# The Preparation and Isomerization of Platinum Metronidazole Complexes: *X*-Ray Crystal and Molecular Structures of *cis*- and *trans*-Dichlorobis[1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole]-platinum(II)

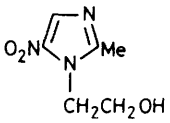
**John R. Bales,[a] Christopher J. Coulson,[b] David W. Gilmour,[b] Muhammed A. Mazid,[a] Stephen Neidle,[c] Reiko Kuroda,[c] Barry J. Peart,[b]* Christopher A. Ramsden,[b] and Peter J. Sadler[a]***

[a] *Department of Chemistry, Birkbeck College, Malet Street, London WC1E 7HX, U.K.*
[b] *The Research Laboratories, May & Baker Ltd., Dagenham, Essex RM10 7XS, U.K.*
[c] *Cancer Research Campaign, Biomolecular Structure Research Group, Department of Biophysics, King's College, 26—29 Drury Lane, London WC2B 5RL, U.K.*

*cis*-Pt(Metronidazole)$_2$Cl$_2$, a radiosensitizer toward hypoxic tumour cells, has been prepared and quantitatively isomerizes at its melting point to the *trans* complex; co-ordination of metronidazole to platinum(II) increases the polarographic reduction potential, and in both isomers the imidazole rings are tilted (69—75°) relative to the Pt(N)$_2$Cl$_2$ square-plane as shown by *X*-ray crystallography.

The properties of *cis*-square-planar platinum(II) complexes containing primary or secondary amines have been extensively investigated largely because they exhibit anti-neoplastic activity.[1] The *trans*-isomers are inactive. Less attention has been paid to platinum(II) complexes of heterocyclic tertiary amines. Imidazole and substituted imidazole complexes have been well characterized[2,3] but exhibit only marginal cytostatic activity.[3] Our interest in therapeutically important 5-nitroimidazoles,[4] especially 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) (**1**), marketed as Flagyl$^R$, has led us to investigate the possibility that they form biologically interesting Pt$^{II}$ complexes. The presence of the $NO_2$ substituent lowers the imidazole basicity, the p$K_a$ of imidazole and metronidazole (**1**) being 7.0 and 2.4 respectively. We now report the preparation of *cis*-Pt(metronidazole)$_2$Cl$_2$ (**2**) and a novel conversion into its *trans*-isomer (**3**).

Addition of $K_2PtCl_4$ (20 mmol) to a suspension of (**1**) (40 mmol) in $H_2O$ (300 ml) at 50 °C resulted in a yellow crystalline



(1)

product (91%) which was isolated after 1 h. After recrystallization from acetone–$H_2O$ it was identified as *cis*-Pt(metronidazole)$_2Cl_2$ (**2**)† by *X*-ray crystallography.‡

We noted that although (**2**) melted at 178—181 °C, this was followed by resolidification and a second m.p. (with decomp.) of 257—259 °C. After recrystallization of the resolidified material from acetone–$H_2O$, it was subsequently identified as *trans*-Pt(metronidazole)$_2Cl_2$ (**3**),† by *X*-ray crystallography.‡

Heating complex (**2**) at its melting point (180 °C) achieves a quantitative isomerization to (**3**), a rare example in $Pt^{II}$ chemistry.[5] The transformation (**2**)→(**3**) can also be achieved, in 95% yield, by heating an ethanolic suspension of (**2**) under reflux (6 h).

Platinum(II) complexes of imidazoles in the *trans*-configuration have been prepared *via* the tetra-imidazolato complex by treatment with acid in non-aqueous solvents.[3] We were unable to prepare $Pt^{II}$ complexes with four metronidazole ligands and therefore could not use this route to prepare compound (**3**).

The molecular structures of (**2**) and (**3**) as determined by *X*-ray crystallography are shown in Figure 1. The geometry at platinum is closely square-planar with bond angles in the range 88.9—90.9°. The dihedral angles between the planes of the imidazole rings and the square plane around platinum, 74.2° and 69.6° for (**2**) and 75.3° for (**3**), are much larger than those found in *cis*-Pt(*N*-methylimidazole)$_2Cl_2$ (41.3°),[6] and *trans*-[Pt(NH$_3$)$_2$(*N*-methylimidazole)$_2$]$^{2+}$ (49.2°),[7] probably to avoid steric interactions between the C-2 methyl group and Cl in (**2**) and (**3**).

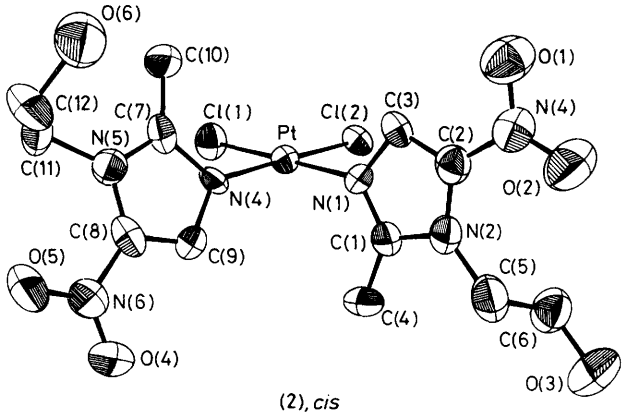
The properties of metronidazole are modified by co-ordination to $Pt^{II}$. Withdrawal of electron density from the imidazole ring results in low-field shifts of the 4-H resonance in the $^1$H n.m.r. spectrum {δ, [$^2H_6$]acetone, (**2**), 8.38; (**3**), 8.10, compared with (**1**), 7.87}, and a hypsochromic shift in the longest wavelength $\pi \rightarrow \pi^*$ electronic transition of (**1**), 318 nm, to 305 nm in (**2**). The polarographic $E_{\frac{1}{2}}$ value increases from −0.47 to −0.27 V (0.1M phosphate buffer, pH 7, 0.15M NaCl) on going from (**1**) to (**2**).

The biological properties of the *cis*-complex (**2**), described elsewhere as FLAP,[8,9] are of considerable interest. It is a radiosensitizer of hypoxic tumour cells towards *X*-irradiation, and is currently undergoing further evaluation.

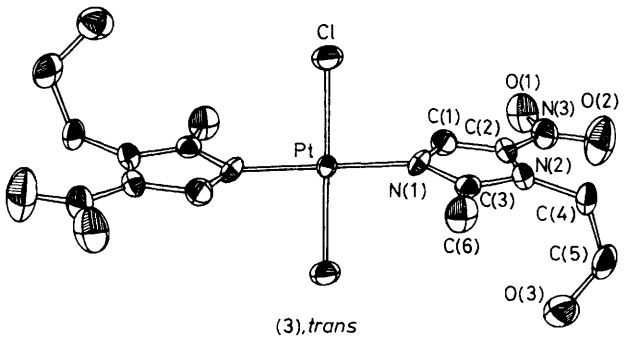
† Satisfactory elemental analyses were obtained for both new compounds.

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

*Crystal data:* (**2**), *cis*, $C_{12}H_{18}Cl_2N_6O_6Pt$, $M_r$ 608.31, monoclinic, space group $P2_1/a$, $a$ = 15.906(4), $b$ = 10.169(1), $c$ = 12.729 (3) Å; $\beta$ = 109.74 (2)°; $U$ = 1937.9 Å$^3$, $Z$ = 4; $D_c$ = 2.08 g cm$^{-3}$; $\mu$(Cu-$K_\alpha$) = 33.3 cm$^{-1}$; (**3**), *trans*, monoclinic, space group $P2_1/a$, $a$ = 6.8110(7), $b$ = 21.858(2), $c$ = 6.9907(3) Å, $\beta$ = 111.19(1)°; $U$ = 970.4 Å$^3$, $Z$ = 2; $D_c$ = 2.082 g cm$^{-3}$; $\mu$(Cu-$K_\alpha$) = 166.6 cm$^{-1}$. Data were collected on an Enraf–Nonius CAD4 diffractometer for the 2θ range 3.5—70° for (**2**) (1.5—65°) [data for (**3**) in parentheses] for crystals of dimensions 0.42 × 0.30 × 0.03 (0.2 × 0.2 × 0.1) mm. Absorption corrections were applied for both (**2**) and (**3**). 3906 (3432) reflections were collected, providing 3833 (1690) unique reflections, of which 2736 (1533) had $I > 3\sigma(I)$. The structures were refined to final $R$ values of 0.074 (0.046), $R_w$ 0.075 (0.054).




(2), *cis*




(3), *trans*

**Figure 1.** The molecular structures of *cis*- and *trans*-Pt(metronidazole)$_2Cl_2$ (**2**) and (**3**). Bond lengths and angles: (**2**): Pt–N, 2.024; Pt–Cl, 2.286 Å; ∠Cl–Pt–Cl, 91.0; N–Pt–N, 89.7, Cl–Pt–N, 88.9, 90.3°; (**3**): Pt–N, 2.003; Pt–Cl, 2.294 Å; ∠Cl–Pt–N, 90.9, 89.1°. Other bond lengths and angles are normal. The shortest intermolecular contact in crystals of (**2**) is 2.75 Å between the oxygen atoms of $CH_2OH$ side chains; all other contacts are >3.2 Å. In crystals of (**3**) the only significant intermolecular contact is a weak interaction (3.18 Å) between Cl and the O of $CH_2OH$; no H-bonding is observed.

We thank the S.E.R.C. (research assistantship for M. A. M. and CASE Studentship for J. R. B.), and the Cancer Research Campaign (for S. N. and R. K.) for support, and Professor A. H. W. Nias and Dr. M. Laverick, Richard Dimbleby Department of Cancer Research, St. Thomas' Hospital, for biological evaluation and valuable discussion. P. J. S. was a Nuffield Foundation Science Research Fellow 1981—2.

*Received, 20th January 1983; Com. 097*

## References

1 B. Rosenberg, *Metal Ions Biol. Systems*, 1982, **11**, 127.
2 J. Reedijk and C. G. van Kralingen, *Inorg. Chem. Acta*, 1978, **30**, 171.
3 J. Reedijk, C. H. van Kralingen, and J. K. De Ridder, *Inorg. Chem. Acta*, 1979, **36**, 69.
4 'Nitroimidazoles. Chemistry, Pharmacology and Clinical Application,' ed. A. Breccia, B. Cavalleri, and G. E. Adams, Plenum Press, New York, 1982.
5 G. K. Anderson and R. J. Cross, *Chem. Soc. Rev.*, 1980, **9**, 185.
6 B. J. Graves, D. J. Hodgson, C. G. van Kralingen, and J. Reedijk, *Inorg. Chem.*, 1978, **17**, 3007.
7 J. W. Carmichael, N. Chan, A. N. Cordes, C. K. Fair, and D. A. Johnson, *Inorg. Chem.*, 1972, **11**, 1117.
8 M. Laverick, J. R. Bales, C. J. Coulson, M. A. Mazid, A. H. W. Nias, and P. J. Sadler, *Br. J. Cancer*, 1982, **45**, 629.
9 J. R. Bales, P. J. Sadler, C. J. Coulson, M. Laverick, and A. H. W. Nias, *Br. J. Cancer*, 1982, **46**, 701.