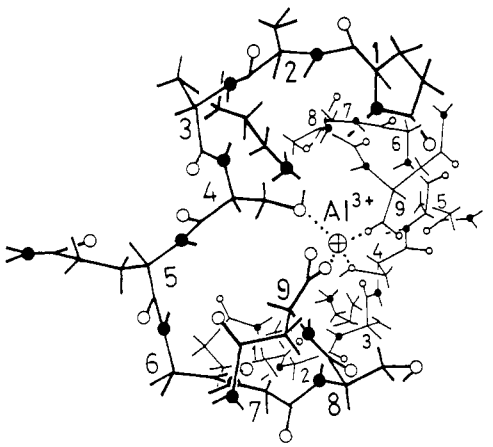

Figure 6. Schematic Dreiding model representation of the 1:2 aluminum:nonapeptide complex in which the long-range NOE effects (<-Glu[1]NH/Ser[4]OH and $Lys^3NH_3^+$/Ser[4]OH) were taken into account.

compact structure. On the basis of our NMR results, the 1:2 complex can be represented as in Figure 6.

The conformation of the Al(III)–nonapeptide complex, as revealed by this NMR study in DMSO solution, may be compared with that of the biologically active Zn(II) complex. Indeed, to interpret the conformational data obtained on our complex, it is of primary importance to determine whether the parameters observed can be correlated with those of the Zn(II) complex. From this comparison, the most significant difference is observed for the hydroxyl group of the Ser[8] residue. From NOESY data, it appears that, with zinc, the Ser[8]OH, which serves as ligand for the metal, gets closer to <Glu[1]NH but that this is not the case with aluminum. These results and those obtained for copper[23] and for thymulin analogues show that the Asn^9COO^- and Ser[4]OH groups play a crucial role in contributing activity but are not sufficient to explain the in vivo behavior of thymulin (FTS–Zn-(II)).

Finally, the results of this study show that the Al(III) complex is identical with one of those formed with Zn(II) (complex 1:2). This similarity may account for the lack of biological activity in vivo of the Al(III)–nonapeptide system. Furthermore, comparisons and correlations between the structure of peptide–metal complexes and their biological activity could lead to better insight into the conformational requirements at receptor sites.

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cis- and *trans*-Dihalotetrakis(dimethyl sulfoxide)ruthenium(II) Complexes ($RuX_2(DMSO)_4$; X = Cl, Br): Synthesis, Structure, and Antitumor Activity

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The chemistry of halogen–dimethyl sulfoxide–ruthenium(II) complexes with the general formula $RuX_2(DMSO)_4$ (X = Cl, Br) is reported. In particular the synthesis and X-ray structure of *trans*-$RuCl_2(DMSO)_4$ and *cis*-$RuBr_2(DMSO)_4$ are described and compared with those of the already known *cis*-$RuCl_2(DMSO)_4$ and *trans*-$RuBr_2(DMSO)_4$. The structure of a new crystal form of *cis*-$RuCl_2(DMSO)_4$ is also reported. Crystal data: for *trans*-$RuCl_2(DMSO)_4$, tetragonal, $I4/m$, a = 9.121 (3) Å, c = 11.167 (4) Å, Z = 2, R = 0.040; for *cis*-$RuBr_2(DMSO)_4$, monoclinic, $P2_1/n$, a = 8.547 (3) Å, b = 27.873 (4) Å, c = 8.637 (2) Å, β = 115.85 (3)°, Z = 4, R = 0.040; for *cis*-$RuCl_2(DMSO)_4$, monoclinic, $P2_1/n$, a = 8.417 (2) Å, b = 27.695 (4) Å, c = 8.598 (2) Å, β = 116.88 (3)°, Z = 4, R = 0.033. While the cis isomers are thermodynamically more stable and form from the trans species, a photochemically driven cis to trans isomerization reaction is observed in dimethyl sulfoxide solution. Kinetic parameters for the thermal trans to cis isomerization reactions for *trans*-$RuCl_2(DMSO)_4$ and *trans*-$RuBr_2(DMSO)_4$, respectively, are $k = 2.58 \times 10^{-6}$ s^{-1} at 25 °C, $\Delta H^{\ddagger} = 128 \pm 2$ kJ·mol^{-1}, and $\Delta S^{\ddagger} = 110 \pm 5$ J·mol^{-1}·K^{-1} and $k = 1.25 \times 10^{-5}$ s^{-1} at 25 °C, $\Delta H^{\ddagger} = 114 \pm 5$ kJ·mol^{-1}, and $\Delta S^{\ddagger} = 79 \pm 18$ J·mol^{-1}·K^{-1}. In chloroform solution the complexes, and in particular the trans isomers, tend to release a dimethyl sulfoxide molecule to give pentacoordinated Ru(II) complexes. However, in aqueous solution, while the cis complexes immediately release one DMSO, the trans ones release two. In both cases, this step is followed by the slow dissociation of a halide ion. For the chloro derivatives the dissociation is completely inhibited at physiological chloride concentrations. Preliminary results from pharmacological tests show that *trans*-$RuCl_2(DMSO)_4$ is more active than the cis isomer against Lewis lung carcinoma, a metastasizing murine tumor. A remarkable dependence of activity on the halogen nature (Cl > Br) is also observed.

Introduction

cis-$PtCl_2(NH_3)_2$ (cisplatin) is, at present, the most widely used drug in anticancer therapy.[1] After the discovery of its antineoplastic activity in the late 1960s,[2] many efforts have been made to understand its mechanism of action and to improve its therapeutic efficacy. In particular, activity against a broader tumor panel and reduced host toxicity has been sought.

Despite the success obtained in understanding the interactions of *cis*-$PtCl_2(NH_3)_2$ with DNA,[3] which are responsible for its cytotoxicity and, probably, for its antitumor activity, the thousands

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of new platinum complexes that have been synthesized and tested brought little enhancement to the antitumor properties of the original cisplatin.[4]

In the same period the screening has been extended also to non-platinum-metal compounds[5] and some promising results have been obtained with complexes of titanium,[6] rhodium,[7] iridium[8] and ruthenium.[9] Interest in the antitumor properties of ruthenium derivatives has been growing continuously in recent years, and a (chloroimidazole)ruthenium(III) complex has been announced to be entering phase I clinical study.[10]

We have reported that a ruthenium(II) complex, *cis*-$RuCl_2(DMSO)_4$, possesses mutagenic properties,[11] exhibits good antineoplastic activity against several murine metastasizing tumors,[12] and interacts "in vitro" with DNA to form covalent bonds with the nucleobases, especially guanine (N7).[13] Recently a nitroimidazole derivative of this complex has been reported to act as a radiosensitizer.[14]

The promising results obtained with *cis*-$RuCl_2(DMSO)_4$ prompted us to undertake a systematic study of halogen–dimethyl sulfoxide–Ru(II) complexes.

Despite the remarkable number of publications on this subject,[15-24] the chemistry of these complexes is not well understood, and many synthetic as well as structural aspects need further investigation.

In this paper we present the structural characterization of a new crystal form of *cis*-$RuCl_2(DMSO)_4$ (F3) together with the synthesis and structural characterization of the previously unknown *trans*-$RuCl_2(DMSO)_4$ and *cis*-$RuBr_2(DMSO)_4$. These results provide a clear idea of the relative stabilities of the cis and trans isomers. Moreover, a comparative study of the chemical behavior of *cis*- and *trans*-$RuCl_2(DMSO)_4$ in aqueous solution and some preliminary results on the antitumor properties of cis and trans isomers are reported.

Experimental Section

Materials. Analytical grade (C. Erba) dimethyl sulfoxide, acetone, chloroform, and diethyl ether were used without further purification. Commercial $RuCl_3 \cdot 3H_2O$ and $RuBr_3 \cdot 3H_2O$ were purchased from Metalli Preziosi S.p.A. and Strem Chemicals, respectively. Cisplatin was obtained from the Drug Synthesis and Chemistry Branch, Division of Cancer Treatment, NCI.

Physical Measurements. Electronic absorption spectra were obtained in stoppered quartz cells with a Perkin-Elmer Lambda 5 UV/vis spectrophotometer equipped with a Julabo F40 thermostatic bath. Infrared spectra (Nujol mull) were recorded between CsI windows on a Perkin-Elmer 983G spectrometer. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded at 80 and 20.1 MHz, respectively, on a Bruker WP-80 spectrometer operating in the Fourier transform mode. All spectra were recorded at room temperature with tetramethylsilane (Me_4Si) as an internal standard for $CDCl_3$ solutions and sodium 2,2-dimethyl-2-2silapentane-5-sulfonate (DSS) for aqueous solutions. Conductivity measurements were carried out on a Beckman RC-18A conductivity bridge equipped with a fill-type cell and thermostated with a Julabo F40 thermostatic bath.

Synthesis of the Complexes. *cis*-Dichlorotetrakis(dimethyl sulfoxide)ruthenium(II) (*cis*-$RuCl_2(DMSO)_4$). The complex was prepared according to the method reported by Evans et al.[16] and recrystallized from hot dimethyl sulfoxide/acetone (1:6) solutions.

***trans*-Dichlorotetrakis(dimethyl sulfoxide)ruthenium(II) (*trans*-$RuCl_2(DMSO)_4$).** Recrystallized *cis*-$RuCl_2(DMSO)_4$ (2.5 g, 5.2 mmol) was dissolved by gentle heating ($T \approx 80$ °C) in dimethyl sulfoxide (40 ml); the solution was transferred into a water-cooled photoreactor equipped with a 125-W lamp and irradiated for 4 h; during the reaction, the solution temperature was kept close to room temperature. The whole procedure was conducted under an inert gas atmosphere.

The reaction product, *trans*-$RuCl_2(DMSO)_4$, gradually separated from the solution as a deep yellow microcrystalline solid, which was filtered, washed with a little DMSO and acetone, and vacuum-dried at room temperature; yield, 2.0 g (80%). The complex can be recrystallized from chloroform/diethyl ether (yield 90%). Anal. Calcd for $RuCl_2(DMSO)_4$ (M_r 484.49): C, 19.83; H, 4.99; Cl, 14.63; S, 26.46. Found: C, 19.9; H, 4.70; Cl, 14.25; S, 26.26. Selected infrared absorptions (Nujol mull, cm^{-1}): ν_{SO} 1080 (s), ν_{RuCl} 336 (s). Electronic spectra (λ_{max}, nm (ϵ, M^{-1} cm^{-1})): in $CHCl_3$ solution, 441 (212), 286 sh (995), 250 (3210); in dimethyl sulfoxide solution, 440.8 (130), 340 sh (165), 298 (216), 261 (2195).

***trans*-Dibromotetrakis(dimethyl sulfoxide)ruthenium(II) (*trans*-$RuBr_2(DMSO)_4$).** The complex was prepared by the method of James et al.[15] (reaction time at 80 °C was 2 h) and carefully recrystallized with the following procedure: 1.5 g of the complex was dissolved in 50 mL of dimethylsulfoxide at a temperature not exceeding 80 °C. The warm solution was then filtered and 150 mL of acetone added. When the mixture was allowed to stand for several days, orange crystals of the product formed, which were filtered off, washed with acetone, and vacuum-dried (yield 70%). Anal. Calcd for $RuBr_2(DMSO)_4$ (M_r 573.39): C, 16.75; H, 4.18; Br, 27.87; S, 22.36. Found: C, 16.8; H, 4.22; Br, 28.3; S, 22.46.

***cis*-Dibromotetrakis(dimethyl sulfoxide)ruthenium(II) (*cis*-$RuBr_2(DMSO)_4$).** A 1-g sample of recrystallized *trans*-$RuBr_2(DMSO)_4$ was dissolved in 15 mL of hot dimethyl sulfoxide and heated to 150 °C for 10 min. The hot solution was then filtered and 70 mL of acetone added. When the mixture was allowed to stand for 2 days, big, light orange crystals of the cis product formed, which were filtered off, washed with acetone, and vacuum-dried (yield 70%). Some small crystals of the starting trans isomer were occasionally found together with the main product. Separation of the two isomers was easily accomplished by sieving. Anal. Calcd for $RuBr_2(DMSO)_4$ (M_r 573.39): C, 16.75; H, 4.18; Br, 27.87; S, 22.36. Found: C, 16.9; H, 4.26; Br, 26.9; S, 22.63. Selected infrared absorptions (Nujol mull, cm^{-1}): ν_{SO} (S-bonded) 1111.5 (m) and 1084 (s), ν_{SO} (O-bonded) 924.5 (s). Electronic spectra (λ_{max}, nm (ϵ, M^{-1} cm^{-1})): in $CHCl_3$ solution, 373 (484), 288 sh (1250), 244 (11 735); in dimethyl sulfoxide solution, 375 (548), 326 sh (409), 259 (8315).

Crystallographic Study. Crystals of *cis*-$RuCl_2(DMSO)_4$ (F3), *cis*-$RuBr_2(DMSO)_4$, and *trans*-$RuCl_2(DMSO)_4$ were mounted on an Enraf-Nonius CAD-4 diffractometer. Lattice parameters were determined by least-squares methods from the setting angles of 25 accurately centered reflections. A summary of the crystal data and details of the intensity data collection and refinement are given in Table I. No decay was observed in the intensities of four standard reflections, monitored periodically during data collection. An empirical absorption correction, based on ψ scans of three close-to-axial reflections, was applied to the intensity of *cis*-$RuX_2(DMSO)_4$ (X = Cl, Br). The structure of *cis*-$RuCl_2(DMSO)_4$ (F3) was solved by Patterson and Fourier methods. *cis*-$RuBr_2(DMSO)_4$ and *trans*-$RuCl_2(DMSO)_4$ were observed to be iso-

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Table I. Experimental Parameters for the X-ray Diffraction Study

	trans-$RuCl_2(DMSO)_4$	*cis*-$RuBr_2(DMSO)_4$	*cis*-$RuCl_2(DMSO)_4$
formula	$C_8H_{24}Cl_2O_4S_4Ru$	$C_8H_{24}Br_2O_4S_4Ru$	$C_8H_{24}Cl_2O_4S_4Ru$
mol wt	484.49	573.49	484.49
cryst syst	tetragonal	monoclinic	monoclinic
space group	$I4/m$	$P2_1/n$	$P2_1/n$
a, Å	9.121 (3)	8.547 (3)	8.417 (2)
b, Å		27.873 (4)	27.695 (4)
c, Å	11.167 (4)	8.637 (2)	8.598 (2)
β, deg		115.85 (3)	116.88 (3)
V, Å^3	929.0 (5)	1851.7 (9)	1787.8 (8)
Z	2	4	4
D_{calcd}, g cm^{-3}	1.73	2.06	1.80
$F(000)$	492	1256	984
abs coeff (Mo Kα), cm^{-1}	15.6	55.5	1.62
cryst size, mm	0.10 × 0.25 × 0.40	0.50 × 0.50 × 0.60	0.30 × 0.35 × 0.40
diffractometer	Enraf-Nonius CAD-4	Enraf-Nonius CAD-4	Enraf-Nonius CAD-4
temp, °C	20 ± 1	20 ± 1	20 ± 1
radiatn (λ, Å)	Mo Kα (0.71069)	Mo Kα (0.71069)	Mo Kα (0.71069)
monochromator	graphite	graphite	graphite
scan type	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$
scan speed, deg min^{-1}	variable (0.78–5.0)	variable (0.78–5.0)	variable (0.78–5.0)
2θ range, deg	6–60	5–60	5–60
orientn monitors[a]	3	3	3
intens monitors[b]	4	4	4
transmissn factors		0.776–0.999	0.974–0.999
total no. of reflcns measd	1502	5800	5642
no. of reflcns with $I > 3\sigma(I)$[c]	591	3612	4107
data/param ratio	21.9	21.0	23.9
R[d]	0.040	0.040	0.033
R_w[e]	0.044	0.048	0.042
GOF[f]	1.89	2.86	1.87

[a] Measured after each 400 reflections, with new orientation matrix if angular change > 0.13. [b] Measured after each 3000 s. [c] Standard deviation from counting statistics. [d] $R = \sum||F_o| - |F_c||/\sum|F_o|$. [e] $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$; $w = 1$. [f] GOF $= [\sum w(|F_o| - |F_c|)^2/(m - n)]^{1/2}$; m = no. of observations; n = no. of variables.

Table II. Fractional Coordinates (×10^4) and Equivalent Isotropic Thermal Parameters (Å^2) for *cis*-$RuCl_2(DMSO)_4$ (F3)

atom	x	y	z	B_{eq}[a]
Ru	2014.8 (4)	1248.4 (1)	3281.7 (4)	1.574 (5)
Cl1	5049 (1)	1381.2 (5)	5486 (1)	3.06 (2)
Cl2	3134 (1)	644.6 (4)	1991 (1)	3.24 (2)
S1	2385 (1)	1813.1 (4)	1601 (1)	2.32 (2)
S2	933 (1)	1742.4 (4)	4693 (1)	2.09 (2)
S3	−816 (1)	1057.2 (4)	1275 (1)	2.31 (2)
S4	3382 (1)	321.1 (4)	5714 (1)	2.25 (2)
O1	1063 (4)	1851 (1)	−237 (4)	3.89 (8)
O2	−192 (5)	2159 (1)	3751 (5)	4.10 (8)
O3	−1811 (5)	756 (2)	1926 (5)	5.36 (9)
O4	1867 (4)	692 (1)	4931 (4)	2.57 (6)
C11	2696 (8)	2412 (2)	2445 (8)	4.5 (1)
C12	4488 (6)	1743 (2)	1574 (7)	4.5 (1)
C21	2564 (7)	1982 (2)	6693 (6)	4.4 (1)
C22	−332 (6)	1405 (2)	5519 (6)	3.7 (1)
C31	−974 (8)	766 (2)	−635 (7)	4.4 (1)
C32	−2211 (6)	1564 (2)	225 (7)	3.7 (1)
C41	2309 (6)	−237 (2)	4901 (6)	3.2 (1)
C42	3714 (7)	271 (2)	7904 (6)	3.8 (1)

[a] B_{eq} is defined as $(4/3)[a^2\beta_{11} + b^2\beta_{22} + c^2\beta_{33} + ab\beta_{12}(\cos\alpha) + ac\beta_{13}(\cos\beta) + bc\beta_{23}(\cos\alpha)]$.

structural with F3 and the dibromo analogue,[23] respectively. Their structures were refined starting from the non-hydrogen atom coordinates of the correspondent analogous derivative. Hydrogen atoms were included at calculated positions and held fixed during the least-squares refinement (B = 5 Å^2). Refinement with anisotropic temperature factors for the non-hydrogen atoms converged to the conventional agreement indices given in Table I. All computations were performed by using the Enraf-Nonius SDP programs on a PDP 11/44 computer. Neutral atomic scattering factors and anomalous dispersion terms were taken from ref 25.

Final positional parameters and equivalent B factors are presented in Tables II–IV for *cis*-$RuCl_2(DMSO)_4$ (F3), *trans*-$RuCl_2(DMSO)_4$, and *cis*-$RuBr_2(DMSO)_4$, respectively.

(25) *International Tables for X-ray Crystallography*: Kynoch: Birmingham, England, 1974; Vol. IV, Tables 2.2 A and 2.3.1.

Table III. Fractional Coordinates (×10^4) and Equivalent Isotropic Thermal Parameters (Å^2) for *trans*-$RuCl_2(DMSO)_4$

atom	x	y	z	B_{eq}[a]
Ru	0	0	5000	1.92 (1)
Cl	0	0	2849 (2)	3.23 (3)
S	2550 (2)	380 (2)	5000	2.86 (3)
O	3391 (5)	−1021 (6)	5000	4.5 (1)
C	3241 (5)	1423 (6)	3776 (5)	3.75 (9)

[a] B_{eq} is defined as $(4/3)[a^2\beta_{11} + b^2\beta_{22} + c^2\beta_{33} + ab\beta_{12}(\cos\alpha) + ac\beta_{13}(\cos\beta) + bc\beta_{23}(\cos\alpha)]$.

Table IV. Fractional Coordinates (×10^4) and Equivalent Isotropic Thermal Parameters (Å^2) for *cis*-$RuBr_2(DMSO)_4$

atom	x	y	z	B_{eq}[a]
Ru	1942.1 (6)	1261.6 (2)	3250.2 (5)	1.509 (7)
Br1	5077.7 (9)	1403.3 (3)	5492.8 (9)	2.91 (1)
Br2	3120 (1)	635.4 (3)	1855.9 (9)	3.21 (1)
S1	22229 (2)	1835.5 (6)	1555 (2)	2.37 (3)
S2	858 (2)	1746.1 (6)	4693 (2)	2.10 (3)
S3	−840 (2)	1057.3 (7)	1324 (2)	2.43 (3)
S4	3292 (2)	331.3 (6)	5667 (2)	2.20 (3)
O1	880 (7)	1876 (2)	−227 (7)	4.2 (1)
O2	−302 (7)	2150 (2)	3751 (7)	3.8 (1)
O3	−1732 (8)	735 (3)	2020 (8)	5.9 (2)
O4	1820 (6)	700 (2)	4890 (5)	2.44 (9)
C11	2520 (1)	2432 (3)	2420 (1)	4.4 (2)
C12	4280 (1)	1791 (4)	1420 (1)	4.7 (2)
C21	2430 (1)	2005 (4)	6630 (1)	4.6 (2)
C22	−330 (1)	1399 (3)	5560 (1)	4.1 (2)
C31	−1080 (1)	783 (4)	−620 (1)	4.7 (2)
C32	−2280 (1)	1552 (4)	360 (1)	4.0 (2)
C41	2250 (1)	−227 (3)	4880 (1)	3.2 (2)
C42	3580 (1)	285 (3)	7835 (9)	3.6 (2)

[a] B_{eq} is defined as $(4/3)[a^2\beta_{11} + b^2\beta_{22} + c^2\beta_{33} + ab\beta_{12}(\cos\gamma) + ac\beta_{13}(\cos\beta) + bc\beta_{23}(\cos\alpha)]$.

Animal Experiments. C57Bl female mice and BD2F1 female hybrids were provided by Charles River, Calco, Como, Italy.

Lewis Lung Carcinoma. The tumor line, conventionally maintained in C57Bl female mice of 20 g, was propagated, for the reported exper-

Table V. Interatomic Bond Distances (Å) and Angles (deg) for *cis*-$RuX_2(DMSO)_4$ (X = Cl (F3), Br)

	cis-$RuCl_2(DMSO)_4$	*cis*-$RuBr_2(DMSO)_4$
Ru-X1	2.424 (1)	2.562 (1)
Ru-X2	2.421 (1)	2.563 (1)
Ru-S1	2.245 (1)	2.253 (2)
Ru-S2	2.274 (1)	2.289 (2)
Ru-S3	2.284 (1)	2.301 (2)
Ru-O4	2.134 (3)	2.143 (5)
S1-O1	1.469 (3)	1.471 (5)
S2-O2	1.479 (3)	1.487 (5)
S3-O3	1.461 (5)	1.466 (8)
S4-O4	1.537 (3)	1.535 (5)
S1-C11	1.781 (6)	1.796 (9)
S1-C12	1.791 (6)	1.808 (10)
S2-C21	1.775 (5)	1.780 (8)
S2-C22	1.787 (6)	1.792 (10)
S3-C31	1.780 (6)	1.772 (10)
S3-C32	1.789 (5)	1.792 (9)
S4-C41	1.767 (5)	1.774 (7)
S4-C42	1.780 (6)	1.784 (9)
X1-Ru-X2	88.41 (4)	87.96 (3)
X1-Ru-S1	89.64 (4)	90.44 (4)
X1-Ru-S2	91.50 (4)	92.05 (4)
X1-Ru-S3	175.21 (4)	174.38 (5)
X1-Ru-O4	86.98 (7)	87.1 (1)
X2-Ru-S2	89.44 (4)	90.10 (6)
X2-Ru-S2	173.10 (4)	173.04 (5)
X2-Ru-S3	89.03 (4)	89.16 (5)
X2-Ru-O4	87.58 (9)	87.5 (1)
S1-Ru-S2	97.46 (4)	96.86 (7)
S1-Ru-S3	94.38 (4)	94.40 (6)
S1-Ru-O4	175.56 (8)	176.6 (1)
S2-Ru-S3	90.55 (4)	90.22 (6)
S2-Ru-O4	85.52 (9)	85.6 (2)
S3-Ru-O4	88.87 (7)	88.0 (1)
Ru-S1-O1	119.0 (2)	118.5 (3)
Ru-S1-C11	115.1 (2)	115.0 (4)
Ru-S1-C12	111.0 (2)	112.1 (3)
O1-S1-C11	105.8 (2)	105.5 (4)
O1-S1-C12	105.4 (3)	106.1 (4)
C11-S1-C12	98.1 (3)	97.3 (5)
Ru-S2-O2	119.2 (2)	118.8 (3)
Ru-S2-C21	114.9 (2)	115.8 (4)
Ru-S2-C22	110.6 (2)	110.4 (3)
O2-S2-C21	105.2 (2)	104.8 (4)
O2-S2-C22	106.0 (2)	105.9 (4)
C21-S2-C22	98.6 (3)	99.0 (4)
Ru-S3-O3	115.2 (1)	114.4 (2)
Ru-S3-C31	114.8 (2)	116.5 (3)
Ru-S3-C32	115.0 (2)	115.4 (3)
O3-S3-C31	106.1 (3)	105.0 (4)
O3-S3-C32	106.4 (3)	106.7 (4)
C31-S3-C32	97.5 (3)	96.9 (4)
O4-S4-C41	103.7 (2)	104.1 (3)
O4-S4-C42	102.6 (2)	102.6 (4)
C41-S4-C42	99.1 (3)	98.9 (4)
Ru-O4-S4	119.2 (2)	120.7 (3)

iments, in BD2F1 female hybrids. For tumor transplantation and evaluation see ref 12.

The dosage employed for each complex is the maximum tolerated dose and corresponds to the $LD_{0.05}$.[26]

Results and Discussion

***cis*-$RuCl_2(DMSO)_4$.** In the crystal structure[24] of *cis*-$RuCl_2(DMSO)_4$, the Ru displays a distorted octahedral coordination.

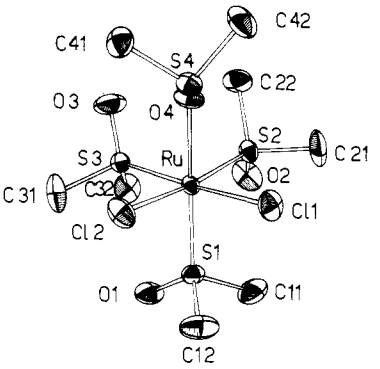


Figure 1. ORTEP drawing of *cis*-$RuCl_2(DMSO)_4$ with the atom-labeling scheme.

Table VI. Selected Torsion Angles (deg) for the Three Crystal Forms of *cis*-$RuCl_2(DMSO)_4$, F1-F3

	F1[a]	F2[b]	F3[c]
S2-Ru-S1-O1	-83.7	-79.1	-101.7
S3-Ru-S1-O1	9.3	15.0	-10.6
S1-Ru-S2-O2	21.5	18.0	33.9
S3-Ru-S2-O2	-73.6	-76.3	-60.6
O4-Ru-S2-O2	-162.2	-163.2	-149.4
S1-Ru-S3-O3	-84.5	-81.9	-168.1
S2-Ru-S3-O3	9.2	11.7	-70.5
O4-Ru-S3-O3	94.3	96.5	15.0

[a] Calculated from parameters given in ref 24. [b] Calculated from parameters given in ref 25. [c] Present work.

Three out of the four DMSO's are S-bonded to the Ru in a facial configuration, while the last one is O-bonded. This structure is substantially different from that of the known dibromo derivative, reported in 1984,[23] which has the two halogens in trans positions and all four DMSO molecules coordinated via their sulfur atoms.

Recently, it has been shown that *cis*-$RuCl_2(DMSO)_4$ is able to crystallize in different forms, depending upon the crystallization conditions. Thus, Mercer and Trotter obtained,[24] from methanol, monoclinic crystals, $P2_1/n$, with an approximative cubic shape, F1, while orthorhombic, *Pccn*, platelike crystals, F2, were obtained by us on cooling a hot dimethyl sulfoxide solution.[27] Both forms exhibit essentially the same molecular structure, and neither contains solvents of crystallization.

A new monoclinic form, F3, $P2_1/n$, has been obtained, as yellow prisms, by adding acetone to a warm dimethyl sulfoxide solution. The molecular structure of F3 is shown in Figure 1. Selected bond lengths and angles are listed in Table V, together with those of the bromo analogue (vide infra). It is easily seen that the molecular geometry of F3 is the same as F1 and F2. Significant differences are only found in the rotation of the S-bonded DMSO's around their Ru-S bonds, which is evident by inspection of the torsion angles around the Ru-S bonds in Table VI. F1 and F2 are seen to have quite similar geometries, while F3 shows a markedly different orientation of the DMSO molecules, mainly for the S3 group.

It is interesting to observe that the different conformations produce slight, but significant, differences in some bond lengths and angles, e.g.: Ru-S3, 2.276 (1) Å in F1, 2.269 (1) Å in F2, 2.284 (1) Å in F3; S3-O3, 1.485 (5) Å in F1, 1.489 (3) Å in F2, 1.461 (3) Å in F3; S1-Ru-S2, 93.44 (5)° in F1, 93.27 (4)° in F2, 97.46 (3)° in F3; C12-Ru-S1, 96.69 (3)° in F1, 94.89 (4)° in F2, 89.44 (3)° in F3. This is indicative of intramolecular steric interactions within the molecule.

The Ru-S1 (trans to O) bond length of 2.245 (1) Å is comparable with the values found in F1 (2.252 (1) Å)[24] and F2 (2.248 (1) Å)[27] as well as with the mean value of 2.25 (1) Å found in $[Ru(DMSO)_6]^{2+}$.[28] This bond length is shorter than the Ru-S

(26) Litchfield, J.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.

(27) Attia, W. M.; Calligaris, M. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1987**, *C43*, 1426.

Table VII. S–O Stretching Frequencies of Coordinated Dimethyl Sulfoxide Molecules in the Three Crystal Forms of *cis*-$RuCl_2(DMSO)_4$, F1–F3

	ν_{SO}, cm^{-1}	
	S bonded	O bonded
F1	1122 (s), 1110 (sh), 1095 (m)	921 (s)
F2	1115 (s), 1096 (sh), 1086 (m)	938 (s)
F3	1108 (m), 1086 (s)	927 (s)

Table VIII. Bond Distances (Å) and Angles (deg) with Esd's for *trans*-$RuCl_2(DMSO)_4$

Ru–Cl	2.402 (2)	S–O	1.491 (5)
Ru–S	2.352 (2)	S–C	1.780 (5)
Ru–S–O	112.5 (2)	C–S–O	106.0 (2)
Ru–S–C	115.4 (2)	C–S–C	100.3 (2)

distances trans to Cl, which average to 2.279 (7) Å. The last value is close to the average values of 2.277 (1) and 2.274 (7) Å found in F1 and F2, respectively,[24,27] as well as to the average value of 2.262 (8) Å found in $[RuCl_3(DMSO)_3]^-$.[29]

Since Cl is not expected to exert a greater trans influence than oxygen, it seems likely that the observed lengthening is essentially due to steric effects that prevent a closer approach of equatorial dimethyl sulfoxide molecules. Further indication of intramolecular steric interactions is derived from the significant distortion of the S atoms from the tetrahedral geometry, with an increase of the Ru–S–O (117°) and Ru–S–C (114°) angles and consequent narrowing of the C–S–O (106°) and C–S–C (98°) bond angles.

The three crystal forms display significantly different solid-state infrared spectra, mainly in the region of S–O stretching (Table VII). It has been observed that the IR spectrum of F2 slowly transforms into that of F3 on standing, showing that the latter polymorph is thermodynamically more stable.

***trans*-$RuCl_2(DMSO)_4$.** Previous efforts to isomerize *cis*-$RuCl_2(DMSO)_4$ to the trans isomer have been ineffective.[23] Moreover, no satisfactory explanation for the sharp structural change between the *cis*-dichloro and *trans*-dibromo derivatives has been offered.

Some reports concerning isomers of $RuCl_2(DMSO)_4$[16-19] and $RuBr_2(DMSO)_4$[18,21,22] have already appeared, but without any structural characterization. IR[22] and, in particular, NMR evidence[18] strongly suggested the existence of a cis and a trans isomer of $RuBr_2(DMSO)_4$, according to the manner of synthesis, but the relations occurring between the two were far from being understood.

The spectroscopic studies of these complexes in solution have been complicated by the presence of more than one isomer in the examined sample.[18,21,23] Unintentional exposure to sunlight may have brought further complications.

We discovered that *trans*-$RuCl_2(DMSO)_4$ can be easily obtained from *cis*-$RuCl_2(DMSO)_4$ through a photochemical isomerization in dimethyl sulfoxide solution at room temperature.

The solid-state infrared spectrum of the isolated complex is substantially similar to that of *trans*-$RuBr_2(DMSO)_4$,[23] except for the sharp single band at 336 cm^{-1} attributed to the Ru–Cl stretching of the two trans halogens.[16] Also the electronic spectrum of the complex in chloroform solution closely resembles that reported for *trans*-$RuBr_2(DMSO)_4$.[23]

The structure of the complex, suggested by the spectroscopic data, has been fully confirmed by X-ray analysis and is shown in Figure 2, together with the atom-numbering scheme. The Ru atom lies at the crystallographic $4/m$ position with the two Cl atoms on the fourfold axis. The S and O atoms lie on the crystallographic mirror plane, so that the Cl–Ru–S and S–Ru–S bond angles are exactly 90°. Bond lengths and angles are listed in Table VIII.

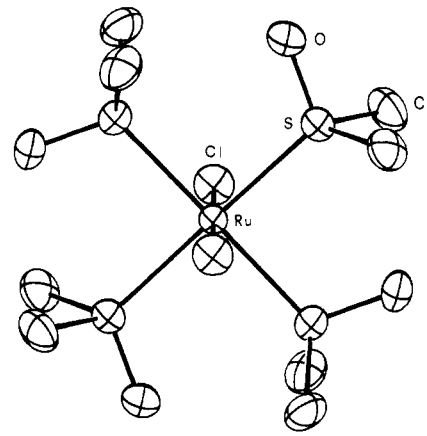


Figure 2. ORTEP drawing of *trans*-$RuCl_2(DMSO)_4$ with the atom-labeling scheme.

The Ru–Cl distance of 2.402 (2) Å in the trans complex is shorter than the mean values found in the three polymorphs of *cis*-$RuCl_2(DMSO)_4$: 2.435 (1) Å in F1, 2.42 (1) Å in F2, and 2.422 (3) Å in F3. This is in agreement with the greater trans influence of DMSO.

The Ru–S distance of 2.352 (2) Å is close to that of 2.360 (1) Å found in the dibromo analogue.[23] This bond length is significantly longer than the average values of the cis isomers. It seems likely that in the trans isomer the lengthening of the Ru–S bond is partly due to the trans influence of S and the greater π back-bonding competition among the trans DMSO ligands,[24,28] and partly due to steric effects arising from the overcrowding in the equatorial plane. In fact, we have seen that steric interactions are active in the cis isomer (see above). Larger effects should be expected in the trans isomer if the in-plane Ru–S distances had to be reduced.

These factors are probably responsible for the lower thermodynamic stability of the trans isomer with respect to the cis one. In the latter the coordination of one DMSO molecule through its oxygen atom causes a stabilization of the facial configuration, through an enhancement of the π back-donation, and relieves the steric repulsive interactions.

The unfavorable situation of the four DMSO molecules in the equatorial plane is confirmed by the behavior of the complex in solution. The ^1H NMR spectrum of the complex in $CDCl_3$ consists of two singlets at δ 3.41 and 2.62, which correspond to S-bonded and free DMSO respectively.[16,18] The relative intensity of the S-bonded resonance to free dimethyl sulfoxide is 3:1. Therefore, in noncoordinating solvents, *trans*-$RuCl_2(DMSO)_4$ thoroughly dissociates one DMSO molecule, relieving the steric demand of the complex, and probably rearranges to a trigonal-bipyramidal species with the three remaining equivalent S-bonded DMSO molecules on the equatorial plane. This hypothesis is confirmed by the $^{13}C\{^1H\}$ NMR spectrum, which presents two singlets at δ 42.78 and 41.14, approximately in a 3:1 ratio, attributed to S-bonded and free DMSO, respectively.[20] The spectral patterns do not change with time upon observation periods of several hours.

Contrary to previous reports,[21,23] a closely similar ^1H (δ 3.51 (s) (S-bonded), 2.61 (s) (free DMSO); ratio 3:1) and $^{13}C\{^1H\}$ (δ 45.07 (S-bonded), 41.16 (free DMSO); ratio approximately 3:1) NMR pattern is found with the dibromo derivative (recrystallized) in $CDCl_3$ solution.

As previously reported,[16,18] *cis*-$RuCl_2(DMSO)_4$ in chloroform solution partially releases the O-bonded dimethyl sulfoxide molecule to give an as yet uncharacterized species. After exposure of the solutions to sunlight, the ^1H NMR spectra show a new singlet at δ 3.41, characteristic of the trans isomer. This points out that the cis to trans photoinduced isomerization readily takes place also in this solvent.

trans-$RuCl_2(DMSO)_4$ is thermodynamically unstable with respect to *cis*-$RuCl_2(DMSO)_4$. It slowly isomerizes in dimethyl sulfoxide solution with first-order kinetics, as indicated spectro-

(28) Davies, A. R.; Einstein, F. W. B.; Farrell, N. P.; James, B. R.; McMillan, R. S. *Inorg. Chem.* **1978**, *17*, 1965.
(29) McMillan, R. S.; Mercer, A.; James, B. R.; Trotter, J. *J. Chem. Soc., Dalton Trans.* **1975**, 1006.

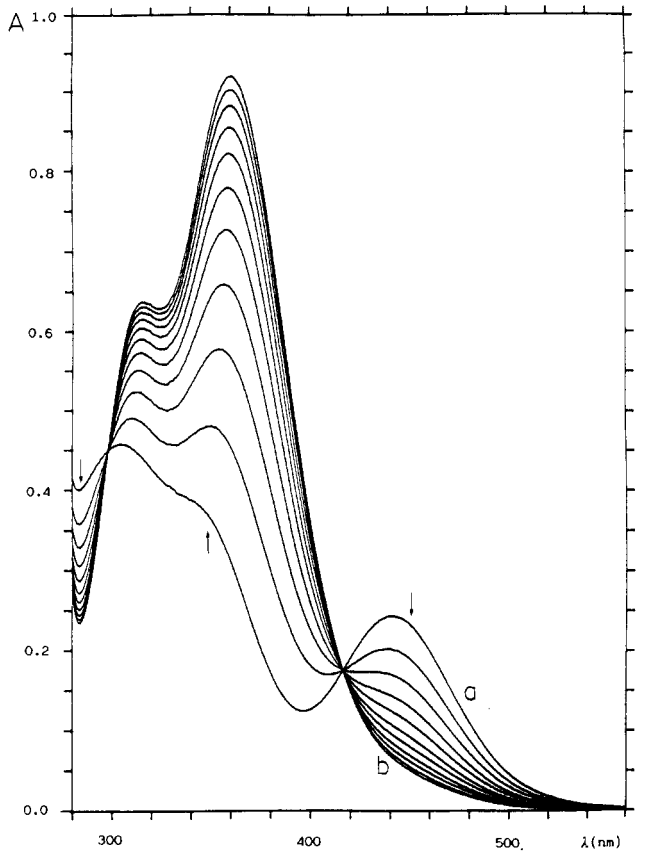


Figure 3. Spectral changes observed during the thermal isomerization of *trans*-$RuCl_2(DMSO)_4$ (2×10^{-3} M) to *cis*-$RuCl_2(DMSO)_4$ in dimethyl sulfoxide solution at 50 °C: (a) *trans*-$RuCl_2(DMSO)_4$, initial spectrum; (b) *cis*-$RuCl_2(DMSO)_4$, final spectrum.

photometrically in Figure 3. Therefore the following reaction[30] can be drawn for the two isomers:

$$cis\text{-}RuCl_2(DMSO)_3(DMSO) \underset{\Delta}{\overset{h\nu}{\rightleftharpoons}} trans\text{-}RuCl_2(DMSO)_4 \quad (1)$$

The trans to cis thermal isomerization has been followed spectrophotometrically. The rate constants have been determined at five temperatures in the range 40–60 °C, and the activation parameters were calculated: $k = 2.58 \times 10^{-6}$ s^{-1} at 25 °C, $\Delta H^{\ddagger} = 128 \pm 2$ kJ mol^{-1}, $\Delta S^{\ddagger} = 110 \pm 5$ J·mol^{-1}·K^{-1}. The positive value of the entropy of activation is in agreement with the assumption of a dissociative loss of dimethyl sulfoxide from the substrate in the rate-determining step.

cis-$RuCl_2(DMSO)_4$ is currently used as a versatile starting material in the synthesis of ruthenium(II) derivatives,[16,31] and both *cis*-$RuCl_2(DMSO)_4$ and *trans*-$RuBr_2(DMSO)_4$ were found to be good catalysts for the selective oxidation of alkyl sulfides to sulfoxides with molecular oxygen.[23,32] Therefore, the facile photochemical synthesis of *trans*-$RuCl_2(DMSO)_4$ opens new possibilities both in inorganic synthesis and homogeneous catalysis. For such purposes, in fact, *trans*-$RuCl_2(DMSO)_4$ might turn out to be superior to its dibromo analogue for the following reasons:

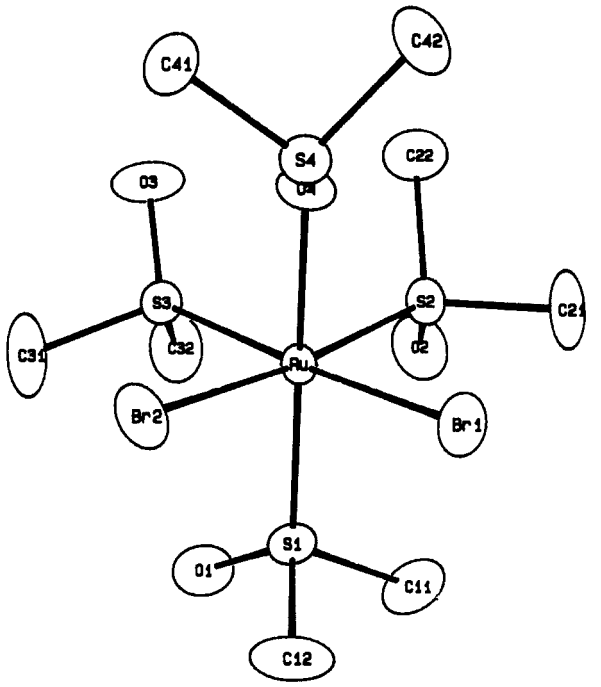


Figure 4. ORTEP drawing of *cis*-$RuBr_2(DMSO)_4$ with the atom-labeling scheme.

the lower cost and easier commercial availability of its precursor $RuCl_3$ with respect to $RuBr_3$, its high synthetic yields, its considerably higher solubility in organic solvents, and the possibility of direct comparison between geometrical isomers.

***cis*-$RuBr_2(DMSO)_4$.** According to the results obtained with the chloro isomers, it appeared unlikely that the change from chloro to bromo might substantially modify the relative stability of the isomers. Therefore we looked for a cis isomer of the known dibromo complex that, in our opinion, should have been the more stable one.

We found that, upon addition of acetone to hot dimethyl sulfoxide solutions of *trans*-$RuBr_2(DMSO)_4$, it is possible to isolate, on cooling, large orange crystals that analyze for $RuBr_2(DMSO)_4$ and have the same solid-state infrared spectrum as *cis*-$RuCl_2(DMSO)_4$, except for the absence of the Ru–Cl stretching bands at 342 cm^{-1}. The same complex had previously been obtained by refluxing $RuBr_3$ in dimethyl sulfoxide.[18]

X-ray analysis of the crystals confirmed that the complex is *cis*-$RuBr_2(DMSO)_4$ and that it is isostructural with *cis*-$RuCl_2(DMSO)_4$. An ORTEP drawing of the molecule is given in Figure 4, showing the strict similarity of its structure with that of F3. Bond distances and angles are given in Table V, together with those of the isostructural dichloro isomer, F3. The trans Ru–S1 and Ru–O4 bond distances of 2.253 (2) and 2.943 (5) Å, respectively, compare favorably with those of F3. On the other hand, the Ru–S2 and Ru–S3 distances of 2.289 (2) and 2.301 (2) Å are significantly longer than the corresponding distances of 2.274 (1) and 2.289 (1) Å in F3. This lengthening is probably due to the greater trans influence of Br with respect to Cl, rather than to steric effects. As with the chloro isomers, the Ru–Br distance of 2.562 (1) Å in the cis isomer is longer than that of 2.540 (1) Å of the trans isomer.[23]

Despite the fact that *trans*-$RuBr_2(DMSO)_4$ has been the only isomer known for many years and used for several synthetic and catalytic purposes,[32] it is the thermodynamically less stable isomer. In dimethyl sulfoxide solution it readily isomerizes, even at room temperature, to the cis derivative with first-order kinetics ($k = 1.25 \times 10^{-5}$ s^{-1} at 25 °C). The high yield of *trans*-$RuBr_2(DMSO)_4$ in its synthesis reaction conducted at 80 °C in dimethyl sulfoxide[15] is attributable to the extremely low solubility of the complex in this solvent, which subtracts it from the isomerization equilibrium.

The activation parameters of the trans to cis thermal isomerization have been calculated by spectrophotometric determination of the rate constant at five temperatures in the range 30–50 °C:

(30) DMSO = S-bonded dimethyl sulfoxide DMS*O* = O-bonded dimethyl sulfoxide

(31) (a) Marks, D. N.; Siegl, W. O.; Gaugè, R. G. *Inorg. Chem.* **1982**, *21*, 3140. (b) Ritchie, G. L. D.; Cooper, M. K.; Calvert, R. L.; Dennis, G. R.; Phillips, L.; Vrbancich, J. *J. Am. Chem. Soc.* **1983**, *22*, 1965. (c) Ravindar, V.; Lingaiah, P.; Veera Reddy, K. *Inorg. Chim. Acta* **1984**, *87*, 35. (d) Marzin, C.; Tarrago, G.; Gal, M.; Zidane, I.; Hours, T.; Lerner, D.; Andrieux, C.; Gampp, H.; Saveant, J. M. *Inorg. Chem.* **1986**, *25*, 1775.

(32) (a) Riley, D. P. *Inorg. Chem.* **1983**, *22*, 1965. (b) Riley, D. P.; Shumate, R. E. *J. Am. Chem. Soc.* **1984**, *106*, 3179. (c) Riley, D. P. *Inorg. Chim. Acta* **1985**, *99*, 5.

(33) Sokal, R. R.; Rohlf, F. J. In *Biometry—The Principles and Practice of Statistics*; W. H. Freeman: San Francisco, CA, 1969; p 201.

Table IX. Comparison of the Antineoplastic Actions of *cis*- and *trans*-$RuCl_2(DMSO)_4$ in Mice Bearing Lewis Lung Carcinoma

compd	dose, mg/(kg·day)	primary tumor wt,[b] mg		lung metastases[c]			
				no.		wt	
		mean ± SE	*I*%[d]	mean ± SE	*I*%	mean ± SE	*I*%
controls		2513 ± 275		41 ± 3		216 ± 32	
cis-$RuCl_2(DMSO)_4$	700	1809 ± 352	28	22 ± 2*	46	104 ± 17*	52
trans-$RuCl_2(DMSO)_4$	37	1960 ± 226	22	18 ± 2*	57	62 ± 11*	71
cis-$PtCl_2(NH_3)_2$	0.52	1608 ± 402	36	14 ± 4*	67	47 ± 19*	78

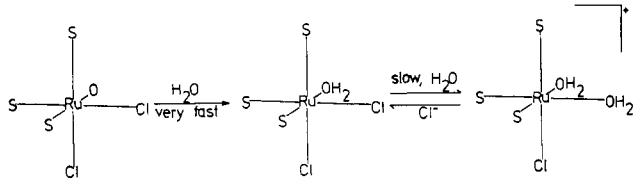
[a] Groups of eight BD2F1 mice, inoculated sc with 100 mm^3 of Lewis lung carcinoma fragments on day 0, were given ip on days 1–14 the reported compounds. An asterisk denotes values statistically different from the corresponding value of the control group by the Student–Newmann–Keuls test,[33] $p = 0.05$. [b] Measured on day 14 from tumor implantation. [c] Measured on day 21 from tumor implantation. [d] *I*%: means percent inhibition compared to the value obtained in control group.

Table X. Effects of *trans*-$RuCl_2(DMSO)_4$ and *trans*-$RuBr_2(DMSO)_4$ on the Growth of Artificial Lung Metastases of Lewis Lung Carcinoma[a]

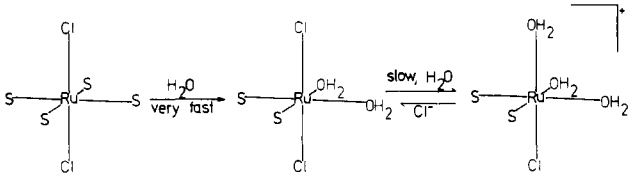
compd	dose, mg/(kg·day)	toxic deaths	lung metastases[b]				animals free[c]
			no.		wt		
			mean ± SE	*I*%	mean ± SE	*I*%	
controls		0/8	9.2 ± 1.1		169 ± 27		0/8
trans-$RuBr_2(DMSO)_4$	150	3/8	7.3 ± 1.4	21	38 ± 2*	78	0/5
trans-$RuCl_2(DMSO)_4$	150	3/8	5	46	15	91	4/5

[a] Groups of eight BD2F1 mice, receiving iv 2.5×10^5 Lewis lung carcinoma cells (artificial metastasis induction) on day 0, were given ip the compounds indicated on days 1–5. An asterisk denotes values statistically different from the corresponding value of control group by the Student–Newmann–Keuls test,[33] $p = 0.05$. [b] Measured on day 14 from iv tumor implantation. [c] Animals free of macroscopically detectable lung colonies.

Scheme I. Chemical Behavior of *cis*-$RuCl_2(DMSO)_4$ in Aqueous Solution



Scheme II. Chemical Behavior of *trans*-$RuCl_2(DMSO)_4$ in Aqueous Solution



$\Delta H^{\ddagger} = 114 \pm 5$ kJ·mol^{-1}; $\Delta S^{\ddagger} = 79 \pm 18$ J·mol^{-1}·K^{-1}.

Also in this case the light-induced reversal isomerization has been experimentally observed.

Therefore, a reaction similar to that of the dichloro derivatives can be drawn for the dibromo isomers:[30]

$$cis\text{-}RuBr_2(DMSO)_3(DMSO) \underset{\Delta}{\overset{h\nu}{\rightleftharpoons}} trans\text{-}RuBr_2(DMSO)_4 \quad (2)$$

Chemical Behavior in Aqueous Solution. The chemical behavior of the isomers in aqueous solution has been studied in view of their potential antitumor activity; particular attention has been devoted to *cis*- and *trans*-$RuCl_2(DMSO)_4$.

The chemical behavior of *cis*-$RuCl_2(DMSO)_4$ is summarized in Scheme I. As shown by others,[18] *cis*-$RuCl_2(DMSO)_4$, once dissolved in water, immediately releases the O-bonded dimethyl sulfoxide molecule. This step is followed by the slow dissociation of a Cl^- anion to give the cationic species.[16] We have followed this step by means of conductivity measurements and repetitive electronic absorption.

Upon dissociation the absorption maxima shift from 355 to 340 nm and from 310 to 300 nm, respectively, with an isosbestic point at 346 nm. The conductivity of diluted (10^{-3} M), light-protected solutions slowly increases over ca. 10 h to that for a 1:1 electrolyte ($\Lambda = 101$ Ω^{-1}·cm^2·mol^{-1} at 25 °C). At 37 °C the equilibrium is reached within 3 h, and it is affected by the presence of free Cl^-. Two significant Cl^- concentrations have been tested, namely 3 and 150 mM, which represent the chloride concentrations inside and outside the cell, respectively. While the equilibrium is not affected in 3 mM NaCl, it is completely inhibited in 150 mM NaCl.

The dibromo analogue shows a similar behavior in water, but for the halogen dissociation rate, which is at least 3 times faster than in the case of the chloro derivative.

trans-$RuCl_2(DMSO)_4$ shows a remarkably different behavior in aqueous solution, as indicated in Scheme II.

The ^1H NMR spectrum of the complex in D_2O consists of two singlets of equal intensities at δ 3.35 and 2.71, which correspond to S-bonded and free DMSO, respectively.[18] A closely similar pattern is shown by the $^{13}C\{^1H\}$ spectrum, which presents two singlets of approximately equal intensity at δ 42.78 (S-bonded DMSO) and 41.14 (free DMSO). Therefore the NMR spectra show that, once dissolved, the trans isomer immediately releases two dimethyl sulfoxide molecules. These, according to their strong trans influence, should be mutually cis and give the *cis*-diaquo, *cis*-bis(dimethyl sulfoxide), and *trans*-dichloro ruthenium(II) complex.

Also the trans isomer slowly releases a Cl^- anion. The conductivity of diluted aqueous solutions (10^{-3} M) of the complex increases in time at a lower rate than *cis*-$RuCl_2(DMSO)_4$. This is in agreement with the lower trans effect of chloride with respect to dimethyl sulfoxide. A molar conductance of 105 Ω^{-1}·cm^2·mol^{-1} is obtained after 24 h at 25 °C, showing the complex to be a 1:1 electrolyte. However, prolonged observation periods (6 days) show that the conductivity still increases very slowly up to values in the range of 2:1 electrolytes.

The chloride dissociation step has also been followed spectrophotometrically by repetitive scanning. As a result of Cl^- dissociation, the two absorption maxima shift from 430 to 415 nm and from 320 to 315 nm, respectively, with an isosbestic point at 421 nm. At 37 °C the equilibrium is reached in more than 6 h, and again it is completely inhibited at the physiological Cl^- concentration.

Both NMR and electronic spectra clearly show that, in aqueous solution at 37 °C, the trans derivative does not isomerize to the corresponding cis one.

The dibromo analogue, although remarkably less soluble, shows a completely similar behavior in water.

Assuming that the coordinated water molecules have a labile nature, while *cis*-$RuCl_2(DMSO)_4$ under physiological conditions has only one coordination site readily available, the trans isomer has immediately two sites open in cis positions. As neutral species they should be able to cross the cell membrane. Once inside the cell, owing to the lower Cl^- concentration, both the complexes should slowly open an additional coordination site.

Accordingly, a higher reactivity in aqueous solution is expected for the *trans* isomer, under both extracellular and intracellular conditions.

Antitumor Activity Tests. On a molar basis, *trans*-$RuCl_2(DMSO)_4$ is more toxic by a factor of 20 than *cis*-$RuCl_2(DMSO)_4$ ($LD_{0.05}$ of 37 vs. 700 mg/(kg·day)), which is in agreement with the higher reactivity expected for the trans isomer.

The results of the comparison of the antitumor activity of *cis*- and *trans*-$RuCl_2(DMSO)_4$ at equitoxic dosages are reported in Table IX. An equitoxic dosage of the clinically used cisplatin is employed as positive control.

The treatment has no statistically significant effect on primary tumor growth. On the contrary, while *cis*-$RuCl_2(DMSO)_4$ reduces the number and weight of spontaneous lung metastases to about 50% of the controls, the effect of *trans*-$RuCl_2(DMSO)_4$ on metastasis weight is slightly superior (inhibition to about 30% of the controls) but at a 20-fold lower dosage. The antimetastatic effect of the trans isomer is of the same order as that obtained with an equitoxic dosage of cisplatin. The absence of significant activity on primary tumor growth is in agreement with separate observations made with *cis*-$RuCl_2(DMSO)_4$, which indicate a strict dependence of the antitumor action on the mass of primary tumor being treated.[12]

The antimetastatic properties of the chloro and bromo trans isomers were investigated in a preliminary experiment in mice with lung tumor colonies artificially induced by iv implantations of Lewis lung carcinoma cells (Table X). The dosage used for the two isomers presents some toxicity for the host, being responsible for toxic deaths within the treated groups (37% with both complexes). Nevertheless, these results show that the efficacy of the *trans*-dichloro isomer is remarkably higher than that of the *trans*-dibromo one, indicating the influence of the halogen on the antitumor effect.

Conclusions

The different behavior of the cis and trans isomers of $[Ru(DMSO)_4X_2]$ in nonprotic solvents provides for the synthesis of homogeneous series of geometrical isomer derivatives. Moreover, their substitution kinetics in aqueous solution directly reflects on their different antitumor properties. The use of *trans*-$RuCl_2(DMSO)_4$ instead of the cis isomer allows for increased tumor toxicity at remarkably lower doses.

Our work is now directed toward the synthesis of homogeneous series of derivatives of both isomers, with the aim of improving the antitumor properties of the original complexes. Moreover, these complexes, due to their high stability towards oxidation,[29] can be used as useful model compounds to study the interactions of octahedral Ru(II) complexes with DNA and oligonucleotides.

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Supplementary Material Available: Tables of anisotropic temperature factors for non-hydrogen atoms (Tables XI-XIII) and positional parameters for hydrogen atoms (Tables XIV-XVI) of *cis*-$RuBr_2(DMSO)_4$, *cis*-$RuCl_2(DMSO)_4$, and *trans*-$RuCl_2(DMSO)_4$, respectively (6 pages); listings of calculated and observed structure amplitudes for *cis*-$RuBr_2(DMSO)_4$, *cis*-$RuCl_2(DMSO)_4$, and *trans*-$RuCl_2(DMSO)_4$ (36 pages). Ordering information is given on any current masthead page.

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Synthesis and Characterization of Diastereomeric (Substituted iminodiacetato)(1,2-diaminocyclohexane)platinum(II) Complexes

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Novel complexes of the type [Pt(DACH)(*N*-R-iminodiacetate)], wherein DACH represents (*R,S*)- and (*R,R*)-1,2-diaminocyclohexane and R represents -Me, -EtOH, and $-CH_2Ph$ groups, have been prepared, purified, and characterized by spectroscopic techniques (^1H, ^{13}C, and ^{195}Pt NMR; MS(FAB); IR) and by the measurement of selected physical properties (pH, pK_a, conductivity, and molecular weights). The data are consistent with the formation of two diastereomeric complexes in unequal proportions in which the *N*-R-iminodiacetate ligand appears to be bonded as a pseudofacial tridentate chelate. One arm of the ligand forms a stable five-membered-ring O,N-chelate while the other arm appears to be involved in ion-pair formation (zwitterion-like) involving the carboxylate anion and the formally positive Pt(II) central metal atom. It has been demonstrated indirectly that an active impurity was present in predictably inactive bulk complexes of the type PtN_3O. The need to characterize unequivocally and certify the purity of prospective antitumor complexes is emphasized.

Introduction

Among the many antitumor-active platinum(II) complexes possessing the common structure *cis*-PtA_2X_2, (1,2-diaminocyclohexane)platinum(II) complexes are of particular interest in the search for a third-generation platinum antitumor drug. Interest in these agents is the result of (1) demonstrated antitumor activity in vivo, including a selectivity based on the isomeric form of the DACH ligand employed[1] and (2) generally good dose potency but, most particularly, (3) effectiveness against cisplatin-resistant tumor systems in vitro and in vivo.[2]

Since $[PtN_3X]^+$ systems are known to be inactive,[3] preliminary reports of the antitumor activity of (*N*-alkyl-substituted iminodiacetato)(*R,R*)-1,2-diaminocyclohexane)platinum(II) complexes[4] suggested the possibility of O,O-chelation rather than the thermodynamically preferred O,N-chelation mode commonly found for metal-amino acid complexes.[5] Interest in resolving this question has led to a study of a series of novel complexes principally of the type [Pt(*R,R*-DACH)X], wherein the X group represents an *N*-alkyl-substituted iminodiacetate dianion, $R-N(CH_2CO_2)_2^{2-}$ (or *N*-R-IDA), and *R,R*-DACH denotes (-)-(*R,R*)-1,2-di-

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