[9] Removal of the TMS group in **7f** leads to the (*R*)-(α-benzylphenylmethyl)ferrocene (95% *ee* determined by HPLC on a chiral phase (Chiracel OD column)). The same enantiomer was obtained by a nucleophilic substitution of the (*R*)-(α-acetoxyphenylmethyl)ferrocene with benzylzinc bromide,[2d] which proved the retention of configuration in the former reaction.
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[11] Synthesis of **8**: a) see reference [5a]; b) see reference [5b]; c) MeOH, AcOH (cat.), 100%, 97% *ee*; d) Recrystallization in MeOH, 83%, *ee* > 99.8%.
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Nucleotide Platination Induced by Visible Light**

Nicole A. Kratochwil, John A. Parkinson, Patrick J. Bednarski, and Peter J. Sadler*

There is increasing interest in the development of photoactive metal complexes as luminescent markers and photocleaving agents for DNA,[1] and in the design of photosensitisers for photodynamic therapy.[2, 3] Photosensitisers catalyze the production of reactive singlet oxygen and therefore rely on the presence of oxygen in the target tissue. An advantage of photo-chemotherapeutic agents is that they can be activated selectively at the target site, thereby minimizing the side-effects of chemotherapy. We are investigating the design of oxygen-independent photoactivated metallodrugs, in particular photoactive analogues of the anticancer drug cisplatin, *cis*-$[PtCl_2(NH_3)_2]$. Iodo complexes of Pt^{IV} are promising in this respect because their cytotoxicity against tumor cells is potentiated by visible light.[4] We show here that stereospecific reactions between a diiododiamine–Pt^{IV} complex and the nucleotide guanosine 5′-monophosphate (5′-GMP) can be induced by visible light, and that photoactivation can be controlled by the axial ligands, which will allow fine-tuning of the photoreactivity of this class of complexes. This appears to be the first report of nucleotide platination induced solely by visible light.

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Photoreactions of the ^{15}N-labelled diiodo–Pt^{IV} complexes ^{15}N-**1** and ^{15}N-**2** in the presence of 5′-GMP were followed by 1D ^1H, 2D [^1H,^{15}N] HSQC and 2D [^1H,^{15}N] HSQC-TOCSY NMR spectroscopy. Photo-irradiation was carried out using an argon ion laser equipped with a fibre optic link designed to deliver light directly into the sample within the magnet of the NMR spectrometer. No reactions between these Pt complexes and 5′-GMP occurred within 30 h in the dark.

trans,cis-$[Pt(OCOCH_3)_2I_2(^{15}N\text{-en})]$ ^{15}N-**1**

trans,cis-$[Pt(OH)_2I_2(^{15}N\text{-en})]$ ^{15}N-**2**

The time-course of the photoreaction of the acetato complex **1** ($\varepsilon_{457.9} = 327\,M^{-1}cm^{-1}$) with 1 equivalent of 5′-GMP (200 μM in water, 298 K, pH 6.2)[5] was observed by 1D ^1H NMR spectroscopy (Figure 1; for the structures and numbering of the complexes see Scheme 1A). After irradiation with low-power visible light ($\lambda_{irr} = 457.9$ nm, $12.2 \times 10^{-3}\,J\,s^{-1}$), the signals for **1** (CH_2: $\delta = 2.7$; CH_3: $\delta = 2.05$) decreased in intensity, and two new multiplets in the en(CH_2) region of the spectrum at $\delta = 3.01$ (***3a***) and $\delta = 2.60$ (***3b***), and a singlet at $\delta = 3.08$ (***4***) appeared. Two new singlets that could be assigned to coordinated acetate ($\delta = 2.09$; ***3***) and to released acetate ($\delta = 1.99$) were detected in the methyl region. During later stages of the photoreaction a new singlet was observed at $\delta = 8.52$, which was assigned to H8 of Pt-bound 5′-GMP (free 5′-GMP: $\delta = 8.10$). A high frequency shift such as this for the H8 resonance of 5′-GMP is typical of metal coordination to N7 of 5′-GMP.[6]

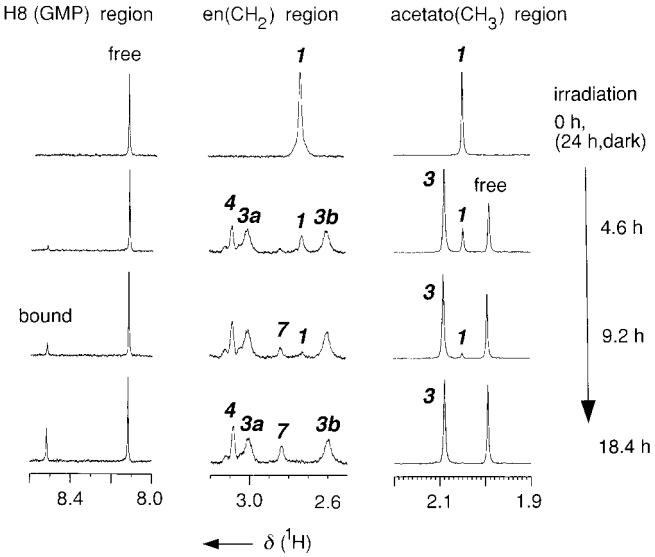

Figure 1. Selected regions of 500 MHz 1D ^1H NMR spectra acquired during the photoreaction ($\lambda_{irr} = 457.9$ nm) of **1** in the presence of 5′-GMP at irradiation times of 0, 4.6, 9.2, and 18.4 h (and 24 h in the dark), pH 6.2, 298 K. Binding of 5′-GMP is preceded by initial light-induced ligand exchange of **1** to give **3**.

The pathway of the photoinduced reaction of ^{15}N-**1** with 5′-GMP was further elucidated by 2D [^1H,^{15}N] HSQC and HSQC-TOCSY NMR spectroscopy (Figure 2). After 1 h irradiation (Figure 2A) the cross peak for **1** with a chemical

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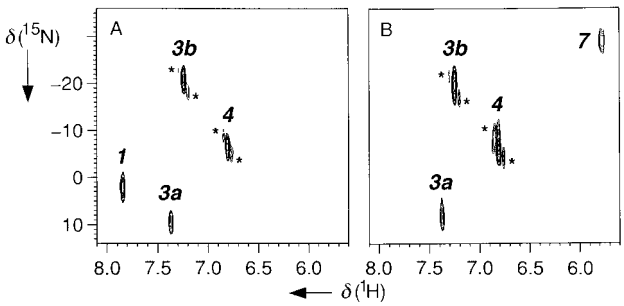


Figure 2. 2D [^{1}H,^{15}N] HSQC NMR spectra for the reaction of ^{15}N-**1** in the presence of 5′-GMP (molar ratio 1:1, 200 μM) at irradiation times of A) 1 h and B) 4.6 h, pH 6.2, 298 K. Asterisks indicate ^{195}Pt satellites.

shift of 7.84/1.98 (^{1}H/^{15}N) and three new cross peaks with chemical shifts of 7.30/9.54 (***3a***), 7.30/ – 20.9 (***3b***), and 6.81/ – 6.45 (***4***) were observed. The corresponding 2D [^{1}H,^{15}N] HSQC-TOCSY NMR spectrum showed that the two multiplets (***3a*** and ***3b***) are part of the same spin system and are correlated with the (en)NH_2 cross peaks at 7.30/9.54 (***3a***) and 7.30/ – 20.9 (***3b***), and the CH_2 singlet at $\delta = 3.08$ with the cross peak at 6.81/ – 6.45 (***4***). The inequivalence of the two CH_2 groups of the coordinated en ligand (***3a*** and ***3b***) and the observation of two ^{1}H/^{15}N cross-peaks, compatible with NH_2 of en *trans* to I (***3a***) and O (***3b***), suggest that *trans,cis*-[Pt(OCOCH$_3$)$_2$(OH)I(^{15}N-en)] ^{15}N-**3** is formed during the photoreaction (Scheme 1 A). The shifts of the peaks for the second, simultaneously formed, photoproduct **4** and the observation of only one ^{1}H/^{15}N cross-peak ($\delta(^1H)/\delta(^{15}N) = 6.81/-6.45$, (en)$CH_2$: $\delta(^1H) = 3.08$), together with the appearance of a peak for free acetate, are consistent with a symmetrical Pt^{IV} complex (equivalent CH_2 groups of the coordinated en ligand), which has lost the two acetato ligands. A mixture of *trans,cis*-[Pt(OH)$_2$I$_2$(^{15}N-en)] ^{15}N-**2**, *mer*-[Pt(OH)$_3$I(^{15}N-en)] ^{15}N-**5**, and [Pt(OH)$_4$(^{15}N-en)] ^{15}N-**6** was studied by 2D [^{1}H,^{15}N] HSQC-TOCSY NMR experiments to aid identification of **4** (Figure 3). However, the differences

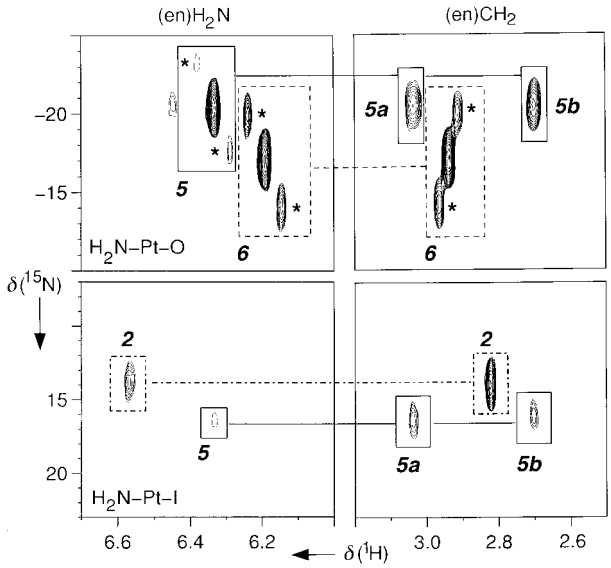
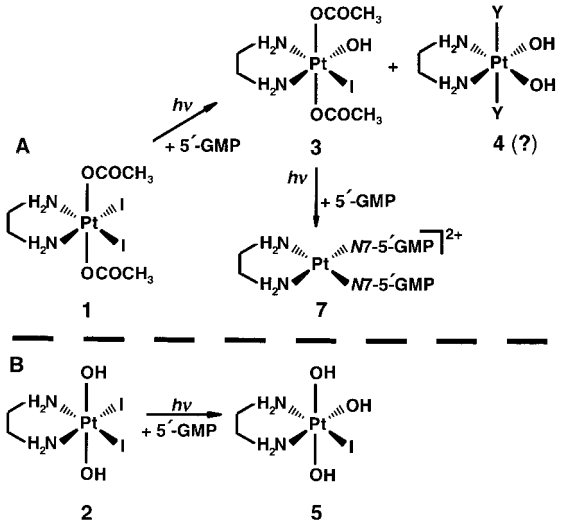


Figure 3. Characterization of a mixture of ^{15}N-labelled ^{15}N-**2**, ^{15}N-**5**, and ^{15}N-**6** at pH 6.2, 298 K by 2D [^{1}H,^{15}N] HSQC-TOCSY NMR spectroscopy. Asterisks indicate ^{195}Pt satellites (see the text for further information).



Scheme 1. Photoreaction pathways for A) **1** and B) **2** in the presence of 5′-GMP. The structure assigned to **4** is tentative; Y may be I or OH.

in chemical shifts (Table 1) rule out the formation of these complexes during the photoreaction of **1**. A possible assignment for **4** is to a dihydroxo – Pt^{IV}(en) complex with one or two axial iodo ligands.

After irradiation of the reaction mixture for 4.6 h (Figure 2 B), two close new ^{1}H/^{15}N cross peaks ($\delta = 5.79/-30.9$ and 5.72/ – 30.9, ***7***), assignable to nonequivalent NH protons of the en ligand, appeared in the 2D [^{1}H,^{15}N] HSQC NMR spectrum. ^{1}H/^{15}N chemical shifts in this range are characteristic of a Pt^{II} rather than a Pt^{IV} complex, and these values are the same as those reported previously for [Pt(5′-GMP-*N7*)$_2$(^{15}N-en)]$^{2+}$ ***7***.[6, 7]

Table 1. Chemical shifts (^{1}H, ^{15}N) and coupling constants $^1J(^{195}Pt,^{15}N)$ [Hz].

Pt complex		CH_3 δ^1H	CH_2 δ^1H	NH_2 δ^1H (*trans* to)	δ^{15}N (*trans* to)	$^1J(^{195}Pt,^{15}N)$ (*trans* to)
trans,cis-[Pt(OCOCH$_3$)$_2$I$_2$(en)]	**1**[4]	2.05	2.72	7.84 (I)	1.98 (I)	
trans,cis-[Pt(OH)$_2$I$_2$(en)]	**2**[4]		2.82	6.56 (I)	14.03 (I)	
trans,cis-[Pt(OCOCH$_3$)$_2$(OH)I(en)]	**3**	2.09	3.01, 2.60	7.30 (I,O)	9.54 (I), – 20.9 (O)	221 (O)
trans,cis-[PtY$_2$(OH)$_2$(en)][a]	**4**		3.08	6.81	– 6.45	213
mer-[Pt(OH)$_3$I(en)]	**5**		3.06, 2.70	6.33 (I,O)	16.32 (I), – 20.07 (O)	268 (O)
[Pt(OH)$_4$(en)]	**6**		2.94	6.19 (O)	– 16.77 (O)	292 (O)
[Pt(5′-GMP-*N7*)$_2$(en)]$^{2+}$	**7**		2.84	5.79, 5.72 (N)	– 30.9 (N)	

[a] tentative assignment; Y = I or OH.

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From the kinetic course of the reaction (Figure 4 A, Scheme 1 A), it is apparent that *trans,cis*-[Pt(OCOCH$_3$)$_2$(OH)I(^{15}N-en)] ^{15}N-**3** is photoreactive towards the nucleotide to give the Pt^{II} – (5′-GMP)$_2$ adduct ***7*** directly, whereas the Pt^{IV} photoproduct **4** is stable.

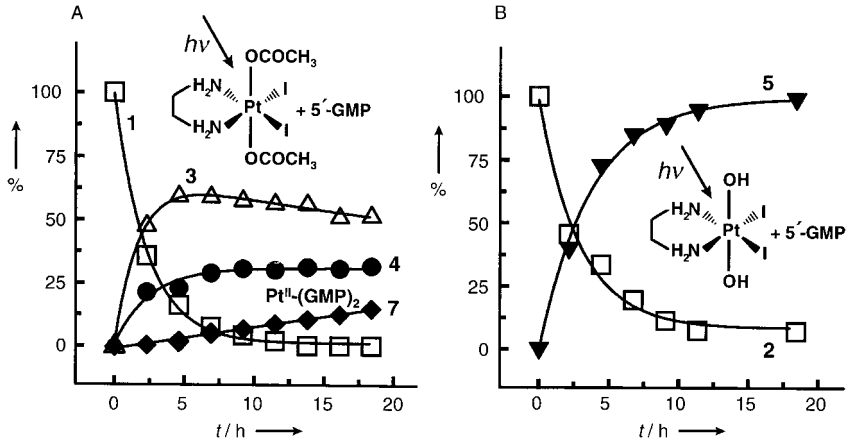

Figure 4. Kinetics of the photoreaction of A) **1** and B) **2**, in the presence of 1 equivalent of 5′-GMP; 200 μM, pH 6.2, 298 K. A) □ **1**, △ **3**, ● **4**, ◆ **7**; B) □ **2**, ▼ **5**. The kinetic data were determined by integration of (en)CH_2 ^{1}H NMR peaks; the total integral of the (en)CH_2 signals was constant during the reaction course.

Similar 1D ^{1}H, 2D [^{1}H,^{15}N] HSQC and 2D [^{1}H,^{15}N] HSQC-TOCSY NMR studies of photoreactions of the dihydroxo complex **2** ($\varepsilon_{457.9} = 246\ M^{-1}cm^{-1}$) in the presence of 5′-GMP (1:1, 200 μM, in water, 298 K, pH 6.2)[5] were carried out. In contrast to irradiation of **1**, only one photoproduct was observed with peaks assignable to *mer*-[Pt(OH)$_3$I(^{15}N-en)] ^{15}N-**5** (Figure 3, Table 1, Scheme 1 B), that is, neither complex **2** nor the photoproduct **5** reacted with the nucleotide over the time period studied (30 h). The rate constant for the light-induced ligand exchange of **1** ($9.27 \times 10^{-5}\ s^{-1}$, half-life 1.61 h, $\phi = 0.16$, Figure 4) is similar to that for **2** ($7.55 \times 10^{-5}\ s^{-1}$; half-life 2.02 h, $\phi = 0.11$), but clearly the axial ligands play a major role in determining the subsequent course of the photoreactions. It can be proposed that the photo-substitution reactions induced by irradiation into the ligand → metal charge transfer (LMCT) band arise from the transfer of a valence electron from I$^-$ into the antibonding d orbitals of d$_6$-Pt^{IV} to give a transient Pt^{III} species. Reactions of Pt^{IV} with nucleotides in the dark are known to be very slow,[8, 9] and in the present case no reactions of complexes **1** or **2** were observed within 30 h in the dark.

Previous reports of photoreactions of Pt^{IV} complexes have been concerned largely with UV irradiation.[10] Light-induced ligand exchange reactions have been investigated, although there appear to be no previous examples of photo-aquation *trans* to am(m)ine ligands. Photoreduction of Pt^{IV} to Pt^{II} is known,[10, 11] and photo-isomerization has been demonstrated for an isomer of the oral Pt^{IV} anticancer drug *cis,trans*-[PtCl$_2$(OAc)$_2$(NH$_3$)(*c*-C$_6$H$_{11}$NH$_2$)] (JM216).[12] However, there appear to be few previous studies of sequential photo-substitution and photo-redox processes and of the influence of the axial ligands on the photoreaction pathways. UV irradiation can result in Pt^{II}-*N7*G bond cleavage for Pt^{II} complexes.[13]

The photoactivation of Pt^{IV} complexes with visible light to give Pt^{II} bis-nucleotide adducts might provide a powerful method for preventing the repair of long-lived mono-Pt^{II}-nucleotide adducts in cancer cells.[14] The success of photochemotherapeutic agents is highly dependent on their stability under physiological conditions, and diiododiamine – Pt^{IV} complexes are likely to be too reactive towards reducing agents, such as glutathione, to be candidates for photochemotherapy.[15] However, there is evidence that by making small changes in the design of the Pt^{IV} complex, photosensitivity can be retained and chemical reactivity towards thiols greatly reduced.

Experimental Section

1 and **2** were synthesized as previously described.[4] Compounds **5** and **6** were obtained by treatment of [PtI$_2$(en)] in water with 1 or 2 equivalents of $AgNO_3$, respectively (6 h, RT), removal of AgI by centrifugation, and reaction with 10 equivalents of H_2O_2 (24 h, RT). The Pt complexes were incubated with 5′-GMP (200 μM, 1 equiv) in H_2O/D_2O (90/10) at 298 K, pH 6.2 in the presence and absence of light. The irradiation was carried out using an argon ion laser (Omnichrome 543-MAP) equipped with a fibre optic (FT-600-UMT, ∅ 600 μm; Elliot Scientific Ltd.) to deliver light ($\lambda_{irr} = 457.9$ nm) directly into the sample within the magnet of the NMR spectrometer. The laser output, after the fibre, was $12.2 \times 10^{-3}\ J\,s^{-1}$ and linear in the range 2.1 to $12.2 \times 10^{-3}\ J\,s^{-1}$, as measured by a LaserMate power meter (Coherent Ltd.). Quantum efficiencies for the decrease of **1** and **2** were determined at 457.9 nm using iron(III) oxalate as a chemical actinometer. 1D ^{1}H, 2D [^{1}H,^{15}N] HSQC, and 2D [^{1}H,^{15}N] HSQC-TOCSY NMR spectra (TOCSY: mixing time of 50 ms) were recorded on a Bruker DMX 500 NMR spectrometer (^{1}H: 500 MHz, ^{15}N: 50.7 MHz).[6] Dioxane was used as internal ^{1}H chemical shift standard ($\delta = 3.764$ relative to [D$_4$]3-trimethylsilyl)propionate (TSP)). All ^{15}N chemical shifts were referenced externally to $^{15}NH_4^+$ at $\delta = 0$. Values of pH were measured with a pH-meter (Corning 145) equipped with a microcombination electrode (Aldrich) calibrated with Aldrich standard buffers (pH 4, 7, and 10) and were adjusted with dilute solutions of $HClO_4$ and NaOH. Rate constants were obtained by fitting the kinetic data to appropriate differential equations by a nonlinear optimization procedure with the program SCIENTIST (version 2.01, MicroMath Inc.).

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Cesium Hydroxide: A Superior Base for the Catalytic Alkynylation of Aldehydes and Ketones and Catalytic Alkenylation of Nitriles**

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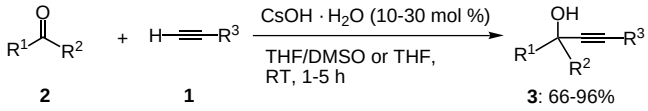
The metal-catalyzed formation of new carbon–carbon bonds is an important synthetic tool.[1] Particularly attractive in this category of reactions are additions to multiple bonds that proceed without the formation of side products (atom economic reactions).[2] Thus, the metal-catalyzed addition of alkynes of type **1** to carbonyl compounds of type **2** that lead to propargyl alcohols of type **3** has a considerable synthetic and industrial importance. Whereas the performance of these reactions that use a stoichiometric amount of a base such as an organolithium or organomagnesium reagent to generate an intermediate metal acetylide[3] has been extensively described, only a few reports concerning the catalytic activation of an alkyne and subsequent addition to the carbonyl derivative have been reported.[4, 5] They are mostly restricted to acetylene itself[4] or are applicable only to some carbonyl compounds such as cycloalkanones.[5] Herein, we report the exceptional activity of cesium hydroxide[6, 7] for the catalytic generation of highly nucleophilic, stabilized organometallic species (Scheme 1). Thus, in the presence of a catalytic



2 **1** **3**: 66-96%

Scheme 1. CsOH-catalyzed alkynylation of aldehydes and ketones with terminal alkynes. R^1, R^2 = alkyl or H, R^3 = alkyl, aryl, alkenyl.

amount of $CsOH \cdot H_2O$ (10 mol%) phenylacetylene (**1a**: 1.5 equiv) adds to cyclohexanone (**2a**) in THF within 1 h at RT. The desired propargyl alcohol (**3a**) is isolated after workup in 88% yield (entry 1 of Table 1). Under these conditions phenylacetylene adds to various aliphatic ketones[8] or to aliphatic aldehydes in yields between 66 and 96%. In many cases, these reactions are complete within five minutes at RT. A 1:1 mixture of THF and DMSO was used as solvent together with $CsOH \cdot H_2O$ (30 mol%) for the addition of less acidic alkynes. Under these conditions most terminal alkynes undergo a smooth addition to secondary or tertiary aliphatic aldehydes or aliphatic ketones to give the corresponding propargyl alcohols of type **3** (Table 1). To avoid competitive aldol reactions a slow addition of the aldehyde with a syringe pump was performed (addition of 0.5 mL h^{-1}). The addition of alkynes to carbonyl compounds with diastereotopic faces such as 2-methylcyclohexanone (**2b**) or the

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