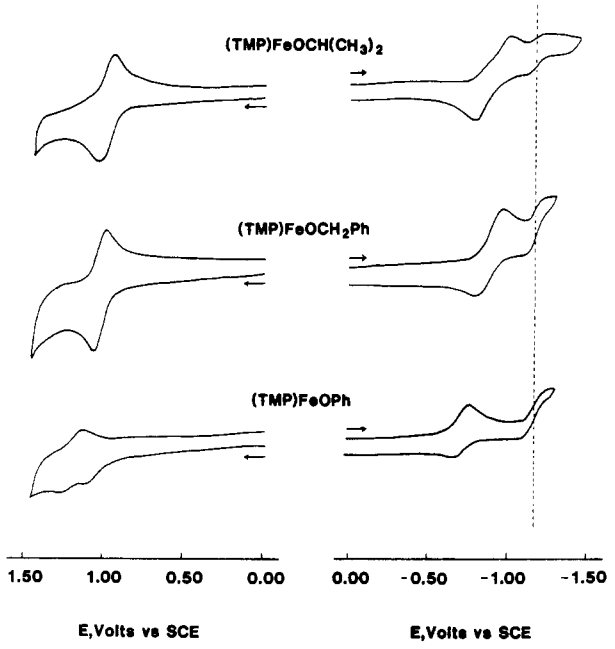

Figure 12. Cyclic voltammograms of (TMP)FeOCH$(CH_3)_2$, (TMP)-FeOCH$_2$Ph, and (TMP)FeOPh in CH_2Cl_2, 0.1 M (TBA)ClO_4.

complexes of (TMP)Fe(OR) from (TMP)FeCl or (TMP)$FeClO_4$, which have meta proton resonances at 16.0, 14.4, and 10.5 ppm, respectively.[1,2]

Figure 12 shows cyclic voltammograms of (TMP)FeOCH-$(CH_3)_2$, (TMP)FeOCH$_2$Ph, and (TMP)FeOPh in the presence of excess coordinating ligand. Half-wave and peak potentials of the (TMP)FeOR complexes are virtually identical with those of (TMP)$FeOCH_3$ and (TMP)FeOH under the same experimental conditions. (TMP)FeOPh has a single anodic peak for the first oxidation, and its reduction potential is shifted positively compared to those of the other alcoholate complexes. This suggests a lower electron density on the metal and indicates that the oxidized product is even less stable than the other complexes.

The first oxidation product can be stabilized at low temperature. The two other alcoholate-bound complexes have essentially the same oxidation behaviors. However, (TMP)FeOCH$(CH_3)_2$ clearly shows a mixture upon reduction. This mixture probably contains [(TMP)FeOCH$(CH_3)_2]^-$, [(TMP)FeOCH$(CH_3)_2]^{2-}$, and (TMP)Fe.

In summary, (TMP)FeOH and (TMP)$FeOCH_3$ have similar physicochemical properties and similar electrochemistries. The only difference between these two complexes is the oxidation products at low temperature in the absence of excess ligand. Similar results are also obtained when other alcoholates are substituted for OH^- or OCH_3^-. The only exception occurs when the axial ligand is not sufficiently electron donating. This is illustrated by (TMP)FeOPh, which is easier to reduce. The electrooxidation product is also unstable, and (TMP)Fe$(OPh)_2$ does not seem to contain iron(IV) at low temprature.

Acknowledgment. The support of the National Institutes of Health (Grant No. GM-25172) is gratefully acknowledged.

Registry No. (TMP)FeOH, 77439-20-4; (TMP)$FeOCH_3$, 93842-72-9; (TMP)FeOPh, 111435-61-1; (TMP)FeOCH$_2$Ph, 111468-45-2; (TMP)FeOCH$(CH_3)_2$, 111435-62-2; (TMP)Fe(ClO_4), 94423-72-0; (TMP)FeCl, 77439-21-5; (TMP)Fe$(OCH_3)_2$, 93862-19-2; (TMP)Fe-$(OCH_3)ClO_4$, 111435-63-3; [(TMP)Fe$(OH)_2]^-$, 111435-64-4; [(TMP)-Fe$(OH_3)_2]^-$, 111435-65-5; (TMP)Fe, 81567-13-7; [(TMP)Fe$(ClO_4)_2]^+$, 111435-60-0; (TMP)Fe$(ClO_4)_2$, 93842-71-8; NaOCH$_2$Ph, 20194-18-7; NaOCH$(CH_3)_2$, 683-60-3; $NaOCH_3$, 124-41-4; (TBA)OH, 2052-49-5; (TBA)ClO_4, 1923-70-2.

Contribution from the Anorganisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, 6900 Heidelberg, FRG

Synthesis, Molecular Structure, and Tumor-Inhibiting Properties of Imidazolium *trans*-Bis(imidazole)tetrachlororuthenate(III) and Its Methyl-Substituted Derivatives

B. K. Keppler,* W. Rupp, U. M. Juhl, H. Endres, R. Niebl, and W. Balzer

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The synthesis, the molecular structure, and the antitumor activity of ImH$(RuIm_2Cl_4)$ and, in addition, the synthesis and antitumor screening data of three methyl-substituted derivatives as well as the molecular structure of one of these are described in this paper. $[ImH]^+[RuCl_4Im_2]^-$ (**1**): $(C_2H_5N_2)^+(C_6H_8Cl_4N_4Ru)^-$; M_r = 448.13; monoclinic; $C2/c$; a = 13.266 (3), b = 8.047 (1), c = 16.514 (4) Å; β = 112.53 (2)°; V = 1628 Å^3; Z = 4; D_{calcd} = 1.83 g cm^{-3}. The final R_w was 0.029 for 1710 reflections and 106 parameters. $[4\text{-MeImH}]^+[Ru(4\text{-MeIm})_2Cl_4]^-$ (**2**): $(C_4H_7N_2)^+(C_8H_{12}Cl_4N_4Ru)^-$; M_r = 490.21; monoclinic; $P2_1/a$; a = 12.947 (3), b = 10.484 (3), c = 14.170 (4) Å; β = 108.22 (2)°; V = 1827 Å^3; Z = 4; D_{calcd} = 1.78 g cm^{-3}. The final R_w was 0.039 for 2563 reflections and 211 parameters. The antitumor activity was investigated in the P 388 leukemia, the Walker 256 carcinosarcoma, and the intramusculary transplanted sarcoma 180. In the P 388 leukemia model, the lifespan of the animals treated with ImH$(RuIm_2Cl_4)$ was increased up to T/C values of 194%. The activity was in the same range as or was slightly better than in the case of cisplatin, which was tested as a positive control. 5-Fluorouracil was less active compared to this metal complex. The compound showed promising activity also in the Walker 256 carcinosarcoma and the sarcoma 180 models.

The aim of our research in the field of antitumor-active metal complexes is to develop new compounds for the treatment of cancer. Preferably these compounds should be active against those human tumors that cannot be treated sufficiently by standard chemotherapy protocols.[1,2]

Recently, we described a new tumor-inhibiting ruthenium complex, bis(imidazolium) (imidazole)pentachlororuthenate(III), $(ImH)_2(RuImCl_5)$.[3] Now we present the synthesis, molecular structure, and antitumor activity of imidazolium *trans*-bis(imidazole)tetrachlororuthenate(III) and, in addition, the synthesis and antitumor screening data of three methyl-substituted derivatives

* To whom correspondence should be addressed.

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as well as the molecular structure of one of these.

Experimental Section

Preparation of the Ruthenium Compounds. The following procedures were carried out under argon.

To obtain a ruthenium solution in the oxidation stage +III, the procedure described below is necessary for purification of commercially available "$RuCl_3 \cdot xH_2O$", which was provided by Degussa, Hanau, FRG. In the following, this solution is termed the "ruthenium solution".

Preparation of the "Ruthenium Solution". $RuCl_3$ (10 g, 38.25 mmol) was dissolved in a mixture of ethanol (250 mL) and 1 N HCl (250 mL), and the mixture was refluxed for 3 h. Then the solution was evaporated to 90 mL, and 1 N HCl was added to give a total volume of 120 mL.

Synthesis of Imidazolium *trans*-Bis(imidazole)tetrachlororuthenate(III), ImH(*trans*-RuIm$_2$Cl$_4$) (ICR). The preparation of this compound has been described previously,[4] but it could not be reproduced that way. The synthesis was improved as described below, with the result that we obtained a crystalline product adequate for X-ray analysis:

A 10-mL sample of ruthenium solution was rapidly added to a suspension of 2.0 g of imidazole (29.4 mmol) in 1 mL of 6 N HCl, and the mixture was stirred for a few minutes. Immediately afterward, the solution was cooled by an ice/$CaCl_2$ mixture. Two hours later the solution was allowed to stand for 2 days at room temperature. Then large, brownish red crystals were filtered off, washed with H_2O/ethanol, and dried under vacuum. Yield: 1.0 g = 60.3%. Anal. Calcd for $C_9H_{13}Cl_4N_6Ru$ (M_r = 448.13): C, 24.12; H, 2.92; N, 18.75; Ru, 22.56; Cl, 31.64. Found: C, 24.4; H, 3.1; N, 18.8; Ru 22.4; Cl, 31.1.

Synthesis of 1-Methylimidazolium *trans*-Bis(1-methylimidazole)-tetrachlororuthenate(III), 1-MeImH[*trans*-Ru(1-MeIm)$_2$Cl$_4$]. A 10-mL quantity of ruthenium solution was added to a suspension of 1.8 g (21.93 mmol) of 1-methylimidazole in 2 mL of 8 N HCl; the mixture was stirred for 2 min and kept at 8 °C for 4 days. Then brownish red crystals were filtered off, washed with water, ethanol, and ether, and dried under P_2O_5. Yield: 0.6 g = 16.74%. Anal. Calcd for $C_{12}H_{19}C_4N_6Ru$ (M_r = 490.05): C, 29.41; H, 3.88; N, 17.15; Cl, 28.94; Ru, 20.62. Found: C, 29.29; H, 3.94; N, 17.13; Cl, 28.78.

Synthesis of 2-Methylimidazolium *trans*-Bis(2-methylimidazole)-tetrachlororuthenate(III), 2-MeImH[*trans*-Ru(2-MeIm)$_2$Cl$_4$]. A 5-mL sample of ruthenium solution was added to a suspension of 2.4 g (30 mmol) of 2-methylimidazole in 2 mL of 8 N HCl, and the mixture was heated up to 50 °C. The solution was then gradually cooled down to room temperature and kept at 8 °C for 1 week. The resulting light red brownish crystals were drawn off, washed with only a little water, and dried under vacuum. Yield: 0.3 g = 6.28%. Anal. Calcd for $C_{12}H_{19}Cl_4N_6Ru$ (M_r = 490.05): C, 29.40; H, 3.88; N, 17.14; Cl, 28.93; Ru, 20.62. Found: C, 29.04; H, 3.80; N, 17.22; Cl, 27.90.

Synthesis of 4-Methylimidazolium *trans*-Bis(4-methylimidazole)-tetrachlororuthenate(III), 4-MeImH[*trans*-Ru(4-MeIm)$_2$Cl$_4$]. A 5-mL quantity of ruthenium solution was added to a suspension of 2.4 g (29.23 mmol) of 4-methylimidazole in 2 mL of 8 N HCl, and the mixture was heated up to 60 °C while being stirred. Then the solution was allowed to stand for 1 day at 8 °C. The resulting brownish red crystals were drawn off, washed with water, ethanol, and ether, and dried under vacuum. Yield: 0.2 g = 20.7%. Anal. Calcd for $C_{12}H_{19}Cl_4N_6Ru$ (M_r = 490.05): C, 29.40; H, 3.91; N, 17.14; Cl, 28.93; Ru, 20.62. Found: C, 29.70; H, 4.0; N, 17.0; Cl, 28.20; Ru, 19.80.

Elemental Analyses. The elemental analysis of chlorine was carried out by argentometry, and that of ruthenium by neutron activation analysis.

Infrared Spectra. Infrared spectra were recorded on a Perkin-Elmer 983 G IR spectrophotometer.

X-ray Investigations. Crystals were mounted on top of glass capillaries, and data collections were carried out at room temperature. Cell dimensions were determined from the setting angles of a number of reflections centered on a diffractometer (Siemens-Stoe AED 2), using monochromated Mo Kα radiation. Weissenberg photographs indicated monoclinic symmetry for both crystals. An empirical absorption correction was performed with a SHELXTL[5] routine. Equivalent reflections were not measured.

Structure Solution and Refinement. The structures were solved by locating the Ru and some of the Cl atoms from Patterson maps, and the positions of the remaining nonhydrogen atoms were obtained from Fourier syntheses. H atoms were not considered. Refinement with anisotropic temperature factors was carried out by block-matrix least squares on an Eclipse computer with the STRUCSY[6] program system, using scattering factors from ref 7 and taking anomalous dispersion into account. The function minimized was $\sum w^{1/2}(||F_o| - |F_c||)$ with weights $w = 1/\sigma^2(F)$ and σ from counting statistics. R and R_w are defined accordingly. The graphical representation was made on a Tektronix plotter with SHELXTL[5] running on a Nova 3 computer.

Table I. Crystal Data and Details of the Structure Determinations and Refinements

	ImH-(*trans*-RuIm$_2$Cl$_4$)	4-MeImH-[*trans*-Ru(4-MeIm)$_2$Cl$_4$]
formula	$C_9H_{13}Cl_4N_6Ru$	$C_{12}H_{19}Cl_4N_6Ru$
mol wt	448.13	490.21
cryst syst	monoclinic	
space group	$C2/c$	$P2_1/a$
a, Å	13.266 (3)	12.947 (3)
b, Å	8.047 (1)	10.484 (3)
c, Å	16.514 (4)	14.170 (4)
β, deg	112.53 (2)	108.22 (2)
vol, Å^3	1628	1827
Z	4	4
d_{calcd}, g cm^{-3}	1.83	1.78
μ, cm^{-1}	14.8	13.2
cryst dimens, mm	0.04 × 0.3 × 0.23	0.08 × 0.2 × 0.27
diffractometer	Siemens-Stoe AED 2	
data collected	$+h,+k,\pm l$	
radiation (λ, Å)	Mo Kα (0.710 69)	
scan technique	θ–2θ	
max 2θ, deg	60	
no. of unique reflcns measd	2375	5330
no. of obsd. reflcns	1710	2563
criterion	$I > 2.5\sigma(I)$	
abs cor	empirical	
min transmission	0.66	0.68
programs used	SHELXTL[5]	
scattering factors	neutral atoms	
R_w, R	0.029, 0.032	0.039, 0.046
goodness of fit	2.71	1.99
no. of params	106	211
max shift/error	0.9	0.14
residual electron density, e/Å^3	0.61	0.71

Animal Experiments. BDF_1 mice were provided by Charles River Wiga, Sulzfeld, FRG, DBA/2 mice and SD rats by Savo-Ivanovas, Kisslegg, FRG, and NMRI mice by Versuchtierzucht Winkelmann, Borchen, FRG.

P 338 Leukemia. P 388 leukemia cells were implanted intraperitoneally into DBA/2 mice for propagation 7 days before the experiment. The tumor cells were taken from these animals at the beginning of the experiment immediately after cervical dislocation. Then we implanted 10^6 of these cells, suspended in 0.2 mL of physiological saline, intraperitoneally into female BDF_1 mice, body weight ~18 g, for testing. The mice were divided arbitrarily into groups consisting of six animals each. Imidazolium *trans*-bis(imidazole)tetrachlororuthenate(III) (ICR) was given to the first group in a single dose (209.3 mg/kg, 0.45 mmol/kg) on day 1, to the second group in three doses (69.8 mg/kg, 0.15 mmol/kg) on days 1, 5, and 9, and to the third group in nine doses (23.3 mg/kg, 0.05 mmol/kg) on days 1–9. 5-Fluorouracil and cisplatin were administered in doses of 60 and 3 mg/kg, respectively, on days 1, 5, and 9. The compounds were given intraperitoneally, dissolved in 20 mL/kg of physiological saline. Evaluation: The median survival time of the treated animals was compared to the median survival time of the untreated control animals. T/C (%) = [(median survival time of treated animals)/(median survival time of control animals)] × 100. The statistical evaluation was done according to the Steel test.

Walker 256 Carcinosarcoma. Walker 256 carcinosarcoma cells were taken from tumor-bearing animals on day 5 after intraperitoneal tumor transplantation. Then 10^6 of these cells, suspended in 0.5 mL of physiological saline, were implanted intraperitoneally into female SD rats, body weight ~150 g, for testing. The rats were divided arbitrarily into two groups consisting of six animals each. The first group of untreated animals served as control. The second group was treated with 50 mg/kg of imidazolium *trans*-bis(imidazole)tetrachlororuthenate(III) (ICR) given intraperitoneally on days 1, 2, and 3. Evaluation: The median

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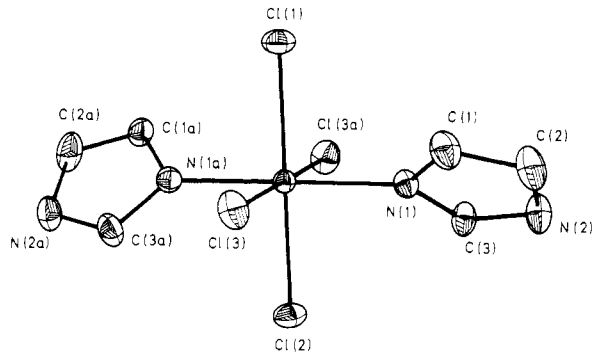

Figure 1. Numbering scheme in the $[RuCl_4Im_2]^-$ anion in **1**. Thermal ellipsoids include 20% probability.

Table II. Atom Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors ($Å^2 \times 10^3$) for ImH(*trans*-$RuCl_4Im_2$)

atom	*x*	*y*	*z*	U_{eq}[a]
Ru(1)	0	1209 (1)	2500	35.5 (2)
Cl(1)	0	4129 (2)	2500	82 (2)
Cl(2)	0	−1700 (2)	2500	47 (1)
Cl(3)	−0116 (1)	1212 (2)	3888 (1)	61 (1)
N(1)	1694 (3)	1201 (5)	3093 (2)	44 (2)
N(2)	3402 (3)	0532 (6)	3383 (3)	68 (3)
N(3)[b]	2998 (6)	2231 (8)	0702 (9)	74 (9)
N(4)[b]	3252 (18)	3071 (47)	0491 (26)	59 (11)
C(1)	2345 (4)	2076 (7)	3815 (4)	59 (3)
C(2)	3388 (4)	1677 (8)	3990 (4)	74 (4)
C(3)	2357 (4)	0288 (6)	2848 (3)	56 (3)
C(4)[b]	2303 (52)	1710 (71)	0465 (50)	102 (20)
C(5)[b]	1887 (38)	8381 (48)	4980 (52)	89 (19)

[a] U_{eq} is defined as one-third of the trace of the U_{ij} tensor. [b] Site occupation factor = 0.5 due to disorder.

survival time of the treated animals was compared to the median survival time of the untreated control animals. The statistical evaluation was done according to the U test.

Sarcoma 180. 10^6 sarcoma 180 tumor cells, suspended in physiological saline, were implanted intramusculary into the left hind leg of female NMRI mice, body weight ~25 g, for testing. These cells had been taken from donor animals of the same species immediately before transplantation. Then the mice were divided arbitrarily into three groups consisting of 12 animals each. The first group served as control. Doses of 81 mg/kg of imidazolium *trans*-bis(imidazole)tetrachlororuthenate(III) were given to the second group and 1.8 mg/kg of cisplatin to the third group on days 6, 8, and 10. Both compounds were dissolved in 20 mL/kg of physiological saline and administered intravenously. The animals were sacrificed on day 15 after tumor transplantation, and the tumor was exactly weighed. Evaluation: The median tumor weight of the untreated animals was compared to the median tumor weight of the treated animals. *T/C* (%) = [(median tumor weight of the treated animals)/(median tumor weight of the control animals)] × 100. Statistical evaluation was done according to the Steel test.

Results and Discussion

The infrared spectra of the four compounds prepared show the following bands in the region responsible for ruthenium ligand bonds: 294 (w), 333 (s), 245 cm^{-1} (m) for ImH(*trans*-$RuIm_2Cl_4$); 273 (m), 320 (s), 244 cm^{-1} (w) for 1-MeImH[*trans*-Ru(1-MeIm)$_2Cl_4$]; 272 (m), 326 cm^{-1} (s) for 2-MeImH[*trans*-Ru(2-MeIm)$_2Cl_4$]; 285 (s), 318 (s), 242 cm^{-1} (w) for 4-MeImH[*trans*-Ru(4-MeIm)$_2Cl_4$] (s = strong, m = medium, and w = weak). From literature data, the first two bands listed in the above order should be assignable to Ru–Cl stretching vibrations.[8] There is, however, not enough literature for assigning the bands between 242 and 245 cm^{-1}, but it might be suggested that these bands can be assigned to Ru–N stretching vibrations, in analogy to Cu(Im)$_4Cl_2$ and Cu(2-MeIm)$_4Cl_2$.[9] UV spectra of ImH(*trans*-$RuIm_2Cl_4$) and some related compounds were recorded previously.[4] Provided that ruthenium is in the oxidation stage +III and is coordinated to a heterocyclic ligand, the spectra are almost identical, each showing an absorption maximum of 300–400 nm.

Description of the Structures. Views of the complex anions in **1** and **2** are shown in Figures 1 and 2, together with the numbering schemes. Atom coordinates are listed in Tables II and III; bond distances and angles, in Tables IV and V. The asymmetric unit of **1** consists of half a complex anion with Ru, Cl(1), and Cl(2)

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Table III. Atom Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors ($Å^2 \times 10^3$) for 4-MeImH[*trans*-Ru(4-MeIm)$_2Cl_4$]

atom	*x*	*y*	*z*	U_{eq}[a]
Ru(1)	0	0	0	28.5 (5)
Cl(1)	1526 (1)	1214 (2)	−30 (1)	47 (1)
Cl(2)	1091 (2)	−1851 (2)	183 (1)	43 (1)
N(1)	439 (4)	202 (6)	1541 (4)	37 (4)
N(2)	806 (5)	1072 (7)	3000 (4)	45 (4)
C(1)	681 (6)	1304 (8)	2021 (5)	46 (5)
C(2)	641 (6)	−226 (7)	3126 (5)	44 (5)
C(3)	401 (6)	−781 (8)	2196 (5)	42 (5)
C(4)	703 (8)	−813 (9)	4116 (6)	69 (6)
Ru(2)	5000	0	5000	29.2 (5)
Cl(3)	3390 (2)	1076 (2)	4973 (1)	44 (1)
Cl(4)	4176 (2)	−1943 (2)	5251 (2)	46 (1)
N(3)	4346 (5)	−256 (6)	3467 (4)	33 (3)
N(4)	3219 (5)	−688 (6)	1991 (4)	44 (4)
C(5)	3329 (5)	−599 (7)	2980 (5)	39 (4)
C(6)	4196 (6)	−368 (6)	1857 (5)	39 (4)
C(7)	4898 (5)	−114 (8)	2781 (5)	41 (4)
C(8)	4350 (7)	−354 (8)	840 (6)	56 (5)
N(5)	3146 (6)	2799 (7)	3039 (6)	60 (5)
N(6)	3057 (5)	4066 (8)	1786 (5)	58 (5)
C(9)	3259 (7)	2864 (10)	2134 (8)	68 (7)
C(10)	2852 (7)	3999 (9)	3282 (6)	55 (6)
C(11)	2797 (5)	4769 (7)	2500 (6)	48 (5)
C(12)	2576 (9)	6166 (9)	2370 (9)	94 (8)

[a] Defined as in Table II.

Table IV. Bond Distances (Å) and Angles (deg) for ImH(*trans*-$RuCl_4Im_2$), Not Including the Disordered Cation

Ru(1)–Cl(1)	2.350 (2)	C(1)–C(2)	1.339 (8)
Ru(1)–Cl(2)	2.342 (1)	C(2)–N(2)	1.367 (8)
Ru(1)–Cl(3)	2.356 (1)	N(2)–C(3)	1.342 (6)
Ru(1)–N(1)	2.079 (3)	C(3)–N(1)	1.324 (6)
N(1)–C(1)	1.369 (6)		
Cl(1)–Ru(1)–N(1a)	90.2 (1)	N(1)–C(1)–C(2)	108.7 (4)
Cl(2)–Ru(1)–N(1a)	89.8 (1)	C(1)–C(2)–N(2)	107.8 (5)
Cl(3a)–Ru(1)–N(1)	89.8 (1)	C(2)–N(2)–C(3)	106.4 (5)
Cl(1)–Ru(1)–Cl(3)	89.9 (1)	N(1)–C(3)–N(2)	110.9 (4)
Cl(2)–Ru(1)–Cl(3)	90.1 (1)	Ru(1)–N(1)–C(3)	125.7 (4)
Ru(1)–N(1)–C(1)	128.7 (4)		

Table V. Bond Distances (Å) and Angles (deg) for 4-MeImH[*trans*-Ru(4-MeIm)Cl_4], Not Including the Cation

Ru(1)–Cl(1)	2.361 (2)	C(6)–C(8)	1.52 (1)
Ru(1)–N(1)	2.087 (6)	Ru(1)–Cl(2)	2.366 (2)
N(1)–C(3)	1.40 (1)	N(1)–C(1)	1.33 (1)
N(2)–C(1)	1.37 (1)	N(2)–C(2)	1.40 (1)
C(2)–C(3)	1.38 (1)	C(2)–C(4)	1.51 (1)
Ru(2)–Cl(3)	2.360 (2)	Ru(2)–Cl(4)	2.369 (2)
Ru(2)–N(3)	2.088 (5)	N(3)–C(5)	1.330 (8)
N(3)–C(7)	1.382 (9)	N(4)–C(5)	1.367 (9)
N(4)–C(6)	1.38 (1)	C(6)–C(7)	1.37 (1)
Cl(1)–Ru(1)–Cl(2)	88.3 (1)	Cl(3)–Ru(2)–Cl(4)	88.5 (1)
Cl(1)–Ru(1)–N(1)	90.5 (2)	Cl(3)–Ru(2)–N(3)	88.7 (2)
C(2)–Ru(1)–N(1)	90.6 (2)	Cl(4)–Ru(2)–N(3)	89.4 (2)
Ru(1)–N(1)–C(1)	124.6 (6)	Ru(2)–N(3)–C(5)	126.0 (5)
Ru(1)–N(1)–C(3)	124.5 (5)	Ru(2)–N(3)–C(7)	125.9 (5)
C(1)–N(1)–C(3)	110.6 (9)	C(5)–N(3)–C(7)	108.1 (7)
C(1)–N(2)–C(2)	109.2 (8)	C(5)–N(4)–C(6)	108.6 (8)
N(1)–C(1)–N(2)	107.5 (6)	N(3)–C(5)–N(4)	108.6 (6)
N(2)–C(2)–C(3)	106.6 (7)	N(4)–C(6)–C(7)	106.2 (6)
N(2)–C(2)–C(4)	123.3 (9)	N(4)–C(6)–C(8)	122.2 (8)
C(3)–C(2)–C(4)	130.2 (10)	C(7)–C(6)–C(8)	131.6 (10)
N(1)–C(3)–C(2)	106.2 (6)	N(3)–C(7)–C(6)	108.5 (6)

Table VI. Antitumor Activity of Imidazolium *trans*-Bis(imidazole)tetrachlororuthenate(III), ImH(*trans*-RuIm$_2$Cl$_4$) (ICR), Compared with Cisplatin and 5-Fluorouracil against the P 388 Leukemia, the Walker 256 Carcinosacoma, and the Intramusculary Transplanted Sarcoma 180

(A) P 388 Leukemia

	no. of mice	ip treatment on days	T/C,[a] %	no. of animals reaching a T/C value of 150%[c]
control animals	18		100	1/18
cisplatin				
3 mg/kg, 0.01 mmol/kg	6	1, 5, 9	175[b]	5/6
5-fluorouracil				
60 mg/kg, 0.46 mmol/kg	6	1, 5, 9	144[b]	3/6
ImH(*trans*-RuIm$_2$Cl$_4$) (ICR)				
209.3 mg/kg, 0.45 mmol/kg	6	1	156[b]	5/6
69.8 mg/kg, 0.15 mmol/kg	6	1, 5, 9	194[b]	5/6
23.3 mg/kg, 0.05 mmol/kg	6	1–9	163[b]	5/6

(B) Walker 256 Carcinosarcoma

	no. of rats	ip treatment on days	T/C,[a] %	no. of animals reaching a T/C value of 150%[c]
control animals	6		100	0/6
50 mg/kg, 0.11 mmol/kg	6	1, 2, 3	230[d]	6/6

(C) Sarcoma 180, Intramusculary Transplanted

	no. of mice	iv treatment on days	T/C,[e] %
control animals	12		100
cisplatin, 1.8 mg/kg, 0.006 mmol/kg	12	6, 8, 10	54
ICR, 81.0 mg/kg, 0.18 mmol/kg	12	6, 8, 10	45[b]

[a] Evaluation parameter = survival time. [b] Significant from control according to the Steel test, $\alpha < 0.05$. [b] Animals that do not reach a T/C value of 50% and animals that reach a T/C value of 300% (long-time survivors) were not observed in any group, including the control group. [d] Significant from control according to the U test, $\alpha < 0.05$. [e] Evaluation parameter = tumor weight.

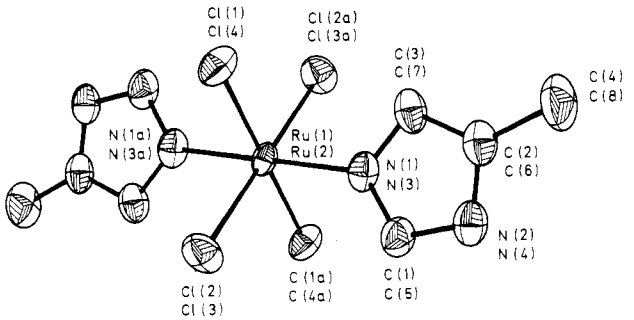

Figure 2. Numbering scheme in the [Ru(4-MeIm)$_2$Cl$_4$]$^-$ anion in **2**. Upper numbers refer to the molecule at 0, 0, 0; lower numbers, to that at 0.5, 0, 0.5. Thermal contours (at 50% probability) are drawn for the first molecule.

on a twofold rotation axis and half a cation disordered around a crystallographic inversion center (at 0.25, 0.25, 0). In a difference Fourier map this cation showed up as an eight-membered ring around the inversion center, which is interpreted as an appropriate superposition of two five-membered rings with occupation parameters 0.5. It was refined accordingly. In **2** there are two independent complex anions with the Ru atoms at crystallographic inversion centers and a cation at a general position. Corresponding bond distances and angles in these two anions are identical within their accuracy. In structure **2** the planes of the two organic trans ligands are parallel by symmetry; in **1** they are nearly perpendicular to one another (84°).

Antitumor Activity Tests. Antitumor activity of ruthenium compounds, e.g. cis-[Ru(NH$_3$)$_4$Cl$_2$]Cl and Ru(DMSO)$_4$Cl$_2$, has been known for some time.[10-13] The former compound has shown better activity against the P 388 leukemia than the latter (T/C = 157%), but there are no sufficient data available on the former compound as to the conditions of the biological experiments carried out. Ru(DMSO)$_4$Cl$_2$ is less active in the P 388 screen (T/C = 125%), but promising results could rather be obtained in inhibiting metastasis of the Lewis lung carcinoma. As to the biodistribution of ruthenium, literature gives evidence that this may be influenced by transferrin binding.[14]

The results of the activity of our test compound ICR against the P 388 leukemia, the Walker 256 carcinosarcoma, and the sarcoma 180 are summarized in Table VI. Preliminary results that indicated antitumor activity were published by us previously.[15] In further experiments we determined the optimum dose of imidazolium *trans*-bis(imidazole)tetrachlororuthenate(III) and tested the compound against three different experimental tumor models. The maximum tolerable dose in the P 388 model (BDF$_1$ mice) turned out to be 0.45 mmol/kg. This dose was given in three different dose schedules: the total dose was applied as a single dose on day 1, divided into three doses on days 1, 5, and 9, and divided into nine doses on days 1–9. The best effect was observed with the treatment schedule of 0.15 mmol/kg on the days 1, 5, and 9, which increased the survival time of the treated animals up to a T/C value of 194%, compared to the control animals. In the other application schemes T/C values of 156% and 162% were reached. Compared with this, 5-fluorouracil and cisplatin increased the survival time of the tumor-bearing animals up to T/C values of 144% and 175%, respectively. When the different compounds in Table VI are compared, it is obvious that the tested ruthenium complex is slightly more effective than cisplatin in treating the animals on days 1, 5, and 9. In any case, the ruthenium complex is more effective than 5-fluorouracil in all treatment schedules. Promising effects of the compound were also obtained in the Walker 256 carcinosarcoma, where survival time of the animals treated with ICR was more than doubled, and in the intramusculary transplanted sarcoma 180 model, where tumor weight of the treated animals was more than halved. In the case

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of the intramusculary transplanted sarcoma 180 tumor, ICR was not given at the site of the tumor, as in the P 388 and Walker 256 tumor model, which are so-called "ip-ip" models, but it was applied intravenously in order to treat a tumor growing in solid form in the left hind leg of the animal. Such models are necessary to evaluate the systemic effect of a compound. Prerequisite for this is an appropriate galenic formulation or a water-soluble compound that is stable enough against hydrolysis during dissolution and treatment, as is the case with our ruthenium compound ICR. The ip-ip models do not take the systemic effect into account, because the drug is applied at the site of the tumor. This is why such additional models are necessary, where a solid tumor is treated by intravenous application, in order to evaluate the systemic effect of a substance that is indispensable for a sufficient cancer therapy. Toxicity in terms of body weight change was tolerable in all three models. From a preliminary P 388 screen it could be concluded that the three methyl-substituted derivatives are less active than the unsubstituted compound. The T/C values obtained were in the range between 130% and 150%. Higher values may be possible by further evaluation of the optimum dose and dose schedule.

The reported activity against the transplantable tumor models described above indicates tumor-inhibiting properties in general, but it cannot guarantee activity of the test compound against specific human organ tumors. Within the range of human tumors, gastrointestinal cancers are one of the major causes of cancer mortality in the western world. No really sufficient chemotherapy against this type of tumors could be established until now. Due to this fact, the title compound, imidazolium *trans*-bis(imidazole)tetrachlororuthenate(III) (ICR), was tested by Garzon et al.[16] against autochthonous colorectal tumors in rats, which are highly predictive for the clinical situation in humans. In this model, promising effects of this compound were observed.

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Registry No. 1, 103875-27-0; 2, 111137-62-3; 2-MeImH[*trans*-Ru(2-MeIm)$_2$Cl$_4$], 111137-60-1; 1-MeImH[*trans*-Ru(1-MeIm)$_2$Cl$_4$], 111026-31-4.

Supplementary Material Available: Tables of anisotropic thermal parameters (3 pages); listings of structure factors (22 pages). Ordering information is given on any current masthead page.

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Contribution from the Laboratoire de Cinétique Chimique, Université Pierre et Marie Curie, 1 Rue Guy de la Brosse, 75005 Paris, France, and Laboratoire de Chimie des Metaux de Transition and Laboratoire de Chimie des Polymères Inorganiques, Université Pierre et Marie Curie, 8 Rue Cuvier, 75252 Paris Cedex 05, France

Heterobimetallic Complexes of Copper(I) with Thiotungstates and Thiomolybdates. Synthesis and Structural Characterization of $(PPh_4)_2[(CuNCS)_2WS_4]$ and of Polymeric $(PPh_4)_2[(CuNCS)_4WS_4]$

C. Potvin,*† J.-M. Manoli,† F. Sécheresse,‡ and S. Marzak§

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Reaction of $(PPh_4)_2MS_4$ (M = Mo, W) with CuCl and KSCN or CuNCS in acetone or acetonitrile affords a new set of mixed metal–sulfur compounds: discrete $[(CuNCS)_2MS_4]^{2-}$ and polymeric $[(CuNCS)_4MS_4]^{2-}$ dianions. $(PPh_4)_2[(CuNCS)_2WS_4]$ crystallizes in monoclinic space group $P2_1/c$ with a = 32.89 (2) Å, b = 9.312 (4) Å, c = 17.993 (5) Å, β = 113.11 (4)°, and Z = 4. Least-squares refinement of 328 variables led to a value of the conventional R index (on F) of 0.053 and an R_w value of 0.049 for 3770 reflections with $I > 3.0\sigma(I)$. The crystal structure of $(PPh_4)_2[(CuNCS)_2WS_4]$ (**1**) reveals the presence of discrete, almost linear trinuclear dianions and involves the coordination of a slightly distorted tetrahedral WS_4 moiety to two copper(I) atoms with each trigonal copper(I) atom also participating in Cu–NCS bond lengths of 1.87 (1) and 1.85 (1) Å. This structure contrasts with the polymeric nature of $(PPh_4)_2[(CuNCS)_4WS_4]$ (**3**), which crystallizes in monoclinic space group $P2_1/n$ with a = 22.641 (9) Å, b = 18.044 (4) Å, c = 14.439 (5) Å, β = 96.22 (4)°, and Z = 4. Least-squares refinement of 400 variables led to a value of the conventional R index (on F) of 0.050 for 6590 reflections with $I > 3.0\sigma(I)$. The crystal structure determination shows that four edges of the tetrahedral WS_4 core are bridged by Cu(I) atoms, giving an aggregate of approximate D_{2d} symmetry with NCS bridges linking different aggregates via two mutually cis pseudotetrahedral coppers to form an infinite zigzag chain running about the 2_1 axis. One of the remaining two copper atoms adopts a trigonal-planar environment as in **1**, while the other copper atom assumes a geometry intermediate between tetrahedral (short nonbonded distance Cu(3)···S(3) = 3.042 (4) Å) and trigonal planar. These weak interactions between copper and the sulfur atom S(3) of a NCS group lead to a two-dimensional-network polymer parallel to the (101) plane. The electronic spectra of the complexes are dominated by the internal transitions of the MS_4^{2-} ligand modified by additional CuNCS units. The structural data have been used to interpret vibrational spectroscopic data of the thiocyanate groups.

The tetrathiometalates MS_4^{2-} (M = Mo, W) have been studied for their ability to coordinate to transition metals[1] and particularly to Cu in connection with the possible relevance of Cu–Mo biological antagonism.[2] The neutral species CuX (X = CN,[3] Cl[4]) coordinate to MS_4^{2-} to form aggregates in which MS_4^{2-} acts as a bi- or tridentate ligand. Other interesting clusters include species stabilized in polymeric form such as $(PPh_4)_2[(CuBr)_4MoS_4]$[5] and $(NMe_4)_2[(CuNCS)_4WS_4]$[6] with MS_4^{2-} acting as a tetradentate ligand. Taking advantage of the fact that nonchelating ambidentate ligands such as CN^- and NCS^- are capable of bridging metal nuclei to form different polymeric anionic compounds, we have expanded our studies on the MS_4^{2-}/CuNCS system. We report herein the synthesis and characterization of the tetra-

† Laboratoire de Cinétique Chimique.
‡ Laboratoire de Chimie des Metaux de Transition.
§ Laboratoire de Chimie des Polymères Inorganiques.

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