Cytotoxicity of (2,2′:6′,2″-Terpyridine)platinum(II) Complexes to *Leishmania donovani, Trypanosoma cruzi,* and *Trypanosoma brucei*

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A range of (2,2′:6′,2″-terpyridine)platinum(II) complexes are shown to possess antiprotozoal activity in vitro against *Leishmania donovani*, *Trypanosoma cruzi*, and *Trypanosoma brucei*, the causative organisms of tropical diseases leishmaniasis and trypanosomiasis. The best compounds caused 100% and 78% inhibition of growth of the intracellular amastigote forms of *L. donovani* and *T. cruzi*, respectively, at a concentration of 1 μM and 100% inhibition of growth of the bloodstream trypomastigote forms of *T. brucei* at a concentration of 0.03 μM. The results obtained with complexes in which the fourth ligand to platinum(II) is capable of being substituted with a substitution inert hydroxyethanethiolate complex are compared. The ammine complexes show high antiprotozoal activity suggesting that the *trans* influence of the 2,2′:6′,2″-terpyridine ligand has a profound effect on the ease of displacement of the fourth ligand in (2,2′:6′,2″-terpyridine)platinum(II) complexes, although nonbonded interaction between the ammine ligand and the 6 and 6″ hydrogens probably also weakens the ligation to Pt(II).

Introduction

(2,2′:6′,2″-Terpyridine)platinum(II) complexes were first reported to bind to double-stranded DNA by intercalation over 20 years ago.[1] The angle by which they unwind the DNA duplex was found to be comparable to that produced by ethidium bromide, while fiber diffraction experiments on the complex between (2-hydroxyethanethiolato)(2,2′:6′,2″-terpyridine)platinum(II) (**1**) and calf thymus (ct) DNA showed the platinum ions to be distributed along the helix axis according to the nearest-neighbor exclusion model.[2]

Early studies on **1** (Chart 1) yielded estimated binding constants between 10^4 and 10^5 M^{-1}, dependent on buffer, ionic strength, and the DNA base-pair composition. Similar data have been reported for complexes with other thiolate, chloride,[3] or hydroxide[4] ions as the fourth ligand. The highest binding constant of these is observed with (2-aminoethanethiolato)(2,2′:6′,2″-terpyridine)-platinum(II) (**2**). In this case the amine group of the fourth ligand is protonated at neutral pH, conferring a second positive charge on the complex. These studies also showed that, while thiolate complexes are only capable of intercalation, the chloride and hydroxide complexes undergo fourth-ligand substitution by the nucleobases of DNA to give a covalent adduct.

In light of the high binding constant of **2**,[3] we investigated pyridines as the fourth ligand. These complexes retain the double-positive charge of platinum(II) centered on the metal complex. (4-Picoline)(2,2′:6′,2″-terpyridine)platinum(II) (**3**; R = H) was prepared and its interaction with DNA studied.[5] Intercalation was evident from a linear dichroism study and an unwinding ligation assay. Fluorescence (ethidium competition) and circular dichroism spectroscopy were used to measure the binding constant. These experiments yielded an initial binding constant to poly[d(A−T)$_2$] of 2×10^7 M^{-1}, associated with a site size of 4 bp, and a secondary binding constant of 1×10^6 M^{-1}, associated with a site size of 2 bp (i.e., showing overall adherence to the nearest-neighbor exclusion model). These figures represent an increase in the binding constant of 1−2 orders of magnitude over **1** and **2** by locating the double charge on the (2,2′:6′,2″-terpyridine)platinum(II) complex.

As a result of attempts to obtain crystals suitable for X-ray analysis of the intercalation complexes with **3** (R = H) or (4,4′-vinylidenedipyridine)bis[(2,2′:6′,2″-terpyridine)platinum(II)] (**4**) and a short synthetic (self-complementary) oligonucleotide, d(CGTACG)$_2$, it became clear that these complexes could also undergo ligand substitution by the oligonucleotide.[6] Although nucleophilic substitution by nucleobases is well-established with the antitumor drug *cis*-platin,[7] there does not appear to be any previous report of the displacement of a pyridine-based ligand by a nucleobase. Indeed, it has been reported that *cis*-[Pt(NH$_3$)$_2$Cl(Py)]$^+$ forms a monofunctional adduct with DNA due to displacement of the chloride ligand, the pyridine ligand (Py) being completely stable.[8]

Further investigation of the platination of d(CGTACG)$_2$ revealed that reaction occurred solely on the 3′-terminal G residue.[6] Experiments with longer sequences have since shown that this selectivity for G residues is not an end effect.[9] These observations have been rationalized by a kinetic and structural investigation of the platination of individual nucleosides by **3**; (R = H). Although all four bases are capable of forming adducts in the order G > A > C > T, only the donor atom of G is not involved in Watson−Crick base pairing in DNA duplexes and therefore available for platination.[10]

Many agents that are active against *Trypanosoma* and *Leishmania* parasites intercalate into nuclear and/

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Chart 1

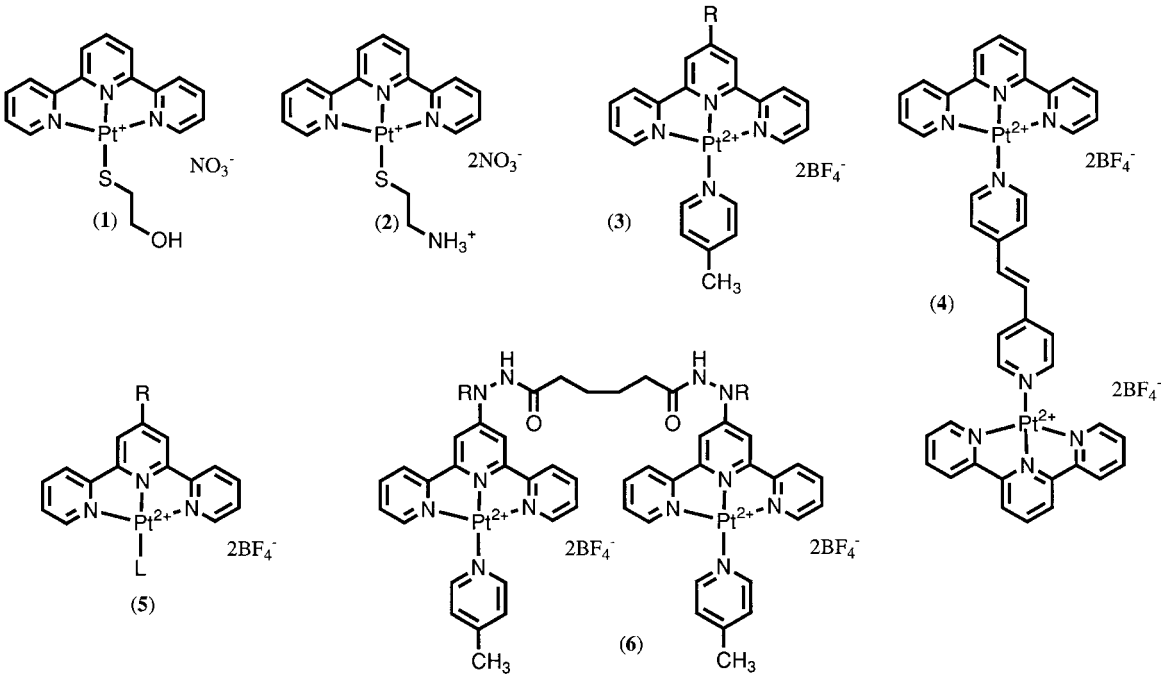

Table 1. Percent Inhibition at a Given Concentration[a]

	L. donovani					*T. cruzi*					*T. brucei*							
5 (R = H), L	30 μM	10 μM	3 μM	1 μM	ED_{50}	30 μM	10 μM	3 μM	1 μM	ED_{50}	30 μM	10 μM	3 μM	1 μM	0.3 μM	0.1 μM	0.03 μM	ED_{50}
4-$CH_3C_5H_4N$	85.7	1.2	4.5	0.5	18	T/100	T/+	T/+			100	100	100	100	100	100	83.3	0.007
4-BrC_5H_4N	54.2	0.2	0	0	28	T/+	T/+	T/+			100	100	100	100	100	100	100	
4-AcC_5H_4N	45.5	27.0	0.2	0	36	T/+	T/+	T/+	3.8		100	100	100	100	86.4	62.7	50.0	0.03
4-$Me_2NC_5H_4N$	97.5	11.6	0	0	41	99.8	100	85.8	30.3	2.0	100	100	100	100	100	44.6		0.15
2-FC_5H_4N	100	31.5	0	0	15	31.3	9.3	6.0	3.0	45	100	100	100	100				
3-FC_5H_4N	96.9	44.9	0	0	12	58.8	43.8	6.5	2.0	19	100	100	100	100				
thiazole	96.7	30.8	2.1	0	16	30.8	5.0	0	0	41	100	100	100	100	100	75.4		0.03
imidazole	94.6	75.1	0	0	7.7	38.0	5.0	0	0	35	100	100	100	93.0	0	0		0.7
CH_3CN	100	82.8	3.9	0	6.8	38.0	4.0	0	0	34	100	100	100	100				
4-$HOCH_2C_5H_4N$	98.7	61.5	0.8	0	8.2	24.7	0	0	0		100	100	100	100	100	32.5		0.15
C_5H_5N	99.5	92.2	0	0	6.2	27.0	0	0	0		100	100	100	100	100	81.6		0.02
H_2O	T/100	T/100	96.5	2.0	2.4	23.8	0	0	0		100	100	100	100	75.5	0		0.13
NH_3	96.1	91.7	27.5	5.0	5.2	100	100	100	72.3	0.5	100	100	100	100	98.5	83.8		
Cl^-	99.1	94.9	22.0	0	5.5	99.3	99.0	76.0	52.0	0.8	100	100	100	100	100	26.2		0.16

[a] T/100 means the compound was toxic to macrophages but more toxic to parasites, i.e., none present, 100% inhibition. T/+ means the compound was toxic to macrophages but parasites still present. The percent inhibition is difficult to determine because the parasites are extracellular when the host cells are destroyed.

or kinetoplast DNA, e.g., acriflavine and ethidium bromide,[11] ellipticine,[12] bleomycin,[13] and platinum/metal complexes.[14,15] Platination of nucleobases could also cause cytotoxicity. Furthermore, ligand substitution reactions are not limited to G residues in DNA. Similar processes could be expected with certain functional groups vital for enzyme activity (e.g., thiols, imidazoles),[16] which could also result in cell death. A series of (2,2′:6′,2″-terpyridine)platinum(II) complexes have been synthesized, therefore, and their antiprotozoal activity has been explored against the closely related hemflagellate protozoa *Leishmania donovani*, *Trypanosoma cruzi*, and *Trypanosoma brucei*, which are the causative agents of leishmaniasis, Chagas disease (South American trypanosomiasis), and sleeping sickness (human African trypanosomiasis). The first-line drugs for these diseases are pentavalent antimonials, nitroheterocyclic compounds and trivalent arsenical compounds, respectively. These therapies are inadequate, have variable efficacy and toxic side effects, and require long courses of administration.[17,18] There is a clear need to develop new drugs for these diseases which are more efficacious and with an improved therapeutic index.

Results and Discussion

Antiparasitic Activity. The data in Table 1 show the percentage inhibition caused by each of the (2,2′:6′,2″-terpyridine)platinum(II) complexes and their ED_{50} values (where these can be calculated), as the fourth ligand to Pt(II) is changed. For *L. donovani* the aqua (**5**, R = H, L = H_2O) and the ammine (**5**, R = H, L = NH_3) complexes were the most effective. For *T. cruzi* the most effective compound is the ammine complex (**5**, R = H, L = NH_3). For *T. brucei* the 4-picoline, the 4-bromopyridine, and the ammine complexes (**5**, R = H, L = 4-CH_3·C_5H_4N; **5**, R = H, L = 4-Br·C_5H_4N; and **5**, R = H, L = NH_3) were the most effective. The low ED_{50} values of the aqua (**5**, R = H, L = H_2O) and chloride (**5**, R = H, L = Cl^-) complexes is not unexpected as the fourth ligand is a good leaving group. We have previ-

Table 2. Percent Inhibition at a Given Concentration[a]

	L. donovani					*T. cruzi*					*T. brucei*							
3, R	30 μM	10 μM	3 μM	1 μM	ED_{50}	30 μM	10 μM	3 μM	1 μM	30 μM	10 μM	3 μM	1 μM	0.3 μM	0.1 μM	0.03 μM	ED_{50}
$N(CH_2CH_2OH)_2$	67.1	8.0	0	0	20	T/+	T/+	0	0	100	100	98.4	81.9	73.0	65.4	66.7	0.015
F	100	97.0	1.1	0	6.6	26.9	0	0	0	100	100	100	100	0	0		
Cl	93.3	89.5	47.9	2.5	3.1	100	97.0	73.5	59.7	100	100	100	100	83.8	99.2		
Br	100	92.8	5.4	0	6.8	T/+	T/+	T/+	T/0	100	100	100	100	100	96.5		
OMe	97.3	0	0	0	20	28.3	4.8	0	0	100	100	100	100	100	40.1		0.13
p-Me·C_6H_4	99.7	93.1	96.2	96.9		T/+	0	0	0	100	100	100	100	100	87.8	50.0	0.03
p-Br·C_6H_4	T/100	T/100	99.8	31.4	1.8	100	100	100	78.2	100	100	100	100	100	0		8
$MeNCH_2CH_2OH$	0	0	0	0		11.0	2.8	3.0	1.0	100	100	100	64.7	15.2	0		0.8
$NH·CH_2CH_2OH$	1.5	0	0	0		18.0	0	0	0	100	100	68.4	0	0	0		2.4
c-NCH_2CH_2	97.9	96.9	0	0		T/0	0	0	0	100	100	100	100	78.9	54.2		0.9
$NH·NH_2$	14.4	0	0	0		60.1	65.8	57.7	60.8	100	100	100	100	29.6	4.9		0.5
$NMeNH_2$	0	0	0	0		33.4	53.3	53.3	60.9	100	100	98.3	44.4	22.5	0		1.4
NH_2	100	100	100	0		0	0	0	0	100	100	100	100	0	0		
6 (R = H)	0	0	0	0		T/0	0	0	0	100	100	100	0	0	0		
6 (R = Me)	0	0	0	0		T/8.3	0	0	0	100	59.8	0	0	0	0		9.0

[a] T/100 means the compound was toxic to macrophages, 100% inhibition. T/+ means the compound was toxic to macrophages but parasites still present.

Table 3. Percent Inhibition at a Given Concentration[a]

5		*L. donovani*				*T. cruzi*					*T. brucei*						
R	L	30 μM	10 μM	3 μM	1 μM	30 μM	10 μM	3 μM	1 μM	ED_{50}	30 μM	10 μM	3 μM	1 μM	0.3 μM	0.1 μM	0.03 μM
Cl	NH_3	T/100	T/100	99	99	T/100	T/100	T/100	50.8	0.95	100	100	100	100	0	0	
p-BrC_6H_4	NH_3	T/100	T/100	T/100	100	T/100	T/100	T/100	64.5	0.6	100	100	100	100	100	100	100

[a] T/100 means the compound was toxic to macrophages, 100% inhibition.

ously shown that pyridine ligands are unusually susceptible to displacement from (2,2′:6′,2″-terpyridine)-platinum(II) complexes and have suggested that this is caused by at least two factors. First, the tridentate bite of the 2,2′:6′,2″-terpyridine ligand is not ideal for a square-planar complex which results in the bond between the nitrogen of the central pyridine moiety and Pt(II) being shorter than a normal Pt(II)−pyridine bond; the bond length to the pyridine acting as the fourth ligand is unusually long. Thus this bond is weak and more easily broken. In addition there is metal-to-ligand change transfer (revealed by the UV spectrum), and this will denude the Pt(II) of electron density and so make it more susceptible to nucleophilic attack. Thus the 2,2′:6′,2″-terpyridine ligand has a powerful *trans* influence on the leaving ability of the fourth ligand in these systems. There remains, however, the still surprising result that the ammine complex is among the best compounds for antiprotozoal activity. The single-crystal X-ray structure of the (2,2′:6′,2″-terpyridine)Pt(II) 4-picoline complex shows the 4-picoline ring to be at an angle of 70° to the (2,2′:6′,2″-terpyridine)Pt(II) plane.[19] It is clear that the 4-picoline cannot be coplanar with the (2,2′:6′,2″-terpyridine)Pt(II) plane because of the severe nonbonded interactions that would arise between the 6 and 6″ hydrogen atoms of the 2,2′:6′,2″-terpyridine and the 2 and 6 hydrogen atoms of the 4-picoline. We have found that with sp^3-hybridized nitrogen ligands it is not possible to form a complex with either trisubstituted or disubstituted amines presumably because, as a model clearly shows, it is not possible to avoid severe nonbonded interaction between at least one of the substituents and a 6 or 6″ hydrogen atom of the 2,2′:6′,2″-terpyridine. Now although ammonia does not carry substituents, there is some nonbonded interaction with the 6 or 6″ hydrogen atoms of the 2,2′:6′,2″-terpyridine, and so although the complex can now be formed, it is intrinsically more susceptible to displacement from Pt(II). Indeed it is possible to show by NMR spectroscopy that the ammine (2,2′:6′,2″-terpyridine)Pt(II) complex (**5**, R = H, L = NH_3) equilibrates with the aqua complex (**5**, R = H, L = H_2O) when dissolved in water at ambient temperature.

The data in Table 2 show the effect of changing the substituent at the 4′-position on the (2,2′:6′,2″-terpyridine)platinum(II) complex keeping the fourth ligand as 4-picoline. For *L. donovani* compounds **3** (R = 4-CH_3·C_6H_4) and **3** (R = 4-Br·C_6H_4) are remarkably effective at 1 μM. For *T. cruzi* compounds **3** (R = 4-Br·C_6H_4), **3** (R = Cl), **3** (R = $NHNH_2$), and **3** (R = $NMeNH_2$) were the most effective at 1 μM. For *T. brucei* compounds **3** (R = Cl), **3** (R = Br), and **3** (R = 4-CH_3·C_6H_4) were the most effective at a concentration of 0.1 μM.

In light of these results a third generation of compounds, namely, **5** (R = Cl, L = NH_3) and **5** (R = 4-Br·C_6H_4, L = NH_3) was prepared and their antiprotozoal activity was investigated. The data are shown in Table 3. For *L. donovani* both of these compounds were more effective than either the first- or second-generation compounds (Tables 1 and 2), both showing effectively complete inhibition at 1 μM concentration. Against *T. cruzi* compounds **5** (R = Cl, L = NH_3) and **5** (R = 4-Br·C_6H_4, L = NH_3) were comparable in effectiveness to the best of the first- and second-generation compounds. Against *T. brucei* **5** (R = 4-Br·C_6H_4, L = NH_3) caused complete inhibition at 0.03 μM.

The (2,2′:6′,2″-terpyridine)platinum(II) complexes (**3**−**6**) are expected to intercalate into DNA and platinate either guanine bases or enzyme functional groups, e.g., thiols and imidazoles essential for enzymic activity.[16] The mechanism of the antiprotozoal activity described above is as yet unknown. To obtain some insight into whether intercalation or platination was the cause of antiprotozoal activity, the 2-hydroxyethanethiolato com-

Table 4. In Vitro Antiprotozoal Activity of **1**

	percent inhibition				
	30 μM	10 μM	3 μM	1 μM	ED_{50} (μM)
L. donovani	99.3	94.6	78.2	0	3.1
T. cruzi	91.7	85.1	39.8	21.6	4.0
T. brucei	100	100	100	100	

plex **1** was investigated. The thiolate ligand possesses a high affinity for Pt(II) and should be inert to substitution by any nucleobase or indeed any normal functional group found in proteins. As such any activity seen with this compound would have to be attributed to intercalation or possibly platination of some functional group in a protein with unusual nucleophilic ability. The results shown in Table 4 are best compared with those in Table 1, i.e., the data for the unsubstituted (2,2′:6′,2″-terpyridine)platinum(II) complexes. Against *L. donovani* the ED_{50} value of 3.1 μM is comparable with that of the best compound in Table 1 (i.e., **5**, R = H, L = H_2O: ED_{50} 2.4 μM). Against *T. cruzi* **1** (ED_{50} 4.0 μM) is almost an order of magnitude less effective than **5** (R = H, L = NH_3: ED_{50} 0.5 μM), and against *T. brucei* it is 100% effective at all concentrations tested. The susceptibility of the parasites to the 2-hydroxyethanethiolato complex **1** is the subject of further investigation.

Although we have not shown directly that the ammine complexes (**5**, L = NH_3) are capable of platinating DNA, their antiprotozoal activity suggests that this is the likely explanation when compared with the activity profile of the hydroxyethanethiolate complex **1**. The remarkable antiprotozoal activity of the ammine complexes (**5**, L = NH_3) can be attributed to the *trans* influence of the 2,2′:6′,2″-terpyridine ligand.[19] Since we have shown that on being kept in aqueous solution the ammine complex (**5**, R = H, L = NH_3) comes to equilibrium with the aqua complex (**5**, R = H, L = H_2O), the question arises as to whether the effective species for antiprotozoal activity is the ammine complex (**5**, R = H, L = NH_3) or the aqua complex (**5**, R = H, L = H_2O). Since, however, the ammine complex (**5**, R = H, L = NH_3) is more effective than the aqua complex (**5**, R = H, L = H_2O) against *T. cruzi* and *T. brucei*, it can be inferred that the ammine complex possesses sufficient stability in aqueous solution for it to be an effective antiprotozoal agent.

Experimental Section

Antiparasitic Activity. Screen 1, Protocol I. *L. donovani* (strain MHOM/ET/67/L82) amastigotes, derived from the spleen of a golden hamster (Wright's strain), were used to infect mouse peritoneal macrophages from CD1 (Charles River Ltd., Margate, U.K.) mice at a parasite:macrophage ratio of 10:1. Infected macrophages were maintained in RPMI 1640 medium plus 10% heat-inactivated fetal calf serum (hiFCS) (Harlan Sera-Lab., Crawley, U.K.) in 16-well Labtek chamber slides (Nunc Inc., IL) at 37 °C in 5% CO_2/air mixture.[18] Infected cultures were exposed to test compounds in medium, in a 3-fold dilution series from 30 μM with quadruplicate cultures at each concentration for 5 days, with medium + drug replaced once during the period. Sodium stilbogluconate (Glaxo Wellcome, U.K.) was included in the assays as the positive control and had an ED_{50} value of 10.4 μg of Sb/mL (M_r of the drug is unknown). Activity was determined, after cultures had been methanol fixed and Giemsa stained, from the proportion of infected cells in treated and untreated cultures, and dose−response curves were analyzed by linear regression to obtain an ED_{50} value where possible.

T. cruzi (strain MHOM/BR/00/Y) trypomastigotes derived from MDCK fibroblasts were used to infect mouse peritoneal macrophages from CD1 mice at a parasite:macrophage ratio of 5:1. Infected cells were maintained in RPMI 1640 medium plus 10% hiFCS in 16-well Labtek chamber slides at 37 °C in 5% CO_2/air mixture. Infected cultures were exposed to test compounds in medium, in a 3-fold dilution series from 30 μM with quadruplicate cultures at each concentration for 3 days. Nifurtimox (Bayer, Germany) was used as the positive control and had an ED_{50} in the range 2.2−4.4 μM. Activity was determined, after cultures had been methanol fixed and Giemsa stained, from the proportion of infected cells in treated and untreated cultures, and dose−response curves were analyzed by linear regression to obtain an ED_{50} value where possible.

T. brucei (strain S427) bloodstream trypomastigotes were cultured in HMI-18 medium containing 20% hiFCS at 37 °C in 5% CO_2/air mixture.[20] Trypomastigotes were exposed to test compounds in medium, in a 3-fold drug dilution series from 30 μM with triplicate cultures at each concentration for 72 h. Pentamidine (Rhone Poulence Rorer Ltd., Dagenham, U.K.) was used as the positive control and had an ED_{50} value of 0.03−0.1 μM. Drug activity was determined by using an MTT-based cytotoxicity assay, and dose response curves were analyzed by linear regression to obtain an ED_{50} value where possible.

Screen 2, Protocol II. The assays follow those outlined in Screen 1, Protocol 1 but include a range of doses in a dilution series from 30 μM. Dose−response curves were analyzed by linear regression and ED_{50} values determined. *T. brucei* numbers/mL were determined using a Coulter counter.

Materials and Methods. Thin-layer chromatography was performed on aluminum sheets precoated with neutral alumina (0.2 mm, Merck aluminum oxide, 60 F_{254}) and unless otherwise indicated eluted with diethyl ether. Plates were visualized under UV light and stained to detect terpyridine with $FeCl_2$ solution (saturated in 1 M HCl). Melting points were recorded on a Kofler block apparatus and are uncorrected.

Mass spectra were recorded by Dr. R. T. Aplin and staff on a V.G. Biotech Bio-Q spectrometer (electrospray ionization (ESI)). Values are quoted in *m*/*z* with only the molecular $[M]^+$ fragments of molecular ions and major peaks being quoted. Routine mass spectra were obtained on a Micromass platform APCI spectrometer. Samples were run in MeOH/CH_2Cl_2 (1:1). Routine proton magnetic resonance spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer. Higher field spectra were recorded at 500 MHz by Mrs. E. McGuinness on a Bruker AM500 spectrometer. Coupling constants (*J*) are recorded in hertz (Hz) to one decimal place.

Chemicals were purchased from Sigma Chemical Co. Ltd. and Aldrich Chemical Co. and were used without further purification. Solvents were obtained from BDH and Fisons at reagent grade and used without distillation.

Synthesis of 4′-Substituted-2,2′:6′,2″-terpyridines. 4′-Chloro-2,2′:6′,2″-terpyridine[21] and 4′-bromo-2,2′:6′,2″-terpyridine[22] were prepared by literature methods. 4′-*p*-Tolyl-2,2′:6′,2″-terpyridine and 4′-*p*-bromophenyl-2,2′:6′,2″-terpyridine were prepared by the method of Spahni and Calzaferri.[23]

4′-(*N*,*N*-Bis(2-hydroxyethyl)amino)-2,2′:6′,2″-terpyridine. $FeCl_2 \cdot 4H_2O$ (1.6 g, 8.1 mmol) and diethanolamine (23.6 g, 224 mmol, 60 equiv) were added to a solution of 4′-chloro-2,2′:6′,2″-terpyridine (1 g, 3.7 mmol) in 2-propanol (80 mL). The purple solution was refluxed for 60 h and then filtered through Celite. The solvent was evaporated in vacuo and the resulting viscous residue adjusted to pH 3 by dropwise addition of a solution of 2 M hydrochloric acid. The acidic solution was treated with $[NH_4][PF_6]$ (2 g), and $[Fe((HOCH_2CH_2)_2Nterpy)_2]$-$[PF_6]_2$ precipitated as a purple solid which was collected by centrifugation, washed with 0.1 M $[NH_4][PF_6]$ and ether, and then air-dried. The solid was then dissolved in a solution of acetonitrile/1M NaOH (20 mL) and the solution so obtained stirred under O_2 until the purple color had disappeared (ca. 20 h). The brown reaction mixture was filtered through Celite and the solid residue washed with acetonitrile. The combined

filtrate and extracts were then concentrated in vacuo, and the white solid so obtained was collected by filtration and recrystallized from dichloromethane to afford white needles of 4′-(*N*,*N*-bis(2-hydroxyethyl)amino)-2,2′:6′,2″-terpyridine (352 mg, 31%): mp 171−172 °C. δ_H (500 MHz, CD_3OD): 8.61 (dd, $^4J(6,4) = 1.4$, $^3J(6,5) = 4.5$, 2H, H−C(6), H−C(6″)); 8.52 (d, $^3J(3,4) = 8.0$, 2H, H−C(3), H−C(3″)); 7.93 (dt, $^4J(4,6) = 1.8$, $^3J(4,3) = {}^3J(4,5) = 7.7$, 2H, H−C(4), H−C(4″)); 7.68 (s, 2H, H−C(3′), H−C(5′)); 7.42 (ddd, $^4J(5,3) = 1.2$, $^3J(5,6) = 4.9$, $^3J(5,4) = 7.5$, 2H, H−C(5), H−C(5″)); 3.85 (t, $^3J_{vic} = 5.9$, 4H, H_2−COH); 3.75 (t, $^3J_{vic} = 5.9$, 4H, H_2−CNterpy). δ_C (50.3 MHz, CD_3OD): 156.92 (C(4′)); 155.66 (C(2)/C(2′), C(6′)/C(2″)); 155.25 (C(2)/C(2′), C(6′)/C(2″)); 148.55 (C(6)/C(6″)); 137.49 (C(4)/C(4″)); 123.49 (C(5)/C(5″)); 121.94 (C(3)/C(3″)); 103.91 (C(3′)/C(5′)); 58.72 (H_2*C*OH); 52.86 (H_2*C*Nterpy). *m*/*z* (+ESI): 377 (MH^+). Anal. ($C_{19}H_{20}N_4O_2$) C, 67.6; H, 6.0; N, 16.4%.

Isolation and Characterization of the Two Alkoxy Side Products. When 2-propanol is replaced by ethanol/methanol (1:1, v/v, 80 mL) in the previous experiment, the dichloromethane filtrate remaining from the recrystallization when evaporated in vacuo gave a solid residue which on chromatography on an alumina preparative plate using petroleum ether (bp 40−60 °C)/EtOAc (7:1) as eluant gave three bands identified as 4′-chloro-2,2′:6′,2″-terpyridine, 4′-methoxy-2,2′:6′,2″-terpyridine, and 4′-ethoxy-2,2′:6′,2″-terpyridine.

4′-Methoxy-2,2′:6′,2″-terpyridine: mp 56−57 °C. Anal. ($C_{16}H_{13}N_3O$) C, 72.8; H, 5.0; N, 15.8. TLC (alumina, petroleum ether (40−60 °C)/EtOAc, 3:1): $R_f = 0.53$. δ_H (200 MHz, $CDCl_3$): 8.71 (d, $^3J(6,5) = 4.7$, 2H, H−C(6), H−C(6″)); 8.64 (d, $^3J(3,4) = 8.0$, 2H, H−C(3), H−C(3″)); 8.04 (s, 2H, H−C(3′), H−C(5′)); 7.87 (dt, $^4J(4,6) = 1.8$, $^3J(4,3) = {}^3J(4,5) = 7.8$, 2H, H−C(4), H−C(4″)); 7.34 (ddd, $^4J(5,3) = 1.1$, $^3J(5,6) = 4.8$, $^3J(5,4) = 7.5$, 2H, H−C(5), H−C(5″)); 4.05 (s, 3H, H_3−COterpy). δ_C (50.3 MHz, $CDCl_3$): 168.15 (C(4′)); 157.35 (C(2)/C(2′), C(6′)/C(2″)); 156.33 (C(2)/C(2′), C(6′)/C(2″)); 149.28 (C(6)/C(6″)); 137.04 (C(4)/C(4″)); 124.03 (C(5)/C(5″)); 121.54 (C(3)/C(3″)); 107.05 (C(3′)/C(5′)); 55.55 (H_3*C*Oterpy). *m*/*z* (+ESI): 264 (MH^+). This compound can be prepared in excellent yield by methanolysis of 4′-chloro-2,2′:6′,2″-terpyridine activated by $FeCl_2 \cdot 4H_2O$ or by reaction of sodium methoxide with 4′-chloro-2,2′:6′,2″-terpyridine without activation.

4′-Ethoxy-2,2′:6′,2″-terpyridine: mp 85−86 °C. Anal. ($C_{17}H_{15}N_3O$) C, 73.3; H, 5.5; N, 15.1. TLC (alumina, petroleum ether (40−60 °C)/EtOAc, 3:1): $R_f = 0.59$. δ_H (200 MHz, $CDCl_3$): 8.70 (d, $^3J(6,5) = 4.1$, 2H, H−C(6), H−C(6″)); 8.63 (d, $^3J(3,4) = 8.1$, 2H, H−C(3), H−C(3″)); 8.02 (s, 2H, H−C(3′), H−C(5′)); 7.86 (*dt*, $^4J(4,6) = 1.8$, $^3J(4,3) = {}^3J(4,5) = 7.3$, 2H, H−C(4), H−C(4″)); 7.34 (ddd, $^4J(5,3) = 1.2$, $^3J(5,6) = 4.8$, $^3J(5,4) = 7.5$, 2H, H−C(5), H−C(5″)); 4.32 (q, 2H, $^3J_{vic} = 7.1$, 2H, H_2−COterpy); 1.50 (t, $^3J_{vic} = 6.9$, H_3−CCH_2). *m*/*z* (+ESI): 278 (MH^+). This compound can be prepared in excellent yield by ethanolysis of 4′-chloro-2,2′:6′,2″-terpyridine activated by $FeCl_2 \cdot 4H_2O$ or by reaction of sodium ethoxide with 4′-chloro-2,2′:6′,2″-terpyridine without activation.

4′-Amino-2,2′:6′,2″-terpyridine. A solution of 4′-azido-2,2′:6′,6″-terpyridine (0.453 g; 1.65 mmol, prepared from 4′-hydrazino-2,2′:6′,6″-terpyridine, vide infra, by treatment with nitrous acid) in dichloromethane (5.0 mL) and methanol (5.0 mL) was saturated with hydrogen sulfide at 0 °C and the solution kept at room temperature for 4h by which time TLC showed no azide to remain. The solution was degassed with argon to remove hydrogen sulfide and then evaporated to dryness. The residue was treated with sulfuric acid (2M, 3.0 mL) and the aqueous mixture filtered and washed with dichloromethane to remove elemental sulfur. The solution was basified by the dropwise addition of sodium hydroxide (50%) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried and evaporated to give the title compound as a pale yellow solid (0.398 g, 97%). Crystallization from light petroleum−dichloromethane gave pale-yellow brown needles: mp 228−230 °C. Anal. ($C_{19}H_{20}N_4O_2$) C, 72.5; H, 4.7; N, 22.2. ν_{max}(Nujol)/cm^{-1}: 3414, 3344, and 3226 (NH_2). δ_H(200 MHz, $CDCl_3$): 4.36 (2H, br s, NH_2); 7.32 (2H, ddd, *J* 1.2, 4.8, and 6.0, terpy H5/5″); 7.75 (2H, s, terpyH3′/5′); 7.84 (2H, td, $J = 1.8$, 7.7, terpy H4/4″); 8.60 (2H, d, $J = 8.0$, terpy H3/3″); 8.66−8.69 (2H, m, terpy H6/6″). *m*/*z* (+ESI): 249 (MH^+).

4′-Fluoro-2,2′:6′,2″-terpyridine. A suspension of 4′-amino-2,2′:6′,6″-terpyridine (0.185 g, 0.75 mmol) in fluoroboric acid (50%; 1.0 mL) was stirred and treated dropwise at 0 °C with a cold solution of sodium nitrite (0.10 g, 1.4 mmol) in water (0.5 mL). Most of the solid dissolved to give a bright-yellow solution. The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stirred for a further 1 h. The mixture was cooled again to 0 °C and basified with aqueous sodium hydroxide (50%). A yellow solid was precipitated, and the mixture was extracted with chloroform (3 × 10 mL). The organic extracts were dried and evaporated and the residual brown gum flash chromatographed over alumina eluting with light petroleum−ether (10:1). The fractions containing terpyridine were combined and evaporated and the material was further purified by preparative TLC on alumina to remove 4′-chloroterpyridine formed as a byproduct (7%). Elution six times with light petroleum−ether (50:1) afforded the title compound as a colorless solid (0.043 g, 23%). Crystallization from light petroleum−dichloromethane gave colorless needles: mp 114−115 °C. Anal. ($C_{15}H_{10}FN_3$) C, 71.4; H, 4.0; N, 16.5. ν_{max}(Nujol)/cm^{-1}: 1597, 1581, 1468, 1403, 1173, 931, and 790. δ_H(200 MHz, $CDCl_3$): 7.36 (2H, ddd, $J = 0.9$, 4.8, and 7.4 Hz, terpy H5/5″); 7.86 (2H, td, $J = 1.8$, 7.7, terpy H4/4″); 8.19 (2H, d, $J_{HF} = 9.7$, terpy H3′/5′); 8.61 (2H, d, $J = 8.6$, terpy H3/3″); 8.70 (2H, d, *J* 4.5, terpy H6/6″). δ_C(50 MHz, $CDCl_3$): 108.5 (d, $J_{CF} = 19.5$, C3′/5′); 121.3 and 124.3 (C3/3″ and C5/5″); 136.9 (C4/4″); 149.2 (C6/6″); 155.0 (C2/2″); 158.6 (d, J_{CF} 7.3, C2′/6′); 170.77 (d, $J_{CF} = 259.8$, C4′); δ_F(235 MHz, $CDCl_3$) −102.0; *m*/*z* ($APCI^+$) 252(MH^+).

4′-(*N*-2-Hydroxyethyl-*N*-methylamino)-2,2′:6′,2″-terpyridine. A solution of 4′-chloro-2,2′:6′,2″-terpyridine (1.61 g, 6 mmol) in 20 mL of dichloromethane was added to a solution of $FeCl_2 \cdot 4H_2O$ (1.35 g, 6.8 mmol) in 2-propanol (100 mL). An excess of *N*-methylethanolamine (20 mL) was then added to the purple solution. The mixture was heated to reflux for 22 h under an atmosphere of argon and with stirring. It was then concentrated by removal of solvent in vacuo to leave a viscous purple oil. Addition of $[NH_4][PF_6]$ (1.66 g, 10 mmol) in methanol (10 mL) followed by diethyl ether (50 mL) gave a purple gum $[HOCH_2CH_2N(Me)terpy)_2Fe][PF_6]$ which was worked up as for 4′-(*N*,*N*-bis(2-hydroxyethyl)amino)-2,2′:6′,2″-terpyridine (see above). The title product was recrystallized from acetone/petroleum ether (bp 40−60 °C) to give 4′-(*N*-2-hydroxyethyl-*N*-methylamino)-2,2′:6′,2″-terpyridine (1.44 g, 78%): mp 148−150 °C. Anal. ($C_{18}H_{18}N_4O$) C, 70.8; H, 5.6; N, 18.4. ν_{max} (KBr)/cm^{-1}: 3219(m,br), 2880−2820(m,br), 1609(m), 1592(s), 1567(s), 1459(m), 1412(m), 1228(w), 1055(s), 1006(m) 851(w), 790(s). δ_H (200 MHz, $CDCl_3$): 8.65 (d, $^3J(6,5) = 4.5$ Hz, 2H, H−C(6)/H−C(6″)); 8.60 (d, $^3J(3,4) = 8.5$, 2H, H−C(3)/H−C(3″)); 7.83 (dt, $^3J(4,5) = 7.77$, $^4J(4,6) = 1.8$, 2H, H−C(4)/H−C(4″)); 7.78 (s, 2H, H−C(3′)/H−C(5′)); 7.30 (ddd, $^3J(5,4) = 7.4$, $^3J(5,6) = 4.8$, $^4J(5,3) = 1.1$, 2H, H−C(5)/H−C(5″)); 3.9 (t, $^3J_{vic} = 5.8$, 2H, terpyNMe·CH_2CH_2OH); 3.7 (t, $^3J_{vic} = 5.8$, 2H, terpyNMe·CH_2CH_2OH); 3.2 (s, 3H, terpyNCH_3·CH_2CH_2OH).

4′-(1-Methylhydrazino)-2,2′:6′,2″-terpyridine. 4′-Chloro-2,2′:6′,2″-terpyridine (148 mg, 0.55 mmol) was dissolved in *iso*butanol (3 mL) with warming. Excess methylhydrazine (0.8 mL) was added. The mixture was then heated to reflux, with stirring, for 28 h. On cooling white needles crystallized out of solution. The solid was collected by filtration and washed with diethyl ether to yield analytically pure 4′-(1-methylhydrazino)-2,2′:6′,2″-terpyridine (132 mg, 86%): mp 217−219 °C. Anal. ($C_{16}H_{15}N_5$) C, 69.5; H, 5.1; N, 25.2. ν_{max}(KBr)/cm^{-1}: 3323(m), 3100−2700(w,br), 2359(w,br), 1562(s), 1582(s), 1470(s), 1408-(s), 1093(m), 1005(m), 826(w). δ_H (200 MHz, $CDCl_3$): 8.70 (d, $^3J(6,5) = 4.7$, 2H, H−C(6)/H−C(6″)); 8.64 (d, $^3J(3,4) = 7.98$, 2H, H−C(3)/H−C(3″)); 7.98 (s, 2H, H−C(3′)/H−C(5′)); 7.85 (dt, $^3J(4,5) = 7.56$, $^4J(4,6) = 1.77$, 2H, H−C(4)/H−C(4″)); 7.33 (ddd, $^3J(5,4) = 7.4$, $^3J(5,6) = 4.8$, $^4J(5,3) = 1.2$, 2H, H−C(5)/H−C(5″));

4.06 (s, 2H, terpyNMe.NH_2); 3.40 (s, 3H, terpyNCH_3.NH_2). *m/z* (+ESI) = 278 (100%, $[MH]^+$).

4′-Hydrazino-2,2′:6′,2″-terpyridine. 4′-Chloro-2,2′:6′,2″-terpyridine (600 mg, 2.2 mmol) was dissolved in isobutanol (12 mL) with warming. Excess anhydrous hydrazine (4 mL) was added. The mixture was then heated to reflux under argon, with stirring, for 30 h. On cooling white crystals precipitated out of solution. These were collected by filtration and washed with a small volume of water to yield analytically pure 4′-hydrazino-2,2′:6′,2″-terpyridine (439 mg, 74%): mp 195−197 °C. Anal. ($C_{15}H_{13}N_5$) C, 68.4; H, 4.6; N, 26.6. ν_{max}(KBr)/cm^{-1}: 3329(w,br), 3277(s), 3181(m), 1644(w), 1605(m), 1585(s), 1565(s), 1466(m), 1403(m), 1229(w), 1069(w), 996(m), 864(m). δ_H (200 MHz, $CDCl_3$): 8.69 (d, $^3J(6,5) = 4.6$, 2H, H−C(6)/H−C(6″)); 8.63 (d, $^3J(3,4) = 8.0$, 2H, H−C(3)/H−C(3″)); 7.87 (s, 2H, H−C(3′)/H−C(5′)); 7.86 (dt, $^3J(4,5) = {}^3J(4,3) = 7.7$, $^4J(4,6) = 1.6$, 2H, H−C(4)/H−C(4″)); 7.34 (ddd, $^3J(5,4) = 7.4$, $^3J(5,6) = 4.9$, $^4J(5,3) = 1.3$, 2H, H−C(5)/H−C(5″)); 5.81 (s, br, 1H, terpyN*H*.NH_2); 3.83 (s, br, 2H, terpyNH·NH_2). *m/z* (+ESI) = 264.26 (100%, $[MH]^+$).

Adipoyl-Linked Bis[4′-hydrazino-2,2′:6′,2″-terpyridine]. Adipoyl chloride (175μL, 1.2 mmol) was added to a solution of 4′-hydrazinoterpyridine (178 mg, 2.2 mmol) in tetrahydrofuran (10 mL). Immediately the solution turned yellow, and a yellow solid became suspended in solution. After the mixture was stirred at room temperature for 2 h, dichloromethane (100 mL) and saturated aqueous sodium bicarbonate solution (100 mL) were added. The yellow solid turned white and collected at the solvent interface. Isolation of this solid by filtration and washing with diethyl ether yielded the title product (387 mg, 55%). A sample for elemental analysis was prepared as the diacetate salt: mp >200 °C. Anal. ($C_{36}H_{32}N_{10}O_2$·$C_4H_8O_4$) C, 63.8; H, 5.2. ν_{max}(KBr)/cm^{-1}: 3283−3012(s, br), 2928−2800(w,br), 1655(s), 1585(s), 1566(s), 1467(s), 1405(s), 989(m), 866(w), 793(s), 745(m), 733(m). δ_H (500 MHz, DMSO-d_6) 9.99 and 8.80 (2s, br, 2 × 2H, [terpyN*H*.N*H*COCH_2CH_2]$_2$); 8.68 (d, $^3J(6,5) = 4.75$, 4H, H−C(6)/H−C(6″)); 8.57 (d, $^3J(3,4) = 7.91$, 4H, H−C(3)/H−C(3″)); 7.95 (dt, $^3J(4,5) = {}^3J(4,3) = 7.76$, $^4J(4,6) = 1.80$, 4H, H−C(4),/H−C(4″)); 7.80 (s, 4H, H−C(3′)/H−C(5′)); 7.44 (dd, $^3J(5,4) = 7.48$, $^3J(5,6) = 4.73$, 4H, H−C(5)/H−C(5″)); 2.34 (m, br, [terpyNH.NHCOCH_2CH_2]$_2$); 1.74 (m, br, [terpyNH.NHCOCH_2CH_2]$_2$). δ_C (125.7 MHz; DMSO) 172.07 ([terpyNH·NH*C*OCH_2CH_2]$_2$); 157.05 (C(4′)); 155.76 (C(2′)/C(6′) or C(2)/C(2″)); 155.34 (C(2′)/C(6′) or C(2)/C(2″)); 149.21 (C(6)/C(6″)); 137.22 (C(4)/C(4″)); 124.14 (C(5)/C(5″)); 120.79 (C(3)/C(3″)); 103.67 (C(3′)/C(5′)); 33.27 ([terpyNH·NHCO*C*H_2CH_2]$_2$); 24.96 (terpyNH·NHCOCH_2*C*H_2]$_2$). *m/z* (+ESI) = 637(<10%, $[MH]^+$), 319 (100%, $[M + 2H]^{2+}$).

Adipoyl-Linked Bis[4′-(1-methylhydrazino)-2,2′:6′,2″-terpyridine]. Adipoyl chloride (430 mL, 3 mmol) was added to a solution of 4′-(1-methylhydrazino)terpyridine (1.49 g, 5.4 mmol) in tetrahydrofuran (20 mL). The white solid at the solvent interface after addition of sodium bicarbonate was collected by filtration and washed with diethyl ether to give the required product (90 mg, 50%): mp > 200 °C. Anal. ($C_{38}H_{36}N_{10}O_2$·$2H_2O$) C, 64.7; H, 5.5; N, 20.0. ν_{max}(KBr)/cm^{-1}: 3291(s,br), 3064(w,br), 2900−2800(m,br), 1657(s), 1585(s), 1564(s), 1511(s), 1467(s), 1283(m), 1111(m), 1007(m), 854(m), 791(s), 731(m); δ_H (500 MHz, DMSO-d_6): 10.52 (s, 2H, [terpyNMe.N*H*COCH_2CH_2]$_2$); 8.70 (d, $^3J(6,5) = 4.69$ Hz, 4H, H−C(6)/H−C(6″)); 8.60 (d, ^3J (3,4) = 7.92, 4H, H−C(3)/H−C(3″)); 7.97 (dt, ^3J (4,5) = $^3J(4,3) = 7.72$, $^4J(4,6) = 1.79$, 4H, H−C(4)/H−C(4″)); 7.81 (s, 4H, H−C(3′)/H−C(5′)); 7.45 (ddd, $^3J(5,4) = 7.4$, ^3J (5,6) = 4.80, $^4J(5,3) = 1.16$, 4H, H−C(5)/H−C(5″)); 3.30 (s, 6H, [terpyNCH_3·NHCOCH_2CH_2]$_2$); 2.33 (s, br, 4H [terpyNMe·NHCO*C*H_2CH_2]$_2$); 1.75 (s, br, 4H [terpyNMe·NHCOCH_2*C*H_2]$_2$). δ_C (125.7 MHz, DMSO)* 171.41 (C, [terpyNMe·NH*C*OCH_2CH_2]$_2$); 156.75 (C(4′)); 155.70 (C(2′)/C(6′) or C(2)/C(2″)); 155.47 (C(2′)/C(6′) or C(2)/C(2″)); 149.24 (C(6)/C(6″)); 137.31 (C(4)/C(4″)); 124.26 (C(5)/C(5″)); 120.94 (C(3)/C(3″)); 103.43 (C(3′)/C(5′)); 33.17 ([terpyNMe·NHCO*C*H_2CH_2]$_2$); 24.80 ([terpyNMe·NHCOCH_2*C*H_2]$_2$). *m/z*(+ESI) = 665 (<10%, $[MH]^+$), 333 (100%, $[M + 2H]^{2+}$). *A signal due to the primary C atom [terpyNCH_3·NHCOCH_2CH_2]$_2$ was not observed, probably due to it being obscured by the DMSO solvent resonance.

4′-(*N*-2-Hydroxyethylamino)-2,2′:6′,2″-terpyridine. A solution of 4′-chloro-2,2′:6′,2″-terpyridine (137 mg, 0.5 mmol) in dichloromethane (2 mL) was added to a solution of $FeCl_2$·$4H_2O$ (112 mg, 0.6 mmol) in 2-propanol (10 mL). An excess of ethanolamine (1 mL) was then added to the purple solution. The mixture was heated to reflux for 19 h under an atmosphere of argon and with stirring. Workup proceeded as in the preparation of 4′-(*N*-2-hydroxyethyl-*N*-methylamino)-2,2′:6′,2″-terpyridine (see above). The resulting powdery solid recrystallized from acetone/petroleum ether (bp 40−60 °C) to give 4′-(*N*-2-hydroxyethylamino)-2,2′:6′,2″-terpyridine (90 mg, 60%): mp 145−147 °C. Anal. ($C_{17}H_{16}N_4O$) C, 69.9; H, 5.2; N, 18.9. ν_{max}(KBr)/cm^{-1}: 3424(m), 3200(m,br), 2935(w), 1608(m), 1588(s), 1565(m), 1480(m), 1465(m), 1400(w), 1083(m), 989(m). δ_H (200 MHz, $CDCl_3$): 8.67 (d, $^3J(6,5) = 4.8$, 2H, H−C(6)/H−C(6″)); 8.61 (d, $^3J(3,4) = 7.89$, 2H, H−C(3)/H−C(3″)); 7.85 (dt, $^3J(4,3) = {}^3J(4,5) = 7.7$, $^4J(4,6) = 1.8$, 2H, H−C(4)/H−C(4″)); 7.71 (s, 2H, H−C(3′)/H−C(5′)); 7.32 (ddd, $^3J(5,4) = 7.6$, $^3J(5,6) = 4.8$, $^4J(5,3) = 1.3$, 2H, H−C(5)/H−C(5″)); 4.92 (s, 1H, terpyN*H*·CH_2CH_2OH); 3.92 (t, $^3J_{vic} = 5.0$, 2H, terpyNH·CH_2CH_2OH); 3.56 (q, $^3J_{vic} = 5.4$, 2H, terpyNH·CH_2CH_2OH). *m/z* (+ESI) = 293.26 (100%, $[MH]^+$).

4′-(*N*-2-Chloroethylamino)-2,2′:6′,2″-terpyridine. A solution of 4′-(*N*-2-hydroxyethylamino)-2,2′:6′,2″-terpyridine (880 mg, 3 mmol) in thionyl chloride (8 mL) was kept at room temperature for 20 h. Excess thionyl chloride was removed in vacuo to leave a green glassy solid. This solid was suspended in dichloromethane (40 mL) and washed with saturated aqueous sodium bicarbonate solution (2 × 25 mL). The aqueous phase was separated and reextracted with further dichloromethane. The organic extracts were then combined and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent in vacuo gave a solid which was purified by elution through a column of activity IV neutral alumina. Initially 100% dichloromethane and then dichloromethane: methanol (50:1) were used as eluants. Impurities remained on the baseline. Removal of solvent in vacuo from the collected fractions yielded the 4′-(*N*-2-chloroethylamino)-2,2′:6′,2″-terpyridine (797 mg, 85%). Recrystallization was achieved from diethyl ether/petroleum ether (bp 40−60 °C): mp 135−137 °C. Anal. ($C_{17}H_{15}N_4Cl$) C, 66.0; H, 4.5; N, 18.2. ν_{max}(KBr)/cm^{-1}: 3256(m,br), 3134−2954(w,br) 1582(s), 1565(s), 1460(m), 1443(m), 1226(m), 985(m), 793(s). δ_H (500 MHz, $CDCl_3$): 8.68 (d, $^3J(6,5) = 4.7$ Hz, 2H, H−C(6)/H−C(6″)); 8.62 (d, $^3J(3,4) = 7.97$, 2H, H−C(3)/H−C(3″)); 7.84 (dt, $^3J(4,3) = {}^3J(4,5) = 7.7$, $^4J(4,6) = 1.79$, 2H, H−C(4)/H−C(4″)); 7.73 (s, 2H, H−C(3′)/H−C(5′)); 7.32 (ddd, $^3J(5,4) = 7.4$, $^3J(5,6) = 4.8$, $^4J(5,3) = 1.1$, 2H, H−C(5)/H−C(5″)); 4.79 (t, $^3J_{vic} = 5.2$, 1H, terpyN*H*·CH_2CH_2Cl); 3.83−3.74 (m, 4H, terpyNH·CH_2CH_2Cl). *m/z*(+ESI) = 311.18 (100%, $[MH]^+$).

4′-Aziridino-2,2′:6′,2″-terpyridine. Sodium hydride (16 mg, 0.6 mmol) was washed with petroleum ether (bp 40−60 °C) and suspended in tetrahydrofuran (1 mL). *tert*-Butanol (38 mL, 0.4 mmol) was added and the mixture stirred for 5 min until effervescence had subsided. After this time a solution of 4′-(*N*-2-chloroethylamino)-2,2′:6′,2″-terpyridine (64 mg, 0.2 mmol) in THF (1 mL) was introduced and reaction allowed to proceed at room temperature; 18 h later all solvent was removed in vacuo to yield a yellow solid. This solid was suspended in water (5 mL) and the solution neutralized by the addition of a few drops of acetic acid. Organic material was extracted into dichloromethane (5 mL), separated, and dried over anhydrous magnesium sulfate. Filtration and evaporation to dryness yielded 4′-aziridino-2,2′:6′,2″-terpyridine as a white crystalline solid (54 mg, 95%). Recrystallization was achieved from acetonitrile: mp 149−151 °C. Anal. ($C_{17}H_{14}N_4$) C, 74.3; H, 4.7; N, 20.4. ν_{max}(KBr)/cm^{-1}: 3050−2000(s,br), 1800−1700(w,br), 1587(s), 1565(s), 1469(m), 1404(s), 1284(m), 1160(m), 991(m), 880(m), 788(s). δ_H (200 MHz, $CDCl_3$): 8.73 (d, $^3J(6,5) = 4.1$, 2H, H−C(6)/H−C(6″)); 8.64 (d, $^3J(3,4) = 7.89$, 2H, H−C(3)/H−C(3″)); 8.12 (s, 2H, H−C(3′)/H−C(5′)); 7.87 (t, $^3J(4,3) = {}^3J(4,5) = 7.7$, 2H, H−C(4)/H−C(4″));

7.36 (ddd, $^3J(5,4) = 7.4$, $^3J(5,6) = 4.8$, $^4J(5,3) = 1.3$, 2H, H−C(5)/H−C(5″)); 2.35 (s, 4H, aziridine CH_2's). δ_C (125.7 MHz, $CDCl_3$): 164.38 (C(4′)); 156.41 (C(2)/C(2″), C(2′)/C(6′)); 149.26 (C(6)/C(6″)); 137.07 (C(4)/C(4″)); 123.98 (C(5)/C(5″)); 121.57 (C(3)/C(3″)); 113.68 (C(3′)/C(5′)); 27.66 (aziridine C(1)/C(2)). m/z(+ESI) = 275 (100%, $[MH]^+$).

Reaction has also been carried out using potassium *tert*-butoxide directly; 1.5 mL of a solution of potassium *tert*-butoxide (1.5 g) in THF (10 mL) was added to a solution of 4′-(*N*-2-chloroethylamino)-2,2′:6′,2″-terpyridine (64 mg, 0.2 mmol) in THF (1 mL). The mixture was stirred at room temperature for 21 h. Workup analogous to the above yielded 4′-aziridino-2,2′:6′,2″-terpyridine (50 mg, 89%) with an NMR spectrum identical to the above.

(2,2′:6′,2″-Terpyridine)platinum(II) and (4′-Substituted-2,2′:6,2″-terpyridine)platinum(II) Complexes. These were prepared in general (except see below) from 2,2′:6′,2″-terpyridine or the appropriate 4′-substituted-2,2′:6′,2″-terpyridine by the method of Lowe and Vilaivan.[24] The preparation of ammine complexes was not described, however, and these are presented below.

(4′-Chloro-2,2′:6′,2″-terpyridine)platinum(II) Ammine Tetrafluoroborate. Cyclooctadienylplatinum(II) diiodide (0.292 g, 0.53 mmol) was treated with a solution of silver tetrafluoroborate (0214 g; 1.1 mmol) in acetone (1.0 mL). The mixture was centrifuged to remove precipitated silver iodide and the supernatant solution added to a suspension of 4′-chloro-2,2:6′,2″-terpyridine (0.133 g, 0.5 mmol) in dichloromethane (0.5 mL). The mixture turned yellow, and a yellow solid was precipitated. This was collected by centrifugation and washed with acetone:ether (1:1) (1.0 mL), ether (1.0 mL), and finally ether saturated with ammonia (2 × 1.0 mL) to form the ammine complex. This afforded the title compound as a pale-yellow solid (0.110 g, 34%) which was dried in vacuo.

(4′-(4-Bromophenyl)-2,2′:6′,2″-terpyridine)platinum-(II) Ammine Tetrafluoroborate. Cyclooctadienylplatinum-(II) diiodide (0.292 g, 0.53 mmol) was treated with a solution of silver tetrafluoroborate (0214 g, 1.1 mmol) in acetone (1.0 mL). The mixture was centrifuged to remove precipitated silver iodide and the supernatant solution added to a suspension of 4′-(4-bromophenyl)-2,2:6′,2″-terpyridine (0.194 g; 0.5 mmol) in dichloromethane (0.5 mL). The mixture turned orange, and a gum was precipitated. On rubbing this triturated to give a yellow solid which was collected by centrifugation and washed with acetone (1.0 mL), acetone:ether (1:1) (1.0 mL), ether (1.0 mL), and finally ether saturated with ammonia (2 × 1.0 mL) to form the ammine complex. This afforded the title compound as a yellow solid (0.265 g, 68%) which was dried in vacuo.

(2,2′:6′,2″-Terpyridine)platinum(II) Ammine Nitrate. Chloroplatinum 2,2′:6′,2″-terpyridine chloride dihydrate (53.5 mg, 0.1 mmol) was dissolved in water (1 mL) by extensive shaking and sonication over a period of 1 h. To this was added a solution of silver nitrate (35.7 mg, 0.21 mmol) in water (0.5 mL), causing immediate precipitation of a red solid which became lighter in color after a few minutes of sonication to remove supernatant entrained in the precipitate. The supernatant was isolated by centrifugation, aqueous ammonia (880 g·L^{-1}, 0.5 mL) added and the solution immediately added to acetone/ether (3:1, v/v, 20 mL). After the suspension stood at 4 °C for 15 min, the product was isolated by centrifugation, washed with ether, and dried in vacuo to leave an orange powdery solid (27 mg, 47.5%). m/z (ES+, from 1:1 MeOH: H_2O): 222.4 (100%, M^{2+}), 445.5 (55%, $[Pt(terpy)OH]^+$), 459.5 (20%, $[Pt(terpy)OMe]^+$). δ_H (500 MHz, D_2O): 8.60 ($2H^a$, d, J = 5.6 Hz, H6,6″^{a}); 8.42 ($3H^a + 2H^b$, m, H4′^{a} + H4,4″^{a} + H6,6″^{b}); 8.30 ($4H^a + 3H^b$, m, H3′,5′^{a} + H3,3″^{a} + H4′^{b} + H4,4″^{b}); 8.09 ($2H^b$, d, J = 7.9 Hz, H3,3″^{b}); 8.01 ($2H^b$, d, J = 8.1 Hz, H3′,5′^{b}); 7.83 ($2H^a$, m, H5,5″^{a}); 7.77 ($2H^b$, m, H5,5″^{b}); 3.75 (s, dioxane reference). Multiplets assigned from COSY cross-peaks: H4,4″^{a} (8.40 ppm); H4′^{a} (8.44 ppm); H6,6″^{b} (8.43 ppm); H3,3″^{a} (8.33 ppm); H3′,5′^{a} (8.29 ppm); H4,4″^{b} (8.29 ppm); H4′^{b} (8.24 ppm). Ratio of species a:b (calculated from integrals) = 3:2 (immediate acquisition); 5:4 (1 h); 1:1 (24 h). Species b was identified as the aqua complex by comparison with the spectrum of an authentic sample, and species a is the ammine complex. Assuming that equilibrium has been reached after 24 h, $K \approx 10^4$.

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