Ruthenium(II)–dimethyl sulfoxide complexes with nitrogen ligands: synthesis, characterization and solution chemistry. The crystal structures of *cis,fac*-$RuCl_2(DMSO)_3(NH_3)$ and *trans,cis,cis*-$RuCl_2(DMSO)_2(NH_3)_2 \cdot H_2O$

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Abstract

In this paper we report the synthesis and characterization of some new derivatives of the isomers *cis*-(**1**) and *trans*-$RuCl_2(DMSO)_4$ (**6**) (DMSO = dimethyl sulfoxide) with monodentate nitrogen donor ligands (L) such as NH_3, imidazole (Im) and benzimidazole (BzIm): *cis,fac*,-$RuCl_2(DMSO)_3(L)$ (L = NH_3 (**2**), Im (**3**)); *cis,cis,cis*-$RuCl_2(DMSO)_2(Im)_2$ (**4**); *fac*-$[Ru(Im)_3Cl(DMSO)_2]PF_6$ (**5**); *trans,cis,cis*-$RuCl_2(DMSO)_2(L)_2$ (L = NH_3 (**7**), Im (**8**), BzIm (**9**)); *trans*,-$RuCl_2(DMSO)_3(Im)$ (**10**). All complexes have exclusively S-bonded DMSOs. Their chemical behavior in aqueous solution is also described. The crystal structures of *cis,fac*-$RuCl_2(DMSO)_3(NH_3)$ (**2**) and *trans,cis,cis*-$RuCl_2(DMSO)_2(NH_3)_2 \cdot H_2O$ (**7**), were determined by three dimensional X-ray analyses. Crystal data: **2**, $a = 9.103(2)$, $b = 12.568(2)$, $c = 13.375(6)$ Å, $\beta = 96.52(2)°$, monoclinic, space group $P2_1/n$, $Z = 4$; **7**, $a = 8.507(4)$, $b = 11.331(4)$, $c = 14.071(4)$ Å, $\beta = 90.99(1)°$, monoclinic, space group $P2_1c$, $Z = 4$. Least-squares refinement based on 4045 (**2**) and 3682 (**7**) reflections converged to $R = 0.026$ and 0.030 for **2** and **7**, respectively. In **2**, the three DMSOs have Ru–S bond distances of 2.2774(6) and 2.2458(5) Å (*trans* to Cl), and 2.2877(5) Å (*trans* to N). The Ru–Cl bond distances are 2.4178(6) and 2.4411(6) Å (*trans* to S), while the Ru–N (*trans* to S) bond length is 2.151(2) Å. In **7**, the *trans* Ru–Cl bond distances are 2.4030(7) and 2.4125(7) Å, while the Ru–S (*trans* to N) bond distances are 2.2350(6) and 2.2469(6) Å, and the Ru–N (*trans* to S) 2.142(2) and 2.156(2) Å.

Introduction

The search for non-platinum antitumor complexes, which should possibly be active against those tumor lines that do not respond to the clinically used platinum drugs, is an item of major research interest [1].

In this field, the two isomeric ruthenium(II) derivatives *cis*- and *trans*-$RuCl_2(DMSO)_4$ (DMSO = dimethyl sulfoxide) [2] were shown to possess antitumor and, in particular, remarkable antimetastatic activity against some murine tumor models (P388 leukemia, platinum resistant P388, Lewis lung carcinoma, B16 melanoma, MCa mammary carcinoma) [3]. According to recent *in vitro* results, *cis*-$RuCl_2(DMSO)_4$ also possesses a differential cytotoxicity towards some human tumor cell lines [4]. Of interest, it exhibits particular activity against ZR-75-1 breast carcinoma cells.

A series of *in vitro* and *in vivo* experiments performed in recent years allowed an insight into the possible mechanism of action of the two complexes. In particular, attention was focused on *trans*-$RuCl_2(DMSO)_4$, as it exhibits an antitumor activity more pronounced than the *cis* isomer. The complex was proved to interact with DNA, with guanine bases as preferential sites of attack [3c]. The study of its interactions with pBR 322 DNA showed that *trans*-$RuCl_2(DMSO)_4$, in analogy to cisplatin, markedly inhibits those restriction enzymes that recognize sequences containing two or more adjacent guanines (e.g. Bam HI: G/GATCC; Ava I: C/TCGGG) [5]. The affinity of the ruthenium complex for guanine N7 was confirmed by an NMR study concerning its interactions with mononucleotides [6].

From the results reported above, the biological activity of the two isomers appears to be strictly

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connected to their *in vivo* interactions with nitrogen bases. This consideration urged us to undertake a detailed study of the reactivity of *cis*- and *trans*-$RuCl_2(DMSO)_4$ with simple molecules such as NH_3, imidazole (Im) and benzimidazole (BzIm), with the aim of building a model that might provide some guidelines for understanding the interactions of the two isomers with nitrogen donor ligands of biological importance. In the course of this study we isolated several new derivatives of the two isomers. In this paper we describe the synthesis and characterization of the following new complexes with exclusively S-bonded DMSOs: *cis,fac*-$RuCl_2(DMSO)_3(L)$ (L= NH_3, Im); *cis,cis,cis*,-$RuCl_2(DMSO)_2(Im)_2$; *fac*-$[Ru(Im)_3Cl(DMSO)_2]PF_6$; *trans*-$RuCl_2(DMSO)_3$-(Im); *trans,cis,cis*-$RuCl_2(DMSO)_2(L)_2$ (L= NH_3, Im, BzIm). Their chemical behavior in aqueous solution is also described. It was studied with the aim of evaluating whether some of the new derivatives had such chemical features that might suggest their use in pharmacological tests. We also report the crystal structures of the ammonia complexes *cis,fac*-$RuCl_2(DMSO)_3(NH_3)$ and *trans,cis,cis*-$RuCl_2$-$(DMSO)_2(NH_3)_2$.

Very little has been reported in the literature about this subject and only a few reports concerning nitrogen ligand derivatives of *cis*-$RuCl_2(DMSO)_4$ could be found. In the early work of Wilkinson's group on *cis*-$RuCl_2(DMSO)_4$, the complex was reported to react with pyridine to give the tetrasubstituted complex $RuCl_2(Py)_4$ [7]. In more recent years, Chan *et al.* reported some well characterized nitroimidazole (NO_2-Im) derivatives of *cis*-$RuCl_2$-$(DMSO)_4$, of general formula *cis,cis,cis*-$RuCl_2$-$(DMSO)_2(NO_2Im)_2$ [8]. Such complexes were shown to possess promising radio-sensitizing properties [8].

Due to the relatively recent publication of the synthesis of *trans*-$RuCl_2(DMSO)_4$ [2], its derivatives described here are the first ever reported.

Experimental

Materials

All solvents and reagents were used as received without further purification

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. Solid state IR spectra (KBr plates and nujol mull) were recorded on a Perkin-Elmer 983G spectrometer; nujol mull spectra were recorded between CsI windows. ^1H NMR spectra were collected on a Bruker AM500 spectrometer. All spectra were recorded at room temperature with sodium 2,2-dimethyl-2,2-silapentane-5-sulfonate (DSS) as an internal standard for aqueous solutions and tetramethylsilane (Me_4Si) for methanol 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- (**1**) and *trans*-$RuCl_2(DMSO)_4$ (**6**) were synthesized and recrystallized according to the procedures reported in ref. 2a. An alternative, not photochemical, synthetic route to **6** was recently reported by the group of James [2b].

cis,fac-Dichlorotris(dimethyl sulfoxide)ammonia-ruthenium(II) (cis,fac-$RuCl_2(DMSO)_3(NH_3)$ (2))

The complex could be synthesized by two different procedures, depending whether gaseous (a) or aqueous (b) ammonia was used.

(a) 0.5 g of recrystallized *cis*-$RuCl_2(DMSO)_4$ (1 mmol) was partially dissolved in 20 ml of methanol in a flask closed with a stop-cock. The flask was first connected to a vacuum line and then to a reservoir of gaseous ammonia. Within 10 min at r.t. the reactant was completely dissolved, the lemon–yellow solution turned pale yellow and the product, of the same colour, formed. After 30 min it was filtered off, washed with methanol and diethyl ether and vacuum dried at r.t. Yield: 0.36 g (85%).

(b) 0.5 g (1 mmol) of recrystallized *cis*-$RuCl_2(DMSO)_4$ was dissolved in 30 ml of a 2:1 absolute ethanol/chloroform mixture and treated with 1 ml of 37% aqueous NH_3. Yellow crystals of the product formed from the clear yellow solution after 24 h at r.t. They were filtered off, washed with cold ethanol and vacuum dried. Yield 0.36 g (85%).

Anal. Calc. for $C_6H_{21}Cl_2NO_3RuS_3$ (M_r 423.43): C, 17.02; H, 5.01; N, 3.31. Found: C, 17.50; H, 5.16; N, 3.15%.

Selected IR absorptions (cm^{-1}): ν_{NH} 3312 (m), 3277 (w), 3180 (m); ν_{so} (S-bonded) 1095 (s), 1073 (vs); ν_{RuS} 423 (s); ν_{Ru-Cl} 338 (w), 303 (w). Electronic spectra (λ_{max}, nm (ϵ, $M^{-1}\,cm^{-1}$)): in H_2O, 351 (321), 296 sh (180); in methanol, 351 (335), 296 sh (200).

cis,fac-Dichlorotris(dimethyl sulfoxide)imidazole-ruthenium(II) (cis,fac-$RuCl_2(DMSO)_3(Im)$ (3))

0.5 g of recrystallized *cis*-$RuCl_2(DMSO)_4$ (1 mmol) was partially dissolved in 20 ml of methanol and treated with 0.15 g (2.2 mmol) of imidazole. The mixture was stirred at room temperature for 8 h. During this period a pale yellow precipitate formed

and was then filtered off, washed with cold methanol and vacuum dried. Yield 190 mg (40%).

Anal. Calc. for $C_9H_{22}Cl_2N_2O_3RuS_3$ (M_r 474.48): C, 22.78; H, 4.68; N, 5.91; Cl, 14.94; S, 20.27. Found: C, 22.90; H, 4.74; N, 5.53; Cl, 15.00; S, 20.19%.

Selected IR absorptions (cm^{-1}): ν_{NH} 3197 (m); ν_{so} (S-bonded) 1092 (s), 1082(s); ν_{RuS} 426 (s); ν_{RuCl} 324 (w), 310 (w). Electronic spectra (λ_{max}, nm (ϵ, M^{-1} cm^{-1})): in H_2O, 356 (375), 309 sh (190); in methanol, 357 (400), 309 sh (187).

cis,cis,cis,-Dichlorobis(dimethyl sulfoxide)bis-imidazoleruthenium(II) (cis,cis,cis,-$RuCl_2$-$(DMSO)_2Im_2$ (4))

A suspension of 0.5 g of recrystallized *cis*-$RuCl_2(DMSO)_4$ (1 mmol) and 0.15 g of imidazole (2.2 mmol) in 20 ml of methanol was heated to reflux. A clear yellow solution was obtained after a few minutes, from which the product gradually formed as a deep yellow precipitate. After 6 h the mixture was cooled to room temperature and the product was filtered off, washed with CH_2Cl_2 and diethyl ether and vacuum dried. Yield 0.3 g (63%).

Anal. Calc. for $C_{10}H_{20}Cl_2N_4O_2RuS_2$ (M_r 464.43): C, 25.86; H, 4.35; N, 12.07. Found: C, 26.0; H, 4.57; N, 12.0%.

Selected IR absorptions (cm^{-1}): ν_{NH} 3132 (br, s); ν_{so} (S-bonded) 1082 (s); ν_{RuS} 426 (m). Electronic spectra (λ_{max}, nm (ϵ, M^{-1} cm^{-1})): in H_2O (to be attributed to the mono-aquo species *cis,cis,cis*-$[Ru(DMSO)_2(Im)_2Cl(H_2O)]^+$), 360 sh (174), 313 (276); in methanol, 370 sh (238), 330 (309).

fac-Trisimidazolechlorobis(dimethyl sulfoxide)-ruthenate(II)-hexafluorophosphate (fac-$[RuIm_3Cl(DMSO)_2]PF_6$) (5))

A suspension of 0.3 g of recrystallized *cis*-$RuCl_2(DMSO)_4$ (0.6 mmol) and 0.14 g of imidazole (2 mmol) in 10 ml of methanol was heated to reflux under an argon stream. The clear yellow solution obtained after a few minutes was further refluxed for 1.5 h. 0.25 g of NH_4PF_6 (1.5 mmol) dissolved in 5 ml was then added to the cooled solution. Bright yellow crystals of the product formed within a few hours and were filtered off, washed with acetone and vacuum dried. Yield 0.25 g (63%). Interestingly, some crystals of complex **8** (see below) could be isolated from the mother liquor of the reaction upon addition of diethyl ether.

Anal. Calc. for $C_{13}H_{24}ClF_6N_6O_2PRuS_2$ (M_r 641.96): C, 24.32; H, 3.76; N, 13.09. Found: C, 24.4; H, 3.67; N, 13.2%.

Selected IR absorptions (cm^{-1}): ν_{NH} 3380 (s), 3150 (m); ν_{so} (S-bonded) 1091 (s) (this region is affected by the presence of imidazole bands); ν_{RuS} 420 (m). Electronic spectra (λ_{max}, nm (ϵ, M^{-1} cm^{-1})): in H_2O, 299 (283), 363 (170); in methanol 301 (295), 361 (194).

A chloride salt of **5** could be also isolated from the mother liquors in the synthesis of **3**, after concentration, addition of diethyl ether and overnight standing at r.t.

trans,cis,cis,-Dichlorobis(dimethyl sulfoxide)bis-ammoniaruthenium(II) (trans,cis,cis,-$RuCl_2$-$(DMSO)_2(NH_3)_2$ (7))

Also in this case the complex could be synthesized by two different procedures, depending whether gaseous (a) or aqueous (b) ammonia was used.

(a) 0.5 g of *trans*-$RuCl_2(DMSO)_4$ (1 mmol) was dissolved in 6 ml of $CHCl_3$ in a flask closed with a stop-cock. The flask was first connected to a vacuum line and then to a reservoir of gaseous ammonia. Within 10 min at r.t. the initially orange solution turned yellow and the product, of the same colour, formed. After 30 min it was filtered off, washed with chloroform and diethyl ether and vacuum dried at r.t. Yield 0.26 g (70%).

(b) 0.5 g of *trans*-$RuCl_2(DMSO)_4$ (1 mmol) was dissolved in 30 ml of a 2:1 absolute ethanol/chloroform mixture and treated with 1 ml of 37% aqueous NH_3. After 24 h at room temperature 20 ml of diethyl ether were added dropwise. The orange microcrystals formed on standing were collected by filtering, washed with chloroform and diethyl ether and vacuum dried. Yield 290 mg (80%). The complex obtained by this procedure has a water molecule of crystallization and therefore can be better formulated as *trans,cis,cis*-$RuCl_2(DMSO)_2(NH_3)_2 \cdot H_2O$.

Anal. Calc. for $C_4H_{18}Cl_2N_2O_2RuS_2$ (M_r 362.33): C, 13.26; H, 5.02; N, 7.73; Cl, 19.57; S, 17.69. Found: C, 13.20; H, 5.20; N, 7.53; Cl, 19.01; S, 17.07%.

Selected IR absorptions (cm^{-1}): ν_{NH} 3511 (m), 3428 (m), 3333 (m), 3251 (w), 3185 (m); ν_{so} (S-bonded) 1064 (s), 1043(s); ν_{RuS} 429 (s, br); ν_{RuCl} 325 (m). Electronic spectra (λ_{max}, nm (ϵ, M^{-1} cm^{-1})): in H_2O, 428 (91), 298 (181); in methanol, 297 (209), 425 (102).

trans,cis,cis-Dichlorobis(dimethyl sulfoxide)bis-imidazoleruthenium(II) (trans,cis,cis,-$RuCl_2$-$(DMSO)_2Im_2$ (8))

0.5 g of *trans*-$RuCl_2(DMSO)_4$ (1 mmol) was dissolved in 30 ml of $CHCl_3$ and 0.17 g of imidazole (2.5 mmol) added. Yellow crystals of the product precipitated from the unstirred solution within 24 h at room temperature. They were filtered off, washed with cold $CHCl_3$ and vacuum dried. Yield 0.3 g (65%).

Anal. Calc. for $C_{10}H_{20}Cl_2N_4O_2RuS_2$ (M_r 464.43): C, 25.86; H, 4.35; N, 12.07. Found: C, 25.75; H, 4.50; N, 12.10%.

Selected IR absorptions (cm^{-1}): ν_{NH} 3195 (s, br); ν_{so} (S-bonded) 1083 (s), 1064 (s) (this region is affected by the presence of imidazole bands); ν_{RuS} 424 (s); ν_{RuCl} 357 (s). Electronic spectra (λ_{max}, nm (ϵ, M^{-1} cm^{-1})): in H_2O, 431 (169), 298 (301); in methanol, 428 (169), 300 (294).

trans,cis,cis-Dichlorobis(dimethyl sulfoxide)bisbenzimidazoleruthenium(II) (trans,cis,cis-$RuCl_2(DMSO)_2(BzIm)_2$ (9))

0.5 g of *trans*-$RuCl_2(DMSO)_4$ (1 mmol) was dissolved in 30 ml of methanol and 0.3 g of benzimidazole (2.5 mmol) added. Orange–yellow crystals of the product precipitated from the unstirred solution within 24 h at room temperature. They were filtered off, washed with cold $CHCl_3$ and vacuum dried. Yield 0.3 g (51%).

Anal. Calc. for $C_{18}H_{24}Cl_2N_4O_2RuS_2$ (M_r 564.55): C, 38.29; H, 4.29; N, 9.33. Found: C, 38.50; H, 4.19; N, 9.60%.

Selected IR absorptions (Nujol mull, cm^{-1}): ν_{so} (S-bonded) 1095 (s), 1077 (s); ν_{RuCl} 357 (s). Electronic spectra (λ_{max}, nm (ϵ, M^{-1} cm^{-1})): in H_2O, 431 (169), 298 (301); in methanol, 428 (169), 300 (294). ^1H NMR (CD_3OD): 3.35 ppm (s, 12H, S-bonded DMSO), 7.01 ppm (t, 2H, H5*), 7.19 ppm (t, 2H, H6*), 7.45 ppm (d, 2H, H4*), 8.16 ppm (d, 2H, H7*), 8.45 ppm (s, 2H, H2) (s, singlet; d, doublet; t, triplet; * tentative attribution).

trans-Dichlorotris(dimethyl sulfoxide)imidazoleruthenium(II) (trans-$RuCl_2(DMSO)_3Im$ (10))

0.12 g of *trans*-$RuCl_2(DMSO)_4$ (0.25 mmol) was dissolved in 15 ml of $CHCl_3$ and a solution of 15 mg of imidazole (0.22 mmol) in 15 ml of absolute ethanol added. The deep yellow solution was vacuum evaporated to 5 ml and 3 ml of diethyl ether were added. After some hours at room temperature a deep yellow precipitate formed and was filtered off, washed with some $CHCl_3$ and vacuum dried. Yield 90 mg (76%).

Anal. Calc. for $C_9H_{22}Cl_2N_2O_3RuS_3$ (M_r 474.48): C, 22.78; H, 4.68; N, 5.91. Found: C, 23.10; H, 4.50; N, 5.91%.

Selected IR absorptions (Nujol mull, cm^{-1}): ν_{so} (S-bonded) 1085 (s), 1061 (s); ν_{RuS} 414 (s); ν_{RuCl} 339 (s). Electronic spectra (λ_{max} nm (ϵ, M^{-1} cm^{-1})): in H_2O, 433 (180), 314 (377); in methanol, 435 (224), 320 (432).

Crystal data

Crystals of **2** were grown by dissolving the crude product in refluxing 95% ethanol followed by slow cooling. Crystals of **7** were obtained directly from the reaction mixture (method b). Unit cell parameters of both compounds were obtained by least-squares methods from the setting angles of 25 accurately centered reflections on an Enraf-Nonius CAD4 diffractometer. A summary of the crystal data and data collection and refinement is given in Table 1. Intensities were corrected for Lorentz–polarization factors and an empirical absorption correction was also applied, by using ψ scan data. No correction for extinction was applied.

Structure determination and refinement

The structures of **2** and **7** were solved by the heavy atom method through Patterson and Fourier syntheses. All hydrogen atoms were included at calculated positions, except for the H atoms of the water molecule 03 in **7**, which were located from a difference Fourier map. Such a water molecule is involved in hydrogen bonds with O1 and N1 atoms. Hydrogen atom parameters were held fixed during refinement with isotropic thermal factors $B = 1.3B_{eq}$ of the carbon atom to which they are bonded. The final full-matrix least-squares refinement, with anisotropic temperature factors for all non-hydrogen atoms, converged to $R = 0.026$ for **2** and 0.030 for **7**.

Neutral atom scattering factors and anomalous dispersion terms were taken from the literature [9]. All calculations were done by using the Enraf-Nonius SDP programs [10] on a PDP 11/44 computer.

The final positional parameters for non-hydrogen atoms of **2** and **7** are listed in Tables 2 and 3, respectively. See also 'Supplementary material'.

Results and discussion

Derivatives of cis-$RuCl_2(DMSO)_4$

cis-$RuCl_2(DMSO)_4$ (**1**) reacts with monodentate nitrogen ligands to give different products (both DMSO and Cl^- can be replaced), depending on the reaction conditions and the ligand to ruthenium ratio. In every case the remaining DMSO ligands are S-bonded to ruthenium, as clearly evidenced by solid state IR spectra (S=O stretching in the range 1100–1070 cm^{-1}; for an exhaustive treatment of the spectroscopic features of coordinated DMSO see ref. 11), and the complexes are quite stable towards air oxidation in solution.

When **1** is treated with an excess of a nitrogen donor ligand (L) in organic solvents at room temperature, the labile O-bonded DMSO is easily replaced by L to give complexes of general formula *cis,fac*-$RuCl_2(DMSO)_3(L)$ (eqn. (1)).

TABLE 1. Crystallographic data for 2 and 7

	2	7
Formula	$C_6H_{21}Cl_2NO_3S_3Ru$	$C_4H_{20}Cl_2N_2O_3S_2Ru$
Molecular weight	423.4	380.3
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/c$
a (Å)	9.103(2)	8.507(4)
b (Å)	12.568(2)	11.331(4)
c (Å)	13.375(6)	14.071(4)
β (°)	96.52(2)	90.99(1)
V (Å^3)	1520.3(8)	1356.1(9)
Z	4	4
D_{calc} (g cm^{-3})	1.850	1.774
λ (Å)	0.71069 (graphite-monochromated Mo Kα)	
μ (Mo Kα) (cm^{-1})	17.6	18.1
Scan type	$\omega/2\theta$	$\omega/2\theta$
θ range (°)	3–30	3–30
Intensity monitors[a]	3	3
Unique data with $I>3\sigma(I)$	4045	3682
R[b]	0.026	0.030
R_w[c]	0.042	0.052
GOF[d]	1.66	2.13

[a]Measured after each 4000 s. [b]$R=\Sigma\|\|F_o\|-\|F_c\|\|/\Sigma\|F_o\|$. [c]$R_w=[\Sigma w(\|F_o\|-\|F_c\|)^2/\Sigma w\|F_o\|^2]^{1/2}$, $w=[1+\sigma^2(F_o)+0.02F_o^2]^{-1}$. [d]$GOF=[\Sigma w(\|F_o\|-\|F_c\|)^2/(m-n)]^{1/2}$; m = no. of observations, n = no. of variables.

TABLE 2. Atomic parameters[a] of *cis,fac*-$RuCl_2(DMSO)_3(NH_3)$ (2) with e.s.d.s. in parentheses

Atom	x	y	z	B (Å^2)
Ru	0.05237(2)	0.18001(1)	0.34713(1)	1.351(3)
C11	0.31423(6)	0.17942(6)	0.33099(6)	3.37(1)
C12	0.04229(6)	−0.00202(5)	0.28305(5)	2.68(1)
S1	−0.19070(5)	0.16368(4)	0.37005(4)	1.486(7)
S2	0.06105(6)	0.34031(4)	0.42177(4)	1.889(8)
S3	0.00866(5)	0.24817(4)	0.18794(4)	1.876(8)
O1	−0.2134(2)	0.1338(2)	0.4751(1)	2.47(3)
O2	−0.0397(2)	0.4241(1)	0.3753(1)	2.91(3)
O3	−0.1472(2)	0.2643(2)	0.1424(1)	2.72(3)
N	0.1209(2)	0.1050(2)	0.4893(1)	2.05(3)
C1	−0.2917(3)	0.0696(2)	0.2894(2)	2.65(4)
C2	−0.3060(2)	0.2766(2)	0.3383(2)	2.35(4)
C3	0.2393(3)	0.3998(2)	0.4428(2)	3.51(5)
C4	0.0238(3)	0.3289(2)	0.5499(2)	2.73(5)
C5	0.1043(3)	0.3693(2)	0.1709(2)	3.29(5)
C6	0.0942(3)	0.1655(3)	0.1018(2)	3.60(5)

[a]Anisotropically refined atoms are given in the form of equivalent thermal parameters defined as: $4/3[a^2\beta_{11}+b^2\beta_{22}+c^2\beta_{33}+ab(\cos\gamma)\beta_{12}+ac(\cos\beta)\beta_{13}+bc(\cos\alpha)\beta_{23}]$.

TABLE 3. Atomic parameters[a] of *trans,cis,cis*-$RuCl_2(DMSO)_2(NH_3)_2$ (7) with e.s.d.s in parentheses

Atom	x	y	z	B (Å^2)
Ru	0.25173(2)	0.20396(1)	0.44425(1)	1.536(3)
C11	0.29678(9)	0.38715(6)	0.52634(5)	2.88(1)
C12	0.20775(9)	0.00819(6)	0.38186(5)	2.93(1)
S1	0.48188(7)	0.21878(5)	0.37095(4)	1.731(9)
S2	0.11212(7)	0.28967(5)	0.32613(4)	2.02(1)
O1	0.6216(2)	0.1763(2)	0.4287(1)	2.73(3)
O2	0.1936(3)	0.3310(3)	0.2389(2)	4.52(5)
O3	0.7527(3)	0.3416(3)	0.5652(2)	4.57(6)
N1	0.0489(3)	0.1852(2)	0.5311(2)	2.82(4)
N2	0.3727(3)	0.1168(2)	0.5604(2)	2.57(4)
C1	0.4917(4)	0.1432(3)	0.2602(2)	3.06(5)
C2	0.5303(3)	0.3640(2)	0.3333(2)	2.82(5)
C3	−0.0466(4)	0.1999(3)	0.2847(3)	4.46(8)
C4	0.0003(4)	0.4142(3)	0.3638(2)	3.67(6)

[a]Anisotropically refined atoms are given in the form of equivalent thermal parameters defined as: $4/3[a^2\beta_{11}+b^2\beta_{22}+c^2\beta_{33}+ab(\cos\gamma)\beta_{12}+ac(\cos\beta)\beta_{13}+bc(\cos\alpha)\beta_{23}]$.

$$cis\text{-}RuCl_2(DMSO)_3(DMSO)+L\longrightarrow cis,fac\text{-}RuCl_2(DMSO)_3(L)+DMSO \quad (1)$$

The products with $L=NH_3$ (2) and imidazole (3) were isolated and thoroughly characterized (the pyridine derivative was also isolated with similar procedures). The crystal structure of 2 was determined by X-ray diffraction, confirming the proposed structure, and is described in a separate section (see below).

The ^1H NMR spectra of freshly prepared D_2O solutions of complexes 1–3 are collected in Table

4. The spectrum of **2** is very similar to that already reported for its parent compound **1** [12] and consists of three peaks of equal intensity (a singlet and two unresolved quartets) in the region of S-bonded DMSOs (see ref. 11). The sharp singlet can be easily attributed to the equivalent methyl groups of the DMSO *trans* to ammonia. On the other hand, because of the low symmetry of the complex (C_s), the two equivalent DMSO ligands *trans* to Cl have inequivalent methyl groups (two enantiotopic pairs of diastereotopic methyl groups [13, 14]). Due to ^1H–$\{^1H\}$ coupling between the diastereotopic methyls on the same DMSO, the signals of such groups appear as poorly resolved quartets [12]. A relatively broad peak at 3.21 ppm is attributed to coordinated ammonia protons. Of interest, the H–D exchange rate is very low, with a $t_{1/2}$ of about 6 h at 25 °C. Beside the decreasing of the resonance of coordinated ammonia, a time dependence of the DMSO signals was also observed. A new set of three resonances of equal intensity for S-bonded DMSOs (3.32, 3.43 and 3.47 ppm, respectively) slowly increases with time at the expense of the initial pattern. The process can be attributed to the slow dissociation of a Cl^- anion. In fact, a molar conductivity characteristic of a 1:1 electrolyte ($\Lambda = 95\ \Omega^{-1}\ cm^2\ mol^{-1}$) is reached within 8 h at 25.0 °C. The dissociation rate is very similar to that reported for **1** [2a] and, as already observed in that case, the process is accompanied by a shift of the electronic spectrum to lower wavelengths (absorbance maximum from 351 to 333 nm); two isosbestic points are maintained during the process. As in the case of **1**, chloride dissociation is almost completely inhibited in the presence of 120 mM Cl^- (extracellular chloride concentration).

Of interest, *cis,fac*-$RuCl_2(DMSO)_3(NH_3)$ can be conveniently regarded as a prochiral complex, the two chlorine atoms being the enantiotopic ligands [13, 14]. In fact, replacement of either one or the other chlorine atom by water will give enantiomeric cationic products having opposite chirality at the ruthenium atom [15] (Fig. 1) (the two optical isomers should rapidly interconvert through an intermediate prochiral trigonal bipyramid). In this regard **2** differs from **1**, or better from its aquo derivative **1a** that is readily obtained upon dissolution of the complex in water by complete replacement of the O-bonded DMSO. In fact, chloride dissociation from **1a** produces a cationic derivative that is not chiral, but is still prochiral with the two coordinated water molecules as enantiotopic ligands. The prochiral nature of **2** can be of considerable relevance when the interactions of its cationic derivative with chiral molecules are considered. In this case two diastereoisomers will form upon replacement of coordinated water.

The chemical behavior of **3** in aqueous solution is more complex than that reported for **2**. The D_2O NMR spectrum of freshly prepared solutions of the complex (Table 4), is characterized by an overlap between the singlet of the DMSO *trans* to imidazole and the more downfield quartet of the two equivalent DMSOs *trans* to chlorine (see above). Coordinated imidazole has three resonances of equal intensity for the three inequivalent protons. The two upfield signals, that appear as partially resolved multiplets, are attributed to the two *cis* protons H4 and H5 [8]. As shown by the trend of molar conductivity versus time, dissociation of the first Cl^- is consid-

TABLE 4. Proton chemical shifts of complexes **1–3** in D_2O

1[a]	3.485 (q) 6H	
	3.385 (q) 6H	
	3.465 (s) 6H	
2	3.21 (s, br) 3H	
	3.457 (q) 6H	
	3.400 (q) 6H	
	3.418 (s) 6H	
3	8.342 (m) 1H	
	7.474 (m) 1H	
	7.209 (m) 1H	
	3.456 (o) 6H	
	3.261 (q) 6H	
	3.456 (o) 6H	

[a]From ref. 12. s = singlet, q = quartet, o = overlapping, br = broad.

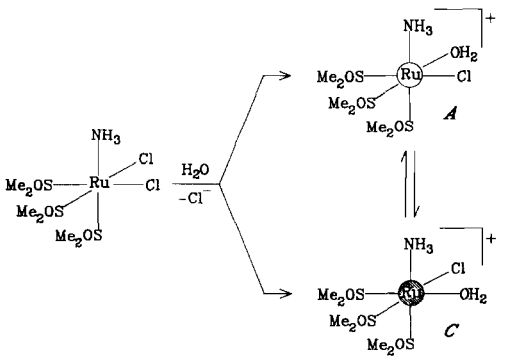
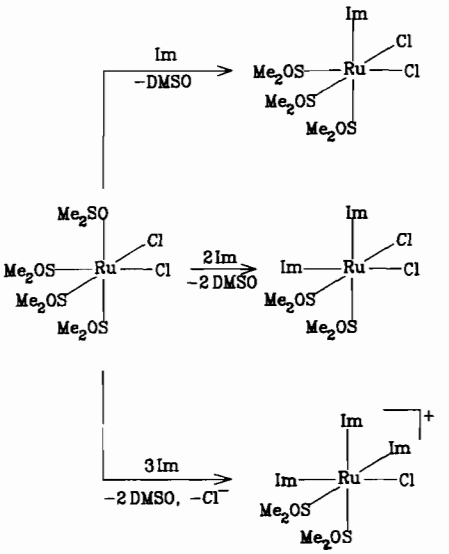


Fig. 1. Schematic representation of the chloride dissociation reaction that transforms the prochiral octahedral complex *cis,mer*-$RuCl_2(DMSO)_3(NH_3)$ into a pair of enantiomeric cationic products having opposite chirality at the ruthenium atom. The chirality symbols *C* and *A* are assigned according to ref. 15. Metal atoms circled with different shadings represent optical isomers.

erably faster than for the ammonia derivative ($\Lambda = 96$ Ω^{-1} cm^2 mol^{-1} after 3 h at 25.0 °C). The NMR spectrum of the solution correspondingly undergoes substantial modifications with time, a new pattern becoming predominant over that observed soon after dissolution of the complex. Three new peaks of equal intensity for coordinated imidazole grow at 7.30, 7.55 and 8.40 ppm, while the main feature of the S-bonded DMSOs region consists of five new signals with an intensity ratio of 1:1:1:1:2 at 3.19, 3.32, 3.35, 3.41 and 3.49 ppm, respectively. A pattern of six resonances of equal intensity would be expected for the six inequivalent methyl groups of the *fac* cationic derivative; an overlap between two of them can easily explain the observed pattern. Although chloride dissociation is the main process occurring in **3** in aqueous solution, a contemporary partial dissociation of dimethyl sulfoxide is also observed in the NMR spectrum (peak of free DMSO at 2.71 ppm corresponding to approximately 5% of the total, accompanied by a pattern of minor intensity in the imidazole and DMSO region). Steric hindrance considerations suggest that the complex should release one of the two enantiotopic DMSO ligands *cis* to imidazole. A further increase of conductivity up to values of 2:1 electrolytes is observed within 24 h and might be explained in terms of dissociation of the second chloride anion. Also in this case the reactions are accompanied by a shift of the electronic spectrum to lower wavelengths (absorption maximum from 356 to 322 nm), but no isosbestic point can be observed. The process is only partially slowed in 120 mM Cl^-.

The formation of **3** represents the first step in the synthesis of poly-substituted imidazole derivatives in organic solvents, as summarized in Scheme 1. In fact, when *cis*-$RuCl_2(DMSO)_4$ is reacted with two equivalents of imidazole in refluxing methanol, the disubstituted all-*cis* derivative $RuCl_2(DMSO)_2(Im)_2$ (**4**) is obtained [8]. Since **3** can be reasonably assumed as an intermediate in the synthesis, the all-*cis* configuration of **4** is in agreement with the expected (see above) more facile dissociation of one of the two enantiotopic DMSOs *cis* to imidazole with respect to the DMSO *trans* to it. As already observed for similar complexes [8], dissociation of one chloride from **4** in aqueous solution is a rather fast process. In fact, within 5 min at room temperature, a molar conductivity of 106 Ω^{-1} cm^2 mol^{-1} is reached and the electronic absorption maximum is correspondingly shifted from 324 to 313 nm. A similar behavior was also found in methanolic solution. The ^{1}H NMR spectrum in D_2O of *cis,cis,cis*-$[Ru(DMSO)_2(Im)_2Cl(H_2O)]^+$ (Table 5) is similar to that reported for the analogous nitro-imidazole derivatives and is consistent with a *cis,cis,cis* geometry of the complex



Scheme 1. Reactivity of *cis*-$RuCl_2(DMSO)_4$ with imidazole in methanol.

[8]. In fact, the four signals of equal intensity occurring in the region of S-bonded DMSO ligands as unresolved quartets, can be safely attributed to the inequivalent methyl groups of the two inequivalent *cis* DMSO ligands. Correspondingly, the two inequivalent *cis* imidazoles have two sets of three signals of equal intensity for the three inequivalent protons.

The all-*cis* disubstituted complex reacts further with excess nitrogen ligand to produce a cationic trisubstituted derivative (Scheme 1). In fact, when **1** is reacted with three equivalents of imidazole in refluxing methanol, a cationic species of formula $[RuCl(DMSO)_2(Im)_3]^+$ (**5**) is obtained. Due to the high solubility of its chloride salt in methanol, this complex could be more easily isolated as a hexafluorophosphate derivative (small amounts of the chloride salt of **5** could be isolated from the mother liquors in the synthesis of **3**). The NMR spectrum of **5** in D_2O (Table 5) reveals that the three imidazole ligands are in a *fac* arrangement. The imidazolic protons give two sets of three signals in a 2:1 intensity ratio, in agreement with the presence of two equivalent ligands. This pattern, however, is consistent either with a *mer* or a *fac* disposition of the three imidazole moieties. The fine structure of the DMSO methyl resonances (two unresolved quartets of equal intensity in the region of S-bonded DMSOs) allows *fac* geometry to be assigned to **5**. In the hypothesis of a *mer* complex, in fact, the two *cis* DMSOs would be inequivalent but have equivalent methyl groups (two sharp singlets expected), while in a *fac* complex the two DMSOs are equivalent but have inequivalent methyl groups (as in the case of **2**, two unresolved quartets expected). The *fac* geometry of complex **5**

TABLE 5. Proton chemical shifts of complexes **4–10** in D_2O

Compound	Imidazole		NH_3	CH_3(DMSO)
	H-2	H-4, H-5		
Free Im	7.30(1H)	7.13(2H)		
4	8.04(1H) 8.08(1H)	7.27(1H), 6.86(1H) 7.30(1H), 7.12(1H)		2.83(q,3H), 2.86(q, 3H) 3.34(q,3H), 3.45(q,3H)
5	8.02(2H) 8.09(1H)	7.23(2H), 7.05(2H) 7.29(1H), 7.07(1H)		2.79(q,6H), 3.34(q,6H)
6[a]				3.35(s,12H), 2.71(s,12H)(free)
7			3.23(s,br,6H)	3.30(s,12H)
8	8.06(2H)	7.38(2H), 7.14(2H)		3.15(s,12H)
9[b]	for the benzimidazole signals see 'Experimental'			3.34(s,12H)
10	8.39(1H)	7.62(1H), 7.28(1H)		3.36(s,6H), 3.09(s,6H) 2.71(s,6H)(free)

s = singlet, q = quartet, br = broad. [a]From ref. 2. [b]In deuterated methanol.

requires that in its most likely precursor, **4**, the chlorine atom *trans* to DMSO is the one that undergoes substitution. This is in agreement with the relatively large *trans* effect of S-bonded DMSO [11b]. As suggested by time-drive NMR and UV–Vis spectroscopy, complex **5** does not undergo any relevant process in aqueous solution over observation periods of some hours.

The reaction pattern between *cis*-$RuCl_2(DMSO)_4$ and imidazole observed in methanol and reported in Scheme 1, cannot however be considered even as a rough model for the interactions of **1** with nitrogen bases in aqueous solution. In fact, according to the changes of the UV–Vis spectra, the interactions of *cis*-$RuCl_2(DMSO)_4$ with imidazole in aqueous solution are considerably more complex and do not always lead to the same products as in methanol. The spectral variations were found to depend both on the imidazole to ruthenium ratio and on the presence free chloride in solution. The more facile Cl^- versus DMSO dissociation in water than in methanol can open new reaction pathways to the complex and might provide an explanation to its rather different behavior in the two media.

Derivatives of trans-$RuCl_2(DMSO)_4$

trans-$RuCl_2(DMSO)_4$ (**6**) easily reacts at room temperature in organic solvent solution with two equivalents of a nitrogen ligand to give complexes of general formula *trans,cis,cis*-$RuCl_2(DMSO)_2(L)_2$ (eqn. (2)).

$$\textit{trans}\text{-}RuCl_2(DMSO)_4 + 2L \longrightarrow \textit{trans,cis,cis}\text{-}RuCl_2(DMSO)_2(L)_2 \quad (2)$$

Complexes with L = NH_3 (**7**), imidazole (**8**) and benzimidazole (**9**) have been isolated and characterized. Upon reaction of **6** with a less than stoichiometric amount of imidazole, the monosubstituted intermediate *trans*-$RuCl_2(DMSO)_3(Im)$ (**10**) could be also isolated. Also in this case the complexes are rather stable towards air oxidation in solution.

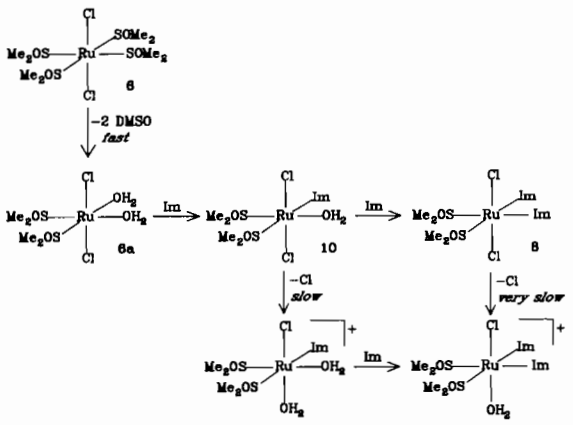
As shown by solid state IR spectra, all derivatives have exclusively S-bonded DMSOs (S=O stretching bands in the region 1100–1040 cm^{-1}). *trans* Disposition of the two chlorine atoms is always suggested by the presence of a strong Ru–Cl stretching band in the region 320–360 cm^{-1}. The structure of the ammonia derivative (**7**) has been confirmed by X-ray analysis (see below). The D_2O ^1H NMR spectra of complexes **7–10** are collected in Table 5. The spectra of the disubstituted derivatives **7–9** are very simple, due to the high symmetry of the complexes (of interest, the chemical shifts of S-bonded DMSOs *trans* to either NH_3 or H_2O are very similar, cf. **6** and **7**). Moreover, owing to the relative inertness of the complexes towards ligand dissociation, their spectra are also time-stable. In fact, no free DMSO or L can be detected in solution even after some hours at room temperature and, as clearly shown by conductivity measurements, the chloride dissociation rate in water for both **7** and **8** is remarkably slower than for their parent compound **6**.

The D_2O NMR spectrum of **10** is more complex, consisting of three singlets of equal intensity for the DMSO methyl groups. The peak at 2.71 ppm (free DMSO) shows that, upon dissolution in water, the complex readily releases one DMSO molecule. Due

to the relatively large *trans* effect of S-bonded DMSO [11b] and in agreement with the behavior of *trans*-$RuCl_2(DMSO)_4$ [2], the molecule released is very likely one of the two DMSOs *trans* to each other. The two remaining inequivalent *cis* DMSOs have equivalent methyl groups which give the sharp singlets at 3.09 and 3.36 ppm. Comparison with the spectra of **6** and **8** suggests that the more downfield signal can be attributed to the DMSO *trans* to coordinated water.

The reactivity of *trans*-$RuCl_2(DMSO)_4$ with imidazole in aqueous solution is similar to that observed in the synthesis of complexes **8** and **10** in methanol and is summarized in Scheme 2. The reactions were followed mainly by means of time-drive UV–Vis spectroscopy and the intermediates and final products were identified by comparing their spectra with those of the imidazole derivatives reported above. The diaquo derivative formed upon dissolution of **6** in water, **6a** [2], reacts with a stoichiometric amount of imidazole to give **10**. The reaction is complete in about 90 min at 27 °C and is followed by the slow dissociation (several hours) of a chloride. The two processes can be easily distinguished spectrophotometrically, since the first involves a small shift to lower wavelengths of the high frequency peak, while the second process requires a shift in the same direction of the low frequency peak (from 433 to 416 nm).

When **6** is reacted with two equivalents of imidazole, the formation of **10** becomes a rather fast process (a few minutes at r.t.) and is followed by the coordination of the second imidazole moiety to give complex **8** in about 90 min. This second step involves a further shift of the high frequency peak in the UV–Vis spectrum to lower wavelengths (see 'Experimental'). The presence of one isosbestic point after the first ten minutes of reaction, suggests that only two species, **8** and 10, are present in solution and that chloride dissociation from **10** can be neglected. The final spectrum is time-stable, in agreement with the observation that chloride dissociation from **8** is a completely negligible process. On increasing the imidazole to ruthenium ratio, the rate of formation of **8** correspondingly increases.



Scheme 2. Reactivity of *trans*-$RuCl_2(DMSO)_4$ with imidazole in water.

Molecular structures

The molecular structures of *cis,fac*-$RuCl_2(DMSO)_3NH_3$ (**2**) and *trans,cis,cis*-$RuCl_2(DMSO)_2(NH_3)_2 \cdot H_2O$ (**7**) are depicted in Figs. 2 and 3, respectively. Bond lengths and angles are given in Tables 6 and 7. Besides giving interesting structural informations, such structures allow the characterization of the completely analogous aquo derivatives, obtained upon dissolution in water of *cis*- and *trans*-$RuCl_2(DMSO)_4$, respectively. They could not be isolated because of their greater solubility and were characterized by means of NMR spectroscopy [2a]. However, in the case of **6**, even though chemical considerations based on *trans*-effect suggested that *trans,cis,cis*-$RuCl_2(DMSO)_2(H_2O)_2$ has to be the complex formed in water, it was not possible to unambiguously distinguish between this structure and the corresponding all-*trans* derivative by means of NMR spectroscopy alone, as both complexes are expected to give a sharp singlet for the two equivalent DMSOs.

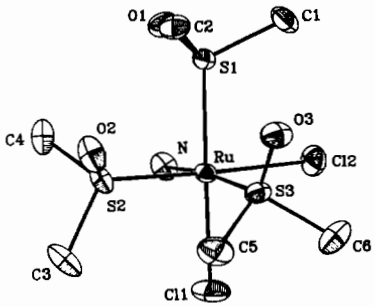


Fig. 2. ORTEP drawing of *cis,fac*-$RuCl_2(DMSO)_3(NH_3)$ (**2**) showing the atom numbering scheme (thermal ellipsoids at 50% probability level).

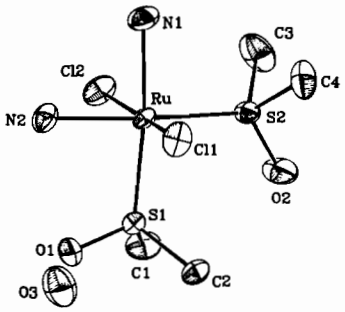


Fig. 3. ORTEP drawing of *trans,cis,cis*-$RuCl_2(DMSO)_2(NH_3)_2$ (**7**) showing the atom numbering scheme (thermal ellipsoids at 50% probability level).

TABLE 6. Bond distances (Å) and angles (°) for **2**

Distances			
Ru–C11	2.4178(6)	S1–C2	1.788(2)
Ru–C12	2.4411(6)	S2–O2	1.486(2)
Ru–S1	2.2774(6)	S2–C3	1.781(3)
Ru–S2	2.2458(5)	S2–C4	1.790(3)
Ru–S3	2.2877(5)	S3–O3	1.493(2)
Ru–N	2.151(2)	S3–C5	1.782(3)
S1–O1	1.491(2)	S3–C6	1.793(3)
S1–C1	1.784(2)		
Angles			
C11–Ru–C12	87.94(2)	Ru–S1–C1	114.86(8)
C11–Ru–S1	174.04(2)	Ru–S1–C2	116.74(8)
C11–Ru–S2	93.28(2)	O1–S1–C1	106.6(1)
C11–Ru–S3	89.26(2)	O1–S1–C2	106.4(2)
C11–Ru–N	83.54(5)	C1–S1–C2	97.7(2)
C12–Ru–S1	87.96(2)	Ru–S2–O2	117.45(7)
C12–Ru–S2	174.16(2)	Ru–S2–C3	115.6(1)
C12–Ru–S3	91.63(3)	Ru–S2–C4	110.64(9)
C12–Ru–N	83.98(5)	O2–S2–C3	106.1(1)
S1–Ru–S2	90.38(2)	O2–S2–C4	106.4(1)
S1–Ru–S3	95.17(2)	C3–S2–C4	98.7(1)
S1–Ru–N	91.74(5)	Ru–S3–O3	119.15(7)
S2–Ru–S3	94.10(2)	Ru–S3–C5	113.76(9)
S2–Ru–N	90.47(5)	Ru–S3–C6	109.9(1)
S3–Ru–N	171.69(5)	O3–S3–C5	106.7(1)
Ru–S1–O1	112.98(7)	O3–S3–C6	106.2(1)
C5–S3–C6	99.1(1)		

TABLE 7. Bond distances (Å) and angles (°) for **7**

Distances			
Ru–C11	2.4030(7)	S1–O1	1.508(3)
Ru–C12	2.4125(7)	S1–C1	1.781(3)
Ru–S1	2.2350(6)	S1–C2	1.779(3)
Ru–S2	2.2469(6)	S2–O2	1.492(2)
Ru–N1	2.142(2)	S2–C3	1.781(4)
Ru–N2	2.156(2)	S2–C4	1.788(3)
O3···O1	2.893(4)	O3···N1′ [a]	3.124(4)
Angles			
C11–Ru–C12	172.58(2)	N1–Ru–N2	84.31(9)
C11–Ru–S1	91.33(2)	Ru–S1–O1	114.61(9)
C11–Ru–S2	93.44(2)	Ru–S1–C1	115.0(2)
C11–Ru–N1	86.27(8)	Ru–S1–C2	114.59(9)
C11–Ru–N2	87.79(6)	O1–S1–C1	105.6(1)
C12–Ru–S1	91.88(2)	O1–S1–C2	105.7(1)
C12–Ru–S2	92.96(2)	C1–S1–C2	99.8(1)
C12–Ru–N1	89.71(8)	Ru–S2–O2	119.6(1)
C12–Ru–N2	85.62(6)	Ru–S2–C3	112.5(1)
S1–Ru–S2	94.72(2)	Ru–S2–C4	113.5(1)
S1–Ru–N1	172.50(7)	O2–S2–C3	105.5(2)
S1–Ru–N2	88.51(7)	O2–S2–C4	105.0(2)
S2–Ru–N1	92.52(7)	C3–S2–C4	98.3(2)
S2–Ru–N2	176.53(7)		

[a]Coordinates referred to those of N1 by $1+x, y, z$.

The S-bonding of all the DMSO ligands supports the suggestion that in Ru(II)–sulfoxide complexes, S-bonding is preferred to O-bonding, in the absence of *trans* π-accepting ligands and strong steric effects [16]. In fact, in **2**, two S atoms are *trans* to Cl and one *trans* to NH_3, while in **7**, both are *trans* to NH_3.

In **2**, the Ru atom displays a highly distorted octahedral coordination, because of intramolecular steric interactions, as shown by the widening of the S–Ru–S bond angles (av. 94.6(8)°) and the narrowing of the Cl–Ru–N bond angles (av. 83.8(3)°). This is also shown by the differences in chemically equivalent bond lengths: 0.023(1) Å for Ru–Cl and 0.032(1) Å for Ru–S *trans* to Cl.

Anyhow, the mean values of 2.43(2) and 2.27(3) Å compare well with the values of 2.428(11) and 2.278(14) Å, reported for Ru(II)–Cl (*trans* to DMSO) and Ru(II)–S (*trans* to Cl) [17]. The Ru–S3 bond distance of 2.2877(5) Å is markedly longer than Ru–S1 and Ru–S2. It seems likely that this lengthening is in part attributable to the greater *trans* influence of NH_3, with respect to Cl, and in part to steric effects.

In **7**, the *trans* Ru–Cl bond lengths (av. 2.408(7) Å) are very close to the value of 2.402(2) Å found in *trans*-$RuCl_2(DMSO)_4$ [2]. As in **2**, the DMSO molecules exhert some steric effect, causing a widening of the S–Ru–S angle, 94.72(2)°, with consequent narrowing of the N–Ru–N bond angle to 84.31(9)°.

As to the Ru–S bond distances *trans* to N, it is interesting to observe that the mean value of 2.241(8) Å is significantly shorter than that of 2.2877(5) Å, found in **2**. This is probably due to the reduction of steric interactions in **7** (two DMSOs versus three in **2**) and to the increased electron charge density on the metal atom, due to coordination of a second NH_3 molecule. This allows a strengthening of the Ru–S bonds because of the increased π-backbonding ability of ruthenium. As a matter of fact, in $[Ru(NH_3)_5(DMSO)]^{2+}$ the Ru–S bond distance is as short as 2.188(3) Å [18]. The importance of the π bonding contribution in the Ru–S bonds is reflected by the variation in the S–O stretching frequencies, which are expected to decrease with the increasing of the Ru to S π-backdonation [17]. In fact, the solid state S–O stretching frequencies are 1095, 1073 cm^{-1} in **2**, 1064, 1043 cm^{-1} in **7**, and 1045 cm^{-1} in the pentaammino complex [19].

Conclusions

The rough model system elaborated for *trans*-$RuCl_2(DMSO)_4$ and based mainly on its interactions

with imidazole suggests that, in biological conditions, the complex should react quite easily with nitrogen bases, regardless of chloride concentration. Therefore, in the hypothesis that it can reach the nitrogen bases of DNA, it might form rather long-lived adducts in the absence of efficient DNA repair systems. On the other hand, **6** should also rapidly react with all the nitrogen ligands present in the biological medium (e.g. amino acids and proteins). Due to the inertness of the disubstituted derivatives, this process might lead to the inactivation of large amounts of the administered complex before it can reach the cellular target [3c].

As for the possible biological applications of the newly synthesized complexes, the disubstituted derivatives of *trans*-$RuCl_2(DMSO)_4$ are not likely to possess any relevant activity due to their large inertness. On the other hand, two chemical features of **2**, that is the availability of one coordination site in low chloride concentration and the possible selective formation of diastereoisomers upon interaction with chiral biological targets, suggest that the complex might be worth some biological tests. Its cytotoxicity is currently being tested on some human tumor cell lines [20], in comparison with that of complexes **1**, **6** and of the corresponding tetramethylene sulfoxide (TMSO) derivatives [16].

Finally, the known radio-sensitizing properties of *cis*,*cis*,*cis*-$RuCl_2(DMSO)_2(NO_2Im)_2$ [8] and the abundance of new, water soluble, DMSO–imidazole complexes (**3**, **5**, **8**, **10**), might suggest performing the synthesis of the corresponding nitroimidazole derivatives for the purpose of testing their radiosensitizing activity.

Supplementary material

Anisotropic thermal parameters, hydrogen atom coordinates and tables of observed and calculated structure factors are available from the authors on request.

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References

1 (a) M. J. Cleare and P. C. Hydes, in H. Sigel (ed.), *Metal Ions in Biological Systems,* Vol. II, Marcel Dekker, New York, 1980, p. 1; (b) G. Mestroni, G. Zassinovich, E. Alessio and A. Bontempi, *Inorg. Chim. Acta, 137* (1987) 63; (c) S. G. Ward and R. C. Taylor, in M. F. Gielen (ed.), *Metal-Based Anti-Tumor Drugs,* Freund, London, 1988, p. 1; (d) I. Haiduc and C. Silvestru, *Coord. Chem. Rev., 99* (1990) 253.

2 (a) E. Alessio, G. Mestroni, G. Nardin, W. M. Attia, M. Calligaris, G. Sava and S. Zorzet, *Inorg. Chem., 27* (1988) 4099; (b) J. S. Jaswal, S. J. Rettig and B. R. James, *Can. J. Chem., 68* (1990) 1808.

3 (a) G. Sava, S. Zorzet, T. Giraldi, G. Mestroni and G. Zassinovich, *Eur. J. Cancer Clin. Oncol., 20* (1984) 841; (b) E. Alessio, W. M. Attia, M. Calligaris, S. Cauci, L. Dolzani, G. Mestroni, C. Monti-Bragadin, G. Nardin, F. Quadrifoglio, G. Sava, M. Tamaro and S. Zorzet, in M. Nicolini (ed.), *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy,* Martinus Nijhoff, Boston, MA, 1988, p. 617; (c) G. Mestroni, E. Alessio, M. Calligaris, W. M. Attia, F. Quadrifoglio, S. Cauci, G. Sava, S. Zorzet, S. Pacor, C. Monti-Bragadin, M. Tamaro and L. Dolzani, *Progress in Clinical Biochemistry and Medicine,* Vol. 10, Springer, Berlin, 1989, p. 71; (d) G. Sava, S. Pacor, F. Bregant, V. Ceschia, E. Luxich, E. Alessio and G. Mestroni, *Pharmacology (Life Sci. Adv.), 9* (1990) 79; (e) A. Nassi, E. Alessio, G. Mestroni, F. Loseto, D. Giordano and M. Coluccia, *Anticancer Res.,* in press.

4 S. P. Fricker, *Metal Ions in Biology and Medicine,* John Libbey Eurotext, Paris, 1990, p. 452.

5 F. Loseto, E. Alessio, G. Mestroni, A. Nassi, G. Lacidogna, D. Giordano and M. Coluccia, *Anticancer Res.,* in press.

6 E. Alessio, Y. Xu, S. Cauci, G. Mestroni, F. Quadrifoglio, P. Viglino and L. G. Marzilli, *J. Am. Chem. Soc., 111* (1989) 7066.

7 I. P. Evans, A. Spencer and G. Wilkinson, *J. Chem. Soc., Dalton Trans.,* (1973) 204.

8 (a) P. K. L. Chan, P. K. H. Chan, D. C. Frost, B. R. James and K. A. Skov, *Can. J. Chem., 66* (1988) 117; (b) P. K. L. Chan, B. R. James, D. C. Frost, P. K. H. Chan, H. L. Hu and K. Skov, *Can. J. Chem., 67* (1989) 508.

9 *International Tables for X-ray Crystallography,* Vol. IV, Kynoch Press, Birmingham, U.K., 1974.

10 *Enraf-Nonius Structure Determination Package,* B. A. Frenz & Associates, Enraf-Nonius, Delft, The Netherlands, 1985.

11 (a) W. L. Reynolds, *Prog. Inorg. Chem., 12* (1970) 1; (b) J. A. Davies, *Adv. Inorg. Chem. Radiochem., 24* (1981) 115.

12 J. A. Barnes and R. J. Goodfellow, *J. Chem. Res. Miniprint,* (1979) 4301.

13 G. Mestroni, E. Alessio, G. Zassinovich and L. G. Marzilli, *Comments Inorg. Chem.,* in press.

14 E. L. Eliel, *Top. Curr. Chem., 105* (1982) 1.

15 (a) M. F. Brown, B. R. Cook and T. E. Sloan, *Inorg. Chem., 14* (1975) 1273; (b) T. E. Sloan, *Top. Stereochem., 12* (1981) 1.

16 E. Alessio, B. Milani, G. Mestroni, M. Calligaris, P. Faleschini and W. M. Attia, *Inorg. Chim. Acta, 177* (1990) 255.
17 E. Alessio, G. Balducci, M. Calligaris, G. Costa, W. M. Attia and G. Mestroni, *Inorg. Chem.*, in press.
18 F. C. March and G. Ferguson, *Can. J. Chem., 49* (1971) 3590.
19 C. V. Senoff, E. Maslowsky Jr. and R. G. Goel, *Can. J. Chem., 49* (1971) 3585.
20 S. P. Fricker, E. Alessio and G. Mestroni, paper in preparation.