

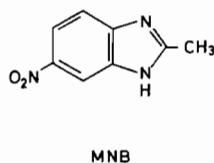
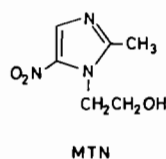
Platinum and Other Metal Complexes of 2-Methyl-5-nitrobenzimidazole and Metronidazole

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Received July 30, 1982

Metronidazole (MTN) (Flagyl) is one of the group
of clinically significant nitroheterocyclic radio-



sensitizing drugs. With the aim of selectively modifying the activity of such compounds we have prepared metal complexes of metronidazole and of some related nitroheterocycles.

Particular interest centres on the platinum complexes because of: (a) the relative stability of the

Pt-N bond in aqueous solution compared with those formed by many other metals, and (b) the effectiveness with which compounds of type *cis*-PtL₂X₂ bind to DNA, especially in tumour cells. We report here the preparation of some platinum and copper complexes of MTN, and of 2-methyl-5-nitrobenzimidazole (MNB). We also describe the results of a survey of the synthesis and some properties of complexes of MNB with a wider range of metal ions, for comparison with those of platinum and copper.

The compounds we have isolated are listed in Table I. The platinum chloride complexes were readily obtained by direct reaction of K₂PtCl₄ with the appropriate proportions of the nitroheterocycle in aqueous ethanol solution, and the corresponding iodides by an analogous reaction from PtI₄²⁻. An attempt to convert Pt(MNB)₂I₂ to the corresponding chloride by the commonly used route of addition of aqueous silver nitrate, removal of the precipitated silver iodide, and addition of potassium chloride was unsuccessful. The addition of the silver nitrate caused the precipitation of solids containing both platinum and silver, presumably because of the formation of Pt-imidazole ring-Ag bridged species, a problem which has previously been encountered [1] with other potentially bridging N-donor ligands.

With metronidazole as ligand the ethanol substituent on one of the ring nitrogens renders such a

TABLE I. Analytical Data for Some Complexes of 2-Methyl-5-nitrobenzimidazole (=L) and metronidazole (=MTN).

Complex	Colour	Found (%)			Calculated (%)		
		C	H	N	C	H	N
MnL ₂ Cl ₂	Pale yellow	40.02	2.89	17.33	40.13	2.92	17.51
MnL ₂ Br ₂	Pale yellow	34.09	2.59	15.01	33.76	2.46	14.77
FeL ₂ Cl ₂	Bright yellow	39.81	2.92	17.43	39.94	2.91	17.47
CoL ₂ Cl ₂	Deep blue	39.51	2.82	17.15	39.69	2.89	17.36
NiL ₂ Cl ₂ · H ₂ O	Yellow	38.24	2.91	16.46	38.28	3.21	16.74
NiL ₂ Br ₂	Blue	33.99	2.81	14.29	33.54	2.45	14.67
CuL ₂ Cl ₂ · 2H ₂ O	Apple green	36.47	3.46	15.75	36.32	3.46	16.01
CuL ₂ Cl ₂	Blue green	39.10	2.85	17.08	39.32	2.89	17.19
CuL ₂ Br ₂	Olive green	33.08	2.32	14.33	33.31	2.42	14.55
CuL ₂ (NO ₃) ₂	Lilac	35.40	2.55	20.49	35.45	2.59	20.68
ZnL ₂ Cl ₂	White	39.08	2.82	16.93	39.16	2.86	17.13
PtL ₂ Cl ₂	Pale yellow	30.64	2.37	13.64	30.97	2.26	13.55
PtL ₂ I ₂	Bright yellow	23.95	1.74	10.50	23.90	1.74	10.46
Cu(MTN) ₂ Cl ₂	Turquoise	30.24	4.00	17.20	30.23	3.80	17.62
Cu(MTN) ₂ Br ₂	Green	26.56	3.35	14.81	25.48	3.21	14.86
Pt(MTN) ₂ Cl ₂	Yellow	23.85	2.98	13.62	23.75	2.92	13.53
Pt(MTN) ₂ I ₂	Bright yellow	18.32	2.27	10.39	18.21	2.27	10.60

TABLE II. Diffuse Reflectance Spectral Band Energies (cm^{-1}).

$\text{Fe}(\text{MNB})_2\text{Cl}_2$	6150
$\text{Co}(\text{MNB})_2\text{Cl}_2$	5710, 6850, 8550, 15 400, 17 100 sh, 20 600sh
$\text{Ni}(\text{MNB})_2\text{Cl}_2 \cdot \text{H}_2\text{O}$	7700 br, 12 500, 13 500 sh, 19 400 w, sh ^a , 21 100 sh ^a
$\text{Ni}(\text{MNB})_2\text{Br}_2$	6250 br, 10 360, 15 400 sh, 17 400, 20 200 sh
$\text{Cu}(\text{MNB})_2\text{Cl}_2$	14 800
$\text{Cu}(\text{MNB})_2\text{Br}_2$	16 000 ^a
$\text{Cu}(\text{MNB})_2(\text{NO}_3)_2$	14 000 sh, 18 400

^aOn edge of strong absorption in U.V. region.

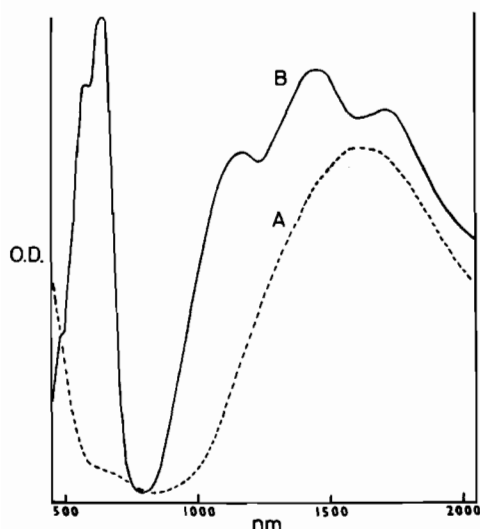


Fig. 1. Reflectance spectra of: A, $\text{Fe}(\text{MNB})_2\text{Cl}_2$; B, $\text{Co}(\text{MNB})_2\text{Cl}_2$.

complication unlikely and we have found that conversion of $\text{Pt}(\text{metronidazole})_2\text{I}_2$ to the chloride via the silver nitrate route is possible in dimethylsulphoxide. However, the direct reaction between metronidazole and K_2PtCl_4 as outlined in the Experimental section, is easier and gives the product in good yield (82%).

The complexes PtL_2Cl_2 ($\text{L} = \text{MTN}$ or MNB) each show two $\nu(\text{Pt}-\text{Cl})$ i.r. bands (at 335 and 350 cm^{-1} for $\text{L} = \text{MTN}$, and at 324 and 338 cm^{-1} for $\text{L} = \text{MNB}$) consistent with *cis*-geometry. The $\nu(\text{Pt}-\text{I})$ bands in the iodo-complexes were below the limit (200 cm^{-1}) of our spectrometer.

We have found that MNB forms complexes with a wide range of metals in addition to platinum (Table I). From their electronic spectra (Table II, Fig. 1) the iron(II) chloride, cobalt(II) chloride, and nickel(II) bromide complexes clearly contain tetrahedral MN_2X_2 chromophores. The electronic spectrum of the nickel(II) chloride complex, on the other hand, shows that it is six-coordinate. The complexes Mn -

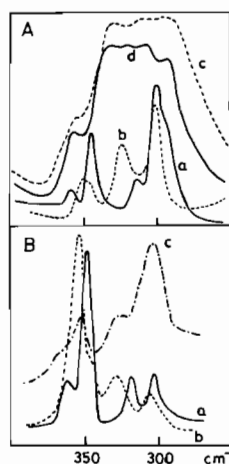


Fig. 2. A. I.R. spectra of: a, MNB ; b, $\text{Mn}(\text{MNB})_2\text{Cl}_2$; c, $\text{Zn}(\text{MNB})_2\text{Cl}_2$; d, $\text{Co}(\text{MNB})_2\text{Cl}_2$. B. Raman spectra of: a, MNB ; b, $\text{Mn}(\text{MNB})_2\text{Cl}_2$; c, $\text{Zn}(\text{MNB})_2\text{Cl}_2$.

$(\text{MNB})_2\text{X}_2$ ($\text{X} = \text{Cl}$ or Br) are halide-bridged polymers, as their X-band e.p.r. spectra show only a strong, broad band in the $g_{\text{eff}} = 2$ region as commonly found for such structures [2], with no evidence of the zero-field splitting shown by monomeric tetrahedral MnL_2X_2 compounds [3].

These conclusions are supported, in the case of the chloro-complexes, by the low frequency i.r. spectra. The nickel chloride and the manganese chloride compounds have no $\nu(\text{M}-\text{Cl})$ bands above 200 cm^{-1} , in accord with observations [4] for halide bridged polymers. The compounds formed by the chlorides of iron(II), cobalt(II), and zinc(II) have quite different i.r. spectra, showing strong absorption in the $290-350 \text{ cm}^{-1}$ region (Fig. 2A) where $\nu(\text{M}-\text{Cl})$ for tetrahedral ML_2Cl_2 species are observed [5]. Ligand i.r. bands in that region overlap the $\nu(\text{M}-\text{Cl})$ bands of the tetrahedral species precluding accurate numerical assignment of $\nu_{\text{symm}}(\text{M}-\text{Cl})$ and $\nu_{\text{asymm}}(\text{M}-\text{Cl})$. However in the complementary Raman spectra (Fig. 2B) of the free ligand and the

six coordinate complexes the ligand bands in the 300–330 cm^{-1} region become much weaker relative to the *ca.* 350 cm^{-1} ligand band.

If this relative intensity pattern extends to the tetrahedral complexes, we may assign $\nu(\text{M}-\text{Cl})$ at 301 and 322 cm^{-1} for $\text{M} = \text{Fe}$, and 302 and 328 cm^{-1} for $\text{M} = \text{Zn}$ from their Raman spectra (good Raman spectra could not be obtained for the cobalt chloride complex).

The electronic spectra of $\text{Cu}(\text{MNB})_2\text{X}_2$ ($\text{X} = \text{Cl}$, Br), (Table II) are of the type usually observed for planar CuN_2X_2 units interlinked by longer $\text{Cu}-\text{X}$ bonds to give very distorted octahedral geometry. Such interlinking appears to be much weaker in the chloride, which has an X-band e.p.r. spectrum of well-defined axial type with $g_{\parallel} = 2.248$ and $g_{\perp} = 2.074$, than in the bromide, where the interaction between the copper ions is strong enough to yield only a single broad e.p.r. band in the $g_{\text{eff}} \approx 2.1$ region. These compounds have $\nu(\text{Cu}-\text{X})$ bands at 311 cm^{-1} ($\text{X} = \text{Cl}$) and at 241 cm^{-1} ($\text{X} = \text{Br}$).

Magnetic concentration is also evident in the e.p.r. spectrum of $\text{Cu}(\text{MNB})_2(\text{NO}_3)_2$, which shows an anisotropic e.p.r. band but without clear resolution of \parallel and \perp features. The nitrate i.r. bands (1025, 1295, and 1475 cm^{-1}) for this complex suggest that $\text{Cu}-\text{Cu}$ bridging may be via these anions.

These results show that MNB forms complexes with a range of metal ions. However, we have not attempted a more complete survey as we find that their formation requires the use of organic solvents and, except for the platinum compounds, the products are decomposed by water. It appears likely, therefore, that in the search for clinically useful metal-modified nitroheterocycles major emphasis should be placed on platinum compounds. However, the possible interaction of such ligands with other biologically important metal ions cannot be ignored in hydrophobic regions of large biomolecules.

Experimental

Preparations

Except where stated below, the complexes were obtained on warming the required stoichiometric amounts of the heterocyclic ligand and the appropriate metal salt in a 4:1 mixture of methanol and 2,2-dimethoxypropane. Microanalyses (Table I) were by the Microanalytical Laboratory, Imperial College. Synthetic details additional to the above general method were as follows:

Complexes of 2-methyl-5-nitrobenzimidazole (=L)

MnL_2Br_2 and ZnL_2Cl_2 . These complexes were induced to crystallise by the dropwise addition of hot toluene to the hot reaction mixture.

FeL_2Cl_2 . This was prepared under nitrogen. The yellow product becomes brown when stored in air.

CoL_2Cl_2 . The complex crystallised when the reaction mixture was stored at -20°C overnight.

NiL_2Br_2 . Concentration of the reaction mixture by partially distilling off the solvent gave a mixture of yellow, green, and blue solids. This mixture was refluxed in toluene to afford a homogeneous, blue, crystalline product.

$\text{CuL}_2\text{Cl}_2 \cdot 2\text{H}_2\text{O}$ and CuL_2Cl_2 . The general method gave the apple green dihydrate, which formed the blue green anhydrate when stored *in vacuo* under concentrated sulphuric acid.

PtL_2Cl_2 . An ethanolic solution (10 cm^3) of L (0.571 g) was added to an aqueous solution of K_2PtCl_4 (0.67 g) (employing sufficient water to produce a clear solution). The pale yellow complex precipitated during overnight stirring (63% yield).

PtL_2I_2 . A very concentrated aqueous solution of KI (0.46 g) was added to a solution of K_2PtCl_4 (0.136 g) in water (4 cm^3). The resulting dark brown solution was stirred for 1 minute at room temperature and then a solution of L (0.116 g) in ethanol (2 cm^3) was added. The resulting deep red solution was stirred for 30 min and then stored at *ca.* 2°C overnight to yield bright yellow crystals in 74% yield.

Complexes of metronidazole (=MTN)

$\text{Cu}(\text{MTN})_2\text{Cl}_2$. This was dried *in vacuo* over conc. H_2SO_4 .

$\text{Cu}(\text{MTN})_2\text{Br}_2$. Green needles were obtained on cooling the reaction mixture to -20°C . Under these conditions the yield was low (*ca.* 12%) as it was difficult to avoid contamination with free metronidazole.

$\text{Pt}(\text{MTN})_2\text{X}_2$ ($\text{X} = \text{Cl}$ or I). These were obtained as for the corresponding complexes with 2-methyl-5-nitro-benzimidazole in 82% ($\text{X} = \text{Cl}$) and 91% ($\text{X} = \text{I}$) yields.

Physical Measurements

Raman spectra were obtained with a Spex Ramalog instrument using a Krypton ion laser. I.R. spectra were measured on a Perkin-Elmer 597 spectrometer for the range 4000–250 cm^{-1} and a Perkin-Elmer 683 instrument for the range 400–200 cm^{-1} (using vaseline mulls between polythene plates for the low frequency region). A Cary 14 spectrometer was used for the diffuse reflectance spectra

and a Varian 14 X-band instrument for the e.p.r. spectra.

Acknowledgements

We thank Mr. N. J. Campbell for the Raman spectra; Dr. G. W. Rayner Canham for the sample of 2-methyl-5-nitrobenzimidazole and Johnson Matthey and Co. for the loan of K_2PtCl_4 .

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