SHORT PAPER

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The effect of 4′-substituents on the kinetics of ligand substitution in 2,2′:6′,2″-terpyridine platinum(II) complexes†

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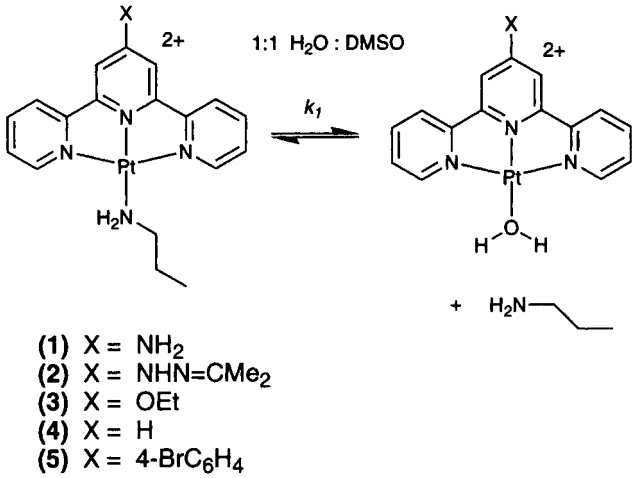
The rates of hydrolysis of five (4′-substituted-2,2′:6′,2″-terpyridine) platinum(II) (*n*-propylamine) complexes exhibit a high sensitivity to the electronic properties of the terpyridine ligand; analysis using the Hammett relationship gives a ρ value of +2.34.

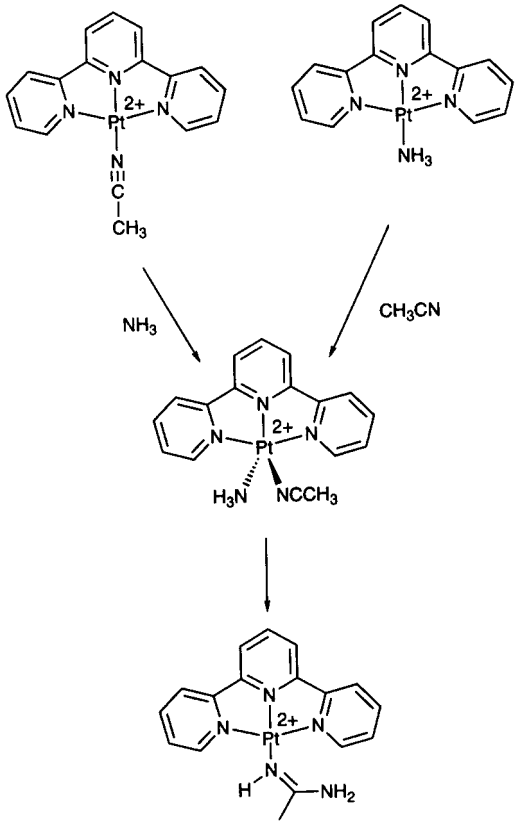
The antiparasitic[1] and antitumor[2] activity of a range of (2,2′:6′,2″-terpyridine) platinum(II) complexes have recently been reported. The mode of action of these complexes is currently uncertain, with intercalation into DNA,[3] platination of DNA[4] and binding to cysteine or histidine donors in proteins all being possible cellular targets.[5] It has been shown previously that ligand substitution reactions of terpyridine platinum(II) chloro complexes are 3–4 orders of magnitude faster than their dien (1,5-diamino-3-azapentane) analogues,[6] but no direct correlation has been made with the electronic properties of the terpyridine ligand.

From an analysis of a wide range of derivatives, it became apparent that *n*-alkylamine complexes of terpyridineplatinum(II) were hydrolysed (see Scheme 1) at a rate which could be followed by ^{1}H NMR spectroscopy. Pt(II)(propylamine) complexes of 4′-amino-2,2′:6′,2″-terpyridine (**1**), (4′-hydrazino-2,2′:6′,2″-terpyridine)acetonide (**2**), 4′-ethoxy-2,2′: 6′,2″-terpyridine (**3**), 2,2′:6′,2″-terpyridine (**4**) and 4′-(4-bromophenyl)-2,2′:6′,6″-terpyridine (**5**) were obtained as their *bis* nitrate salts using a modified literature synthesis (see Table 1).[7]



Scheme 1
Hydrolysis of terpyridine platinum(II) complexes **1–5**

Modification of the synthetic procedure was necessary due to the formation of by-products if acetonitrile was used in the synthesis. These by-products were attributed to nucleophilic attack of amines (or ammonia) at the coordinated nitrile centre to give complexed amidines, as illustrated in Scheme 2. These impurities were readily observed by electrospray mass spectrometry, and were also shown to occur irrespective of the order of addition of CH_3CN and amine to the Pt(II) centre.



Scheme 2
Formation of coordinated amidines at terpyridine platinum(II) centres

^{1}H NMR spectra of complexes **1–5** were recorded in d_6-dimethylsulfoxide over 24 hours to demonstrate that the complexes were stable in DMSO. An equivalent volume of D_2O was then added and ^{1}H NMR spectra were recorded at 25(±0.3)°C at fixed time intervals until no further spectral changes were observed and equilibria had been attained. The changes in the aliphatic region of the ^{1}H NMR spectrum for complex **4** (unsubstituted terpyridine) are illustrated in Fig. 1.

It has been shown previously that chloro (2,2′:6′,2″-terpyridine)platinum(II) chloride is reactive towards thiol and

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 ESI-MS and ^{1}H NMR spectroscopic data for n-propylamine(2,2′;6′,2″-terpyridine)platinum(II) *bis* nitrate complexes **1–5**

	m/z (2+)	δH (500 MHz, d_6-DMSO)
1	251(100%)	0.95 (3H, t, *J* = 7 Hz, CH_3), 1.85 (2H, m, CH_2), 2.90 (2H, m, CH_2N), 6.13 (2H, s br, NH_2), 7.50 (2H, s, $ArNH_2$), 7.84 (2H, s, H3′,5′), 7.96 (2H, m, H5,5″), 8.37 (2H, d, *J* = 8 Hz, H3,3″), 8.50 (2H, m, H4,4″) and 8.81 (2H, d, *J* = 5 Hz, H6,6″)
2	278(100%)	0.93 (3H, t, *J* = 7.5 Hz, CH_3), 1.83 (2H, m, CH_2), 2.05 (3H, s, N=CMe_2), 2.13 (3H, s, N=CMe_2), 2.90 (2H, m, CH_2N), 6.11 (2H, s br, NH_2), 7.83 (2H, m br, H3′,5′), 7.95 (2H, m, H5,5″), 8.40 (2H, s br, H3,3″), 8.48 (2H, m, H4,4″), 8.80 (2H, m, H6,6″) and 10.57 (1H, s br, NH)
3	265(100%)	0.96 (3H, t, *J* = 8 Hz, CH_3), 1.49 (3H, t, *J* = 7 Hz, CH_3CH_2O), 1.89 (2H, m, CH_2), 2.75 (2H, m, CH_2N), 4.49 (2H, q, *J* = 7 Hz, CH_3CH_2O), 6.29 (2H, s br, NH2), 8.03 (2H, m, H5,5″), 8.37 (2H, s, H3′,5′), 8.61 (2H, m, H4,4″), 8.77 (2H, d, *J* = 8 Hz, H3,3″) and 8.87 (2H, d, *J* = 6 Hz, H6,6″)
4	243(100%)	0.97 (3H, t, *J* = 8 Hz, CH_3), 1.99 (2H, m, CH_2), 2.95 (2H, t br, *J* = 8 Hz, CH_2N), 6.39 (2H, s br, NH_2), 8.06 (2H, m, H5,5″), 8.60 (2H, m), 8.70 (5H, m, H3′,5′,3,3″,4′) and 8.89 (2H, d, *J* = 6 Hz, H6,6″)
5	321(100%)	0.97 (3H, t, *J* = 8 Hz, CH_3), 1.88 (2H, m, CH_2), 2.96 (2H, m, CH_2N), 6.38 (2H, s br, NH_2), 7.95 (2H, d, *J* = 8 Hz, H3‴,5‴), 8.09 (2H, m, H5,5″), 8.20 (2H, d, *J* = 8 Hz, H2‴,H6‴), 8.66 (2H, m, H4,4″), 8.91 (2H, d, *J* = 5 Hz, H6,6″), 8.94 (2H, d, *J* = 8 Hz, H3,3″) and 9.08 (2H, s, H3′,5′)

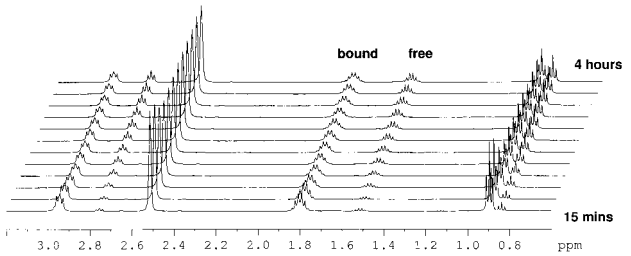

Fig. 1 ^{1}H NMR spectra during the hydrolysis of **4**, showing Pt(II)-bound propylamine (δ = 0.91, 1.81, 2.95 ppm) and free propylamine (δ = 0.84, 1.50, 2.77 ppm). The signal at 2.52 ppm is due to partially deuterated DMSO.

imidazole groups of cysteine and histidine protein residues, but not towards methionine or cystine residues. This has been attributed to steric hindrance between the 6,6″ hydrogen atoms on the terpyridine and the thioether substituents.[5] Dimethyl sulfoxide also does not react with terpyridineplatinum(II) centres for the same reason and is not involved in the kinetic analysis. The data were analysed (assuming a first-order forward reaction and a second-order back reaction) using the integrated rate equation shown below;[8]

$$\frac{x_e}{(2a-x_e)} \ln \frac{ax_e + x(a-x_e)}{a(x_e-x)} = k_1 t$$

where a = initial concentration of propylamine complex, x = concentration of aqua complex at time t and x_e = equilibrium concentration of aqua complex.

The rate constants for the first order hydrolysis reactions were calculated to be 2.03, 3.40, 17.9, 81.6 and 125 ($\times 10^{-6}$ s^{-1}) for complexes **1–5** respectively. It is immediately apparent that the rates are strongly dependent upon the terpyridine substituent. The data were analysed using the Hammett equation and found to give good agreement with the Hammett σ_p parameters.[9] A Hammett plot of $\log(k/k_o)$ (where $k_o = k$ for the unsubstituted terpyridine complex **4**) *vs* σ_p gives a straight line with a ρ value of +2.34 (see Fig. 2).

Ligand substitution reactions at Pt(II) centres normally proceed *via* an associative mechanism with a five-coordinate transition state.[10] The straight-line correlation of the kinetic data with the Hammett σ_p parameters indicates that the same step is rate-limiting (if a transient intermediate is formed) for the five different substituents (X). The positive ρ value indicates that there is a build-up of electron-density in this transition state, which can be reduced by electron-withdrawing groups, in accord with an associative mechanism. The magnitude of ρ (2.34) indicates that the transition state is sensitive to substituents at the 4′ position on the terpyridine ring. Comparisons

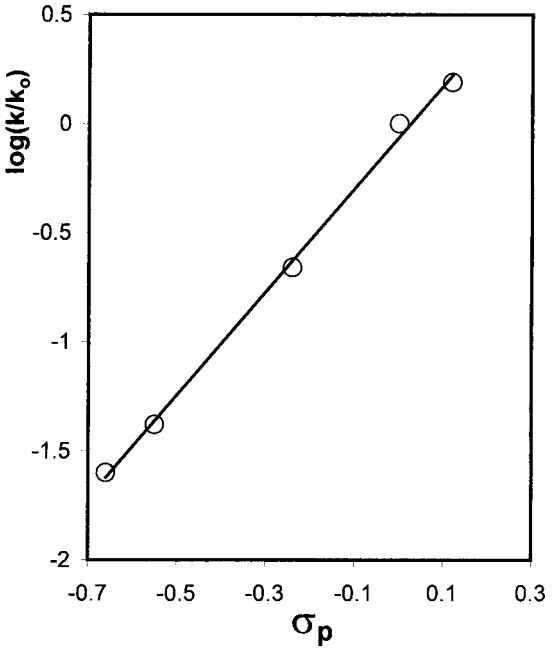

Fig. 2 Plot of $\log(k/k_o)$ *vs* σ_p for hydrolysis of complexes **1–5** (σ_p values taken from ref. 9)

can be drawn to the base-catalysed hydrolysis of aromatic carboxylic acid esters, which have a ρ value of +2.61.[11]

The data are consistent with attack of water at the Pt(II) centre being the rate determining step for these hydrolysis reactions. The high reactivity of the terpyridine platinum(II) class of compounds to ligand substitution (compared to other aliphatic tridentate donor ligands) can be rationalised in terms of good overlap of the platinum(II) d-orbitals with the terpyridine π^* orbitals.

We have shown previously that terpyridine platinum(II) complexes exhibit antiparasitic[1] and antitumor[2] activity. The ability to now control and predict the ligand substitution behaviour of these complexes should aid in the rational design and study of further derivatives.

Experimental

Synthesis: ^{1}H NMR spectra were recorded on a Bruker AMX500 instrument and assignments were confirmed using 2D techniques. 2,2′:6′,2″-Terpyridine and 4′-chloro-2,2′:6′,2″-terpyridine were used as supplied (Aldrich Chemical Co.). 4′-Ethoxy-, 4′-amino- and 4-hydrazino-2,2′:6′,2″-terpyridine were prepared as described previously.[1] Complexes **1–5** were prepared as their *bis* nitrate salts (in 40–60% yields) by a modified route based on that described previously.[7] $AgNO_3$ (0.2 mmol) was reacted with $Pt(COD)I_2$ (0.1 mmol) in

20% aqueous acetone (700 μl) for 2–3 minutes, then centrifuged to remove AgI. The supernatant was added to a suspension of the appropriate terpyridine ligand (0.85 mmol) in acetone (300 μl) and vortexed for 5 minutes. The precipitate was isolated by centrifugation and washed three times with ether:acetone (3:1, 1 ml). The intermediate $[Pt(Xterpy)(solvent)](NO_3)_2$ was then dissolved in DMF (1 ml) and added to a solution of propylamine (0.2 mmol) in DMF (1 ml). The solution was sonicated for 30 minutes, then acetone:ether (1:1, 20 ml) was added and the precipitate was isolated, washed with ether and dried *in vacuo*. Slight impurites were occasionally observed due to side reactions. However, these were less than 3% and did not interfere with the kinetic measurements. Complexes **1**–**5** all gave satisfactory ^{1}H NMR and ESI-MS data (Table 1). 4′-hydrazinoterpyridine was used as the starting ligand for complex **2**, although the complex was isolated as the acetonide, due to the presence of acetone in the synthetic procedure. The acetonide structure was confirmed by elemental analysis ($C_{21}H_{26}N_8O_6Pt.H_2O$ requires % C 36.1, H 4.0, N 16.0, found C 36.3, H 3.8, N 15.9), in addition to ^{1}H NMR and ESI-MS data.

Kinetic analysis: Complexes **1–5** were each dissolved in 700 μl d_6-DMSO / D_2O (1:1 v/v) to give final concentrations of around 10–20 mmol/dm^3. ^{1}H NMR spectra were then recorded over fixed time intervals until the solvolysis reactions had reached equilibria. Total reaction times ranged from 30 minutes (complex **5**) to 6 days (complex **1**) and final equilibria were between 25 and 90% hydrolysis of starting complex. Concentrations of starting materials and products were calculated at a given time *t* and at equilibrium by averaging the integrals of selected (well-separated) ^{1}H NMR resonances at each time interval. These data were then analysed using the integrated rate equation shown in the text, with the logarithmic term being plotted against time. σ_p values for the Hammett plot were taken from ref.9. The σ_p value for the acetonide group (–0.54 ± 0.1) was estimated from the ^{19}F NMR shift of the acetonide of 4-fluorophenylhydrazine (–125.9 ppm) as compared to the ^{19}F NMR shifts of fluorobenzene (–113.5 ppm) and 4-fluorophenyl hydrazine (–126.2 ppm) in dilute $CDCl_3$ solution (see ref. 9).

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