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Synthesis, Characterisation and Radiosensitizing Properties of some Nitroimidazole Adducts of Rhodium(II) Carboxylates; X-ray Structure of $\{Rh(CH_3CO_2)_2$-[1-(2-hydroxy-3-methoxypropyl)-2-methyl-5-nitroimidazole]$\}_2$

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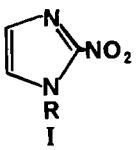
Abstract

The synthesis is reported of the complexes $[Rh(CH_3CO_2)_2L]_2$ where L = misonidazole, desmethylmisonidazole, 2-nitroimidazole-1-ethanol and 1-(2-hydroxy 3-methoxypropyl)-2-methyl-5-nitroimidazole (Roll-3696), and of the rhodium(II) butyrate analogues with the last two nitroimidazole ligands Crystals of $[Rh(CH_3CO_2)_2$(Roll-3696)$]_2$ are triclinic $P\bar{1}$ with $a = 7.982(2)$, $b = 8.121(3)$, $c = 13.327(3)$ Å, $\alpha = 77.23(2)$, $\beta = 82.47(2)$, $\gamma = 87.74(2)^\circ$, $Z = 1$. The structure was refined on 1833 reflections to $R = 0.031$. The molecule has the standard rhodium(II) acetate dinuclear structure with Rh–Rh = 2.399 Å, and with the ligand Roll-3696 coordinated to rhodium in terminal positions via N3 of the imidazole ring (Rh–N = 2.248 Å). The rhodium(II) carboxylate complexes with misonidazole, desmethylmisonidazole and Roll-3696 were examined for their ability to act as radiosensitizers of Chinese hamster mammalian cells *in vitro*. The rhodium(II) butyrate complex is substantially more toxic than the corresponding acetate and showed no sensitization at non-toxic concentrations. However, the acetates do sensitize and are up to 50X more efficient than the corresponding nitroimidazole ligand, when measured as the concentration required to give a similar increase in the radiation sensitivity of hypoxic cells. Some sensitization of aerobic cells is also observed but this is small compared to that seen under hypoxic conditions. The compounds containing the 2-nitroimidazole ligands are more efficient sensitizers than the complex containing the 5-nitroimidazole.

Introduction

A major limitation to radiotherapy for cancer treatment is the comparative radiation resistance of hypoxic cells in the tumour. In efforts to overcome this, attempts have been made in recent years to identify compounds which enhance the radiation sensitivity of hypoxic tumour cells, relative to that of aerobic cells. Nitroheterocycles, and especially nitroimidazoles, have been particularly favoured as radiosensitizers. Misonidazole, 1-(2-hydroxy-3-methoxypropyl)-2-nitroimidazole **(Ia)** was found



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a: R = $CH_2CH(OH)CH_2OMe$, misonidazole
b: R = $CH_2CH(OH)CH_2NH_2$, RSU 1111
c: R = $CH_2CH(OH)CH_2OH$, desmethylmisonidazole
d: R = CH_2CH_2OH, 2-nitroimidazole-1-ethanol

to have some effectiveness as a clinical radiosensitizer [1, 2] but its use is limited by its neurotoxicity. Attempts have been made to overcome this limitation by synthesising related compounds with good radiosensitizing properties but lower toxicity [3–7].

As an alternative approach, other workers have explored the radiosensitizing abilities of *cis*-$Pt(NH_3)_2Cl_2$, its 'second-generation' analogues, and complexes of these with nitroimidazoles. Such studies have recently been reviewed [8]. We recently reported [9] that the adduct of a misonidazole analogue RSU 1111 **(Ib)** with rhodium(II) acetate was an effective radiosensitizer towards Chinese hamster V79 cells. This observation prompted us to study a wider range of rhodium(II) carboxylate complexes with nitroimidazoles and to determine by X-ray diffraction methods the way in which the nitroimidazole ligand binds to the rhodium. We report here the results of that work.

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Experimental

Preparations

The nitroimidazoles (misonidazole, **Ia**; desmethylmisonidazole, **Ic**; 2-nitroimidazole-1-ethanol, **Id**, 1-(2-hydroxy-3-methoxypropyl)-2-methyl-5-nitroimidazole, **II**) were kindly supplied by Dr. C. E. Smithen, Roche Products Ltd., Welwyn Garden City, Herts, U.K. Rhodium(II) acetate and butyrate were prepared by standard literature methods [10, 11].

The nitroimidazole complexes of the rhodium(II) carboxylates were prepared by refluxing equimolar amounts of the appropriate rhodium(II) carboxylate and the nitroimidazole in ethanol for 30–60 min. The complexes, which precipitated in good yield (60–95%) either from the hot solution or on subsequent cooling, were filtered off, washed with ethanol and air-dried. Analytical results (Microanalytical Laboratory, Imperial College) and other details are listed in Table I. Attempts were also made to prepare adducts of rhodium(II) butyrate with misonidazole and with desmethylmisonidazole. In both cases brown products were obtained but they were of insufficient purity for further studies.

Physical Measurements

Infrared spectra were obtained on a Perkin-Elmer 597 Spectrometer using nujol mulls and KBr plates. Solid state electronic spectra were by the reflectance technique using a Beckman DK2 spectrometer.

X-ray Study

$[Rh(O_2C_2H_3)_2L]_2$ crystallizes as deep violet prisms. The crystal data are $C_{24}H_{38}N_6O_{16}Rh_2$, triclinic $a = 7.982(2)$, $b = 8.121(3)$, $c = 13.327(3)$ Å, $\alpha = 77.23(2)$, $\beta = 82.47(2)$, $\gamma = 87.74(2)^\circ$, $U = 835$ Å^3, space group $P\bar{1}$, $Z = 1$, $M_r = 872.4$, $D_c = 1.74$ g cm^{-3}, μCu Kα = 89 cm^{-1}. Refined unit cell parameters were obtained by centering 12 reflections on a Nicolet R3m diffractometer. 1833 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, $\theta < 55^\circ$] were measured with Cu Kα radiation (graphite monochromator) using ω-scans. The data were corrected for Lorentz and polarisation factors, and a numerical absorption correction was applied.

The structure was solved by the heavy atom method, and the non-hydrogen atoms refined anisotropically. The position of the hydroxy hydrogen atom and the orientations of the methyl groups were determined from a ΔF map. The ΔF map also revealed a residual peak of height = 1.7 e Å^{-3} at a distance of 1.2 Å from C(7). Clearly this peak was too high to be accounted for by the C(7) hydrogen atom alone. The peak was in a tetrahedral position with respect to C(7), and it was interpreted as due to a combination of the C(7) hydrogen atom and a partial weight hydroxy oxygen atom, indicating a degree of inversion at the C(7) centre. The occupancy of this

TABLE I. Analytical and Spectroscopic Data for the Complexes

Complex[a]	Colour	Analytical results						Melting Point (°C)	Reflectance spectra (nm)		$\nu(CO_2)$ (cm^{-1})	
		Found (%)			Calculated (%)				Band I[b]	Band II[b]	ν_{asym}	ν_{sym}
		C	H	N	C	H	N					
$Rh(CH_3CO_2)_2(LIa)$[a]	brown–red	30.70	3.95	9.30	31.30	4.10	9.90	186–188 dec	540	455	1585	1445
$Rh(CH_3CO_2)_2(LIc)$	pinkish brown	29.61	3.69	10.05	29.43	3.70	10.29	224–227 dec	556	424	1585	1440
$Rh(CH_3CO_2)_2(LId)$	red–brown	28.73	3.43	10.95	28.59	3.47	11.11	215–217 dec	536	449	1587	1430
$Rh(CH_3CO_2)_2(LII)$	red	33.16	4.35	9.63	33.04	4.39	9.64	228–230 dec	529	~440sh	1595	1440
$Rh(C_3H_7CO_2)_2(LId)$	yellow–brown	35.95	4.87	9.68	35.88	4.75	9.69	186–188	550	413br[c]	1584	1410
$Rh(C_3H_7CO_2)_2(LII)$	red–brown	38.81	5.46	8.49	39.03	5.53	8.54	150–152	523	396br[c]	1584	1410

[a]Ligand abbreviations: LIa = misonidazole; LIc = desmethylmisonidazole; LId = 2-nitroimidazole-1-ethanol; LII = 1-(2-hydroxy-3-methoxypropyl)-2-nitroimidazole [b]For explanation of notation see ref. 14, section F. [c]Bands II and III unresolved into separate components.

oxygen atom was estimated at 0.2. This oxygen and the hydroxy hydrogen atom were refined isotropically. The remaining hydrogen atoms (with the exception of both partial weight C(7) hydrogen atoms, which were omitted) were placed at idealised positions (C–H = 0.96 Å), assigned isotropic thermal parameters, $U(H) = 1.2\ U_{eq}(C)$, and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full matrix least-squares to $R = 0.031$, $R_w = 0.031$ $[w^{-1} = \sigma^2(F) + 0.00044\ F^2]$. It should be noted that the inclusion of the partial weight hydroxy oxygen atom in place of the C(7) hydrogen atom reduced R from 0.034 to 0.031. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system [12]. Atomic scattering factors were from ref. [13]. The fractional atomic coordinates of the non-hydrogen atoms are listed in Table II. Table III lists the bond lengths and valence angles.

TABLE II. Atom Coordinates ($\times 10^4$) and Temperature Factors ($Å^2 \times 10^3$)

Atom	x	y	z	U_{eq}[a]
Rh	−70(1)	4090(1)	846(1)	29(1)
N(1)	139(5)	−145(5)	3535(3)	35(1)
C(2)	871(6)	1113(6)	2768(4)	36(2)
N(3)	−274(5)	2221(5)	2376(3)	38(2)
C(4)	−1803(7)	1646(6)	2898(4)	39(2)
C(5)	−1566(6)	213(6)	3587(4)	36(2)
C(6)	1036(7)	−1697(6)	3987(4)	42(2)
C(7)	939(7)	−3025(6)	3341(5)	47(2)
O(7*)	1392	−2308	2306	64(6)
O(7)	−724(5)	−3590(6)	3452(4)	44(2)
C(8)	2176(7)	−4445(7)	3626(6)	60(3)
O(8)	3825(5)	−3775(6)	3371(4)	80(2)
C(9)	5068(9)	−5002(10)	3498(8)	99(4)
N(10)	−2840(6)	−772(6)	4312(3)	46(2)
O(10)	−2441(6)	−1616(5)	5124(3)	64(2)
O(11)	−4268(6)	−675(6)	4072(4)	71(2)
C(12)	2699(7)	1202(7)	2399(5)	51(2)
C(13)	1476(6)	2565(6)	−804(4)	36(2)
O(13)	1246(4)	3973(4)	−1428(3)	37(1)
O(14)	1125(4)	2287(4)	164(3)	39(1)
C(15)	2191(8)	1136(7)	−1270(5)	50(2)
C(16)	−2852(6)	3766(6)	−264(4)	35(2)
O(16)	−2161(4)	4924(4)	−999(3)	42(1)
O(17)	−2325(4)	3252(4)	602(3)	39(1)
C(18)	−4403(7)	2984(8)	−470(5)	53(2)

[a]Equivalent isotropic U_{eq} defined as one third of the trace of the orthogonalised U_{ij} tensor.

Mammalian Cells

Asynchronous, exponentially growing cultures of Chinese hamster V79-379A cells were used in all experiments. Cells were grown in spinner culture in Eagles' minimal essential medium (MEM) supplemented with 7.5% foetal calf serum (fcs).

Irradiation Procedure

Cells were harvested, diluted and allowed to attach to 5 cm glass petri dishes containing MEM + 10% fcs at 37 °C for 2 h before the medium was removed and replaced with 1 cm^3 of phosphate buffered saline containing the test compound. Irradiations with ^{60}Co γ-rays were carried out in Dural vessels containing four petri dishes. The vessels were rendered hypoxic by purging with N_2 for 30 min, sealed and irradiated at room temperature at a dose rate of ~3 Gy min^{-1}. After irradiation the drug solution was removed and the cells overlaid with fresh MEM + 10% fcs. Dishes were incubated at 37 °C in a humidified atmosphere of air + 5% CO_2 for 7–9 days and colonies with 50 or more cells scored as indicating survival of a single treated cell.

Results and Discussion

When reacted with rhodium(II) acetate in ethanol all four of the nitroimidazoles used here gave reddish brown adducts of the type $[Rh(CH_3CO_2)_2L]_2$ in good yield, and two of them, ligands **Id** and **II**, gave analogous complexes with rhodium butyrate (Table I). There was evidence for the formation of similar complexes of rhodium(II) butyrate with misonidazole and desmethylmisonidazole but they formed in an impure state and we have not characterized them further.

The colours, solid state electronic spectra and ν(CO) carboxylate frequencies of the rhodium compounds listed in Table I are consistent with the retention of the dinuclear rhodium(II) carboxylate structure and coordination of the nitroimidazole ligands to rhodium in the terminal positions [14].

All four of the nitroimidazoles are potentially ambidentate ligands, being able to coordinate by the unsubstituted ring nitrogen or by an oxygen atom in the side chain on N1. The colours of the complexes and, particularly, the positions of the lowest energy electronic band in the UV–Vis spectra, conventionally termed band I [14], are in accord with the terminal group donor atom being a nitrogen atom. However, as colour is not an infallible guide to the nature of the terminal donor atom [15] and as it is important to determine unambiguously how the nitroimidazoles are bonded, so as to provide a firm basis for assessing the radiosensitization results, we have determined by X-ray diffraction methods the molecular structure of one of the complexes, $[Rh(CH_3CO_2)_2(Roll\text{-}3696)]_2$.

The X-ray study (Fig. 1) confirms that the dinuclear structure is retained by the rhodium(II) acetate after reaction with the nitroimidazole and that ligand II (Roll-3696) binds to the rhodium via the unsubstituted ring nitrogen atom N(3). There is

TABLE III. Bond Lengths and Angles

Bond lengths (Å)			
Rh–N(3)	2.248(4)	Rh–O(14)	2.032(3)
Rh–O(17)	2.039(4)	Rh–Rh′	2.399(1)
Rh–O(13′)	2.046(3)	Rh–O(16′)	2.033(4)
N(1)–C(2)	1.363(6)	N(1)–C(5)	1.376(6)
N(1)–C(6)	1.473(6)	C(2)–N(3)	1.330(6)
C(2)–C(12)	1.477(7)	N(3)–C(4)	1.368(6)
C(4)–C(5)	1.338(6)	C(5)–N(10)	1.440(6)
C(6)–C(7)	1.532(9)	C(7)–O(7*)	1.380
C(7)–O(7)	1.401(7)	C(7)–C(8)	1.504(8)
C(8)–O(8)	1.415(7)	O(8)–C(9)	1.377(9)
N(10)–O(10)	1.219(6)	N(10)–O(11)	1.218(7)
C(13)–O(13)	1.279(5)	C(13)–O(14)	1.255(6)
C(13)–C(15)	1.494(8)	O(13)–Rh′	2.046(3)
C(16)–O(16)	1.281(5)	C(16)–O(17)	1.257(6)
C(16)–C(18)	1.496(8)	O(16)–Rh′	2.033(4)
Bond angles (deg)			
N(3)–Rh–O(14)	88.9(1)	N(3)–Rh–O(17)	88.7(1)
O(14)–Rh–O(17)	89.1(1)	N(3)–Rh–Rh′	175.4(1)
O(14)–Rh–Rh′	87.9(1)	O(17)–Rh–Rh′	87.9(1)
N(3)–Rh–O(13′)	95.3(1)	O(14)–Rh–O(13′)	175.8(1)
O(17)–Rh–O(13′)	91.3(1)	Rh′–Rh–O(13′)	87.9(1)
N(3)–Rh–O(16′)	95.5(1)	O(14)–Rh–O(16′)	92.0(1)
O(17)–Rh–O(16′)	175.7(1)	Rh′–Rh–O(16′)	87.9(1)
O(13′)–Rh–O(16′)	87.4(1)	C(2)–N(1)–C(5)	104.8(4)
C(2)–N(1)–C(6)	123.7(4)	C(5)–N(1)–C(6)	130.0(4)
N(1)–C(2)–N(3)	111.5(4)	N(1)–C(2)–C(12)	124.1(4)
N(3)–C(2)–C(12)	124.4(4)	Rh–N(3)–C(2)	129.1(3)
Rh–N(3)–C(4)	121.7(3)	C(2)–N(3)–C(4)	105.9(4)
N(3)–C(4)–C(5)	109.2(4)	N(1)–C(5)–C(4)	108.6(4)
N(1)–C(5)–N(10)	124.4(4)	C(4)–C(5)–N(10)	126.9(5)
N(1)–C(6)–C(7)	109.9(5)	C(6)–C(7)–O(7*)	109.5(3)
C(6)–C(7)–O(7)	109.8(5)	C(6)–C(7)–C(8)	110.7(5)
O(7*)–C(7)–C(8)	106.6(3)	O(7)–C(7)–C(8)	112.5(4)
C(7)–C(8)–O(8)	108.0(5)	C(8)–O(8)–C(9)	112.8(5)
C(5)–N(10)–O(10)	118.8(5)	C(5)–N(10)–O(11)	116.8(4)
O(10)–N(10)–O(11)	124.4(5)	O(13)–C(13)–O(14)	125.1(5)
O(13)–C(13)–C(15)	117.2(5)	O(14)–C(13)–C(15)	117.7(4)
C(13)–O(13)–Rh′	118.9(3)	Rh–O(14)–C(13)	120.1(3)
O(16)–C(16)–O(17)	125.0(5)	O(16)–C(16)–C(18)	116.3(5)
O(17)–C(16)–C(18)	118.6(4)	C(16)–O(16)–Rh′	119.3(3)
Rh–O(17)–C(16)	119.5(3)		

a crystallographic centre of symmetry at the centre of the Rh–Rh bond.

The axial N–Rh–Rh′–N′ chain is very nearly linear with NRhRh angles of 175.4(1)°. The two groups of four equatorial oxygen atoms are nearly perfectly eclipsed with respect to each other, with a maximum ORhRhO torsion angle of 1°. The atoms of the imidazole ring are coplanar, with a maximum deviation from their least squares plane of 0.009 Å (for N(1)). N(3) shows a degree of pyramidisation, being displaced by 0.16 Å from the plane of its substituents. The plane of the imidazole bisects the O(16′)RhO(14) and O(17)RhO(13′) angles causing a small splaying of these angles (92.0(1) and 91.3(1)° respectively) and a corresponding contraction of those for O(16′)RhO(13′) and O(14)RhO(17) (87.4(1) and 89.1(1)° respectively). The greater splaying of the O(16′)RhO(14) angle can be accounted for by the close approach of the methyl group C(12) to O(14) and O(16′), 3.31 and 3.33 Å respectively. The nitro group is rotated by 26° from the plane of the imidazole ring.

The four independent Rh–O bonds do not differ significantly from each other and have an average length of 2.038 Å (*cf.* 2.036 Å in [15]). The Rh–Rh distance (2.399(1) Å) is similar to that observed in

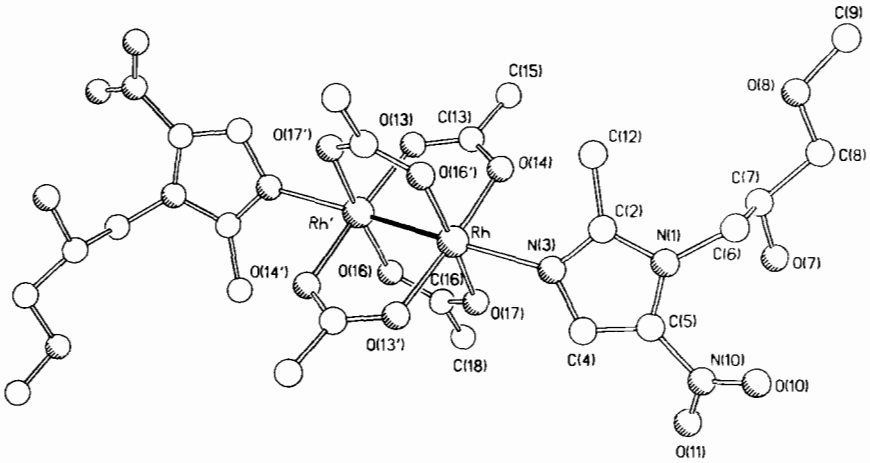

Fig. 1. Molecular structure of $\{Rh(CH_3CO_2)_2[1\text{-}(2\text{-hydroxy-3-methoxypropyl})\text{-}2\text{-methyl-5-nitroimidazole}]\}_2$.

other rhodium carboxylate bridged systems [14] and the Rh–N bond lengths (2.248(4) Å) are also unexceptional [14]. There is an intermolecular hydrogen bond between the major occupancy hydroxy hydrogen atom and one of the carboxylate oxygen atoms (O(7)···O(13') 2.87 Å, OHO = 140°). There are also fairly short intermolecular contacts between the minor occupancy hydroxy oxygen atom O(7) and the carboxylate oxygen atoms O(16') and O(13'), both 3.03 Å. There are no other significant intermolecular contacts, the packing of the molecules being normal Van der Waals.

In the light of this structural result we conclude that the nitroimidazole ligands in the other complexes listed in Table I also bind to rhodium via the unsubstituted ring nitrogen atom.

Enhancement ratios (*ER*) for radiosensitization of hypoxic V79 cells were determined using previously-described protocols [16–18]. At the maximum drug concentrations tested, the rhodium(II) complexes reduced the plating efficiency of unirradiated cells by no more than 20% after a one hour contact time in hypoxia at room temperature. This allows concentrations of up to 50 μmol of the rhodium acetates to be used. In contrast, $[Rh(C_3H_7CO_2)_2$Roll-3696$]_2$ was toxic below 0.5 μmol dm^{-3} and no sensitization is observed for this compound at non toxic concentrations. Generally, radiation dose log-survival curves were obtained at a number of concentrations for each compound. Some representative examples are shown in Fig. 2. At these concentrations $[Rh(CH_3CO_2)_2$misonidazole$]_2$ clearly increases the radiation response of hypoxic cells *in vitro*. *ER* values derived from the ratio of the slopes of the exponential portions of the survival curves obtained in the absence or presence of 10 or 20 μmol dm^{-3} rhodium(II) complex are 1.5 and 1.7 respectively. Figure 2 also shows that some sensitization of aerobic cells can be observed but it is small when compared to that occurring under

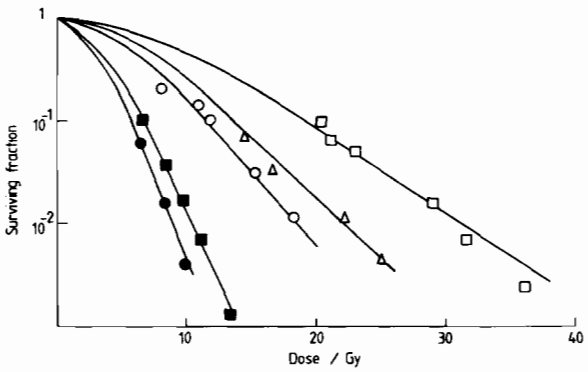

Fig. 2. Survival curves for V79 cells irradiated under aerobic (closed symbols) or hypoxic (open symbols) conditions in the presence of 10 μmol dm^{-3} (△) or 20 μmol dm^{-3} (○, ●) $[Rh(CH_3CO_2)_2$misonidazole$]_2$. Squares, no Rh(II) complex present.

hypoxic conditions. *ER* values for certain concentrations were derived from single survival points (usually between 2×10^{-2} and 10^{-1}) obtained by appropriate choice of radiation dose and by assuming an unchanged extrapolation number. Figure 3 shows the concentration dependence for the *ER* values determined for each compound. The ratios for hypoxic cells irradiated in the presence of misonidazole or Roll-3696 are indicated by the dashed lines. It is quite apparent that substantially lower concentrations of the rhodium(II) complexes are required to sensitize hypoxic cells compared to the nitroimidazoles, misonidazole and Roll-3696. A measure of sensitizing efficiency for any particular compound is given by the term $C_{1.6}$, which is the concentration required to give an *ER* of 1.6. The lower the value of $C_{1.6}$, the higher the sensitizing efficiency. Values of $C_{1.6}$ determined for the rhodium complexes are given in Table IV together with literature values for the nitroimidazoles alone and rhodium(II) acetate.

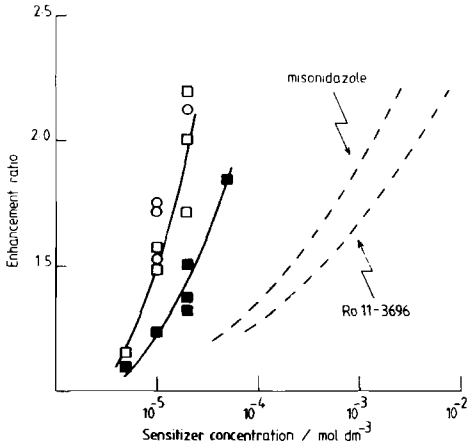

Fig. 3. Dependence of enhancement ratio (*ER*) for irradiated hypoxic cells in the presence of various concentrations of $[Rh(CH_3CO_2)_2L]_2$; where L = misonidazole, □; L = desmethylmisonidazole, ○; L = Roll-3696, ■. Dashed lines are taken from some of our previously published data [16] comparing the sensitizing efficiency of the free ligands, misonidazole and Roll-3696.

TABLE IV. Radiosensitizing Efficiencies of the Complexes, $[Rh(CH_3CO_2)_2L]_2$

Compound	$C_{1.6}$ (mol dm^{-3})
Rhodium complexes	
L = Misonidazole	1.2×10^{-5}
L = desmethylmisonidazole	1.0×10^{-5}
L = Ro 11-3696	2.5×10^{-5}
Ligands alone	
Misonidazole	$(0.3-1.0) \times 10^{-3}$ [16, 21]
Desmethylmisonidazole	0.9×10^{-3} [16]
Roll-3696	1.0×10^{-3} [16]
Rhodium(II) acetate	1.0×10^{-4} [20]

For the complexes $[Rh(CH_3CO_2)_2L]_2$ sensitizing efficiency is greater for L = misonidazole and desmethylmisonidazole compared to that observed for L = Roll-3696. A similar difference is seen for sensitization by the ligands alone, which is attributable to the difference in one-electron red-ox potential between the 2- and 5-nitroimidazoles [16]. The substantial increase in sensitizing efficiency obtained with the rhodium complexes may be due to an increase in red-ox potential of the complex relative to that of the ligand alone. This red-ox change would be likely to occur because of co-ordination of the metal center directly to the aromatic nucleus via N(3). Such an increase in red-ox potential, E_7^1, has recently been measured for *cis*-dichlorobis(1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole-N_3)-platinum(II), (*cis*-Flap) [19]. For metronidazole alone the value of E_7^1 is −476 mV [16, 19] compared to −375 mV for *cis*-Flap [19]. However, in our hands, co-ordination of metronidazole to platinum does not lead to an increase in sensitizing efficiency relative to the ligand alone [9]. Therefore, we cannot assume a red-ox change to be the explanation for the sensitizing properties of the rhodium complexes.

We have recently reported radiosensitization by a range of rhodium(II) carboxylates [20]. It was strongly suggested that sensitization by these compounds was due, at least in part, to their ability to react with and deplete intracellular thiols. Such an effect can lead to a small amount of sensitization under aerobic conditions and this is observed in the present work. Further, combination experiments with rhodium(II) acetate plus misonidazole resulted in a higher level of sensitization than could be achieved with either compound individually; e.g. 100 μmol dm^{-3} rhodium(II) acetate plus 50 μmol dm^{-3} misonidazole gave an *ER* of 1.8 [20]. However, in the work reported here, a concentration of only 20 μmol dm^{-3} $[Rh(CH_3CO_2)_2$misonidazole$]_2$ gives this level of *ER*. This suggests the complex to be operating more efficiently than the combination of misonidazole with rhodium(II) acetate.

The observations we have made demonstrate the value of exploring a wider range of metal complexes as radiosensitizers, either, as in the present work, in combination with known organic radiosensitizers, or as metal complexes possessing radiosensitizing ability in their own right. The potential of such systems is considerable, because of the number of factors that can be exploited to generate, and to modify, radiosensitizing activity. Such factors include: variation in the identity of the metal, its formal oxidation state when administered, the accessibility of alternative oxidation states *in vivo*, and the influence of the nature of the accompanying ligand set on the question of biological transport. The large range of redox potentials available to metal complexes is a particularly attractive factor in this context.

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