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Biological Activity and Crystallographic Study of a Rhodium Propionate-Metronidazole Adduct

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A estrutura do aduto entre propionato de ródio e metronidazol foi caracterizada cristalograficamente por difração de raios X monocristal. Avaliou-se a atividade antibacteriana e antineoplásica bem como a toxicidade aguda do propionato de ródio e de seu aduto com metronidazol. Ambos os compostos apresentaram toxicidades e capacidades inibitórias sobre a síntese de DNA semelhantes. O aduto exibiu, contudo, maior poder inibitório sobre *S. aureus* e *P. aeruginosa* que seus dois componentes isolados.

The structure of the adduct between rhodium propionate and metronidazole has been characterized by single crystal X-ray diffraction. Antitumor and antibacterial activities, as well as acute toxicity for rhodium propionate and its adduct with metronidazole were also studied. Both compounds exhibit similar toxicity and ability to inhibit DNA synthesis. However, the metronidazole adduct is more active than rhodium propionate or metronidazole alone against *S. aureus* and *P. aeruginosa*.

Keywords: *rhodium carboxylates, chemotherapeutic metal complexes, metronidazole*

Introduction

Rhodium carboxylates and nitroimidazoles both exhibit chemotherapeutic activities. Metronidazole (**metro**) is a well established antimicrobial and antiprotozoal agent while several rhodium carboxylates have been prepared and evaluated against cancer in the last twenty years[1-3].

Adducts of nitroimidazoles with dirhodium tetraacetate and butyrate were examined for their radiosensitizing properties[4]. The antichagasic activities of several rhodium carboxylates and their adducts with metronidazole and benznidazole, including rhodium propionate (**prop**) and its adducts (**meprop and benzprop**), have also been evaluated[5,6]. The dirhodium tetraacetate-metronidazole complex

had its genotoxicity evaluated as a radiosensitizer[7] and was later characterized by spectroscopic, electrochemical and crystallographic measurements[8]. Rhodium(III) salts have been assayed as antibacterial agents against selected Gram-positive and Gram-negative bacteria[9].The present work describes assays on the acute toxicity and on the antibacterial and antitumor activities of **prop** and **meprop**, as well as a structural study by X-ray diffraction of the latter.

Chemical Studies

Syntheses and X-ray diffraction

Rhodium propionate and its adduct with metronidazole were prepared as previously described[6]. Brown reddish X-ray-quality crystals of **meprop** were obtained by desiccation of filtered crystals formed in ethanolic solutions left in a refrigerator for 24 hours.

A single crystal with maximum linear dimensions of 0.5 mm was mounted on an *Enraf-Nonius CAD-4 diffractometer* for cell dimension measurements and intensity data collection, at room temperature. The crystallographic data for $Rh_2(prop)_4L_2$ are: F_w = 844.44, monoclinic, P_c, a = 9.658(1), b = 20.505(1), c = 9.026(1) Å, β = 110.23(1)^0, V = 1677(1) Å^3, z = 2, D_c = 1.672 g cm^{-3}, λ (MoKα) = 0.71073 Å, μ(MoKα) = 10.37 cm^{-1}.

The crystal was stable under radiation and a total of 2,924 unique reflections were collected in the range $0<\theta<24.99^0$, the intensities being corrected for Lp and for absorption 1450 with $I > 3\sigma(I)$ retained for structure refinement[10].

The structure was solved by Patterson and differential Fourier methods. In the final cycles of the least-square refinement, all non-H atoms were treated anisotropically. Hydrogen atoms were included in the structure factor calculations with their positional coordinates determined by geometrical bond considerations and a common isotropic temperature factor was assumed as 6.0 Å^2, but not included in the refinement. The function to be minimized was

$\Sigma_w(|F_o| - |F_c|)^2$ with $w^{-1} = [\sigma^2(F_o) + 0.00095\ F_o2]$, with 432 parameters being refined, excluding the unobserved reflections. The refinement converged to R = 0.0257, R_w = 0.0299, and R = 0.0385 for all reflections. The largest peaks in the final differential Fourier synthesis were approximately 0.3 eÅ^{-3}. Atomic scattering factor and anomalous dispersion terms were taken from the literature[11-13]. The programs used were SHELX76[14] and ORTEP[15].

Description of the structure

A projection of the molecule showing atomic identification is given in Fig. 1.

Final positional and equivalent isotropic thermal parameters are listed in Table 1 while isotropic thermal parameters, hydrogen coordinates and structure factors are available as supplementary material.

Table 1. Atomic coordinates and isotropic equivalent temperature factors (Å^2) with e.s.d.'s.

Atom	X/a	Y/b	Z/c	Beq (Å)
Rh (1)	0.07384 (5)	0.30577 (4)	0.18796 (5)	2.11 (3)
Rh (2)*	0.00075	0.19448 (4)	0.12157	2.18 (3)
O (1)	0.2118 (5)	0.2950 (2)	0.0682 (6)	3.0 (1)
O (2)	0.1477 (6)	0.1901 (2)	0.0011 (7)	4.0 (2)
O (1A)	0.2391 (5)	0.2717 (2)	0.3847 (5)	3.0 (1)
O (2A)	0.1713 (4)	0.1675 (2)	0.3247 (5)	2.6 (1)
O (1B)	-0.0655 (6)	0.3071 (2)	0.3103 (6)	2.7 (1)
O (2B)	-0.1456 (5)	0.2041 (2)	0.2409 (6)	3.0 (1)
O (1C)	-0.0925 (6)	0.3314 (2)	-0.0057 (6)	3.4 (1)
O (2C)	-0.1640 (6)	0.2268 (2)	-0.0704 (6)	4.0 (2)
O (11)	0.5514 (8)	0.4968 (3)	0.435 (1)	9.2 (3)
O (12)	0.4254 (8)	0.5859 (3)	0.432 (1)	8.0 (3)
O (13)	0.010 (1)	0.5989 (3)	0.0668 (8)	6.9 (2)
O (21)	-0.3549 (8)	-0.0802 (3)	-0.169 (1)	8.8 (3)
O (22)	-0.4747 (7)	0.0033 (4)	-0.146 (1)	9.6 (3)
O (23)	0.0808 (7)	-0.1003 (3)	0.2578 (7)	6.5 (2)
N (11)	0.1508 (6)	0.4090 (3)	0.2580 (7)	3.4 (2)
N (12)	0.1667 (7)	0.5139 (2)	0.3198 (7)	3.2 (1)
N (13)	0.441 (1)	0.5263 (4)	0.435 (2)	8.5 (4)
N (21)	-0.0687 (6)	0.0903 (2)	0.0629 (6)	2.5 (1)
N (22)	-0.0821 (6)	-0.0146 (3)	-0.0010 (6)	2.8 (1)
N (23)	-0.3567 (7)	-0.0257 (3)	-0.1088 (8)	4.6 (2)
C (1)	0.2128 (7)	0.2439 (3)	0.0003 (8)	2.8 (2)
C (2)	0.3267 (7)	0.2344 (3)	-0.0856 (9)	3.3 (2)
C (3)	0.445 (1)	0.1736 (5)	-0.003 (2)	6.6 (4)
C (1A)	0.2622 (7)	0.2118 (3)	0.4087 (7)	2.4 (2)
C (2A)	0.3975 (8)	0.1919 (4)	0.527 (1)	4.1 (2)
C (3A)	0.404 (1)	0.1182 (3)	0.589 (1)	4.4 (2)
C (1B)	-0.1592 (7)	0.2605 (3)	0.3046 (8)	2.4 (2)
C (2B)	-0.271 (1)	0.2620 (4)	0.376 (1)	4.9 (3)
C (3B)	-0.3674 (9)	0.3128 (3)	0.3313 (9)	3.5 (2)
C (1C)	-0.1731 (8)	0.2894 (4)	-0.0874	4.0 (2)
C (2C)	-0.309 (1)	0.3139 (4)	-0.235 (1)	5.9 (3)
C (3C)	-0.350 (2)	0.3674 (6)	-0.243 (2)	12.7 (6)
C (11)	0.0768 (7)	0.4681 (3)	0.2540 (8)	2.8 (2)
C (12)	0.3042 (8)	0.4885 (4)	0.3438 (9)	3.8 (2)
C (14)	0.1195 (8)	0.5837 (3)	0.3293 (8)	3.2 (2)
C (13)	0.2872 (7)	0.4259 (3)	0.3230 (9)	3.4 (2)
C (15)	0.115 (1)	0.6243 (4)	0.199 (1)	5.3 (3)
C (17)	-0.0891 (8)	0.4694 (3)	0.1844 (9)	3.5 (2)
C (21)	0.0087 (7)	0.0402 (3)	0.0550 (7)	2.4 (2)
C (22)	-0.2257 (8)	0.0097 (3)	-0.0515 (9)	3.4 (2)
C (23)	-0.2209 (8)	0.0743 (3)	0.0061 (9)	3.6 (2)
C (24)	-0.0301 (9)	-0.0783 (3)	-0.0220 (8)	3.8 (2)
C (25)	-0.022 (1)	-0.1236 (3)	0.1230 (9)	4.4 (2)
C (27)	0.1716 (7)	0.0340 (3)	0.1018 (8)	3.2 (2)

* used to fix the space group origin

Table 2. Bond lengths (Å) with e.s.d's in parentheses.

Rh (1)	Rh (2)	2.403 (1)	C (1A)	C (2A)	1.432 (9)	N (12)	C (14)	1.514 (8)
Rh (1)	O (1)	1.998 (6)	C (2A)	C (3A)	1.61 (2)	N (13)	C (12)	1.51 (1)
Rh (1)	O (1A)	2.057 (4)	O (1B)	C (1B)	1.305 (7)	C (11)	C (17)	1.51 (1)
Rh (1)	O (1B)	2.015 (7)	O (2B)	C (1B)	1.318 (7)	C (12)	C (13)	1.30 (1)
Rh (1)	O (1C)	1.993 (4)	C (1B)	C (2B)	1.44 (1)	C (14)	C (15)	1.43 (1)
Rh (1)	N(11)	2.259 (5)	C (2B)	C (3B)	1.36 (2)	O (21)	N (23)	1.25 (1)
Rh (2)	O (2)	2.067 (8)	O (1C)	C (1C)	1.223 (9)	O (22)	N (23)	1.225 (9)
Rh (2)	O (2A)	2.072 (4)	O (2C)	C (1C)	1.29 (2)	O (23)	C (25)	1.363 (9)
Rh (2)	O (2B)	2.062 (7)	C (1C)	C (2C)	1.59 (2)	C (21)	C (27)	1.487 (9)
Rh (2)	O (2C)	2.017 (5)	C (2C)	C (3C)	1.17 (2)	C (21)	N (21)	1.287 (8)
Rh (2)	N (21)	2.247 (5)	O (11)	N (13)	1.23 (1)	C (21)	N (22)	1.407 (7)
O (1)	C (1)	1.216 (8)	O (12)	N (13)	1.24 (2)	C (22)	C (23)	1.418 (9)
O (2)	C (1)	1.272 (9)	O (13)	C (15)	1.37 (1)	C (22)	N (22)	1.394 (8)
C (1)	C (2)	1.56 (1)	N (11)	C (11)	1.402 (8)	C (22)	N (23)	1.394 (9)
C (2)	C (3)	1.68 (1)	N (11)	C (13)	1.290 (9)	C (23)	N (21)	1.418 (9)
O (1A)	C (1A)	1.254 (7)	N (12)	C (11)	1.277 (8)	C (24)	C (25)	1.58 (2)
O (2A)	C (1A)	1.308 (7)	N (12)	C (12)	1.37 (1)	C (24)	N (22)	1.435 (9)

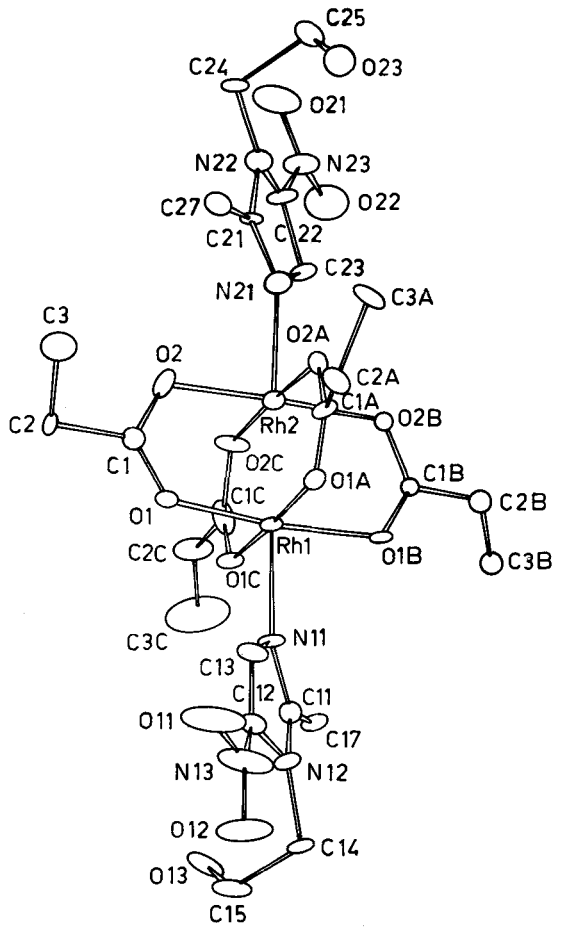

Figure 1: Tridimensional model for meprop, based on crystallographic data.

Interatomic distances and angles are given in Tables 2 and 3, respectively.

Biological Studies

Acute toxicity

LD_{50} and LD_{10} studies were performed on eight different groups of ten healthy male Balb-c mice weighing 18-22 g. The animals were treated intraperitonially (ip) with four different doses of **prop** (groups 1 to 4) and **meprop** (groups 5 to 8). Deaths were registered after 48 h. LD_{10} and LD_{50} were determined by probit analysis[16].

LD_{10} values for **prop** and **meprop** were found to be 0.9×10^{-5} M/kg (4.48 mg/kg) and 1.0×10^{-5} M/kg (8.40 mg/kg), respectively. Concentrations of LD_{50} were 1.7×10^{-5} M/kg (fiducial limits 1.1×10^{-5} to 2.4×10^{-5} M/kg) for **prop** and 1.6×10^{-5} M/kg (fiducial limits 1.2×10^{-5} to 2.0×10^{-5} M/kg) for **meprop** (8.46 mg/kg and 13.45 mg/kg, respectively), as shown in Table 4.

Antitumor studies

Mice were implanted ip or intramuscularly (im) with 5×10^5 Ehrlich tumor cells. Twenty four hours after implantation the animals were randomly divided into groups of ten mice and treated with single doses of **prop**, **meprop**,and **metro** applied ip or im. The drugs were administered from solutions prepared by dissolving 5 mg of either **prop**, **meprop** or **metro** in 1 ml of acetone and diluting to 50 ml with 0.9% saline. Control group mice received injections of a saline-acetone mixture. Observations were continued for 45 days in order to allow the calculation of ILS_{40} (the dose capable of providing a 40% increase in life span)[17]. The following assays were performed: (a) tumor cells im-

Table 3. Intramolecular bond angles (°) with e.s.d's in parentheses.

Rh(2)	Rh(1)	O(1)	87.3(1)	Rh(1)	Rh(2)	O(2)	88.7(1)
Rh(2)	Rh(1)	O(1A)	88.0(1)	Rh(1)	Rh(2)	O(2A)	87.7(1)
Rh(2)	Rh(1)	O(1B)	87.4(1)	Rh(1)	Rh(2)	O(2B)	88.5(1)
Rh(2)	Rh(1)	O(1C)	87.3(1)	Rh(1)	Rh(2)	O(2C)	88.8(1)
Rh(2)	Rh(1)	N(11)	177.7(1)	Rh(1)	Rh(2)	N(21)	179.1(2)
O(1)	Rh(1)	O(1A)	88.0(2)	O(2)	Rh(2)	O(2A)	88.5(2)
O(1)	Rh(1)	O(1B)	174.4(2)	O(2)	Rh(2)	O(2B)	177.0(2)
O(1)	Rh(1)	O(1C)	92.3(2)	O(2)	Rh(2)	O(2C)	92.5(2)
O(1)	Rh(1)	N(11)	92.3(2)	O(2)	Rh(2)	N(21)	92.2(2)
O(1A)	Rh(1)	O(1B)	89.9(2)	O(2A)	Rh(2)	O(2B)	92.4(2)
O(1A)	Rh(1)	O(1C)	175.3(2)	O(2A)	Rh(2)	O(2C)	176.2(2)
O(1A)	Rh(1)	N(11)	89.8(2)	O(2A)	Rh(2)	N(21)	92.1(2)
O(1B)	Rh(1)	O(1C)	89.4(2)	O(2B)	Rh(2)	O(2C)	86.4(2)
O(1B)	Rh(1)	N(11)	93.0(3)	O(2B)	Rh(2)	N(21)	90.6(2)
O(1C)	Rh(1)	N(11)	94.9(2)	O(2C)	Rh(2)	N(21)	91.5(2)
Rh(1)	O(1)	C(1)	119.4(5)	Rh(2)	O(2)	C(1)	113.3(6)
Rh(1)	O(1A)	C(1A)	121.4(4)	Rh(2)	O(2A)	C(1A)	119.8(4)
Rh(1)	O(1B)	C(1B)	123.7(4)	Rh(2)	O(2B)	C(1B)	120.1(4)
Rh(1)	O(1C)	C(1C)	119.7(5)	Rh(2)	O(2C)	C(1C)	115.4(4)
Rh(1)	N(11)	C(11)	133.4(4)	Rh(2)	N(21)	C(21)	129.9(4)
Rh(1)	N(11)	C(13)	124.3(4)	Rh(2)	N(21)	C(23)	119.5(4)
O(1)	C(1)	O(2)	130.9(8)	O(1)	C(1)	C(2)	119.2(6)
O(2)	C(1)	C(2)	109.2(6)	C(1)	C(2)	C(3)	111.1(7)
O(1A)	C(1A)	O(2A)	122.5(5)	O(1C)	C(1C)	O(2C)	128.7(6)
O(2A)	C(1A)	C(2A)	119.4(5)	O(2C)	C(1C)	C(2C)	114.5(6)
O(1A)	C(1A)	C(2A)	118.0(5)	O(1C)	C(1C)	C(2C)	116.8(7)
O(1B)	C(1B)	O(2B)	119.2(7)	C(1A)	C(2A)	C(3A)	116.4(6)
O(1B)	C(1B)	C(2B)	125.8(7)	C(1B)	C(2B)	C(3B)	115.2(9)
O(2B)	C(1B)	C(2B)	114.7(6)	C(1C)	C(2C)	C(3C)	121.0(9)
C(11)	N(12)	C(12)	105.0(6)	C(21)	N(22)	C(22)	105.0(5)
C(11)	N(11)	C(13)	102.2(6)	C(21)	N(21)	C(23)	110.2(5)
C(11)	N(12)	C(14)	123.5(6)	C(21)	N(22)	C(24)	124.8(6)
C(12)	N(12)	C(14)	130.1(6)	C(22)	N(22)	C(24)	129.5(5)
O(11)	N(13)	O(12)	126.0(2)	C(21)	N(23)	O(22)	118.0(7)
O(11)	N(13)	C(12)	110.1(8)	O(21)	N(23)	C(22)	118.8(8)
O(12)	N(13)	C(12)	115.0(8)	O(22)	N(23)	C(22)	119.2(6)
N(11)	C(11)	N(12)	111.4(5)	N(21)	C(21)	N(22)	110.8(6)
N(11)	C(11)	C(17)	119.1(5)	N(21)	C(21)	C(27)	129.1(5)
N(12)	C(11)	C(17)	129.4(6)	N(22)	C(21)	C(27)	120.0(5)
N(12)	C(12)	N(13)	120.6(7)	N(22)	C(22)	N(23)	127.5(6)
N(12)	C(12)	C(13)	106.6(6)	N(22)	C(22)	C(23)	108.1(5)
N(13)	C(12)	C(13)	129.0(7)	N(23)	C(22)	C(23)	122.3(7)
N(11)	C(13)	C(12)	112.9(6)	N(21)	C(23)	C(22)	104.4(6)
N(12)	C(14)	C(15)	115.4(7)	N(22)	C(24)	C(25)	110.1(7)
O(13)	C(15)	C(14)	107.3(7)	O(23)	C(25)	C(24)	110.1(6)

Table 4. Lethal doses for 10 and 50% for meprop and prop.

Compound	DL_{10} (mol/kg)	DL_{50} (mol/kg)
meprop	1.0×10^{-5}	1.6×10^{-5}
	(8.40 mg/kg)	(13.45 mg/kg)
prop	0.9×10^{-5}	1.7×10^{-5}
	(4.48 mg/kg)	(8.46 mg/kg)

planted ip and drugs injected ip or im, or given orally; (b) tumor cells implanted subcutaneously (sc) and drugs injected ip.

Metronidazole alone did not increase the life span of mice bearing an Ehrlich tumor, while **prop** and **meprop**, when given ip to mice whose tumors had been implanted ip, did produce an increased life span. ILS_{40} doses were found to be $5x10^{-6}$ M/kg and $4x10^{-6}$ M/kg for **prop** and **meprop**, respectively. In trials in which tumors were implanted and drugs administered through different routes, no ILS was observed.

The therapeutic Index (TI), defined as the relation LD_{10}/ILS_{40}, was determined as being 2.0 for **prop** and 2.2 for **meprop**.

Inhibition of DNA Synthesis

15,000 to 40,000 cells of a subconfluent stock culture of malignant adrenocortical Y-1 cell line[18] were plated in Dulbecco's modified Eagle's medium (DME) containing 10% fetal calf serum (FCS). Twenty-four hours before the addition of the test compounds, the medium was replaced with a fresh medium of equal composition. **Prop, meprop,** and **metro** solutions were prepared by dissolving the drugs in acetone and performing further dilutions with PBSA (buffered saline without Ca^{+2} and Mg^{+2}) in order to achieve final concentrations in a culture ranging from 10^{-5} to 10^{-8} M. Twelve hours after addition of the drugs, [methyl ^{3}H] thymidine (Amersham, 70-90 Ci/mmol) was added to a final concentration of 0.25 μCi/ml, 10^{-7} M.

The incorporation was monitored for the subsequent twelve hours, the uptake of the [methyl 3H] thymidine being determined by scintillography, as previously described[3].

Figure 2 shows the results of [3H]-thymidine incorporation into the Y-1 cells. A nearly 100% inhibition of incorporation was observed at drug concentrations above 10^{-6} M for **prop** and **meprop**. Metronidazole did not show any inhibiting effect, on level with acetone (10 μl, equivalent to the maximum volume present in the wells containing drugs), or untreated control cells.

Antimicrobial Activity

Minimal inhibitory concentrations (MIC) for **prop, meprop** and **metro**, were performed against bacteria (*Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 100031, *Pseudomonas aeruginosa* ATCC 227853) and yeasts (*Candida albicans* ICB 12, *Cryptococcus neoformans* ICB 59).

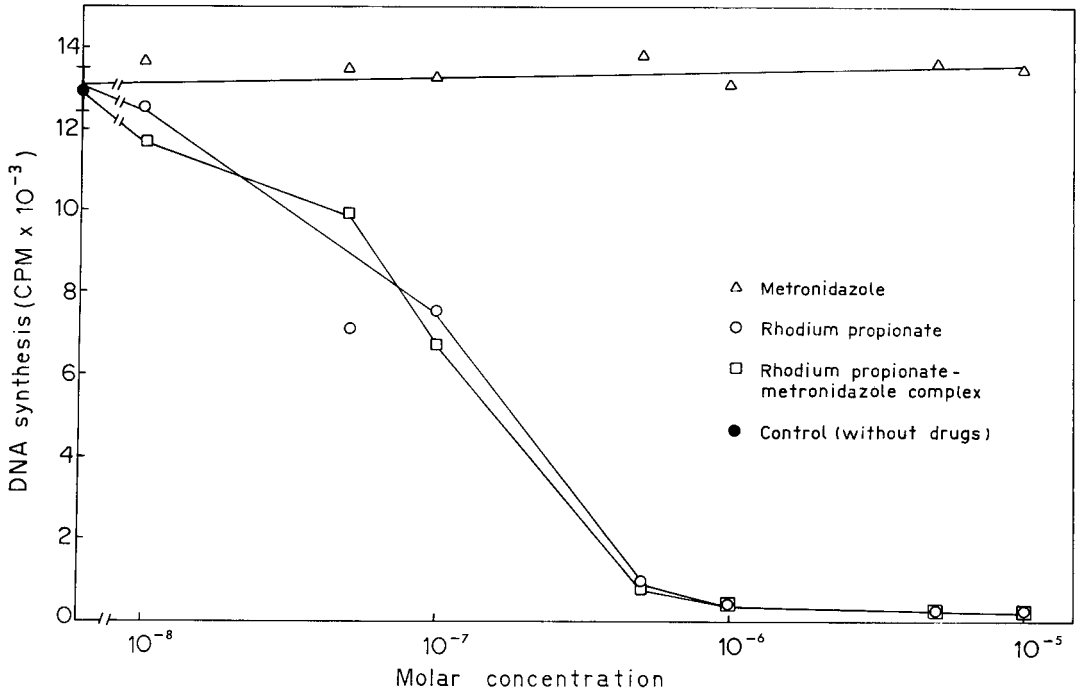

Figure 2. Inhibition of [^{3}H] – thymidine incorporation by meprop.

Table 5. MIC values for the assayed compounds in 10^{-8} M/ml and μg/ml.

Compound	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*	*E. coli*
meprop	0.6	7.0	60	60
	(5)	(60)	(500)	(500)
prop	1.0	20	> 100	> 100
	(5)	(500)	(500)	(500)
metro	290	290	290	290
	(500)	(500)	(500)	(500)

Preliminary assays with bacteria and yeasts were carried out by the cupplate agar diffusion method[19], using respectively Trypticase soy agar (Difco) and Sabouraud-dextrose agar (Difco). The compounds were dissolved in an acetone-water mixture and tested in concentrations of 500, 100, 50 and 10 μg/ml. The plates were incubated at 37 °C and the activities measured as the diameter (in mm) of the zone of inhibition surrounding the agar well, after 24 and 48 h.

A two-fold serial dilution method in liquid medium (Trypticase soy broth-Difco)[19], was employed for determining MICs. Two sets of controls were used, the organism control, without samples, and the solvent control. Antibiotic samples (streptomycin sulfate or nystatin, 0.5 mg/ml) were also tested in the agar diffusion method.

MIC values for **prop** and **meprop** in bacterial cultures are listed in Table 5.

Discussion

While studying dimeric 'lantern' type complexes bearing the general structure $[Rh_2(RCO_2)_4L_2]$, several authors attempted to correlate the nature of the axial ligands L with Rh-Rh distances. It has been suggested that an increase in the basicity of L ligands measured by their pK_b values shortens the bond. Although the correlation seemed obvious with some ligands coordinated through oxygen atoms[20], the interpretation turned into a more complex task when ligands coordinate simultaneously through σ and π interactions, as is the case with nitroimidazole ligands, and taking into account the occurrence of steric effects[21,22].

The work of Goodgame *et al.*[4] characterizes the structure of several nitroimidazole adducts with rhodium acetate and butirate. The X-ray diffraction data of these complexes evidences typical dimeric structures, the ligands binding axially to the metal atoms via their unsubstituted ring nitrogen atoms. A Rh-Rh distance of 2.399 Å was determined for the rhodium acetate-1-(2-hydroxy-3-methoxypropyl)-2-methyl-5-nitroimidazole adduct. The value is close to that found for **meprop** (2.403 Å), and similar to the distances determined for the Rh-Rh distance in other binuclear rhodium carboxylate adducts such as rhodium propionate-7-azaindole (2.403 Å)[22], rhodium acetate-DMSO (2.406 Å)[23] and rhodium propionate-DMSO (2.407 Å)[21]. Dimethylsulfoxide binds with rhodium carboxylates via the sulfur atom in these cases.

The remaining interatomic distances and angles associated with the propionate cage, in particular the distances Rh-O and Rh-N and the nearly 180° angle between Rh-Rh-N bonds are in good agreement with those found in rhodium carboxylate complexes bearing nitrogen-donor ligands[22, 24-29].

The results obtained in the acute toxicity assays are within those previously published for analogous complexes[2, 30]. LD_{10} values for rhodium acetate, propionate, and butyrate have been shown to range from 19 mg/kg to 0.7 mg/kg, indicating the occurrence of a direct correlation between toxicity and hydrophobicity.

It should be noted that the DL_{10}, DL_{50} and ILS_{40} values for **prop** and **meprop** were virtually identical. One possible explanation for this is that **meprop** may be exerting its toxic and antitumoral actions after breaking down into its two components, **metro** and **prop**, the latter being the active compound. In addiction, the antitumor activity of both complexes could be detected only when the drugs were injected ip for the treatment of an ascitic tumor. A similar behavior has been described by Fimiani *et al.* while testing rhodium(II) formamidinate[31]. This suggests that these compounds have their actions limited to the injection site due to distribution restrictions.

Although **prop** and **meprop** exhibited the same ability to inhibit DNA synthesis *in vitro,* their activities against bacteria differ significantly. Both **prop** and **meprop** strongly inhibited the development of Gram-positive (*S. aureus*) as well as Gram-negative bacteria (*P. aeruginosa*). A comparative evaluation of the MIC values shown in Table 5, expressed in M/ml and in μg/ml, indicates that the metronidazole adduct is approximately two and three times as active as the parent compound, **prop**, against *S. aureus* and *P. aeruginosa*, respectively. *E. coli* and *K. pneumoniae* showed lower sensitivities to these drugs, reacting only at concentrations equal to or above 500 g/mL. **Metro** alone inhibited *S.aureus* in concentrations equal to or above 500 μg/ml. None of the tested compounds showed activity against yeasts.

Supplementary Material

Tables of anisotropic thermal parameters, H-atom coordinates, and structure factors are available from the authors on request.

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References

1. R. G. Hughes, J. L. Bear, and A. P. Kimball, *Proc. Am. Assoc. Cancer Res.* **13**, 120 (1972).
2. A. Erck, L. Rainen, J. Whileyman, I. Chang, A. P. Kimball and J. L. Bear, *Proc. Soc. Exp. Biol. Med.* **145**, 1278 (1974).
3. S. Zyngier, E. Kimura and R. Najjar, *Braz J. Med. Biol. Res.* **22**, 397 (1989).
4. D. Goodgame, A. S. Lawrence, A. M. Z. Slawin, D. J. Williams and I. Stratford, *Inorg. Chim. Acta* **125**, 143 (1986).
5. M. S. Nothenberg, *Adutos de carboxilatos de ródio com nitroimidazóis - síntese, caracterização e avaliação de potencial antichagásico*. Doctoral Thesis, Instituto de Química, USP (1989).
6. M. S. Nothenberg, G. K. F. Takeda and R. Najjar, *J. Inorg. Biochem.* **42**, 217 (1991).
7. L. D. Dale, T. M. Dyson, D. A. Tocher, J. H. Tocher and D. I. Edwards, *Anti-Cancer Drug Des.* **4**, 295 (1989).
8. T. M. Dyson, E. C. Morrison, D. A. Tocher, L. D. Dale and D. I. Edwards, *Inorg. Chim. Acta* **169**, 127 (1990).
9. R. J. Bromfield, R. H. Dainty, R. D. Gillard and B. T. Heaton, *Nature* **223**, 735 (1969).
10. N. Walker and D. Stuart, *Acta Cryst.* **A39**, 158 (1983).
11. R. F. Stewart, E. R. Davidson and W. T. Simpson, *J. Chem. Phys.* **42**, 3175 (1965).
12. D. T. Cromer and D. Liberman, *J. Chem. Phys.* **53**, 1891 (1970).
13. D. T. Cromer and J. B. Mann, *Acta Cryst.* **A24**, 321 (1968).
14. G. M. Sheldrick, *SHELX76, Program for crystal structure determination*, University of Cambridge, U.K. (1976).
15. C. K. Johnson, *ORTEP, Rep. ORNL-3794*, Oak Ridge National Laboratory, TN (1965).
16. J. H. Burn, *Biological Standardization*, 2nd Ed. Vol. 1, Oxford Univ. Press (1950).
17. H. E. Skipper and L. H. Schmidt, *Cancer Chemoth. Rep.* **17**, 1 (1962).
18. Y. Yasumura, V. Buonassini and G. Sato, *Cancer Res.* **26**, 529 (1966).
19. V. Lorian, *Antibiotics in Laboratory Medicine*, Williams and Wilkins, Baltimore (1980).
20. M. Moszner, T. Glowiak and J. J. Ziolkowski, *Polyhedron* **4**, 1413 (1985).
21. F. A. Cotton and T. R. Felthouse, *Inorg. Chem.* **19**, 2347 (1980).
22. F. A. Cotton and T. R. Felthouse, *Inorg. Chem.* **20**, 600 (1981).
23. F. A. Cotton and T. R. Felthouse, *Inorg. Chem.* **19**, 320 (1980).
24. E. B. Boyar and S. D. Robinson, *Coord. Chem. Rev.* **50**, 109 (1983).
25. T. R. Felthouse, *Prog. Inorg. Chem.* **29**, 73.(1982).
26. N. Farrell, M. D. Vargas, Y. P. Mascarenhas and M. T. P. Gambardella, *Inorg. Chem.* **26**, 1426 (1987).
27. F. A. Cotton and T. R. Felthouse, *Acta Cryst.* **C40**, 42 (1984).
28. Y. B. Koh and G. G. Christoph, *Inorg. Chem.* **17**, 2590 (1978).
29. Y. B. Koh and G. G. Christoph, *Inorg. Chem.* **18**, 1122 (1979).
30. R. A. Howard, E. Sherwood, A. Erck, A. P. Kimball and J. L. Bear, *J. Med. Chem.* **20**, 943 (1977).
31. V. Fimiani, T. Ainis, A. Cavallaro and P. Piraino, *J. Chemother.* **2**, 319 (1990).