, which is particularly pronounced in the case of **5**. The formation of Pt^{II} compounds is established on the basis of the *J* coupling constants of ^{195}Pt with selected ^1H NMR resonances. The results obtained herein are possibly also relevant to the chemistry of Cl-containing Pt^{IV} antitumor agents and their reactions with DNA.

Keywords: oxidation · platinum · reductive elimination · solvolysis

Introduction

It was originally a Pt^{IV} compound, *cis*-$[PtCl_4(NH_3)_2]$, which opened the field of platinum antitumor drugs by demonstrating the effect of filamentous growth of bacteria when present in solution.[1] Pt^{II} compounds soon dominated, however, and despite encouraging phase I–III clinical trials with three Pt^{IV} drugs (Tetraplatin, Iproplatin, and JM-216), no Pt^{IV} compound is presently in clinical use.[2] Nevertheless, there is still considerable interest in active Pt^{IV} compounds, primarily for two reasons, namely the relative kinetic inertness of Pt^{IV} coordination compounds as compared to Pt^{II} compounds, and the possibility of tuning the lipophilicity of Pt^{IV} compounds by the choice of axial ligands. The basic chemistry underlying the pharmacological activity of Pt^{IV} drugs still remains a major challenge. Widely seen as a prodrug for an active Pt^{II} reduction product, questions remain as to whether Pt^{IV} complexes are inherently unable to bind to biomolecules, such as DNA, without prior reduction; whether reduction occurs outside or/and inside the cells; and how the ligand set around the metal center (type of

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donor atoms, bulk of ligands, and so forth) influences the reactivity and rate of reduction.[2,3] Maybe there is no universal answer to these questions. Another crucial point of interest and the subject of ongoing research is whether the reductant of Pt^{IV} may be the target, for example, DNA. In other words: are Pt^{IV} species capable of oxidizing DNA bases and, specifically, the base to be oxidized most easily, guanine? It has been reported that this is indeed possible.[4] Today it is well established that oxidative transformations of nucleobases, and in particular of guanine, can take place by metal ions directly[5] or indirectly, namely, through processes in which the metal ion acts as a catalyst.[6] Intracomplex redox chemistry between a Pt^{IV} center and a ligand coordinated to the metal has indeed been demonstrated.[7] In addition, we are interested in the question: which factors make such redox chemistry possible, especially in the case of coordinated nucleobases?

Herein, we report our initial study into the behavior of selected Pt^{IV} coordination compounds in the absence of nucleobases to separate redox processes that occur with or without nucleobases. The Pt^{IV} compounds we chose contain 2,2′-bipyridine (2,2′-bpy) as a chelating ligand. Although Pt^{IV} compounds with 2,2′-bpy ligands have not been studied either structurally or pharmacologically in great detail,[8] we considered the use of 2,2′-bpy potentially advantageous for our purpose in that it should lead to a more positive redox potential. The choice of methylamine rather than the more frequently applied NH_3 ligands was motivated by solubility considerations and the wish to have another resonance in the ^1H NMR spectra (CH_3) for the identification of the reaction products. In the course of our studies, we noticed a distinct influence of light on some of the samples of Pt^{IV} compounds when dissolved in water and specifically reduction to Pt^{II} species. In this context, light-induced platination reactions of 5′-guanosine monophosphate (5′-GMP) by Pt^{IV}–iodo[9a] and Pt^{IV}–azide[9b–d] complexes are of interest.

Results and Discussion

Synthesis: The yellow form of $[PtCl_2(2,2'\text{-bpy})]$ (**1**) was prepared according to a previously reported procedure.[10] A mixture of $[PtCl(2,2'\text{-bpy})(MeNH_2)]Cl$ (**2**) and $[Pt(2,2'\text{-bpy})(MeNH_2)_2]Cl_2$ (**3**) was obtained by treating **1** with $MeNH_2$ in aqueous solution. The perchlorate analogue of **2**, $[PtCl(2,2'\text{-bpy})(MeNH_2)]ClO_4$ (**2′**), was eventually isolated in pure form following addition of $NaClO_4$ to a mixture of **2** and **3**. The ^1H NMR spectrum of **2′** was identical with that of **2**, as expected. The Pt^{IV} compounds *mer*-$[PtCl_3(2,2'\text{-bpy})(MeNH_2)]Cl\cdot H_2O$ (**4**) and *trans*-$[PtCl_2(2,2'\text{-bpy})(MeNH_2)_2]Cl_2$ (**5**) were isolated from aqueous solutions upon treatment of a mixture of **2** and **3** with gaseous Cl_2. Compound *trans*-$[Pt(2,2'\text{-bpy})(MeNH_2)_2(OH)_2]Cl_2$ (**6**) was prepared by oxidation of **3** with H_2O_2. For comparison, $[PtCl_4(2,2'\text{-bpy})]$ (**7**) was also prepared by oxidation of **1** with Cl_2[11] and by reaction of $Na_2[PtCl_6]$ with 2,2′-bpy, respectively.[12]

^1H NMR spectroscopy as an analytical tool: As briefly indicated above, our conclusions drawn from the changes in the ^1H NMR spectra were largely based on an analysis of the ^{195}Pt satellites. In addition, the observed pD changes were taken into consideration. Because of severe signal overlap, most of the bipyridine resonances were of no significant help in the analysis, except for the H6 (H6′) signals of 2,2′-bpy, which occurred the furthest downfield in the spectrum and which exhibited ^{195}Pt satellites. Other useful resonances were those of the $MeNH_2$ ligands, which likewise displayed ^{195}Pt satellites. Given a constant donor set in the equatorial plane, the differentiation between the Pt^{II} and Pt^{IV} nuclei is usually straightforward considering that the ^{195}Pt coupling constants are always smaller for Pt^{IV} than for Pt^{II} species. This behavior is a consequence of the lower s contribution in the d^2sp^3-hybridized Pt^{IV} species relative to the dsp^2 hybridized Pt^{II} center.[13,14] Thus the $^3J(^{195}Pt,^1H)$ coupling constants for the H6 (H6′) protons of 2,2′-bpy are around 26–29 Hz for the Pt^{IV} complexes **4**–**7** and are typically 29–32 Hz for the CH_3 protons of the $MeNH_2$ ligands in **4**–**6**. There is a second qualitative difference in the ^{195}Pt satellites of ^1H NMR resonances between the Pt^{IV} and Pt^{II} species: the satellites in the Pt^{IV} species are always considerably sharper than those of the Pt^{II} compounds as a consequence of the octahedral geometry and smaller anisotropy of the Pt^{IV} nucleus (Figure 1).[14] Moreover, the broadening of the satellites in the Pt^{II} species as a result of the chemical shift anisotropy (CSA) relaxation was so pronounced that with higher field instruments (>300 MHz) these satellites were usually broadened beyond resolution.

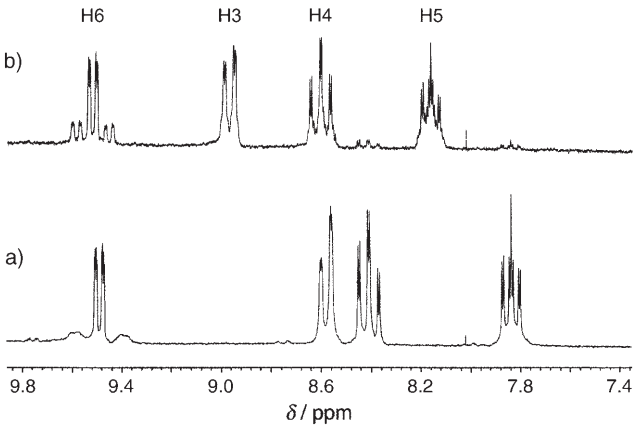


Figure 1. ^1H NMR spectra (200 MHz) of a) $[PtCl_2(2,2'\text{-bpy})]$ (**1**) and b) $[PtCl_4(2,2'\text{-bpy})]$ (**7**) in $[D_6]Me_2SO$ with $^3J(^{195}Pt,^1H)$ coupling of the H(6) resonances. Note the difference in line width of the ^{195}Pt satellites in (a) and (b).

Although, in principle, ^{195}Pt NMR spectroscopy seems to be highly suitable as an analytical tool for the kind of questions raised herein because of its large shift range and the ease of differentiating the Pt^{II} and Pt^{IV} oxidation states, the relative insensitivity of this technique for mixtures containing a number of Pt species eventually prompted us to disregard this method.

^{1}H NMR spectra of Pt^{II} precursors: As ^{1}H NMR spectroscopy was instrumental in analyzing the changes that occurred with the Pt^{IV} compounds in aqueous solution, ^{1}H NMR spectra of the Pt^{II} precursors **1**–**3** were recorded as references (Table 1). Although the spectrum of **1** could only be obtained in [D$_6$]Me$_2$SO because of its poor solubility in D$_2$O, there is a fair degree of similarity in terms of the 2,2′-bpy resonances of **1** with those of **2** and **3** in aqueous solutions. For the C_{2v}-symmetrical compounds **1** and **3**, single sets of bipyridine resonances (H3–H6) were observed, whereas for the C_1-symmetrical compound **2** and its hydrolysis product [Pt(2,2′-bpy)(MeNH$_2$)(H$_2$O)]$^{2+}$ (**2″**), these resonances were doubled (e.g., H6, H6′, and so forth). As a result of the hydrolysis of the Cl$^-$ ions, the spectrum of **2** underwent additional changes with time, which were substantial for H6 (H6′) in particular. The assignment of individual bipyridine resonances was carried out according to previous reports, with H6 and H3 resonances representing doublets and H4 and H5 appearing as triplets, with additional splitting as a result of long-range coupling.[15] If spectra were recorded at low field (200 MHz), the H6 resonance of 2,2′-bpy and the H6′ resonance of **2**, could frequently be identified by their ^{195}Pt satellites. The ^3J coupling constants were 39.6 (**1**) and approximately 30–37 Hz (**2** and **3**). The ^{195}Pt satellites of the methyl resonances of the MeNH$_2$ ligands were likewise helpful in differentiating species and assigning the metal oxidation states (see below) for **2** and **3**. The ^3J coupling constants of these methyl groups were approximately 40 (**2**) and 43 Hz (**3**).

Table 1. ^{1}H NMR chemical shifts [ppm] of selected resonances and $^3J(^{195}\text{Pt},^1\text{H})$ coupling constants [Hz].

Compound	δ (H6, H6′)[a]	δ (NH–CH$_3$)	Solvent (pD value)
1	9.48, d (^3J=39.6 Hz)	–	[D$_6$]Me$_2$SO
2, **2′**	9.11, d; 8.67, d ($^3J \approx$30; 36.8 Hz)	2.64 (^3J=39.5 Hz)	D$_2$O (6.2)
2″	8.74, d; 8.62, d (^3J not identified)	2.70 (^3J=38.2 Hz)	D$_2$O (6.2)
3	8.64, d (^3J=31.1 Hz)	2.76 (^3J=42.8 Hz)	D$_2$O (8.2)
4	9.48, d; 8.88, d ($^3J\approx$22 Hz; $^3J\approx$24 Hz)	2.65 (^3J=29.8)	D$_2$O (3.4)
4a (hydrolysis product)	9.17, d; 8.81, d ($^3J\approx$22 Hz; $^3J\leq$22 Hz)	2.56 (?)	D$_2$O (3.4)
4b (hydrolysis product)	9.52, d; 8.94, d (^3J not identified)	2.50 (?)	D$_2$O (4.2)
4′ (isomerization product)	9.54 (^3J=26.9 Hz)	1.91 (^3J=36.4 Hz)	D$_2$O (3)
5	ca. 8.77 ($^3J\approx$19 Hz)	2.71 (^3J=31.6 Hz)	D$_2$O (4.6)
5a (hydrolysis product)	?	2.56 (^3J=31.6 Hz)	D$_2$O (3.3)
5′ (isomerization product)	9.53, d; 8.96, d ($^3J\approx$22 Hz; $^3J\approx$24 Hz))	1.98 (^3J=36.0 Hz)	D$_2$O (3)
6	8.89, d (^3J=20.4 Hz)	2.52 (^3J=29.2 Hz)	D$_2$O (7)
7	9.52, d (^3J=26.3 Hz)	–	[D$_6$]Me$_2$SO

[a] d: The H6 and H6′ doublets (5.9 Hz) are frequently split in four components each as a result of long-range ^{1}H,^{1}H coupling; ^3J values refer to ^{195}Pt,^{1}H coupling.

Crystal structure analyses of 4–6: Views of the cations of **4**–**6** are given in Figure 2. Selected structural features are compiled in Table 2. In keeping with common usage in the literature,[2] "equatorial" ligands will be referred to as those coplanar with the 2,2′-bpy heterocycle, whereas the "axial" ligands are those lying above and below the bipyridine plane. The crystal structure of **4** consists of a *mer*-[PtCl$_3$(2,2′-bpy)(MeNH$_2$)]$^+$ ion, a Cl$^-$ ion, and a water molecule of crystallization per asymmetric unit, whereas **5** and **6** contain the

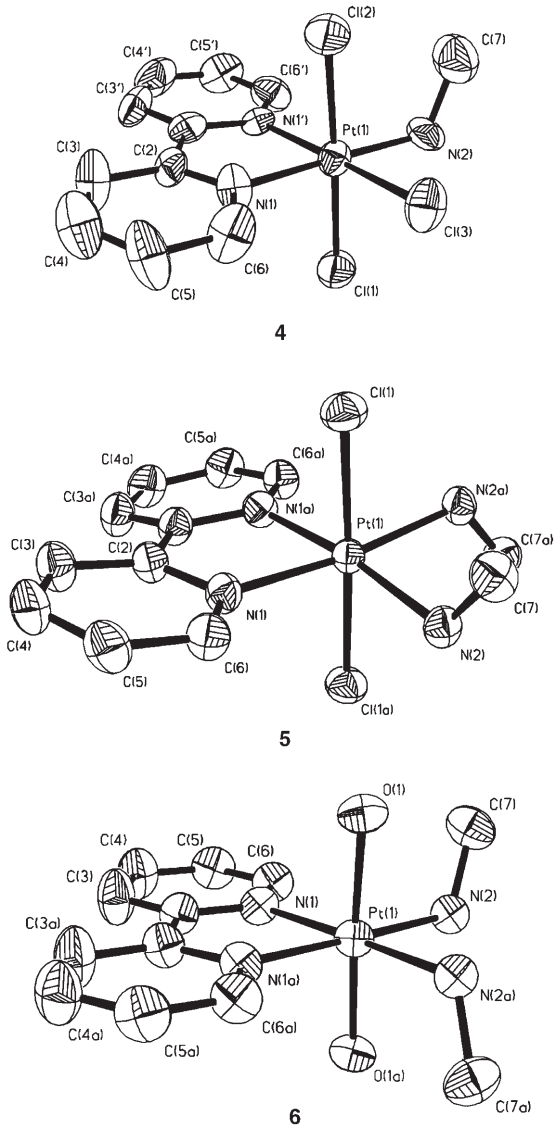


Figure 2. Views of the cations of *mer*-[PtCl$_3$(2′,2′-bpy)(MeNH$_2$)]Cl·H$_2$O (**4**), *trans*-[PtCl$_2$(2,2′-bpy)(MeNH$_2$)$_2$]Cl$_2$ (**5**), and *trans*-[Pt(2,2′-bpy)(MeNH$_2$)$_2$(OH)$_2$]Cl$_2$ (**6**).

Table 2. Crystal data and structure refinement for **4**–**6**.

	4	**5**	**6**
formula	$C_{11}H_{15}Cl_4N_3OPt$	$C_{12}H_{18}Cl_4N_4Pt$	$C_{12}H_{20}Cl_2N_4O_2Pt$
M_r	542.15	555.19	518.31
crystal habit	yellow cube	pale yellow block	yellow cube
crystal dimensions [mm]	0.3×0.3×0.3	0.40×0.25×0.15	0.20×0.20×0.20
crystal system	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$C2/c$	$C2/c$
a [Å]	13.202(1)	16.829(1)	11.915(1)
b [Å]	16.634(1)	10.369(1)	19.281(1)
c [Å]	7.678(1)	12.708(1)	8.221(1)
β [°]	96.21(1)	127.03(1)	119.74(1)
V [Å^3]	1676.2(3)	1770.3(2)	1639.9(3)
Z	4	4	4
$F(000)$	1024	1056	992
λ [Å]	0.71069	0.71069	0.71069
ρ_{calcd} [g cm^{-3}]	2.148	2.083	2.099
$\mu(Mo_{K\alpha})$ [mm^{-1}]	0.901	0.853	0.889
θ limits [°]	3.2–27.4	3.3–28.7	3.6–28.50
reflections collected/unique	3126/3048 (R_{int}=0.071)	6940/2099 (R_{int}=0.064)	5847/1775 (R_{int}=0.042)
observed reflections[a]	2067	1867	1490
parameters	200	96	97
$R1$[a,b]	0.053	0.030	0.018
$wR2$[a,c]	0.127	0.071	0.046
(Δ/ρ) max/min [e Å^{-3}]	1.187/−1.212	1.256/−2.592	0.652/−0.599

[a] Observation criterion: $I>2\sigma(I)$. [b] $R1=\Sigma||F_o|-|F_c||/\Sigma|F_o|$. [c] $wR2=[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

trans-$[PtCl_2(2,2'\text{-bpy})(MeNH_2)_2]^{2+}$ and *trans*-$[Pt(2,2'\text{-bpy})(MeNH_2)_2(OH)_2]^{2+}$ ions and two Cl^- ions. The octahedral coordination geometries of the Pt centers in the three complexes are distorted as a consequence of the narrow bite angle of the 2,2′-bpy ligand. The N-Pt-N angles are 80.4(4) (**4**), 80.2(2) (**5**), and 80.1(2)° (**6**), thus falling in the typical range for Pt–bpy chelates.[8] The Pt–N and Pt–Cl bond lengths in **4**–**6** show no unusual features. The Pt–N(2,2′-bpy) bond lengths, which range from 2.03(1) to 2.052(3) Å, compare well with those found in $[PtCl_4(2,2'\text{-bpy})]$ (2.038(8)–2.044(9) Å).[8a] The Pt–Cl bond lengths are between 2.278(4) and 2.306(4) Å (2.306(3)–2.320(3) Å in $[PtCl_4(2,2'\text{-bpy})]$), and the differences between the bond lengths to the mutually *trans*-arranged Cl group and those *trans* to the N atom fall within the three σ criterion. The two six-membered rings of 2,2′-bpy are essentially coplanar in **4** and **6**, with the dihedral angle between the two rings being 2.8(3) (**4**) and 1.1(2)° (**6**). The best weighted plane through 2,2′-bpy in **6** is coplanar with the plane defined by the Pt1, N1, N1a, N2, and N2a atoms (angle: 0.4(2)°). The 2,2′-bpy ligand and the PtN_3Cl plane in **4** meet at an angle of 3.3(2)°; by contrast, the two six-membered rings of the 2,2′-bpy ligand of **5** include an angle of 15.8(6)°. Deviations from a least-squares plane through the Pt1, N1, N1a, N2, and N2a atoms in **5** are as follows: Pt1: 0.885(2), N1: −0.371(2), N1a: 0.005(2), N2: −0.495(2), N2a: −0.024(2) Å.

The crystal packing of the three complexes is illustrated in the Supporting Information. The structures are stabilized by hydrogen bonds, with the amino groups acting as donors and the chloride anions acting as acceptors (Tables 3–5). Hydrogen bonds are also formed between the amine nitrogen atom and the water molecules of crystallization in **4** and between the amine nitrogen atoms and hydroxy groups in **6**.

Solution behavior of Pt^{IV} compounds: During the routine characterization of the Pt^{IV} compounds **4** and **5** by ^{1}H NMR spectroscopy, we noticed in several examples time-dependent changes in the spectral appearances that exhibited poor reproducibility but eventually suggested an influence of ordinary laboratory daylight. We subsequently observed that deliberate irradiation of the NMR tubes with a 50-W halogen lamp potentiated these differences. We therefore decided to record time-dependent spectra of illuminated samples and samples kept in the dark.

Solvolysis of Cl ligands: Samples of **4** and **5** become more acidic with time when kept in D_2O. Typically, the pD value

Table 3. Selected bond lengths [Å], angles [°], and hydrogen-bonding interactions for **4**.

Pt1–N1	2.04(1)	Pt1–N1′	2.03(1)
Pt1–N2	2.07(1)	Pt1–Cl1	2.295(4)
Pt1–Cl2	2.306(4)	Pt1–Cl3	2.278(4)
N1-Pt1-N1′	80.4(4)	N1′-Pt1-N2	99.0(5)
N1-Pt1-N2	177.9(5)	N1′-Pt1-Cl1	91.1(3)
N1-Pt1-Cl1	92.0(3)	Cl1-Pt1-Cl2	177.6(2)
N2-Pt1-Cl1	86.0(4)	Cl1-Pt-Cl3	90.8(2)
N1-Pt1-Cl3	95.1(3)	Cl2-Pt-Cl3	91.4(2)
C2-N1-C6	122(1)	C2′-N1′-C6′	119(1)
Pt1-N1-C2	115.2(9)	Pt1-N1′-C2′	113.6(9)
Pt1-N1-C6	123(1)	Pt1-N1′-C6′	128(1)
hydrogen bonds			
	d(D···A)	∢(D–H···A)	
N2···Cl4[a,b]	3.19(2)	141	
N2···Cl5[a]	3.27(2)	163	
N2···Ow[a,b]	2.94(3)	152	

[a] Occupancy factor = 0.5. [b] Symmetry operation: $1-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$.

Table 4. Selected bond lengths [Å], angles [°], and hydrogen-bonding interactions for **5**.

Pt1–N1	2.052(3)	Pt1–N2	2.072(3)
Pt1–Cl1	2.306(1)		
N1-Pt1-N1[a]	80.2(2)	N2-Pt1-Cl1	95.3(1)
N1-Pt1-N2	96.4(2)	Cl1-Pt1-Cl1[a]	177.67(4)
N1-Pt1-Cl1	87.5(1)	C2-N1-C6	119.2(3)
Pt1-N1-C2	113.8(2)	Pt1-N1-C6	126.3(3)
hydrogen bonds			
	d(D···A)	∢(D–H···A)	
N2···Cl2	3.146(4)	158	
N2···Cl2[b]	3.225(3)	154	

[a] Symmetry operation: $1-x$, y, $\frac{1}{2}-z$. [b] Symmetry operation: $1-x$, $-y$, $-z$.

Table 5. Selected bond lengths [Å], angles [°], and hydrogen-bonding interactions for **6**.

Pt1−N1	2.047(3)	Pt1−O1	1.998(3)
Pt1−N2	2.056(3)		
N1-Pt1-N1[a]	80.1(2)	N2-Pt1-O1	93.4(1)
N1-Pt1-N2	96.1(1)	O1-Pt1-O1[a]	177.0(1)
N1-Pt1-O1	94.8(1)	C2-N1-C6	119.6(3)
Pt1-N1-C2	114.1(2)	Pt1-N1-C6	126.2(2)
hydrogen bonds			
	d(D···A)	∢(D−H···A)	
N2···Cl2	3.118(4)	158	
N2···O1[b]	2.776(5)	165	
O1···Cl1	3.119(3)		

[a] Symmetry operations: $1-x, y, {}^1/_2-z$. [b] ${}^1/_2+x, {}^1/_2-y+1, {}^1/_2+z$.

drops by 1–1.7 units over a period of 4–7 days, with samples having a concentration of 5 mM. This effect is seen regardless of whether the sample is kept in the dark, in daylight, or if it is irradiated. For samples of **4** (see Figure 3) and **5**

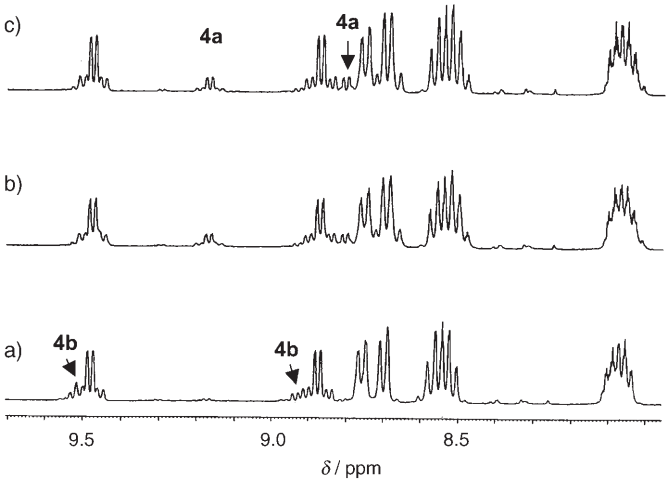
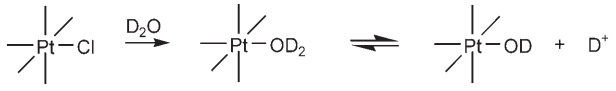


Figure 3. ^{1}H NMR spectra of *mer*-[$PtCl_3$(2,2′-bpy)($MeNH_2$)]Cl (**4**) in D_2O (pD 4.4) initially and at different times: a) after mixing, b) after 48 h, and c) after 72 h. The H6 and H6′ resonances of the hydrolysis product **4a** are clearly discernable, whereas the resonances of the other species **4b** are too weak to be unambiguously assigned.

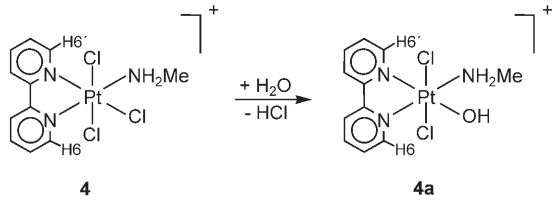
kept in the dark, inspection of the $^3J(^{195}Pt,^1H)$ coupling constants of the newly formed species reveals no indication of the formation of Pt^{II} reduction products. A logical conclusion is that hydrolysis of the Cl^- groups is taking place, thus leading to Pt^{IV}–OH species and liberation of protons (Scheme 1). Such an interpretation is in agreement with the low pK_a values of aqua ligands bonded to Pt^{IV} centers, which are generally in the range ≤ 1.[16] This view is further supported by the fact that in this process is in part suppressed for both compounds in a 0.1 M NaCl solution.



Scheme 1.

The ^{1}H NMR spectrum of a freshly prepared solution of **4** (D_2O) consists of two doublets (ca. 6 Hz) in the low-field region that are further split by long-range coupling and that both exhibit ^{195}Pt satellites. One of the doublets is centered at $\delta = 9.48$ ppm (H6) and the other at $\delta = 8.88$ ppm (H6′). The other six bpy protons give rise to four overlapping signals centered at $\delta = 8.76$, 8.70, 8.54, and 8.08 ppm, with the relative intensities being 1:1:2:2. The ^{195}Pt coupling constants of H6 and H6′ are slightly different: approximately 22 and 24 Hz, respectively. We tentatively assign the signal at $\delta =$ 8.88 ppm, which has the somewhat larger ^{195}Pt coupling constant, to the H6′ resonance in the pyridine ring *trans* to the more electronegative Cl^- ligand in **4**.[17] The CH_3 resonance of the methylamine ligand occurs at $\delta = 2.65$ ppm, with ^{195}Pt satellites of 29.8 Hz.

Even in the first spectrum obtained after sample preparation, a growing new resonance, centered at $\delta = 9.17$ ppm, between the H6 and H6′ signals of **4** is observed. With time, the new resonance proves to be similar in appearance to the original H6 and H6′ resonances, with ^{195}Pt satellites of approximately 22 Hz (Figure 3). Within seven days in the dark, and with the pD value decreased by one unit, the intensity of this new resonance amounts to approximately 15–20% of the original signals. Its counterpart has a chemical shift of $\delta = 8.81$ ppm and likewise displays ^{195}Pt satellites of comparable or slightly smaller values for ^3J. We tentatively assign this evolving species to a Pt^{IV} hydrolysis product of **4**, namely to *trans*-[$PtCl_2$($MeNH_2$)(2,2′-bpy)(OH)]$^+$ (**4a**; Scheme 2), hence to a derivative of **4**, in which the equatori-



Scheme 2.

al Cl^- ligand has been replaced by a hydroxy group. This interpretation is based on the assumption that "equatorial" interactions between H6 and the *cis*-positioned ligand (Cl^- versus OH_2/OH^-) has a more profound influence on the chemical shift of the aromatic proton involved than a change in the axial position. We consequently assign the signal at $\delta = 9.17$ ppm to H6. If hydrolysis takes place at pD 8 (achieved by the addition of 1 equiv of $NaHCO_3$),[18] the new H6 and H6′ resonances dominate by 2:1 over the original signals within three days and hydrolysis is complete within five days. In this case, the methyl resonances of the two species are superimposed at $\delta = 2.53$ ppm, with ^{195}Pt satellites of approximately 29 Hz.

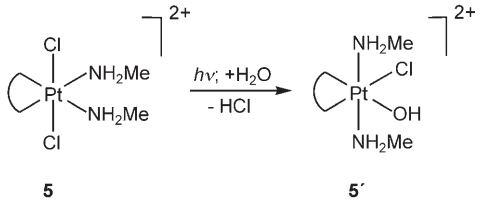
Inspection of the methyl resonances range ($\delta = 2.4$–2.7 ppm) reveals several additional peaks, which we cannot assign with confidence owing to their weak intensities. Similarly, in the spectra recorded at low pH value (see Figure 3),

there are very weak resonances close to the H6 and H6′ signals of **4** at approximately $\delta = 9.52$ and 8.94 ppm, which could be due to the additional hydrolysis species **4b**, in which the axial chloride ligand in **4** has been replaced by an OH^- moiety. Because of their difference in chemical shift, we rule out the possibility that these resonances are due to the presence of **5** as an impurity (see below).

In the spectrum of **5** (D_2O, pD 4.6; sample kept in the dark), the H6 and H3 resonances of the 2,2′-bpy ligand strongly overlap at approximately $\delta = 8.77$ ppm. Two of the four expected ^{195}Pt satellites of H6 are visible (^3J value estimated at ca. 19 Hz). The CH_3 resonances of the methylamine ligands occur at $\delta = 2.71$ ppm ($^3J(^{195}\text{Pt}-^1\text{H})$, 31.6 Hz). Within seven days in the dark, the bpy part of the spectrum remains virtually unaffected and the only change seen is a new weak CH_3 signal (5% intensity of **5**) at $\delta = 2.56$ ppm with ^{195}Pt satellites of 31.6 Hz. The latter change, together with the drop in pD value from 4.6 to 3.3, suggests that partial hydrolysis of an axial chloro ligand is taking place (**5a**). The Pt^{IV} oxidation state is clearly retained.

Photoisomerization of 4 and 5: Normal daylight, also in particular illumination with a 50-W halogen lamp, results in the reduction of the Pt^{IV} complexes **4** and **5** to Pt^{II} species. However, prior to these events, relatively fast (a few hours) light-induced processes take place within **4** and **5** that appear to be independent of the other processes that are occurring (see below). These light-induced processes are assigned as isomerization reactions, in which the methylamine ligand(s), originally in "equatorial" positions, move into "axial" sites. Ready isomerization reactions with Pt^{IV} complexes have been reported previously.[19]

In the case of **5**, the following observations are made (Figure 4): First, a new methylamine resonance at $\delta =$ 1.98 ppm, upfield from the original signal at $\delta = 2.71$ ppm, emerges and displays ^{195}Pt satellites of $^3J = 36.0$ Hz. Second, two new sets of H6, H6′ 2,2′-bpy resonances grow simultaneously. The resonances at $\delta = 9.53$ and 8.96 ppm are of equal intensity and have ^{195}Pt satellites of 22 and 24 Hz, respectively. Third, there are no other 2,2′-bpy resonances, for example, the resonance for H5 is below $\delta = 8$ ppm, which is the shift range in which some of the 2,2′-bpy resonances occur in Pt^{II} species. These findings are consistent with the formation of a Pt^{IV} complex with its symmetry lowered relative to **5**, even though the ^{195}Pt coupling constant of the methylamine ligand is admittedly at the upper end of what can be expected for a Pt^{IV} species in relation to Pt^{II}. We assign the newly formed compound to *cis,trans*-[PtCl-$(MeNH_2)_2$(2,2′-bpy)(OH)]Cl_2 (**5′**) on the basis of the nonequivalency of the two H6 and H6′ protons of the 2,2′-bpy ligand and the fact that a single set of $MeNH_2$ resonances is present (see Scheme 3). The quite substantial upfield shift ($\Delta\delta = 0.7$ ppm) of the methyl resonances of the $MeNH_2$ ligands reflects their position above the π-aromatic 2,2′-bpy ligand.



5 **5′**

Scheme 3.

The behavior of **4** after several hours of illumination is similar to that of **5** in that there is rapid growth of a new methylamine resonance upfield ($\delta = 1.91$ ppm) from that of **4**, which displays ^{195}Pt satellites of 36.4 Hz. Within 8 h in light, 50% of **4** is converted into the new compound **4′**. Again, there are no signs of any 2,2′-bpy resonances below $\delta = 8$ ppm (to be assigned to a Pt^{II} complex of 2,2′-bpy), yet there is a new H6 signal at $\delta = 9.54$ ppm with clear ^{195}Pt satellites of 26.9 Hz. Taken together, we assign the new species **4′** to a geometrical isomer of **4**, *fac*-[$PtCl_3$(2,2′-bpy)-$(MeNH_2)$]$^+$, or a hydrolysis product thereof, *cis,trans*-[$PtCl_2$-$(MeNH_2)_2$(2,2′-bpy)(OH)]$^+$ (Scheme 4). Addition of NaCl (0.1 M) slows down the isomerization process, yet does not prevent it.

Prolonged illumination: loss of methylamine, spontaneous reduction, and formation of HOCl: Prolonged illumination times (up to 50 h) of samples of **4** and **5** in D_2O lead to increasingly complicated ^{1}H NMR spectra. These changes are accompanied by a drop in pD value from 4.2 to 2.5. Figure 5 shows a spectrum obtained from **5** after 40 h in light: Two major $MeNH_2$ resonances, assigned to the isomerization products of **4** and **5** (see above), at around $\delta =$ 2 ppm are observed in addition to one or two minor, unidentified sets of resonances. In the range $\delta = 2.4$–2.8 ppm, the most intense resonance is that

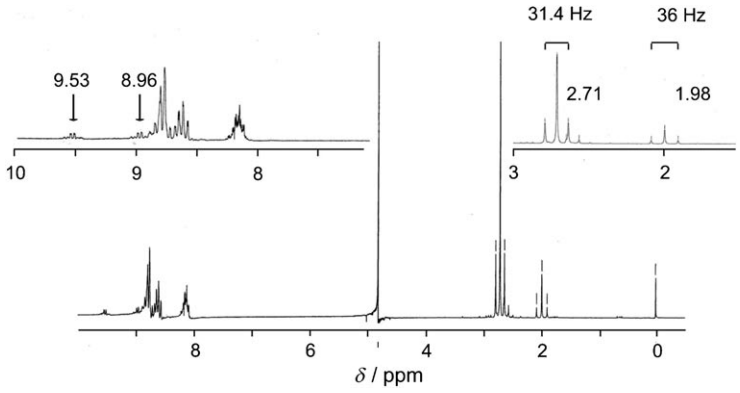
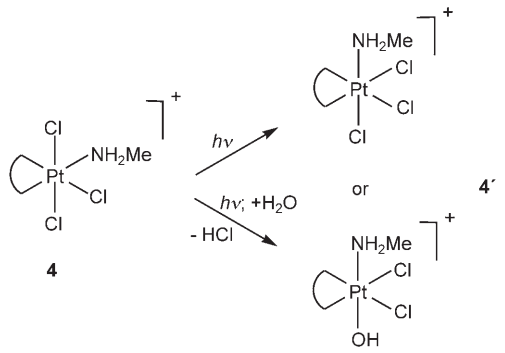


Figure 4. ^{1}H NMR spectrum of **5** in D_2O after 5 h in light (50-W halogen lamp).



Scheme 4.

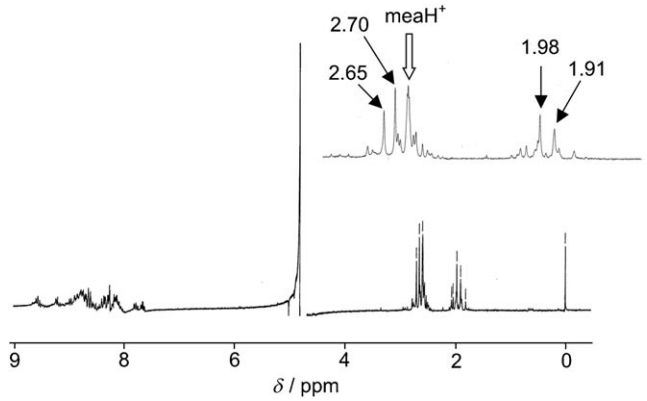


Figure 5. ^{1}H NMR spectrum of **5** in D_2O after 40 h in light (50-W halogen lamp). $meaH^+ = MeNH_3^+$.

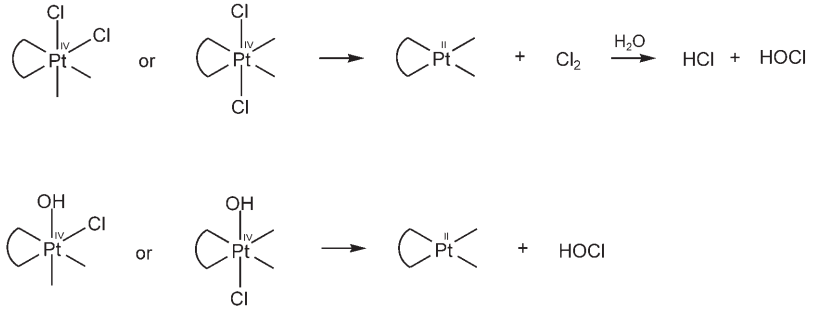
due to free, protonated methylamine ($MeNH_3^+$), as confirmed independently. The second most intense resonance at $\delta = 2.70$ ppm is due to the starting compound **5**. The third most intense signal, centered at $\delta = 2.65$ ppm, is most likely due to the Pt^{II} species $[PtCl(2,2'bpy)(MeNH_2)]^+$ or its hydrolysis species $[Pt(2,2'\text{-bpy})(MeNH_2)(OH_2)]^+$. The ^{195}Pt satellites cannot be identified unambiguously, and other minor $MeNH_2$ resonances in this shift range are likewise not assigned. After 50 h, the CH_3 resonance of the starting compound **5** has strongly diminished and that of the reduction product at $\delta = 2.65$ ppm has further increased in intensity. The upfield-shifted CH_3 resonances ($\delta = 1.9$–2.0 ppm) are still present, although they have decreased in intensity.

As can be seen from Figure 5, there are numerous 2,2′-bpy resonances between $\delta = 7.6$ and 9.65 ppm. Two multiplets centered at $\delta = 7.65$ and 7.76 ppm are well within the range of the resonances found in $[PtCl(2,2'\text{-bpy})(MeNH_2)]^+$ or its hydrolysis species. These resonances as a result of a Pt^{II} compound are first detected after 10 h of illumination of a sample of **5** and a subsequent increase in time. The release of methylamine is likely to occur from a Pt^{IV} species because the pale-yellow precipitate that forms during prolonged illumination is unambiguously identified by its ^{1}H NMR spectrum in $[D_6]Me_2SO$ (Figure 2b) as $[PtCl_4(2,2'\text{-bpy})]$.

The appearance of the Pt^{II} reduction product ($MeNH_2$ signal, H6 and H6′ resonances) is accompanied by the formation of HOCl, as qualitatively demonstrated by a decoloration test of indigo. Only in the presence of light and either **4** or **5** is there a bleaching of the blue color of indigo, whereas neither indigo itself (in water) nor indigo in the presence of **6** undergo decoloration when illuminated. The formation of hypochlorous acid conceivably takes place through the direct reductive elimination of HOCl or reductive elimination of Cl_2 and subsequent disproportionation of Cl_2 (Scheme 5).

Complex *mer*-$[PtCl_3(2,2'\text{-bpy})(MeNH_2)]Cl$ (**4**) behaves in a similar manner to **5**, in that there is partial displacement of the methylamine ligand, although this process is less pronounced relative to **5**. Again, precipitated $[PtCl_4(2,2'\text{-bpy})]$ has been identified (see above), and bleaching of indigo by HOCl is observed.

Inertness of *trans*-$[Pt(2,2'\text{-bpy})(MeNH_2)_2(OH)_2]Cl_2$ (6): Unlike **4** and **5**, the Pt^{IV} complex **6** proved to be stable in aqueous solution in the dark. The pD value of the sample did not change with time and remained virtually constant at pD 7, even after 13 days. In the presence of light (irradiation of the sample), within a period of several days at room temperature, the only ^{1}H NMR spectroscopic change was the



Scheme 5.

appearance of a trace amount of a free $MeNH_3^+$ ($\delta = 2.59$ ppm). Release of $MeNH_2$ from **6** was consistent with a slight rise in pD value from 7.0 to 7.5. There was no formation of a precipitate of $[PtCl_4(2,2'\text{-bpy})]$ (**7**), as in the case of **4** and **5**.

The obvious inertness of Pt^{IV} compounds with two axial hydroxo ligands correlates with the known more negative reduction potentials of these compounds relative to those of the corresponding compounds with two axial chloro ligands.[3d,h]

Summary

The work reported herein had at its onset the aim of gaining a better understanding into the ways in which octahedral Pt^{IV} compounds can interact with guanine nucleobases. This question goes back to controversial reports on findings that Pt^{IV} compounds are prodrugs that are always reduced to Pt^{II} prior to DNA binding, on the one hand, and the view that Pt^{IV} compounds can directly interact with DNA,[3d] even to the extent of oxidizing guanine, on the other hand.[4] As it turned out, the situation proved to be considerably more complicated than anticipated, given the fact that even the Pt^{IV} compounds **4** and **5**, in the absence of guanine, displayed different reaction patterns, as outlined above; only **6** was rather robust. Based on our ^{1}H NMR spectroscopic studies, we conclude the following: First, **4** and **5** undergo hydrolysis of the Cl^- group in the dark. Hydrolysis of the equatorial chloride moiety is definitely preferred for **4**, whereas hydrolysis of **5** implies that an axial chloride is replaced by an OH^- species. Second, both **4** and **5** isomerize quickly (within hours) when illuminated with light. As a consequence, the formerly equatorial methylamine ligand(s) moves into axial positions. Third, both compounds, in particular *trans*-$[PtCl_2(2,2'\text{-bpy})(MeNH_2)_2]Cl_2$ (**5**), lose $MeNH_2$ ligands (more than 50% in the case of **5**) in light. The ease (room temperature, moderately acidic pH value) with which the substitution of methylamine by Cl^- to give $[PtCl_4(2,2'\text{-bpy})]$ (**7**) occurs is remarkable and contrasts with the thermal displacement of NH_3 in complexes of *cis*-$[Pt^{II}(NH_3)_2]$.[20] Fourth, both **4** and **5** undergo photoreduction to Pt^{II} species with the formation of HOCl. In both cases $[Pt(X)(MeNH_2)(2,2'\text{-bpy})]^+$ (with X = Cl or OH) is the major product. We consider the finding that the potentially strong oxidant HOCl is formed in this "spontaneous" reduction remarkable and noteworthy in that, to the best of our knowledge, it has not been considered in earlier reports. In principle, this product formed from the reductive elimination of Pt^{IV} compounds could very well be a species capable of damaging biomolecules oxidatively.[21] As to practical applications for mechanistic Pt^{IV}–DNA work: be aware of light! What has generally been termed "spontaneous" can in fact be caused by light.

Experimental Section

The starting materials were of commercial origin and were used without further purification. $[PtCl_2(2,2'\text{-bpy})]$ (**1**) was prepared as reported.[10]

The Pt^{II} precursors $[PtCl(2,2')(MeNH_2)]X$ (X = Cl (**2**), ClO_4^- (**2′**), and $[Pt(2,2'\text{-bpy})(MeNH_2)_2]Cl_2$ (**3**) were prepared as follows: $MeNH_2$ (40%; 25 mL) was added to a suspension of **1** (4.6 mmol) in water (50 mL), and the reaction mixture was kept in a stoppered flask at 50 °C. After 5 h, the suspension had become a yellow solution, which was filtered and subsequently evaporated under reduced pressure at 50 °C. To remove all $MeNH_2$, the resulting solid was treated twice with water, and the evaporation process was repeated twice. According to ^{1}H NMR spectroscopic analysis, the yellow solid obtained (2.1 g) was an approximate 1:1 mixture of two main compounds **2** and **3**. This product mixture was later used for the oxidation experiments with Cl_2 to obtain **4** and **5** (see below).

Attempts to separate **2** and **3** (Cl^- salts) on the basis of differences in their solubilities in water were not successful. However, the addition of an excess of $NaClO_4$ to a mixture of **2** and **3** in water eventually allowed the separation of $[PtCl(2,2'\text{-bpy})(MeNH_2)]ClO_4$ (**2′**) as a result of its somewhat lower solubility relative to the bis(methylamine) complex. Specifically, $NaClO_4$ (10.6 mmol) in water (10 mL) was added to the mixture of **2** and **3** (2.1 g) in water (30 mL), and the resulting precipitate (580 mg), which consisted predominantly of **2′**, was washed with water (50 mL) and dissolved in water (400 mL, 50 °C). The solution was concentrated by rotary evaporation to a volume of 80 mL, and orange–yellow microcrystals of $[PtCl(2,2'\text{-bpy})(MeNH_2)]ClO_4$ (**2**) (428 mg) were obtained upon filtration. Elemental analysis (%) calcd for $PtC_{11}H_{13}Cl_2N_3O_4$ (**2′**; 517.26): C 25.54, H 2.54, N 8.13; found: C 25.55, H 2.55, N 8.20; ^{1}H NMR (D_2O, pD 6.2): $\delta = 9.11$ (d, $J = 8$ Hz, $^3J(^{195}Pt,^1H) \approx 39.5$ Hz), 8.67 (d, 5.8 Hz, $^3J(^{195}Pt,^1H) = 36.8$ Hz), 8.36–8.15 (m), 7.76 (t, $J = 6.5$ Hz), 7.58 (t, $J = 6.5$ Hz), 2.64 ppm (s, $^3J(^{195}Pt,^1H) = 39.5$ Hz).

Treatment of **1** with a larger excess of $MeNH_2$ and a longer reaction time (5 days at 50 °C), filtration of a red precipitate, and evaporation of the aqueous solution to dryness (to remove $MeNH_2$ and $MeNH_3^+Cl^-$) yielded a product containing **3** in >95% yield, according to ^{1}H NMR spectroscopic and elemental analysis.

The hydrolysis product of **2′** $[Pt(H_2O)(2,2'\text{-bpy})(MeNH_2)]^{2+}$ (**2″**) was prepared in situ by adding $AgNO_3$ (1 equiv) to a solution of **2′** in D_2O and filtration of AgCl. Complex **2″** has H6 and H6′ doublets at $\delta = 8.74$ and 8.62 ppm (D_2O, pD 6.2) that overlap the H3, H3′, H4, and H4′ signals between $\delta = 8.33$ and 8.21 ppm and the H5 and H5′ triplets at $\delta = 7.76$ and 7.67 ppm. The Me–NH_2 resonance is at $\delta = 2.70$ ppm ($^3J(^{195}Pt–^1H) = 38.2$ Hz). As expected, resonances of **2″** are dependent on the pD value because of the acid–base equilibrium between the aqua complex **2″** and its hydroxo species. Signals as a result of **2″** also appear with time in spectra of the Cl^- species **2′** in D_2O.

Compounds *mer*-$[PtCl_3(2,2'\text{-bpy})(MeNH_2)]Cl{\cdot}H_2O$ (**4**) and *trans*-$[PtCl_2(2,2'\text{-bpy})(Me\ NH_2)_2]Cl_2$ (**5**) were obtained upon bubbling Cl_2 gas through a suspension of **2** and **3** (0.5 g) in water (15 mL) for 90–120 s. Excess Cl_2 gas quickly evaporated and an unidentified red–brown precipitate was filtered off. Subsequently the clear yellow solution was partly evaporated under reduced pressure in a 40 °C water bath and allowed to crystallize in a refrigerator (3 °C). Typically, **5** crystallized first as pale-yellow blocks, was subsequently recrystallized from water, and was obtained in a yield of 0.22 g. Elemental analysis (%) calcd for $PtC_{12}H_{18}Cl_4N_4$ (**5**; 555.19): C 25.96, H 3.27, N 10.09; found: C 25.95, H 3.15, N 10.25. A mixture of **5** and **4** crystallized, especially after longer treatment with Cl_2 (120 s), which was separated by hand under a microscope. Yellow cubes of **4** (0.17 g) were thus obtained. Elemental analysis (%) calcd for $PtC_{11}H_{15}Cl_4N_3O$ (**4**; 542.15): C 24.37, H 2.79, N 7.75; found: C 24.25, H 2.65; N 7.65. Both **4** and **5** were also characterized by X-ray crystallographic analysis.

Compound *trans*-$[Pt(OH)_2(2,2'\text{-bpy})(MeNH_2)_2]Cl_2$ (**6**) was obtained by stirring a mixture of **2** and **3** (1.2 g) with an excess of H_2O_2 (3% w/v; 29 mL) for 1 h at 40 °C. The yellow solution was evaporated under reduced pressure at 45 °C and kept in a refrigerator. The yellow, crystalline precipitate that formed was collected, recrystallized from water, and obtained in a yield of 0.42 g for **6**. Elemental analysis (%) calcd for $PtC_{12}H_{20}Cl_2N_4O_2$ (**6**; 518.31): C 27.81, H 3.90, N 10.81; found: C 27.90, H 3.80, N 10.85. The composition of **6** was also confirmed by X-ray crystallographic analysis.

Compound **7** was obtained either by oxidation of **1** with Cl_2[11] or through reaction of $Na_2[PtCl_6]$ with 2,2′-bpy in a way similar to related compounds.[12]

X-ray data: The crystal data of **4**–**6** were collected at room temperature with an Enraf-Nonius-KappaCCD diffractometer[22] using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å). The programs DENZO and SCALEPACK were used for data reduction and cell refinement.[23] The structures were solved by conventional Patterson methods and subsequent Fourier syntheses and refined by full-matrix least squares on F^2 using the SHELXTL PLUS and SHELXL93 program.[24] The scattering factors were those given in the SHELXTL PLUS program. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were generated geometrically and given fixed isotropic thermal parameters (**4**) or isotropic thermal parameters equivalent to 1.2

(1.5 for methyl groups) times those of the atom to which they were attached (**5** and **6**). The chloride counterion in **4** was found to be disordered over two positions with site occupancy factors of 0.5. Likewise, the water molecule of crystallization occupies two positions to which site occupancy factors of 0.5 were assigned on the basis of the peak height in the Fourier map. Crystallographic data and details of refinement of **4**–**6** are reported in Table 1. CCDC-615447 (**5**), CCDC-615448 (**4**) CCDC-615449 (**6**) are contained in the supplementary crystallographic data and can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data request/cif.

^{1}H NMR spectra and other measurements: ^{1}H NMR spectra were recorded on Bruker AC 200 and AMX 400 instruments with samples prepared in D_2O or $[D_6]Me_2SO$ and kept at room temperature (20 °C). Sample concentrations were typically 0.005 M for Pt. Chemical shifts were referenced to internal sodium 3-(trimethylsilyl)propanesulfonate (TSP) and tetramethylsilane (TMS), respectively. Indigo was added to samples at a concentration of approximately 0.5 mg per 0.5 mL. pD values of aqueous solutions (D_2O) were obtained by adding 0.4 to the pH meter reading (uncorrected = pH*). Samples "kept in the dark" were prepared in ordinary laboratory light and subsequently stored in a cupboard. The illumination of samples with a 50-W halogen lamp took place in a box covered with Al foil. UV/Vis spectra of the Pt^{IV} compounds **4**–**6** were recorded in water on a Cary 100 instrument. All three compounds displayed two absorption bands of comparable intensity at approximately 309 and 320 nm and extinction coefficients of $(9\pm1)\times10^3\,L\,mol^{-1}\,cm^{-1}$.

Acknowledgement

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