Platinum(II) Complexes of Nitroimidazoles: Synthesis, Characterisation, and *X*-Ray Crystal Structures† of *cis*-Dichlorobis[1-(2'-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole)platinum(II) and *trans*-Dichlorobis-[1-(2'-hydroxy-3'-methoxypropyl)-2-nitroimidazole]platinum(II)

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A range of complexes of the type $[PtL_2X_2]$ (where L is a substituted 5-nitroimidazole, and X_2 is a dihalide or a dicarboxylate) has been prepared and characterised by a variety of methods, including ^{195}Pt n.m.r. spectroscopy. These 5-nitroimidazole complexes had a *cis* stereochemistry as exemplified by the *X*-ray crystal-structure determination of *cis*-dichlorobis[1-(2'-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole)platinum(II) [orthorhombic crystals: a = 8.643(1), b = 24.052(3), c = 9.119(1) Å, Z = 4, space group *Pcan*]. In addition, a number of analogous complexes of 2- and 4-nitroimidazoles were prepared. The 2-nitroimidazoles appeared to form the thermodynamically favoured *trans* complexes, rather than the kinetically favoured *cis* products. This was verified for *trans*-dichlorobis[1-(2'-hydroxy-3'-methoxypropyl)-2-nitroimidazole]platinum(II) [monoclinic crystals: a = 8.134(1), b = 13.014(1), c = 11.323(2) Å, β = 91.469(9)°, Z = 2, space group $P2_1/a$]. This complex showed an unusual loss of planarity between the nitro-group and the imidazole ring, giving a dihedral angle of 45.6°. The geometry of the 4-nitroimidazole complexes was not determined. Co-ordination of the nitroimidazole ligand to Pt^{II} lowered the wavelength of the π–π^* electronic absorption band, and reduced the polarographic reduction potential by *ca.* 0.15—0.2 V.

Nitroimidazoles are widely used as chemotherapeutic agents, particularly in the field of bacterial infections.[1] They have also been proposed as radiosensitisers,[2] *i.e.* compounds that enhance the effect of radiation damage preferentially in hypoxic tumour cells. The effectiveness of nitroimidazoles as radiosensitisers has been correlated with their electron affinity,[3] the most electron affinic molecules exhibiting the highest radiosensitisation. Complexes of platinum, another electron affinic centre, have also been shown to exhibit radiosensitisation to a lesser extent.[4] We have investigated whether the co-ordination of nitroimidazoles to platinum(II) increases their electron affinity. These platinum complexes may be more effective radiosensitisers and, by analogy to *cis*-$[Pt(NH_3)_2Cl_2]$,[5] may also have intrinsic anti-tumour activity, and associated ability to bind to DNA, itself a target for radiation damage.[6]

Previous work on metal–nitroimidazole complexes is limited to two brief reports: a copper(II) complex, containing tetrakis[1-(2'-hydroxyethyl)-2-methyl-5-nitroimidazole]copper,[7] and *trans*-dichlorotetrakis(1-methyl-5-nitroimidazole)rhodium(III).[8]

Several platinum(II) complexes with other imidazole (Him) derivatives have been reported.[9] These include *cis*- and *trans*-$[Pt(Him)_2X_2]$ and $[Pt(1Me\text{-}im)_2X_2]$, where X = halide and 1Me-im = 1-methylimidazole; *cis*-$[Pt(1Me\text{-}im)_2(C_2O_4)]$, and the tetrakis complexes $[Pt(Him)_4]^{2+}$ and $[Pt(1Me\text{-}im)_4]^{2+}$. In preliminary papers we have reported the synthesis of *cis*-$[Pt(L^6)_2Cl_2]$ [**1g**; L^6 = 1-(2'-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole)],[10–12] its ability to sensitise cells in culture to radiation,[10] and its conversion to the *trans* isomer, (**1h**).[11] Subsequently two other groups have reported the synthesis of platinum(II)–nitroimidazole complexes.[13]

We report here the synthesis of a wide range of neutral platinum(II) complexes containing 5-nitroimidazoles, together with halides or a dicarboxylate, as ligands (Table 1). In addition 2- and 4-nitro-imidazole complexes of Pt^{II} have been prepared (Table 2) and their properties compared to those of the 5-nitroimidazole complexes.

Results and Discussion

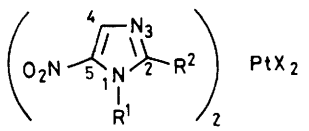
The reactions of $K_2[PtCl_4]$ with 5-nitroimidazoles at 50 °C were rapid and gave good yields of complexes of formula $[PtL_2X_2]$ (X = halide, L = substituted 5-nitroimidazole) (Table 1). These complexes were neutral, and had low water solubilities. Reactions with 2- and 4-nitroimidazoles, on the other hand, proceeded more slowly and were therefore carried out at higher temperatures, *ca.* 95 °C.

Initially, attempts were made to prepare a bis(2-nitroimidazole) complex with the ligand L^{17} [1-(2'-hydroxy-3'-methoxypropyl)-2-nitroimidazole (misonidazole)] at the lower reaction temperature (*ca.* 50 °C) used for the 5-nitroimidazole analogues. These were unsuccessful. The course of the reaction was followed by differential pulse polarography. At the start of the reaction a single reduction peak due to free misonidazole (at −0.41 V) was observed. This diminished in intensity, to *ca.* half height over a 24-h period, and gave rise to a new peak at −0.27 V due to $[Pt(L^{17})Cl_3]^-$ (**3a**), which was subsequently isolated as a K^+ salt and further characterised (see Experimental section). Evidently the incorporation of a second ligand into the complex does not proceed readily under these conditions.

Since the '*trans* effect' of nitrogen-donor ligands is expected to be greater than that of a halide,[14] the kinetically favoured

† *Supplementary data available* (No. SUP 56141, 8 pp.): H-atom co-ordinates for (**3c**), thermal parameters and least-squares planes data for (**1k**) and (**3c**). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1985, Issue 1, pp. xvii—xix. Structure factors are available from the editorial office.

Table 1. Characterisation of 5-nitroimidazole Pt^{II} complexes, $[PtL_2X_2]$

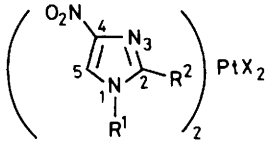


L

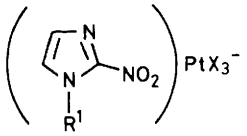
Complex	L	Generic name of ligand	R^1	R^2	X_2	M.p.[a]/ °C	Yield/ %	Geometry	Empirical formula	Elemental analysis (%); calc. (found) C	H	N	X	S
(**1a**)	L^1		CH_3	H	Cl_2	320—330 (d)	100	*cis*	$C_8H_{10}Cl_2N_6O_4Pt$	18.5 (18.1)	1.9 (1.7)	16.2 (16.2)	13.7 (13.7)	
(**1b**)	L^2	Dimetridazole	CH_3	CH_3	Cl_2	174—176	83	*cis*	$C_{10}H_{14}Cl_2N_6O_4Pt$	21.9 (21.5)	2.6 (2.7)	15.3 (14.7)	13.0 (13.2)	
(**1c**)	L^2	Dimetridazole	CH_3	CH_3	Cl_2	276—277 (d)	94	*trans*	$C_{10}H_{14}Cl_2N_6O_4Pt$	21.9 (21.9)	2.6 (2.5)	15.3 (15.3)		
(**1d**)	L^3		CH_3	CH_2OH	Cl_2	110	94	*cis*	$C_{10}H_{14}Cl_2N_6O_6Pt$	20.7 (20.6)	2.4 (2.5)	14.5 (14.6)	12.2 (12.0)	
(**1e**)[b]	L^4		CH_2CO_2H	CH_3	Cl_2	223—225	75	*cis*	$C_{12}H_{14}Cl_2N_6O_8Pt$	21.1 (21.1)	2.8 (2.5)	12.3 (12.3)	10.4 (10.8)	
(**1f**)	L^5	Ronidazole	CH_3	$CH_2OC(O)NH_2$	Cl_2	207	81	*cis*	$C_{12}H_{16}Cl_2N_8O_8Pt$	21.6 (21.5)	2.4 (2.5)	16.8 (17.2)	10.4 (10.4)	
(**1g**)	L^6	Metronidazole	CH_2CH_2OH	CH_3	Cl_2	178—181	90	*cis*	$C_{12}H_{18}Cl_2N_6O_6Pt$	23.7 (23.7)	3.0 (3.1)	13.8 (14.0)	11.7 (11.6)	
(**1h**)	L^6	Metronidazole	CH_2CH_2OH	CH_3	Cl_2	257 (d)	71	*trans*	$C_{12}H_{18}Cl_2N_6O_6Pt$	23.7 (23.4)	3.0 (2.8)	13.8 (13.7)	11.7 (11.5)	
(**1i**)	L^6	Metronidazole	CH_2CH_2OH	CH_3	Br_2	193—195	95	*cis*	$C_{12}H_{18}Br_2N_6O_6Pt$	20.7 (20.6)	2.6 (2.5)	12.0 (11.9)	22.9 (22.6)	
(**1j**)	L^6	Metronidazole	CH_2CH_2OH	CH_3	I_2	161—163	72	*cis*	$C_{12}H_{18}I_2N_6O_6Pt$	18.1 (17.8)	2.3 (2.4)	10.6 (10.7)	32.1 (32.2)	
(**1k**)	L^7		CH_2CH_2OH	CH_2OH	Cl_2	187—189	82	*cis*	$C_{12}H_{18}Cl_2N_6O_8Pt$	22.5 (22.4)	2.8 (3.0)	13.1 (13.0)	11.1 (11.9)	
(**1l**)	L^8	Bamnidazole	$CH_2CH_2OC(O)NH_2$	CH_3	Cl_2	130	100	*cis*	$C_{14}H_{20}Cl_2N_8O_8Pt$	24.2 (23.9)	2.9 (2.9)	16.1 (16.2)	10.2 (10.2)	
(**1m**)	L^9	Ornidazole	$CH_2CH(OH)CH_2Cl$	CH_3	Cl_2	148—149	91	*cis*	$C_{14}H_{20}Cl_4N_6O_6Pt$	23.8 (23.9)	2.9 (2.9)	11.9 (12.0)	20.1 (19.8)	
(**1n**)	L^{10}	Ipronidazole	CH_3	$CH(CH_3)_2$	Cl_2	220 (d)	64	*cis*	$C_{14}H_{22}Cl_2N_6O_4Pt$	27.8 (27.1)	3.6 (3.6)	13.9 (13.5)	11.8 (11.9)	
(**1o**)	L^{11}	Secnidazole	$CH_2CH(OH)CH_3$	CH_3	Cl_2	120—130	90	*cis*	$C_{14}H_{22}Cl_2N_6O_6Pt$	26.4 (26.1)	3.5 (3.6)	13.2 (12.9)	11.1 (10.9)	
(**1p**)	L^{12}	Tinidazole	$CH_2CH_2S(O)_2C_2H_5$	CH_3	Cl_2	145—147	88	*cis*	$C_{16}H_{26}Cl_2N_6O_8PtS_2$	25.3 (25.6)	3.4 (3.6)	11.1 (11.0)	9.3 (9.4)	8.4 (8.5)
(**1q**)[c]	L^6	Metronidazole	CH_2CH_2OH	CH_3	etmal[d]	223—225		*cis*	$C_{17}H_{24}N_6O_{10}Pt$	29.0 (28.7)	4.0 (3.8)	11.9 (11.8)		
(**1r**)	L^6	Metronidazole	CH_2CH_2OH	CH_3	cbda[e]	219—233 (d)		*cis*	$C_{18}H_{24}N_6O_{10}Pt$					
(**1s**)	L^{13}	Nimorazole	CH_2CH_2N⟨O⟩	H	Cl_2	184—186 (d)	70	*cis*	$C_{18}H_{28}Cl_2N_8O_6Pt$	30.1 (29.6)	3.9 (3.9)	15.6 (15.5)	9.9 (9.9)	
(**1t**)	L^{14}	Flunidazole	CH_2CH_2OH	*p*-C_6H_5F	Cl_2	203—205	86	*cis*	$C_{22}H_{20}Cl_2F_2N_6O_6Pt$	34.4 (34.5)	2.6 (2.7)	10.9 (10.9)		

[a] d = Decomposition. [b] (**1e**) Contains $2.5H_2O$ as determined by thermogravimetric analysis. [c] (**1q**) Contains $2H_2O$. [d] etmal = Ethylmalonate, ^-O_2C–$CH(C_2H_5)$–CO_2^-. [e] cbda = Cyclobutane-1,1-dicarboxylate, CH_2–CH_2–CH_2–$C(CO_2^-)_2$.

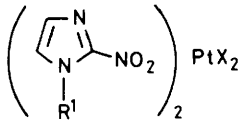
Table 2. Characterisation of 4- and 2-nitroimidazole Pt^{II} complexes



(2a), (2b)



(3a)



(3b), (3c)

Complex	L	R^1	R^2	X	M.p.[a]/°C	Yield/%	Geometry	Empirical formula	Elemental analysis (%); calc. (found) C	H	N	X
(2a)	L^{15}	CH_3	CH_3	Cl	260 (d)	80		$C_{10}H_{14}Cl_2N_6O_4Pt$	21.9 (21.7)	2.6 (2.5)	15.3 (15.5)	12.9 (12.9)
(2b)	L^{16}	CH_2CH_2OH	CH_3	Cl	225 (d)	76		$C_{12}H_{18}Cl_2N_6O_6Pt$	23.7 (23.4)	3.0 (2.9)	11.7 (11.8)	13.8 (13.7)
(3a)[b,c]	L^{17}	$CH_2CH(OH)$-$CH_2(OCH_3)$		Cl	175 (d)	43		$C_7H_{11}Cl_3KN_3O_4Pt$	15.5 (14.5)	2.0 (1.9)	7.8 (6.9)	19.7 (23.5)
(3b)	L^{18}	CH_3		Cl	240 (d)	52	*trans*	$C_8H_{10}Cl_2N_6O_4Pt$	18.5 (18.5)	1.9 (2.2)	16.2 (15.5)	13.7 (13.6)
(3c)[c]	L^{17}	$CH_2CH(OH)$-$CH_2(OCH_3)$		Cl	220—221	41	*trans*	$C_{14}H_{22}Cl_2N_6O_8Pt$	25.1 (24.9)	3.3 (3.3)	12.6 (12.3)	

[a] d = Decomposition. [b] (3a) Contains a small amount of unreacted $K_2[PtCl_4]$. [c] Generic name of ligand = misonidazole.

products from reactions of $[PtX_4]^{2-}$ with two equivalents of an imidazole ligand would be the *cis* isomers. Indeed, the crystal structure obtained here for complex (**1k**) (see later), and previously for (**1g**),[11] support the conclusion that for 5-nitroimidazoles the *cis* isomers do form preferentially.

The *cis* complex (**1g**) melts at 180 °C, resolidifies at *ca.* 185 °C, and finally melts with decomposition at 256 °C. The solid which formed at 185 °C was identified as the *trans* isomer (**1h**). Its structure has been confirmed by *X*-ray crystallography.[11] The isomerisation of (**1g**) to (**1h**) was also achieved by heating in ethanol solution. We have observed a similar isomerisation of the *cis* complex of dimetridazole, (**1b**) to (**1c**). These results suggest that the *trans* isomers are the thermodynamically more stable isomers, as might be expected with bulky nitroimidazole ligands.

The products obtained from reactions of $K_2[PtCl_4]$ with 2- and 4-nitroimidazoles formed more slowly. This may be due to the lower basicity of the co-ordinating nitrogen[15] and/or steric interactions between the nitro-group, which is now adjacent to the co-ordinating nitrogen and the metal co-ordination plane. Steric interactions may be so severe when a second ligand co-ordinates that the complex is forced to adopt a *trans* geometry. Indeed, the crystal structure of (**3c**) does show that it is the *trans* isomer. We have already noted[11] that 5-nitroimidazoles co-ordinated to Pt^{II} are tilted further away from the square plane around Pt than for 1-methylimidazole,[16] probably to avoid such steric interactions.

Attempts to establish co-ordination geometries using i.r., far-i.r., and Raman spectroscopy were unsuccessful. The absorbance bands were broad and unresolved in the region expected for Pt–Cl stretches (*ca.* 320—350 cm^{-1}).[9,17]

Description of the X-Ray Structures.—The *X*-ray crystal structures obtained for (**1k**) and (**3c**) (Figures 1 and 2 respectively) both show platinum(II) with square-planar geometry. The imidazole ligands are co-ordinated *via* the N^3 position. The Pt–N and Pt–Cl distances, Tables 3 and 4, are comparable with values for the related complexes (**1g**) and (**1h**)[11] and for 1-methylimidazole–platinum(II) complexes.[16] The dihedral angles between the co-ordination plane of platinum and the imidazole ring are 57.8° for (**1k**) and 55.8° for (**3c**). These are smaller than those observed for (**1g**) (74.2 and 69.6°) and (**1h**) (75.3°),[11] but are significantly larger than those for 1-methylimidazole complexes.[16]

Complex (**1k**) adopts a *cis* configuration (Figure 1) and resides on a crystallographic *C*2 site. The symmetry-related imidazole rings take the dihedral angle of 75°. The hydroxyethyl group is partially disordered and there are two sites each for O(3) and C(5) with 60% and 40% site occupancy factors. In either position, O(31) or O(32), O(3) can participate in intramolecular hydrogen bonding [O(31)···O(2), 2.95 Å and O(32)···O(4), 3.01 Å] which may account for this disorder. The O(4) atom of the hydroxymethyl group may form a weak intramolecular hydrogen bond to Cl [O(4)···Cl, 3.13 Å]. Intermolecular hydrogen bonding is also possible between O(31) and O(4), 2.80 Å, and O(32) and O(4), 2.83 Å.

Figure 2 shows a view of molecule (**3c**) looking down the normal to the plane Pt–N(1)–Cl(1). It has a crystallographic centre of inversion through the Pt atom and hence is the *trans* isomer. The closest intermolecular contact involving non-hydrogen atoms is between two nitro-group oxygens [O(1)···O(2), 2.813 Å]. It is interesting to note that the nitro-group and the imidazole ring are not co-planar, the dihedral angle being 45.6°. In contrast, planarity is observed for the eight-atom 5-nitroimidazole moieties of complexes (**1k**), (**1g**), and (**1h**),[11] and for the free ligand metronidazole.[18] An *X*-ray crystal structure of misonidazole has not been published, but 2-nitro-5-vinylimidazole was found by *X*-ray crystallography to be totally planar.[19] Therefore the observed loss of planarity in complex (**3c**) may be an indication that the co-ordinated ligand is strained.

N.M.R. Spectroscopy.—Proton and ^{195}Pt n.m.r. chemical shifts for the complexes are listed in Table 5. The ^1H n.m.r. resonances of the imidazole ring protons of the 2-, 4-, and 5-nitroimidazole complexes are shifted to high frequency with respect to their free ligand positions. For example, the chemical shifts of the free ligand 1,2-dimethyl-5-nitroimidazole (dimetridazole) in [$^2H_6$]acetone are 7.84 (C^4–H), 2.45 (C^2–CH_3), and 3.92 p.p.m. (N^1–CH_3) compared to 8.30, 3.01, and 4.04 p.p.m. respectively in complex (**1b**). The magnitudes of these shifts appear to depend on the distance from the platinum atom. Where coupling to platinum is resolved, values of *ca.* 25 Hz were

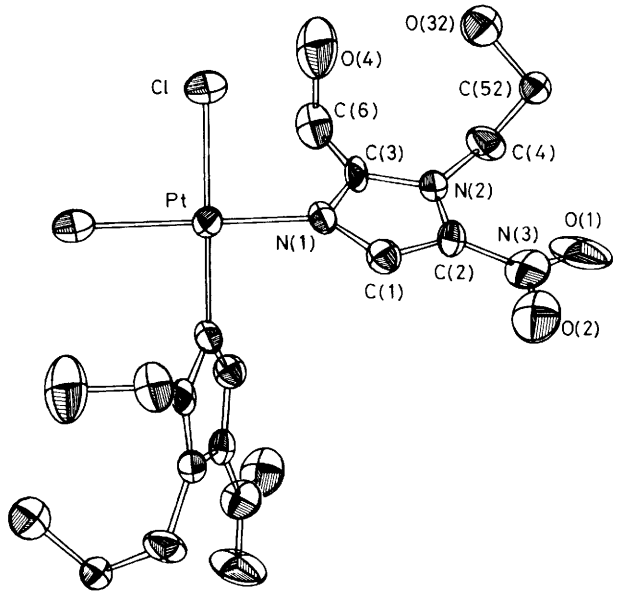


Figure 1. ORTEP *X*-ray crystal structure of *cis*-$[Pt(L^7)_2Cl_2]$ (**1k**)

resonances with those for analogous *cis*-(diammine)platinum(II) complexes.[24,25] On removal of the two chlorides from (**1g**) in H_2O a new resonance, at −1 590 p.p.m. (Table 6), was observed and assigned to the *cis*-diaqua complex. Addition of ethylmalonate (etmal) produced a new resonance 112 p.p.m. to higher frequency. This is a similar shift to that seen for the formation of *cis*-$[Pt(NH_3)_2(etmal)]$ from its diaqua analogue (104 p.p.m.[25]) and therefore was assigned to complex (**1q**). The structure of the related cyclobutane-1,1-dicarboxylate (cbda) complex, (**1r**), was consistent with the ions observed by field-desorption mass spectroscopy (M + Na = 702 for ^{195}Pt isotope).

Electronic Absorption Spectroscopy and Polarography.—The long-wavelength π–π* electronic absorption bands of all the ligands in this study shifted to shorter wavelength on co-ordination of the nitroimidazole to platinum. The peak potentials for the reduction of the nitroimidazole, as measured by differential pulse polarography, also showed a common trend and shifted to less negative values. These are listed in Table 7.

The lowering of the polarographic reduction potential of the nitroimidazole, by 0.15—0.24 V, on metal co-ordination may be important when these complexes are considered as potential

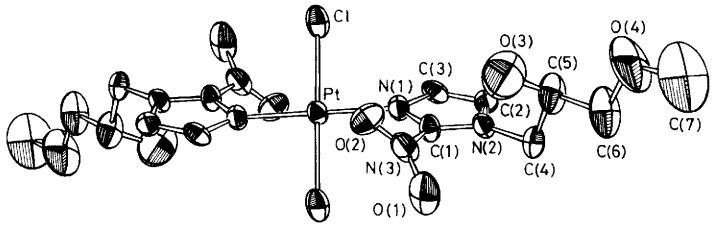


Figure 2. ORTEP *X*-ray crystal structure of *trans*-$[Pt(L^{17})_2Cl_2]$ (**3c**)

measured for the three-bond coupling constant, ^3J(Pt–H). These are comparable to those for imidazole and 1Me-im complexes.[9] The satellites were broadened at higher magnetic field strengths (4.7 and 9.4 T) due to relaxation *via* chemical shift anisotropy of ^{195}Pt.[20] This effect is proportional to the square of the applied field. For complex (**1g**) the C^4 imidazole ring proton was coupled to ^{195}Pt, with ^3J(Pt–H) = 25 Hz, and at 80 MHz the satellites had the expected peak height ratio of 1:4:1. However at 200 MHz the satellites broadened and this ratio became 1:30:1. At 400 MHz the satellites were hardly distinguishable from the baseline.

The ^{195}Pt chemical shifts for the dichlorobis(5-nitroimidazole)platinum(II) complexes were all within the range −2 049 to −2 075 p.p.m. (Table 5). ^{195}Pt N.m.r. shifts are very sensitive to small changes in the distribution of bonding electrons[21] and this suggests that the ring substituents do not greatly affect the N-donor properties of the imidazoles in this series and that the resultant Pt–N bonds are all of similar strength. The resonances were broad, with linewidths of *ca.* 200—300 Hz, attributable to unresolved coupling to the quadrupolar ^{14}N nuclei.[22] On changing the halide ligand from Cl^- to Br^- to I^-, in complexes (**1g**), (**1i**), and (**1j**), the successive shifts to lower frequency, *viz.* 330 and 889 p.p.m., are of the same order as those observed for a variety of other Pt^{II} complexes.[23] The 4- and 2-nitroimidazole complexes, (**2b**) and (**3b**), have ^{195}Pt chemical shifts of −1 850 and −1 856 respectively, reflecting the lower donor strength of these ligands giving rise to weaker Pt–N bonds.

The characterisation of the dicarboxylate complex (**1q**) was aided by comparison of the ^{195}Pt chemical shifts of n.m.r.

new radiosensitisers. It has been shown that more electron affinic nitroimidazoles are more effective radiosensitisers, and that there is a linear correlation between the one-electron reduction potential and the logarithm of the sensitiser concentration required to achieve a specific radiosensitising enhancement ratio.[3] The polarographic reduction process cannot be directly related to electron affinity, but for nitroimidazoles a correlation between polarographic peak potentials and electron affinity has been reported.[26] A recent pulse-radiolysis study by Butler *et al.*[27] of metronidazole and complex (**1g**) gave values for E_7^1 (one-electron, pH 7) of −476 and −370 mV respectively, confirming that there is an increase in electron affinity on metal co-ordination.

Experimental

$K_2[PtCl_4]$ was purchased from Johnson Matthey plc (Royston). Nitroimidazole ligands for the complexes (**1p**), (**1s**), and (**3a**)—(**3c**) were kindly supplied (to P. J. S.) by the following: L^{12}, Pfizers Ltd. (Sandwich, Kent); L^{13}, St. Thomas' Hospital (London); and L^{17} and L^{18} by Roche (Welwyn Garden City, Herts.). Those for complexes (**1f**) (L^5) and (**1t**) (L^{14}) were kindly supplied to May and Baker Ltd. by Merck, Sharp, and Dohme Ltd. (Hoddesdon, Herts.).

Instrumentation.—^1H N.m.r. spectra were recorded on JEOL FX200, Varian CFT20 and XL200, and Bruker WH400 spectrometers at ambient probe temperature and using ^2H_2O, [$^2H_6$]acetone, or [$^2H_7$]dimethylformamide as solvent with

Table 3. Bond distances (Å) and angles (°) with estimated standard deviations for complex (**1k**)

Pt–Cl	2.289(2)	N(3)–O(2)	1.194(9)
Pt–N(1)	2.006(6)	N(2)–C(4)	1.486(9)
N(1)–C(1)	1.357(9)	C(4)–C(51)	1.51(2)
C(1)–C(2)	1.330(10)	C(4)–C(52)	1.49(3)
C(2)–N(2)	1.392(9)	C(51)–O(31)	1.48(2)
N(2)–C(3)	1.342(9)	C(52)–O(32)	1.44(3)
C(3)–N(1)	1.357(8)	C(3)–C(6)	1.49(1)
C(2)–N(3)	1.394(11)	C(6)–O(4)	1.41(1)
N(3)–O(1)	1.238(9)		
Cl–Pt–Cl′	89.4(1)	O(1)–N(3)–O(2)	123.1(9)
Cl–Pt–N(1)	178.8(2)	C(2)–N(2)–C(3)	106.2(6)
Cl–Pt–N(1′)	90.2(2)	C(2)–N(2)–C(4)	128.7(6)
N(1)–Pt–N(1′)	90.3(3)	C(3)–N(2)–C(4)	124.7(7)
Pt–N(1)–C(1)	127.6(5)	N(2)–C(4)–C(51)	110.3(8)
Pt–N(1)–C(3)	127.9(5)	N(2)–C(4)–C(52)	110.8(10)
C(1)–N(1)–C(3)	104.5(6)	C(4)–C(51)–O(31)	108(1)
N(1)–C(1)–C(2)	111.6(7)	C(4)–C(52)–O(32)	106(2)
C(1)–C(2)–N(2)	106.5(6)	N(2)–C(3)–N(1)	111.2(7)
C(1)–C(2)–N(3)	129.0(7)	N(2)–C(3)–C(6)	124.4(6)
N(2)–C(2)–N(3)	124.4(7)	N(1)–C(3)–C(6)	124.3(7)
C(2)–N(3)–O(1)	115.4(7)	C(3)–C(6)–O(4)	111.7(7)
C(2)–N(3)–O(2)	121.5(9)		

Primed atoms are related to the corresponding unprimed atoms by a two-fold axis of rotation.

Table 4. Bond distances (Å) and angles (°) with estimated standard deviations for complex (**3c**)

Pt–Cl(1)	2.299(2)	Pt–N(1)	2.012(7)
N(1)–C(1)	1.34(1)	N(3)–O(1)	1.20(1)
C(1)–N(2)	1.31(1)	N(3)–O(2)	1.23(1)
N(2)–C(2)	1.38(1)	C(4)–C(5)	1.46(1)
C(2)–C(3)	1.34(1)	C(5)–O(3)	1.46(1)
C(3)–N(1)	1.35(1)	C(5)–C(6)	1.57(1)
C(1)–N(3)	1.46(1)	C(6)–O(4)	1.35(1)
N(2)–C(4)	1.48(1)	O(4)–C(7)	1.47(1)
Cl(1)–Pt–N(1)	91.7(2)	C(1)–N(2)–C(2)	105.7(7)
Pt–N(1)–C(1)	128.1(5)	C(1)–N(2)–C(4)	129.2(5)
Pt–N(1)–C(3)	126.1(6)	C(2)–N(2)–C(4)	125.1(6)
C(1)–N(1)–C(3)	104.9(6)	N(2)–C(2)–C(3)	107.2(6)
N(1)–C(1)–N(2)	112.5(6)	N(2)–C(4)–C(5)	108.6(5)
N(1)–C(1)–N(3)	122.1(6)	C(4)–C(5)–C(6)	109.5(7)
N(2)–C(1)–N(3)	125.2(6)	C(4)–C(5)–O(3)	109.7(8)
C(1)–N(3)–O(1)	119.4(3)	O(3)–C(5)–C(6)	105.0(9)
C(1)–N(3)–O(2)	114.5(3)	C(5)–C(6)–O(4)	111.4(7)
O(1)–N(3)–O(2)	126.1(3)	C(6)–O(4)–C(7)	115.5(5)
N(1)–C(3)–C(2)	109.7(6)		

3-trimethylsilyl[$^2H_4$]propionic acid or $SiMe_4$ as internal references.

^{195}Pt N.m.r. spectra were recorded on JEOL FX60 (12.8 MHz), Varian XL200, or Bruker WM200 (43 MHz) spectrometers using dimethylformamide (dmf) or H_2O as solvent and ^2H_2O as an external or internal field-frequency lock respectively. Chemical shifts were referenced with respect to $Na_2[PtCl_6]$ (1 mol dm^{-3}) in ^2H_2O.[28] Broad-band proton decoupling and 45° pulses were used. The pulse repetition rate was *ca.* 0.1 s. Fast pulsing was possible as ^{195}Pt relaxation rates were considerably shortened *via* ^{14}N quadrupolar relaxation.

Electronic absorption spectra were recorded on Perkin-Elmer 402 and 554, or Unicam SP8-500 spectrometers using phosphate buffer (0.1 mol dm^{-3}, pH 7.0) as solvent. Polarographic measurements were made using a Princeton E,G and G model 174A instrument operating in differential pulse mode coupled to an E,G and G model 303 dropping mercury electrode with a Ag–AgCl reference electrode (+20 mV relative to a saturated calomel electrode). Phosphate buffer (0.1 mol dm^{-3}, pH 7.0) was used as solvent.

Table 5. Proton and ^{195}Pt n.m.r. spectroscopy

	δ(^{1}H)[a]/p.p.m.				δ(^{195}Pt)[b]/
Complex	C^4–H	C^2–R^2	N^1–R^1	X	p.p.m.
(**1a**)	8.24 (s)	8.58 (s)	4.14 (s)		
(**1b**)	8.30 (s)	3.01 (s)	4.04 (s)		−2 060
(**1c**)	8.05 (s)	3.0 (s)	4.1 (s)		
(**1d**)	8.3 (s)	5.45 (s)	4.2 (s)		
(**1e**)	8.45 (s)	2.99 (s)	4.36 (s)		−2 074
(**1f**)	8.40 (s)	5.86 (s)	4.20 (s)		
(**1g**)	8.32 (s)	2.98 (s)	3.90 (t) 4.61(t)		−2 071
(**1h**)	8.10 (s)	3.07 (s)	3.97 (t) 4.68 (t)		−2 067
(**1i**)	8.43 (s)	3.04 (s)	3.90 (t) 4.61 (t)		−2 401
(**1j**)	8.52 (s)	3.06 (s)	3.93 (t) 4.64 (t)		−3 290
(**1k**)	8.40 (s)	5.43 (s)	3.95 (t) 4.79 (t)		
(**1l**)	8.34 (s)	3.05 (s)	4.44 (m) 4.80 (m)		
(**1m**)	8.32 (s)	3.0 (s)	3.75 (d) 4.25—4.9 (m)		
(**1n**)	8.41 (s)	4.98 (m) 1.56 (d)	4.13 (s)		
(**1o**)	8.3 (s)	2.95 (s)	1.25 (d) 4.1—4.7 (m)		
(**1p**)	8.34 (s)	2.96 (s)	1.32 (t) 3.24 (q) 3.78 (t) 4.97 (t)		−2 075
(**1q**)	8.32 (s)	2.94 (s)	3.88 (t) 4.52 (t)	1.09 (t) 2.67 (m)	−1 614
(**1r**)	8.3 (s)	2.9 (s)	3.88 (t) 4.58 (t)	1.9 (q) 2.9 (m)	
(**1s**)	8.03 (d)	8.76 (d)	2.50 (t) 2.82 (t) 3.58 (t) 4.71 (t)		−2 049
(**1t**)	7.4—8.0 (m)		3.80 (t) 4.50 (t)		
	C^5–H	C^2–R^2	N^1–R^1		
(**2a**)	8.55 (s)	3.06 (s)	3.96 (s)		
(**2b**)	8.2 (s)	2.85 (s)	3.95 (m) 4.6 (m)		−1 850
	C^4–H	C^5–H	N^1–R^1		
(**3a**)	7.39 (d)	7.53 (d)	3.36 (s) 4.12 (m) 4.46 (m) 4.74 (m)		
(**3b**)	7.61 (d)	7.67 (d)	4.18 (s)		−1 856
(**3c**)	7.50 (d)	7.64 (d)	3.26 (s) 4.04 (m) 4.48 (m) 4.68 (m)		

[a] All ^{1}H shifts in [$^2H_6$]acetone except: (**1a**) and (**2a**) in [$^2H_7$]dmf; and (**1q**) and (**1r**) in ^2H_2O, *ca.* pH 7.0. For labelling of groups see Tables 1 and 2. s = Singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. [b] All ^{195}Pt shifts in dmf except (**1e**) and (**1q**) in H_2O, *ca.* pH 7.0. ^{195}Pt shifts referenced to $Na_2[PtCl_6]$ (ref. 28).

Table 6. ^{195}Pt N.m.r. data for bis(metronidazole)platinum(II) and (diammine)platinum(II) complexes

Complex	Solvent	$\delta(^{195}Pt)^a$/p.p.m. L = NH_3[b]	L = metronidazole[c]
cis-$[PtL_2Cl_2]$	dmf	−2 223	−2 071
cis-$[PtL_2(H_2O)_2]^{2+}$	^2H_2O, pH* 4[d]	−1 590	−1 502
cis-$[PtL_2(etmal)]$	^2H_2O, pH* 7	−1 694	−1 614

[a] Shifts referenced to 1 mol dm^{-3} Na_2PtCl_6 in ^2H_2O (ref. 28). [b] From refs. 24 and 25. [c] Metronidazole = 1-(2′-hydroxyethyl)-2-methyl-5-nitroimidazole. [d] pH* = pH meter reading in ^2H_2O.

Table 7. Electronic absorption spectroscopy and polarography*

Complex	L	$\lambda_{max.}$/nm	E_p/V
(1a)	L^1	294	−0.24
(1b)	L^2	304 (318)	−0.34 (−0.53)
(1c)	L^2	307.5 (318)	−0.29 (−0.53)
(1d)	L^3	295.5	−0.24
(1e)	L^4	305 (318)	−0.32 (−0.52)
(1f)	L^5	292	−0.21
(1g)	L^6	304 (318)	−0.27 (−0.47)
(1h)	L^6	309.5 (318)	
(1i)	L^6	302 (318)	
(1j)	L^6	300 (318)	
(1k)	L^7	291 (310)	−0.22 (−0.45)
(1l)	L^8	304	−0.28
(1m)	L^9	305.5	−0.28
(1n)	L^{10}	308 (320)	−0.32 (−0.56)
(1o)	L^{11}	305.5	
(1p)	L^{12}	302 (315)	−0.37 (−0.52)
(1q)	L^6	303 (318)	
(1s)	L^{13}	291 (303)	
(1t)	L^{14}	314.5	−0.24
(2a)	L^{15}	297	−0.47
(2b)	L^{16}	294	−0.46
(3a)	L^{17}	313 (324)	−0.27 (−0.41)
(3b)	L^{18}	308 (323)	−0.25 (−0.45)
(3c)	L^{17}	310 (324)	

* All measured in phosphate buffer (0.1 mol dm^{-3}, pH 7.0); values for the free ligand are given in parentheses.

Preparation of the 5-Nitroimidazole Complexes.—(i) *cis*-$[PtL_2Cl_2]$ [L = L^1 (**1a**), L^2 (**1b**), L^3—L^6 (**1d**)—(**1g**), L^7—L^{12} (**1k**)—(**1p**), L^{13} (**1s**), *or* L^{14} (**1t**)]. Solid ligand (2 mmol) was added to a solution of $K_2[PtCl_4]$ (0.415 g, 1 mmol) in water (25 cm^3). The suspension was stirred at *ca.* 50 °C for 1 h. The resulting precipitate was filtered off, washed with ethanol–diethyl ether, followed by diethyl ether, and dried *in vacuo*. In certain cases, yields were improved by reducing the solvent volume prior to filtration. Some products were crystallised by slow evaporation of a acetone–water (1:1) solution.

(ii) *cis*-$[Pt(L^6)_2X_2]$ [X = Br (**1i**) *or* I (**1j**)]. The procedure was the same as (i) above except that initially a 20-fold excess of KBr or KI was added to the $K_2[PtCl_4]$ solution to produce $[PtBr_4]^{2-}$ and $[PtI_4]^{2-}$ respectively.

(iii) *cis*-$[Pt(L^6)_2X_2]$ (X_2 = etmal *or* cbda). A quantity (1 mmol) of complex (**1g**), (**1i**), or (**1j**) was added to a solution of $AgNO_3$ (2 mmol) in water (25 cm^3). The suspension was stirred at *ca.* 60 °C for 3 h resulting in a clear yellow solution and a precipitate of AgCl. The solution was filtered and the pH was adjusted to *ca.* 7 by addition of NaOH (*ca.* 2 mol dm^{-3}). A solution of the dicarboxylic acid (1 mmol) in water (10 cm^3), also neutralised by addition of NaOH, was then added. The volume of the solvent was reduced and the product was filtered off, washed with ethanol–diethyl ether, and then diethyl ether, and finally dried *in vacuo*.

(iv) *trans*-$[PtL_2Cl_2]$ [L = L^2 (**1c**) *or* L^6 (**1h**)]. A suspension of the corresponding *cis* complex (0.7 mmol) in ethanol (100 cm^3) was refluxed for 6 h. The solvent was removed under reduced pressure to yield a yellow solid. Crystallisation by slow evaporation of an acetone–water (1:1) mixture gave the *trans* complexes. Alternatively, the *cis* isomer (3 mmol) was heated for 5 min at 10 °C above its melting point and then cooled to room temperature. The resultant solid was recrystallised as above to give the *trans* complex.

Preparation of the 4-Nitroimidazole Complexes.—(v) $[PtL_2Cl_2]$ [L = L^{15} (**2a**) *or* L^{16} (**2b**)]. Complexes were prepared as for (i), but reactions were carried out by heating on a steam-bath for 8 h.

Preparation of the 2-Nitroimidazole Complexes.—(vi) $K[PtL^{17}Cl_3]$ (**3a**). Preparation was the same as for (i), but the reaction was carried out at 50 °C for 24 h. The resulting orange solution was lyophilised and the solid was recrystallised from acetone after adding excess diethyl ether to induce crystallisation.

(vii) *trans*-$[PtL_2Cl_2]$ [L = L^{18} (**3b**) *or* L^{17} (**3c**)]. Complexes were prepared as for (i), but reactions were carried out by heating on a steam-bath for 6 h.

Microanalyses, yields, and melting points for all complexes are given in Tables 1 and 2. N.m.r. data are given in Tables 5 and 6, and u.v. absorption maxima and polarographic reduction potentials in Table 7. Spectra and reduction potentials of complexes in aqueous solution were measured soon after dissolution to minimise hydrolysis.

X-*Ray Crystallography.*—Accurate cell dimensions were obtained from crystals of compounds (**1k**) and (**3c**) by measurement of 25 θ values on an Enraf-Nonius CAD-4 diffractomer, following preliminary examination of Weissenberg photographs. The intensity data were collected with Mo-K_α radiation for (**1k**) and Cu-K_α for (**3c**). A periodic check on the intensities of the standard reflections showed that no crystal deterioration occurred in either case during the data collection. Details of the crystals, data collection and structure refinement are given in Table 8.

The structures were solved by the heavy-atom method and difference electron-density synthesis. Isotropic full-matrix least-squares refinement of the non-hydrogen atoms followed by anisotropic refinement gave R values of 0.044 for (**1k**) and 0.060 for (**3c**). For (**1k**), only H(1) was located from a difference-Fourier map. The positions of all the other hydrogen atoms were generated at their ideal positions and their contributions included in the structure factor calculation. One common $U_{iso.}$ was included in the refinement of all hydrogen atoms.

The data reduction, absorption correction, and structure solutions were carried out on a PDP-11/34A computer using the SDP crystallographic program system.[29] All other calculations were performed on a CDC-7600 computer using programs SHELX-76,[30] XANADU,[31] ORTEP,[32] and PLUTO.[33] Part of the hydroxyethyl group of (**1k**) was disordered. The positions of the disordered atoms were refined with isotropic thermal parameters. The scattering factors for neutral atoms were taken from refs. 34 (H), 35 (Cl, O, N, C), and 36 (Pt), with those for the heavier elements modified for anomalous dispersion using $\Delta f'$ and $\Delta f''$ values from ref. 37.

Intramolecular bond distances and angles are given in Tables 3 and 4 for (**1k**) and (**3c**) respectively. Fractional atom co-ordinates for the non-hydrogen atoms (with estimated standard

Table 8. *X*-Ray crystallography; data collection and structure analysis

	cis-[Pt(L^7)$_2$Cl$_2$] (**1k**)	*trans*-[Pt(L^{17})$_2$Cl$_2$] (**3c**)
Formula	$C_{12}H_{18}Cl_2N_6O_8Pt$	$C_{14}H_{22}Cl_2N_6O_8Pt$
M	640.31	668.13
Crystal system	Orthorhombic	Monoclinic
Space group	*Pcan*	$P2_1/a$ (no. 14)
a/Å	8.643(1)	8.134(1)
b/Å	24.052(3)	13.014(1)
c/Å	9.119(1)	11.323(2)
β/°		91.469(9)
U/Å^3	1 895.7(8)	1 198.2
Z	4	2
D_c/g cm^{-3}	2.243	1.85
F(000)	1 232	647.9
λ/Å	0.7107 (Mo-K_α)	1.5418 (Cu-K_α)
μ/cm^{-1}	81.3 (Mo-K_α)	136.2 (Cu-K_α)
Crystal size/mm	0.25 × 0.03 × 0.25	0.46 × 0.05 × 0.18
Colour (shape)	Yellow (thin plate)	Yellow (needle)
Scan mode	ω–2θ (+h,+k,+l)	ω–2θ (+h,+k,l)
θ Range/°	1.5—28	1.5—70
No. of reflections	2 304	2 715
Unique reflections	2 281	2 545
Observed reflections	1 102, $I > 1.5\sigma(I)$	1 706, $I > 2.0\sigma(I)$
Weighting scheme	Unit	$w = 1/[\sigma^2(F_o) + 0.009(F_o)^2]$
Final R [$= \Sigma\|\Delta F\|/\Sigma\|F_o\|$]	0.038	0.054
R' {$= [\Sigma w\Delta F^2/\Sigma w\|F_o\|]$, where $\Delta F = \|F_o\| - \|F_c\|$}	0.054	0.057

Table 9. Positional parameters and their estimated standard deviations for *cis*-[Pt(L^7)$_2$Cl$_2$] (**1k**)

Atom	x	y	z
Pt	−0.012 45(8)	0.000	0.250
Cl	−0.200 7(5)	0.016 7(2)	0.318 3(6)
O(1)	0.517(2)	−0.064 8(7)	−0.090(2)
O(2)	0.559(2)	−0.144 3(6)	0.007(2)
O(31)	0.292(3)	−0.217(1)	−0.053(3)
O(32)	0.113(5)	−0.227(2)	0.056(5)
O(4)	−0.041(2)	−0.169 4(7)	0.300(2)
N(1)	0.151(1)	−0.055 1(5)	0.194(2)
N(2)	0.291(1)	−0.132 7(6)	0.179(2)
N(3)	0.483(2)	−0.103 0(6)	−0.005(2)
C(1)	0.264(2)	−0.048 8(7)	0.091(2)
C(2)	0.351(2)	−0.094 3(7)	0.080(2)
C(3)	0.169(1)	−0.108 0(6)	0.243(2)
C(4)	0.335(2)	−0.191 9(7)	0.200(2)
C(51)	0.242(3)	−0.229(1)	0.099(3)
C(52)	0.298(6)	−0.225(2)	0.067(6)
C(6)	0.072(2)	−0.133 8(8)	0.359(2)

Table 10. Positional parameters and their estimated standard deviations for *trans*-[Pt(L^{17})$_2$Cl$_2$] (**3c**)

Atom	x	y	z
Pt	0.5	0.5	0.0
Cl(1)	0.403 5(2)	0.364 1(1)	0.107 8(2)
N(1)	0.278 4(9)	0.521 6(5)	−0.079 1(7)
C(1)	0.180 9(8)	0.451 6(5)	−0.131 7(6)
N(2)	0.033 7(11)	0.487 9(4)	−0.157 8(7)
C(2)	0.035 6(8)	0.589 1(5)	−0.120 4(6)
C(3)	0.185 0(9)	0.607 4(5)	−0.072 9(6)
N(3)	0.240 9(4)	0.349 7(3)	−0.164 3(4)
O(1)	0.372 7(4)	0.341 8(3)	−0.208 5(4)
O(2)	0.146 8(4)	0.278 9(3)	−0.142 2(4)
C(4)	−0.106 7(4)	0.436 8(3)	−0.219 7(4)
C(5)	−0.092 1(12)	0.453 1(9)	−0.346 3(7)
O(3)	0.064 2(11)	0.411 1(8)	−0.385 5(7)
C(6)	−0.227 8(12)	0.389 2(9)	−0.414 6(8)
O(4)	−0.231 1(11)	0.411 3(8)	−0.531 4(6)
C(7)	−0.353 9(11)	0.356 0(8)	−0.602 4(6)

deviations) are given in Tables 9 and 10 for (**1k**) and (**3c**) respectively.

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