case of the molybdenum blue bronze $A_{0.3}MoO_3$ (A = K, Rb),[8b,e] thermal excitation of electrons can occur from the π_+ and δ_1 bands into the bottom portion of the δ_2 band. This thermal excitation, which increases with temperature, shrinks the occupied region of wave vectors in both part a and and part b of Figure 2. As a consequence, the two pieces of the Fermi surface of either the π_+ and the δ_1 band come closer to each other upon losing electrons by thermal excitation. Then, the c^* component of $\mathbf{q}_1$ would decrease from $0.73c^*$ upon increasing temperature, whereas that of $\mathbf{q}_2$ would remain nearly temperature-independent.

Concluding Remarks

The present band electronic structure calculations on an $Mo_2O_7^{6-}$ slab show that $La_2Mo_2O_7$ is a pseudo-1D metal, with the strongest electric conductivity along the crystallographic c direction, and has two partially filled bands. These bands give rise to two nesting vectors $\mathbf{q}_1 \simeq (0.5a^*, 0.73c^*)$ and $\mathbf{q}_2 \simeq (0, 0.27c^*)$. Thus the CDW's associated with these nesting vectors are likely to be responsible for the phase transition in $La_2Mo_2O_7$, which occurs around 125 K. As in the case of the molybdenum blue bronze $A_{0.3}MoO_3$ (A = K, Rb), $La_2Mo_2O_7$ has the bottom of an empty band lying above but very close to the Fermi level. Thus, to fully understand the nature of the phase transition in $La_2Mo_2O_7$, it would be important not only to search for the presence of CDW's but also to probe their temperature dependence.

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Contribution from the Anorganisch-Chemisches Institut der Universität Heidelberg, 6900 Heidelberg, FRG

Synthesis, Antitumor Activity, and X-ray Structure of Bis(imidazolium) (Imidazole)pentachlororuthenate(III), $(ImH)_2(RuImCl_5)$

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The X-ray structure, an improved synthesis, and the antitumor activity of $(ImH)_2(RuImCl_5)$ are described. $(ImH)_2(RuImCl_5)$, $(C_3H_5N_2)_2[RuCl_5(C_3H_4N_2)]$, $M_r = 484.59$, is orthorhombic, space group C_{2v}^{12}-$Bm2_1b$, with $a = 8.464$ (2) Å, $b = 14.406$ (3) Å, $c = 14.936$ (4) Å, $V = 1821$ Å^3, $Z = 4$, $D_{calcd} = 1.77$ g cm^{-3}, and final $R_w = 0.038$, for 764 reflections and 75 variables. The antitumor activity was investigated in the P 388 leukemia model. The lifespan of the animals treated with $(ImH)_2(RuImCl_5)$ was increased up to T/C values of 150–162%. This effect was in the same range as that observed with the positive controls 5-fluorouracil and cisplatin. These clinically used drugs increased the lifespan in the same experiment up to T/C values of 144% and 175%, respectively.

Introduction

During the last 20 years, since *cis*-diamminedichloroplatinum(II) (INN: cisplatin) was discovered as a potent tumor-inhibiting agent that, in clinical studies, turned out to be a drug with its best activity against testicular cancer, much more work has been done in the field of antitumor-active metal complexes than before this date.[1] Most of the efforts were concentrated on platinum as the central metal. Thousands of platinum complexes were synthesized for this reason, and more than 1000 were investigated in preclinical tests for antitumor activity. But the clinical trials with a number of new platinum compounds, selected by way of these methods for the first treatment of patients, demonstrated clearly the relatively close pharmacological and toxicological behavior of the new derivatives compared with the original cisplatin. The spectrum of tumors the derivatives exhibited activity against was not broader than that of cisplatin, and myelosuppression was the dose-limiting side effect, as in the case of cisplatin, also. A small amount of success was achieved with a few derivatives concerning the nephrotoxicity and neurotoxicity.[2-6]

Owing to these facts, it is necessary to search for non-platinum complexes, which may exhibit tumor-inhibiting properties against other tumors than the established antitumor agents and which may prove to have less severe side effects. We recently discovered the tumor-inhibiting bis(β-diketonato)metal complexes. One of these compounds, diethoxybis(1-phenylbutane-1,3-dionato)titanium(IV) (INN: budotitane), has reached clinical phase 1 studies now.[7]

Interesting work in the field of antitumor-active ruthenium complexes has been done previously.[8] In this paper we will present bis(imidazolium) (imidazole)pentachlororuthenate(III), $(ImH)_2(RuImCl_5)$, as a representative of a new class of water-soluble, heterocycle-coordinated ruthenium complexes with anticancer activity.

The antitumor activity of $ImH(RuIm_2Cl_4)$, another compound of this class, was described by us recently.[9]

Table I. Crystallographic and Experimental Details

cryst shape; size, mm	prism; 0.08 × 0.1 × 0.15
cryst syst	orthorhombic
space group	$Bm2_1b$ (C_{2v}^{12}, No. 36)
a, b, c, Å	8.464 (2), 14.406 (3), 14.936 (4)
λ, Å	0.7107
μ, cm^{-1}	15.9
min transmission (max = 1)	0.87
max 2θ, deg	60
range of hkl	000 to 7,19,20
possible observns	1328
observns used in refinement ($I > 2.5\sigma(I)$)	764

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Experimental Section

5-Fluorouracil was contributed by Hoffmann-La Roche. Cisplatin was prepared and purified by methods previously described.[10,11]

Preparation of Bis(imidazolium) (Imidazole)pentachlororuthenate(III), $(ImH)_2(RuImCl_5)$. The preparation of this compound was described previously.[12] To obtain a higher yield and a crystalline product, we have improved the preparation in the following way: $RuCl_3$ (4.4 g, 21.2 mmol) was dissolved in a mixture of H_2O (100 mL) and ethanol (100 mL) and was refluxed for 2 h. Then the solution was evaporated to give 50 mL. Into this solution was rapidly dropped imidazole (10 g, 147 mmol), dissolved in 6 N HCl (20 mL). The clear, dark red mixture was stirred for 3 min and evaporated at room temperature to give 40 mL. Then 1.8 mL of 8 N HCl was added, and the solution was heated to 85 °C and then chilled by an ice/$CaCl_2$ mixture. After 30 min red crystals were drawn off and washed with ethanol; yield 2.75 g, 27%. Anal. Calcd for $(ImH)_2(RuImCl_5)$ (M_r = 484.59): C, 22.31; H, 2.91; N, 17.34; Cl, 36.58; Ru, 20.86; Found: C, 22.35; H, 2.68; N, 17.15; Cl, 36.46; Ru, 20.70. Chlorine was determined by argentometry and ruthenium by neutron activation analysis.

X-ray Structure. Data were collected at room temperature with monochromated (graphite monochromator) Mo Kα radiation. A Nicolet R3 diffractometer was used together with its commercial software. An empirical absorption correction was performed with a SHELXTL routine.[13] Equivalent reflections were not measured. Further details of the data collection are given in Table I. The data were accidentally measured corresponding to the nonstandard setting $Bm2_1b$ of space group No. 36, and the structure was solved with this setting. The standard setting is $Cmc2_1$, which transforms to the chosen one by the matrix

$$\begin{matrix} 1 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{matrix}$$

The Ru position was derived from a Patterson map, and completion of the structure was tried in both acentric space groups that are in accord with the systematic absences, No. 36 and No. 40. The centric one, No. 63, can be rejected due to the impossible point symmetry required for the fourfold Rh position. The structure could only be completed in space group No. 36, and it subsequently turned out that the distribution of the cations would not be compatible with the symmetry operations of the rejected space group No. 40.

Ru and Cl atoms were refined with anisotropic temperature factors and the light atoms with isotropic ones. H atoms were inserted at calculated positions, except those of the disordered cation, and refined <<-lrqtriding" on the parent atoms. The disordered imidazolium cation (N(4)–C(8)) posed a refinement problem: A difference Fourier map placed two atoms (C(6) and C(8)) on a mirror plane; the other three had to be assumed to be disordered over two positions above and below the mirror plane. This model refined well except for C(6), the temperature factor of which became unreasonably large. Inspection of the bond lengths suggested that this atom is also disordered over two sites close to the mirror plane. Therefore, it was placed at a position that gave reasonable bond distances. It then refined well, and R_w was lowered from 0.040 to 0.038.

Refinement of the 75 variables based on the F values of 764 reflections with weights $w = 1/\sigma^2(F)$, where σ was taken from counting statistics, by full-matrix least squares converged with R = 0.054, R_w = 0.038, maximum shift/esd = 0.07, and goodness of fit 1.62. The function minimized was $\sum w^{1/2}(||F_o| - |F_c||)$; R and R_w are defined accordingly. The largest features in a final difference Fourier map were +0.91 and −0.76 e Å^{-3}. Calculations were carried out on a Nova 3 computer with the SHELXTL program system,[13] which uses scattering factors from ref 14 and takes anomalous dispersion into account, with f' and f'' from ref 14.

Animal Experiments. BDF_1 mice were provided by Charles River Wiga, Sulzfeld, FRG, and DBA/2 mice were provided by Savo-Ivanovas, Kisslegg, FRG.

Table II. Atom Coordinates (×10^4) and Temperature Factors (×10^3 Å^2)

atom	x	y	z	U^a
Ru	0	7500	5900	31 (1)*
Cl(1)	0	8511 (3)	7215 (2)	36 (1)*
Cl(2)	−1975 (3)	8419 (3)	5216 (2)	44 (1)*
Cl(3)	−1992 (3)	6573 (2)	6579 (2)	41 (1)*
N(1)	0	6634 (9)	4816 (8)	36 (3)
N(2)	0	5388 (10)	3991 (10)	55 (4)
C(1)	0	5705 (12)	4828 (12)	51 (4)
C(2)	0	6125 (13)	3429 (13)	62 (5)
C(3)	0	6884 (12)	3926 (11)	51 (4)
N(3)	3763 (11)	8627 (8)	7239 (7)	58 (3)
C(4)	5000	8289 (14)	6841 (12)	67 (5)
C(5)	4196 (12)	9246 (11)	7871 (9)	65 (4)
N(4)	−876 (20)	1501 (20)	199 (16)	73 (7)
N(5)	535 (19)	1428 (16)	1388 (12)	58 (6)
C(6)	−597 (30)	1976 (23)	937 (26)	91 (11)
C(7)	890 (31)	704 (26)	859 (25)	85 (9)
C(8)	0	720 (17)	128 (17)	83 (6)

[a] Asterisks denote an equivalent isotropic U, defined as one-third of the trace of the orthogonalized U_{ij} tensor.

Table III. Bond Lengths (Å) and Angles (deg)

Ru–Cl(1)	2.446 (4)	Ru–Cl(2)	2.364 (3)
Ru–Cl(3)	2.378 (3)	Ru–N(1)	2.044 (12)
N(1)–C(1)	1.34 (2)	N(1)–C(3)	1.38 (2)
N(2)–C(1)	1.33 (2)	N(2)–C(2)	1.35 (2)
C(2)–C(3)	1.32 (3)	N(3)–C(4)	1.30 (2)
N(3)–C(5)	1.35 (2)	N(4)–C(6)	1.32 (5)
C(5)–C(5a)	1.36 (2)	N(5)–C(6)	1.41 (4)
N(4)–C(8)	1.35 (3)	C(7)–C(8)	1.33 (4)
N(5)–C(7)	1.34 (4)		
Cl(1)–Ru–Cl(2)	90.8 (1)	Cl(1)–Ru–Cl(3)	89.5 (1)
Cl(2)–Ru–Cl(3)	89.9 (1)	Cl(1)–Ru–N(1)	178.9 (4)
Cl(2)–Ru–N(1)	90.0 (3)	Cl(3)–Ru–N(1)	89.7 (3)
Ru–N(1)–C(3)	127.2 (11)	Ru–N(1)–C(1)	126.9 (11)
C(1)–N(2)–C(2)	108.3 (15)	C(1)–N(1)–C(3)	106.0 (13)
N(2)–C(2)–C(3)	107.5 (17)	N(1)–C(1)–N(2)	109.2 (15)
C(4)–N(3)–C(5)	110.5 (11)	N(1)–C(3)–C(2)	109.0 (15)
N(3)–C(5)–C(5a)	105.7 (6)	N(3)–C(4)–N(3a)	107.5 (16)
C(6)–N(5)–C(7)	107.8 (24)	C(6)–N(4)–C(8)	113.5 (23)
N(5)–C(7)–C(8)	110.1 (26)	N(4)–C(6)–N(5)	103.3 (25)
		N(4)–C(8)–C(7)	105.2 (25)

P 388 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. Then the mice were divided arbitrarily into groups consisting of six animals each. Bis(imidazolium) (imidazole)pentachlororuthenate(III) was applied in the first group with a single dose (218.5 mg/kg = 0.45 mmol/kg) on day 1, in the second group with three doses (72.8 mg/kg = 0.15 mmol/kg) on days 1, 5, and 9, and in the third group with nine doses (24.3 mg/kg = 0.05 mmol/kg) on days 1–9. The compound was applied intraperitoneally (ip), dissolved in physiological saline, 20 mL/kg.

5-Fluorouracil and cisplatin were administered ip in the doses 60 and 3 mg/kg, respectively, on days 1, 5, and 9.

Evaluation. The median survival time of the treated animals was compared with the median survival time of the untreated control animals:

$$T/C = [(\text{median survival time of the treated animals})/(\text{median survival time of the control animals})] \times 100$$

The statistical evaluation was done according to the Kruskal–Wallis test.[15,16]

Results and Discussion

Description of the Structure. The asymmetric unit contains half of the $[RuCl_5(C_3H_4N_2)]^{2-}$ anion lying on a mirror plane that accommodates Cl(1), Ru, and the atoms of the imidazole ligand

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Table IV. Antitumor Activity of Bis(imidazolium) (Imidazole)pentachlororuthenate(III), $(ImH)_2(RuImCl_5)$, Compared with That of Cisplatin and 5-Fluorouracil against P 388 Leukemia

	no. of animals	treatment on days	T/C^a	no. of animals reaching $T/C = 150$	body wt change until day 5, %
control animals	18		100	1/18	+7
cisplatin					
3 mg/kg (0.01 mmol/kg)	6	1, 5, 9	175[b]	5/6	−15
5-fluorouracil					
60 mg/kg (0.46 mmol/kg)	6	1, 5, 9	144[b]	3/6	+4
$(ImH)_2(RuImCl_5)$					
218.5 mg/kg (0.45 mmol/kg)	6	1	150[b]	5/6	+8
72.8 mg/kg (0.15 mmol/kg)	6	1, 5, 9	162.5[b]	6/6	+1
24.3 mg/kg (0.05 mmol/kg)	6	1–9	156[b]	6/6	+9

[a] 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. [b] Significant from control according to the Kruskal–Wallis test; $\alpha \leq 0.005$.

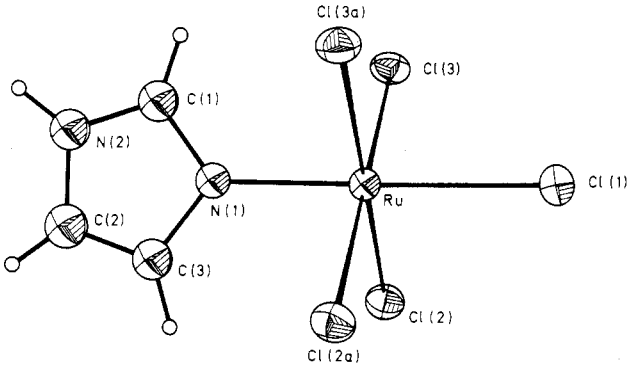

Figure 1. The $[RuCl_5(C_3H_4N_2)]^+$ cation. Thermal contours are drawn at the 30% probability level; calculated H atoms are drawn with arbitrary radius.

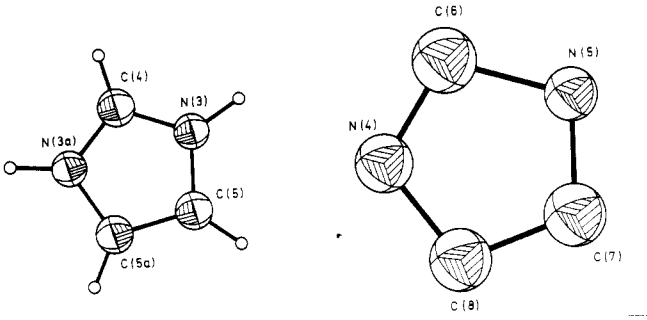

Figure 2. Ordered (left) and disordered (right) $[C_3H_5N_2]^+$ cations, analogous to Figure 1.

(N(1)–C(3)), half of an imidazolium cation (N(3)–C(5)) bisected normally by a mirror plane passing through C(4), and another half-cation (N(4)–C(8)) with one atom on a mirror plane (C(8)) and the rest disordered over two positions above and below this mirror plane. Atom coordinates are given in Table II and bond distances and angles in Table III. The numbering scheme is shown in Figures 1 and 2.

In the complex anion it may be noted that the Ru–Cl(1) bond trans to the imidazole ligand is considerably longer than the other two independent bonds, 2.446 (4) vs. 2.364 (3) and 2.378 (3) Å. This can be explained as an often-observed structural trans effect.

Antitumor Activity Tests. The results of the antitumor activity tests are summarized in Table IV. Bis(imidazolium) (imidazole)pentachlororuthenate(III) increases the lifespan of the tumor-bearing animals up to T/C values of 150–162%. The effect was not very dependent on the different dose schedules, in which the same total dose was applied at different times and separated in different single doses. The clinically used antitumor agents 5-fluorouracil and cisplatin, which were used as positive controls, increased the T/C values of the tumor-bearing animals up to 144% and 175%, respectively. Compared to the tested ruthenium compound, 5-fluorouracil was slightly less and cisplatin slightly more effective in this experimental tumor model. The effects of all compounds were highly statistically significant according to the Kruskal–Wallis test. Long-time survivors were not observed in any group. During the treatment, no body-weight loss indicating toxicity could be observed for the animals treated with 5-fluorouracil and the ruthenium compound. The animals treated with cisplatin lost 15% of their former weight, which gives evidence of some toxicity. Yet, this must also be seen in connection with its better therapeutic effect, compared to that of the other two compounds.

Activity against transplantable tumor models such as the P 388 leukemia indicates tumor-inhibiting properties in general, but this model cannot illustrate activity of the test compounds against specific human organ tumors. Owing to this fact, $(ImH)_2(RuImCl_5)$ will be tested against autochthonous tumor models and against a broader spectrum of human tumor xenografts. These models are more appropriate to find out the particular field of indication for this compound in tumor therapy. First results in testing an autochthonous tumor model exhibited good activities in colonic tumors.[17] More details of this will be published later. Further toxicological experiments are also under way.

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Registry No. $(ImH)_2(RuImCl_5)$, 105085-56-1.

Supplementary Material Available: A listing of anisotropic temperature factors (1 page); a listing of calculated and observed structure amplitudes (5 pages). Ordering information is given on any current masthead page.

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