Synthesis and Characterization of Nitroimidazole Complexes of Platinum and Palladium and the Crystal and Molecular Structure of *trans*-Dichlorobis-(misonidazole)platinum(II)

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The synthesis and properties of some nitroimidazole complexes of platinum and palladium starting from the MCl_4^{2-} salts are described. Both 5-NO_2-imidazole and metronidazole give cis-*$[MCl_2L_2]$ complexes whereas* trans-*$[MCl_2L_2]$ is obtained for 2-NO_2-imidazole and misonidazole. The crystal structure of* trans-*dichlorobis(misonidazole)platinum(II) was determined by three-dimensional X-ray methods. The compound crystallized in space group $P2_1/c$ in discrete monomeric units with* a = *11.303(5),* b = *13.002(5) and* c = *8.125(3)* Å, *B = 91.39(3)°, Z = 2 and the observed and calculated densities are 1.83 and 1.859 respectively. The final full-matrix least-squares refinement gave values of R_1 = 0.037 and R_2 = 0.045 for 142 variables. The complex is square-planar with Pt–Cl and Pt–N distances of 2.294(3) and 2.016(9)* Å *respectively. The mean plane of the misonidazole ring is twisted 56° with respect to the $PtCl_2L_2$ square plane and the Cl–Pt–N angles are 89.4(3) and 90.6(3)°; the nitro group also lies out of the plane of the misonidazole ring. The closest nonbonded contact between non-hydrogen atoms in the unit cells is 2.80* Å *suggesting hydrogen bonding between the hydroxyl proton and the ether oxygen in the misonidazole side-chain,* i.e. *O–H···O. Aspects of the chemistry of these species in relation to their biological activity are discussed.*

Introduction

Platinum metal complexes are now firmly established as clinically useful antitumour agents [1]. A further relatively recent advance in this area is the demonstration that the original complex of this family, *cis*-$[PtCl_2(NH_3)_2]$, and some analogues act as radiosensitizers in both bacterial and mammalian cells [2]. Radiosensitization refers to the enhancement of radiation-induced damage by certain drugs, especially in hypoxic (oxygen-deficient) cells. This is critical because there are cases where tumour cure by radiotherapy is limited by the greater resistance of hypoxic cells, in comparison to normally oxygenated cells [3].

The classic radiosensitizers are the nitroheterocycles as exemplified by nitrofurans [4] and nitroimidazoles [5]; a general (but simplified) rationale being that the 'electron-affinic' nitro groups may interact with damage on DNA induced by radiation in a manner analogous to oxygen producing subsequently lethal hits [6]. The identification of DNA as the ultimate target of radiation damage naturally prompts the question as to how new species may be designed with potential radiosensitizing and DNA-binding properties. In this respect, the strong binding of platinum, in its complexes, to purine and pyrimidine bases suggested that platinum complexes of known radiosensitizers could have interesting biological properties. We have therefore synthesized and studied platinum-metal complexes of the nitroimidazoles and this paper reports on their characteri-

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TABLE I. Elemental Analyses for New Metal–Nitroimidazole Complexes.

Complex	%C	%H	%N
$PtCl_2$(2-NO_2 Imidazole)$_2$	14.35(14.64)	1.54(1.23)	18.09(17.07)
$PtCl_2$(5-NO_2 Imidazole)$_2$	14.55(14.64)	1.15(1.23)	17.93(17.07)
$PdCl_2$(Misonidazole)$_2$	29.08(29.00)	3.68(4.00)	14.45(14.00)
$PdCl_2$(Metronidazole)$_2$	27.59(27.21)	3.39(3.42)	16.07(15.83)

*Calculated in parentheses.

zation and the X-ray crystal structure determination of one of them, *trans*-dichlorobis(misonidazole)platinum(II).

Experimental

Potassium tetrachloroplatinate and sodium tetrachloropalladate were gracious gifts of Johnson-Matthey and Co. Ltd. Metronidazole (or Flagyl) (1,2′-hydroxyethyl-2-methyl-5-nitromidazole) was obtained commercially. Misonidazole (1-(2-nitro-1-imidazolyl)-3-methoxy-propanol) was a gift from Roche Products Ltd., England. The 2-NO_2 and 5-NO_2-imidazoles used were from Sigma. All were used as obtained without further purification.

Physical Methods

Infrared spectra were recorded as KBr discs and Nujol mulls on a Perkin-Elmer 467 instrument. Ultraviolet spectra were recorded on a Cary-17 spectrophotometer.

Preparation of the Complexes

The synthesis of the complexes is represented by that of *trans*-[$PtCl_2$(Misonidazole)$_2$]. For the palladium complexes the solvent used was MeOH. The elemental analyses for the other reported complexes are given in Table I. All complexes may be recrystallised from methanol–ether or acetone–ether.

trans-*[$PtCl_2$(Misonidazole)$_2$]*

To a solution of K_2PtCl_4 (0.0415 g; 0.1 mmol) in H_2O (1 ml) was added misonidazole (0.041 g; 0.2 mmol in CH_3OH (3 ml). The solution was stirred for 2 days and then evaporated to dryness to give a yellow solid which was recrystallised from MeOH–ether to give yellow crystals (0.03 g; 44%). *Anal.* Calcd. for $C_{14}H_{22}Cl_2N_6O_8Pt$: C, 25.16; H, 3.32; N, 12.58. Found: C, 24.87; H, 3.02; N, 12.00.

Solution of the Structure

The crystal data are given in Table III. A yellow crystal (0.03 × 0.05 × 0.18) was mounted in a Lindemann glass capillary. Precession and Weissenberg photographs were used to obtain approximate unit cell dimensions and to uniquely define the space group as $P2_1/c$ (systematic absences: 0k0, k = 2n + 1; h0l, l = 2n + 1). Accurate cell dimensions were determined by least-squares refinement of 18 accurately centred reflections (2θ = 27.5–33.0°; Mo-Kα = 0.70926 Å) from various regions of reciprocal space. Data were collected, at 292 K, using a Picker FACS-I four-circle diffractometer with a graphite monochromator and a scintillation detector with pulse height discrimination. The take-off angle was 3° and symmetrical θ–2θ scans (1° min^{-1}) of (1.6 + 0.692 tanθ)° were used. Stationary crystal, stationary counter background counts of 20% of the scan time were taken at each side of the scan. Measurement of three standards every 50 reflections showed slight oscillation in intensity (<±2%) which was corrected appropriately.

Intensities were measured for 1573 independent reflections ($2\theta < 45°$), of which 1064 were classed observed $I > 2\sigma.3(I)$. Lorentz, polarisation and absorption corrections have been made (transmission coefficients varied from 0.5–0.7).

The structure was solved by Patterson and Fourier methods. The data set was observed to be systematically weak (hkl, k + l = 2n + 1), which together with the value of $Z = 2$, derived from the crystal density, suggested that the Pt atom lay on a centre of symmetry. The Patterson map confirmed this inference and also revealed the position of the Cl atom. Subsequent difference Fourier syntheses gave rise to the remaining non-hydrogen atoms in the unit cell. Wherever possible, hydrogen atoms were included in structure factor calculations as fixed contributions in their calculated positions. Following further refinement a subsequent difference Fourier map based on low angle data ($2\theta < 30°$) did not clearly reveal the positions of the methoxy and hydroxyl hydrogen atoms. Block-diagonal least-squares refinement of the coordinates of all the atoms of the molecule with variable anisotropic temperature factors for non-hydrogen atoms and fixed isotropic temperature factors, for hydrogen atoms, proportional to those of their parent carbon atoms, gave final agreement factors of R_1 = 0.037 and R_2 = 0.045 for 142

TABLE II. Physical Properties of $[MX_2(Nitroimidazole)_2]$ Complexes.

M	X	Nitroimidazole	Configuration	Colour	M.p. (°C)	λ_{max} nm (logϵ)	ν(M–Cl) cm^{-1}
Pt	Cl	Misonidazole	*trans*	Yellow	108–110	310 (4.237)	340
Pt	Cl	2-NO_2 Imidazole	*trans*	Yellow	>200	–	325
Pt	Cl	5-NO_2 Imidazole	*cis*	Yellow	>200	–	325(broad) 310(sh)
Pd	Cl	Misonidazole	*trans*	Pale-Yellow	192–196	300 (4.512)	361
Pd	Cl	Metronidazole	*trans*	Cream	246–250	300 (4.538)	370
Pd	Br	Metronidazole	*trans*	Yellow	–	305	–

TABLE III. Crystal Data.

$C_{14}H_{22}Cl_2N_6O_8Pt$	Mol. wt. 668.32
Space group $P2_1/c$	μ = 62.10 cm^{-1}
a 11.303(5)	ρ_o[a] = 1.83
b 13.002(5)	ρ_c (Z = 2) 1.859
c 8.125(3)	Final R_1[b] = 0.037
β 91.39(3)	Final R_2[c] = 0.045
U 1193.71	

[a]Floatation in a CH_2Cl_2/CH_2I_2 mixture. [b]$R_1 = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$. [c]$R_2 = (\Sigma w(|F_o| - |F_c|)^2/\Sigma w(F_o)^2)^{1/2}$.

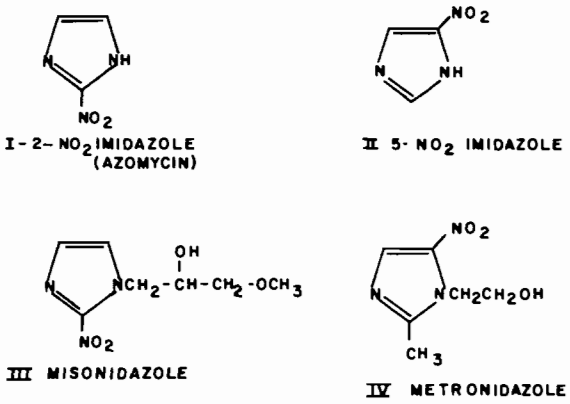

Fig. 1. Structures of nitroimidazoles and substituted derivatives.

variables. The major feature in the final difference map was a peak of [0.75(1) eÅ^3] close to Pt; the remainder of the map was essentially flat. Analysis of the data set as a function of F_o and sinθ suggested the employment of a weighting scheme of the form $w = 1/(\sigma F^2 + 0.0006\ F^2)$. Atomic scattering factors including anomalous dispersion were taken from International Tables for X-ray Crystallography (1974) [7]. Final positional parameters and B_{iso} temperature factors are given in Table IV*. The computer programs used here are those belonging to 'The PDP-8e crystal structure system' [8].

TABLE IV. Final Positional and Thermal Parameters[a] for $[PtCl_2(L)_2]$ (e.s.d.'s refer to the last digit printed).

Atom	X	Y	Z	B_{iso}
Pt	0.(0)	0.(0)	0.(0)	2.701(25)
Cl	0.1075(3)	−0.1360(2)	−0.0965(4)	4.01(17)
O(22)	0.208(1)	0.159(1)	0.128(1)	6.6(7)
O(23)	0.142(1)	0.222(1)	0.352(1)	6.8(8)
O(33)	0.385(1)	0.088(1)	0.432(2)	9.7(12)
O(35)	0.534(1)	0.087(1)	0.731(2)	10.4(12)
N(1)	0.079(1)	−0.018(1)	0.223(1)	2.8(5)
N(21)	0.164(1)	0.151(1)	0.262(1)	4.0(6)
N(3)	0.158(1)	0.012(1)	0.467(1)	2.7(4)
C(2)	0.133(1)	0.049(1)	0.317(1)	2.8(5)
C(31)	0.221(1)	0.063(1)	0.606(1)	3.4(7)
C(32)	0.355(1)	0.049(1)	0.592(2)	4.6(8)
C(34)	0.412(1)	0.108(1)	0.733(2)	6.6(12)
C(36)	0.601(2)	0.143(3)	0.849(3)	16.9(40)
C(4)	0.120(1)	−0.090(1)	0.465(1)	3.1(6)
C(5)	0.073(1)	−0.107(1)	0.318(1)	3.3(6)

[a]For anisotropic atoms, *i.e.*, all non-hydrogen atoms, $B_{iso} = 8\pi^2\ (U_{11}^2 + U_{22}^2 + U_{33}^2)^{1/2}$. For isotropic atoms, *i.e.*, all hydrogen atoms, $B_{iso} = 8\pi^2 U$.

Results and Discussion

For purposes of metal complexation, the nitroimidazoles of current interest may be divided into two structurally distinct groups, 2- and 5-nitroimidazoles. Adaptation of the basic structure, Fig. 1, has led to various compounds of clinical interest,

*Anisotropic thermal parameters, calculated hydrogen positions and listings of structure factors have been deposited.

TABLE V. Bond Parameters for *trans*-[$PtCl_2$(Misonidazole)$_2$].

Distances (Å)			
Pt–Cl	2.294(3)	N(3)–C(31)	1.47(1)
Pt–N(1)	2.016(9)	C(31)–C(32)	1.53(2)
		C(32)–O(33)	1.45(2)
N(1)–C(2)	1.30(1)	C(32)–C(34)	1.51(2)
C(2)–N(3)	1.33(1)	C(34)–O(35)	1.40(2)
N(3)–C(4)	1.40(2)	O(35)–C(36)	1.41(2)
C(4)–C(5)	1.32(2)		
C(5)–N(1)	1.39(1)		
C(2)–N(21)	1.46(2)		
N(21)–O(22)	1.20(1)		
N(21)–O(23)	1.21(1)		
Angles (°)			
Cl–Pt–Cl[a]	180	N(1)–C(2)–N(21)	122.9(10)
Cl–Pt–N(1)	89.4(3)	N(3)–C(2)–N(21)	124.1(10)
N(1)–Pt–N(1)[a]	180	C(2)–N(21)–O(22)	117.5(10)
		C(2)–N(21)–O(23)	117.3(10)
Pt–N(1)–C(2)	129.9(8)	O(22)–N(21)–O(23)	125.2(11)
Pt–N(1)–C(5)	124.6(7)	C(2)–N(3)–C(31)	129.0(10)
		C(4)–N(3)–C(31)	125.4(9)
N(1)–C(2)–N(3)	113.0(10)	N(3)–C(31)–C(32)	110.5(10)
C(2)–N(3)–C(4)	105.4(9)	C(31)–C(32)–C(34)	107.1(11)
N(3)–C(4)–C(5)	107.0(9)	C(31)–C(32)–O(33)	106.2(10)
C(4)–C(5)–N(1)	109.5(10)	O(33)–C(32)–C(34)	113.1(13)
C(5)–N(1)–C(2)	105.1(10)	C(32)–C(34)–O(35)	107.4(12)
		C(34)–O(35)–C(36)	113.7(14)

[a]These atoms are related to others in Table III by the symmetry transformation –x, –y, –z.

the two species most studied being misonidazole-(III) and metronidazole(IV) and these were therefore chosen for complexation. The characterizing data for the complexes obtained are given in Table II.

Whereas simple imidazole and 1-Me imidazole complexes are readily formed with palladium and platinum [9–11], the presence of the deactivating nitro group was expected to reduce the basicity of the nitrogen donor atom; this being more important for 2-NO_2 derivatives. That this is indeed the case is borne out by experimental conditions required for obtention of similar complexes. This deactivation is general, causing difficulties in isolation of desired isomers and precluding any general preparative procedures.

The *trans*-influence of imidazole is, like pyridine, considered to be less than that of chloride and so *cis*-isomers are expected to be formed from reaction with MCl_4^{2-} salts [9]. In the case of nitro-substituted derivatives, however, the isomer isolated is dependent on the ligand employed. Thus, with metronidazole and K_2PtCl_4 in H_2O the *cis*-isomer precipitates readily [12]. However, isomerization to the *trans* isomer is very facile and the structures of both isomers have recently been determined by researchers using a similar rationale to ours. The I.R. spectra of *cis*-[PtX_2(Metronidazole)$_2$], (X = Cl, I) have also been recently discussed [13]. We have found that use of H_2O/CH_3OH, (1:1), as solvent gives the *trans*-isomer directly. With misonidazole the spectrum of the product obtained (see discussion below) indicated that only the *trans*-isomer was obtained. To confirm this point an X-ray crystal structure determination was carried out.

Description of the Structure of trans-*[$PtCl_2$(Misonidazole)$_2$]*

The [$PtCl_2(L)_2$] complex exists as discrete monomeric units in which chlorine atoms and misonidazole ligands are mutually *trans* to one another. The molecular structure and labelling scheme is shown in Fig. 2. Bond parameters are given in Table V. The coordination environment around Pt is, as expected, 'square planar' as found in a number of other *trans*-[$PtCl_2(L)_2$] complexes (L = N-donor ligand) [10, 14–22]. The mean plane of the heterocyclic ring is twisted 56° with respect to the $PtCl_2$-

TABLE VI. Comparison of the Coordination Environments in Some *trans*-$[PtCl_2(L)_2]$ Complexes (L = N-donor ligand).

Ligand	Pt–Cl (Å)	Pt–N (Å)	Cl–P–N (degrees)
Cyclohexylamine [14]	2.302(2)	2.078(5)	85.4(1), 94.6(1)
Cycloheptylamine [15]	2.296(2)	2.065(9)	88.5(2), 91.5(2)
1-Methylcytosine-N3 [16]	2.288(5)	2.04(1)	89.1(5), 90.5(4)
	2.296(5)	2.03(1)	89.4(4), 91.4(4)
Pyrimidine [17]	2.296(2)	2.008(5)	89.8(2), 90.2(2)
Metronidazole [12]	2.294	2.003	89.1, 90.9

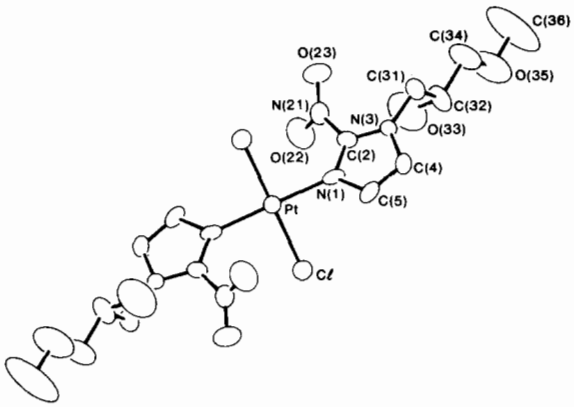

Fig. 2. ORTEP [30] diagram of *trans*-$[PtCl_2$(misonidazole)$_2]$, showing the atomic numbering scheme. Thermal ellipsoids enclose 50% of probability.

$(L)_2$ 'square plane'; the equivalent values in two related complexes are 41.7° for *cis*-$[PtCl_2(L)_2]$ [10] and 49.2° for *trans*-$[Pt(NH_3)_2(L)_2]$ [18] (L = N-methylimidazole). The Cl–Pt–N angles of 89.4(3)° and 90.6(3)° compare favourably with the equivalent angles found in some related complexes which have appeared in the literature recently (Table VI). The Pt–Cl distance of 2.294(3) Å and Pt–N(1) distance of 2.016(9) Å are also similar to values recently reported (Table V).

The misonidazole ring is planar within error and its bond parameters do not differ significantly from those found in *cis*-$[PtCl_2$(N-methylimidazole)$_2]$ and other related complexed imidazole rings [9]. The dimensions of the substituents attached to the heterocyclic ring are all normal, with the nitro group lying out of the plane of the ring.

The closest nonbonded contact between non-hydrogen atoms in the unit cells is 2.80 Å, *i.e.*, between O(33) and O(35) (at $\bar{x}$, $\bar{y}$, $\bar{z}$). This distance indicates that there is hydrogen bonding between the hydroxyl proton attached to O(33) and O(35), *i.e.*, O(33)–H$\cdots$O(35), although there is no observable increase in the O–H stretching frequency. As previously stated, the hydroxyl proton could not be located.

Spectroscopic Data

Definitive structural characterizations on both a *cis*- and *trans*-isomer in this series allows for configuration assignment for the remaining complexes. Both steric and electronic effects have been shown to influence complex formation of imidazoles with metal ions [23, 24] and these factors have to be considered in the present case. To assist in drawing a general picture we also prepared palladium derivatives of III and IV as well as platinum complexes of the parent ligands, 2-NO_2- and 5-NO_2-imidazole.

For palladium, the complex with misonidazole shows an I.R. spectrum superimposable on that of the platinum complex, allowing for frequency shifts, and is therefore also assigned the *trans*-configuration. The value of ν(Pd–Cl) is shifted to 361 cm^{-1} from the value of 340 cm^{-1} obtained for platinum, in accord with observations on simple imidazole systems (for *trans*-$[MCl_2(Im)_2]$, ν(Pd–Cl) = 373 cm^{-1}, ν(Pt–Cl) = 350 cm^{-1}) [9]. The same product is obtained using $[PdCl_2(PhCN)_2]$ or $[PdCl_2$-$(DMSO)_2]$ (reflux in MeOH, 3 hr). For $[PdCl_2$-(Metronidazole)$_2]$ two well defined bands appear at 370 and 321 cm^{-1}, which disappear upon bromide exchange. However, an identical product is obtained with $[PdCl_2(DMSO)_2]$, known to have the *trans* configuration [25]. This fact, together with the facile isomerisation of the platinum complex, which should be even faster for palladium, leads us to conclude that the product obtained is the *trans*-isomer, the nature of the band at 321 cm^{-1} being undefined at this stage.

The different configurations obtained could be due to a combination of steric and electronic effects or simply due to the greater water solubility of the misonidazole complexes, with isomerisation occurring readily in solution. To examine this factor, and as part of the general series of complexes, the reactions of the parent unsubstituted 2- and 5-NO_2 imidazoles were examined. Both ligands give yellow crystalline complexes, the features of their I.R.

spectra in the ν(Pt–Cl) region being similar to that described above; the *trans*- and *cis*-configurations are thus assigned respectively.

Thus, a general pattern emerges that reaction with $PtCl_4^{2-}$ salts gives *trans*-$[PtCl_2L_2]$ for 2-NO_2 imidazoles, the *cis*-isomer being obtained with the 5-NO_2 analogues. Misonidazole is less reactive than metronidazole due to the greater influence exerted by the NO_2 group in the neighbouring 2-position. This is further evidenced by the inability of misonidazole to displace completely labile donor groups in *cis*-$[PtCl_2L_2]$ (L = PhCN, DMSO, Et_2S). The products of these reactions are mixed species apparently containing only one misonidazole.

All complexes studied are moderate radiosensitizers with greatly reduced toxicity compared with the simple platinum–amine complexes [26]. It is of interest to note that the *cis*-configuration is not essential for radiosensitization; both *cis*- and *trans*-$[PtCl_2(NH_3)_2]$ are also active in this respect [27]. Electrochemical studies indicate modification of $E_{1/2}$ values upon complex formation and clearly this will have implications in the biological medium. For *cis*-$[PtCl_2(Metronidazole)_2]$ the reduction potential is increased by 0.2 V from –0.47 to –0.27 V [12]; the corresponding increase for *trans*-$[PtCl_2(Misonidazole)_2]$ is 0.15 V [28]. For *trans*-$[PdCl_2(Metronidazole)_2]$ however, only the wave corresponding to the free ligand is observed, indicating rapid dissociation in solution. The integrity of these complexes in aqueous solution must therefore be considered. In the series $[Ru(NH_3)_5B]^{2+}$ (B = NH_3, Im, py), the imidazole is labile towards acid hydrolysis in comparison to both the amine and pyridine ligands [29]. Relevant data are not available for platinum complexes but these aspects must be studied to obtain a better picture of the utility and potential of the complexes described.

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