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Article

EPR and Electrochemistry of [NH_4]*trans*-[$RuCl_4$(DMSO)(L)] complexes (L = DMSO, py). X-Ray Molecular Structure of [pyH][$RuCl_4$(DMSO)(py)].

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O complexo [$(DMSO)_2$H]*trans*-[$RuCl_4(DMSO)_2$], com simetria axial, apresenta em seu espectro de RPE dois valores de g ($g_\perp$=2,35 e $g_{//}$=1,87). O complexo [NH_4]*trans*-[$RuCl_4(DMSO)_2$] apresenta somente um valor de g no espectro RPE no estado sólido, indicando acoplamento entre os microcristais. Em solução recém-preparada, utilizando-se MeOH, detectam-se por RPE os compostos [NH_4]*trans*-[$RuCl_4$(DMSO)(MeOH)] e o [$RuCl_3$(DMSO)$(MeOH)_2$]. Após aproximadamente 15 h apenas este último composto encontra-se em solução. Estas espécies são detectadas por voltametria cíclica. A espécie [$RuCl_2$(DMSO)$(MeOH)_3$] é gerada eletroquimicamente a partir do [$RuCl_3$(DMSO)$(MeOH)_2$]. O complexo [pyH]*trans*-[$RuCl_4$(DMSO)(py)], obtido a partir da reação entre o [$(DMSO)_2$H]*trans*-[$RuCl_4(DMSO)_2$] e py, cristalizou no grupo espacial P (No.2), Z=2 com a=7,7608(1), b=8,5451(1), c=15,095(5)Å, β=79,33(2)º. A estrutura foi resolvida pelas técnicas de Patterson e diferenciais de Fourier e refinadas para R = 0,0886. O espectro de RPE (T = -160 ºC) confirmou a presença de Ru(III) paramagnéticamente ativo e é consistente com uma simetria axial para o complexo ($g_\perp$=2,42 e $g_{//}$=1,81). O voltamograma cíclico do complexo com a piridina apresenta $E_{1/2}$= - 0,15 V (vs. Ag/AgCl).

The [$(DMSO)_2$H]*trans*-[$RuCl_4(DMSO)_2$] complex presents an axial symmetry in the solid state and its EPR spectrum shows two g values ($g_\perp$=2.35 e $g_{//}$=1.87). The complex [NH_4]*trans*-[$RuCl_4(DMSO)_2$] presents only one-g value in the solid state EPR spectrum indicating coupling of micro-aggregates. In a fresh solution of MeOH it is possible to detect the [NH_4]*trans*-[$RuCl_4$(DMSO)(MeOH)] and [$RuCl_3$(DMSO)$(MeOH)_2$] by EPR. After approximately 15 h only the latter complex is detected in solution. These species are also detected by cyclic voltammetry and the [$RuCl_2$(DMSO)$(MeOH)_3$] complex is generated electrochemically from [$RuCl_3$(DMSO)$(MeOH)_2$]. The [pyH]*trans*-[$RuCl_4$(DMSO)(py)] was obtained from the reaction of [(DMSO)2H]*trans*-[$RuCl_4(DMSO)_2$] with py, and was crystallized in the space group P (No.2), Z=2 with a=7.7608(1), b=8.5451(1), c=15.095(5)Å, β=79.33(2)º. The structure was solved by Patterson and difference Fourier techniques and refined to R = 0.0886. EPR (T = -160 ºC) data confirmed the presence of the paramagnetically active Ru(III), consistent with the axial symmetry of the complex. The cyclic voltamogram of the pyridine complex shows a redox potential with $E_{1/2}$ = - 0.15 V (vs. Ag/AgCl).

Keywords: EPR, cyclic voltammetry, tetrachlororuthenate(III), X-ray structure analyses

Introduction

The ruthenium(III) complex *trans*-HIm[$RuCl_4(Im)_2$] (Im = imidazole) is active against chemically induced colorectal tumours of the rat, reducing the tumour volume to 20 or even 10%[1]. This complex may find clinical use, as colorectal tumors are not responsive to cisplatin and it is currently undergoing preclinical tests[2]. It has been reported that the imidazole complex binds to DNA and blocks DNA-polymerase-catalyzed synthesis[3].

The above imidazole complex belongs to a new promising tumor-inhibiting class of metal complexes of the type HB-*trans*-[$Ru^{III}Cl_4B_2$] (B = nitrogen heterocycle). At pH=4 one chloride ion of the imidazole complex is hydrated to produce a neutral species, presumably [$RuCl_3(Im)_2(H_2O)$][4]. This seems to be transported to the cancer cell where the low Cl^- concentration causes a subsequent hydration to produce higher aqua complexes that can then bind to DNA[2]. This aqua complex is more labile than the corresponding chloro complexes and are therefore considered to be the

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active species for the antitumor activity[5-16]. This information reveals that the development of these complexes as an alternative to platinum metal inhibitors is of special interest and ruthenium compounds have been studied extensively for this purpose. Due to the increasing interest in this class of ruthenium(III) complexes, we recently published the synthesis and characterization of the M-ImH [$RuCl_4$(CO)(M-Im)], [pyH]*trans*-[$RuCl_4(py)_2$] and [pyH]*trans*-[$RuCl_4$(CO)(py)][17,18] and here we report some characteristics of [$RuCl_4$(DMSO)(L)]$^-$ (L = DMSO, py) complexes which are particularly attractive, being structurally very similar to the Ru(III) compounds with heterocyclic nitrogen donor ligands such as those mentioned above.

Experimental

Solvents for the preparation of the complexes and measurements were chemically pure grade and were dried prior to use. Elemental analyses were performed at the Department of Chemistry of the Federal University of São Carlos, São Paulo.

Preparations

*[(DMSO)$_2$H]*trans-*[RuCl$_4$(DMSO)$_2$]* **(1)**[19]

Commercial (Degussa) hydrated ruthenium trichloride (0.75 g 2.87 mmol), was partially dissolved in dimethylsulfoxide (3.5 mL) and aqueous HCl 37% (0.5 mL) was added to the solution. This vigorously stirred mixture was heated for 80 °C and kept at this temperature for 20 min, until $RuCl_3$ was completely dissolved. The deep red solution was then heated to 100 °C for 10 min. A bright orange solution formed which was cooled and 15 mL of acetone was added. Yellow crystals formed after four days. They were collected by filtration and washed with acetone. (yield: 1.23 g, 80%). Anal. Calc. for $C_8H_{25}S_4O_4Cl_4Ru$: C, 17.3; H, 4.53; S, 23.04. Found: C, 17.37; H, 4.70; S, 20.53 %

*[NH$_4$]*trans-*[RuCl$_4$(DMSO)$_2$]* **(2)**

Commercial (Degussa) hydrated ruthenium trichloride (1.5 g 5.74 mmol), was partially dissolved in methanol (5.0 mL) and nitric oxide was passed through the solution for 30 h. 1.0 mL of DMSO was added to the solution which was then stirred for 2 h after which 0.32 g (5.37 mmol) of NH_4Cl dissolved in 1.0 mL of water was slowly added droppwise. The red precipitate was filtered and washed with cold acetone. (yield: 1.91 g; 80%). Anal. Calc. for $C_4H_{16}NS_2O_2Cl_4Ru$: C, 11.52; H, 3.89; N, 3.36; S, 15.37% Found; C, 11.33; H, 3.89, N, 3.47; 15.56 %. This synthesis can be carried out without bubbling NO.

*[pyH][*trans-*RuCl$_4$(DMSO)(py)]* **(3)**[20]

The procedure used for preparation of this complex was a modification of a literature procedure for the analogous sodium salt. In our work we modified the procedure.

[$(DMSO)_2$H]*trans*-[$RuCl_4(DMSO)_2$] (0.1 g 0.18 mmol), was partially dissolved in DMSO (0.17 mL) and acetone (2.0 mL). The mixture was left at room temperature for 7 h. The volume of the solution was reduced (*ca.* 1.0 mL) and pyridine was added (0.03 mL) followed by ether 10.0 ml to precipitate a yellow solid (yield: 0.078 g; 80%). Anal. Calc. for $C_{12}H_{17}N_2SOCl_4Ru$: C, 30.17; H, 3.98; N, 5.03; %. Found; C, 29.62; H, 3.64, N, 4.65. The powder was recrystallized from dichloromethane/ether affording yellow crystals.

X-ray diffraction data

Complete data sets were collected on an Enraf-Nonius CAD-4 four circle diffractometer. Experimental details are given in Table 1. 3289 reflections were measured of which 2909 were independent. The intensity of one standard reflection was essentially constant over the duration of both experiments. Data were corrected for Lorentz, polarization and absorption effects, following the procedure of Walker and Stuart[21].

Table 1. Crystal data, data collection details and structure refinement results for the [pyH]*trans*-[$RuCl_4$(DMSO)(py)] complex.

Formula	$C_{13}H_{18}N_2SO\ Cl_6Ru$
M	562.11
System	Triclinic
Space group	P
a (Å)	7.7608(1)
b (Å)	8.5451(1)
c (Å)	15.095(5)
β (°)	79.33(2)
V (Å^3)	983.2(4)
Z	2
D_c (g cm^{-3})	1.899
λ (Å)	(CuKα) 1.54184
Sample dimensions (mm)	0.53 x 0.35 x 0.20
Linear absorption coefficient (μ) (mm^{-1})	15.001
Absorption correction factors	1.16, 0.86
Scan technique	ω-2θ
θ range (°)	2.98- 59.94
F(000)	556
Reflections measured	3289
Rint	0.03
Reflections above 3σ(I)	1553
R	0.0886
Rw	0.2184
Range h; k; l	-8.8; -9.9; -1.16
Max., min. residual ρ (eÅ^{-3})	4.228, -2.007

Crystal structure determination and refinement

The determination and refinement of the structures was performed with the SHELX 93[22] system of programs. The structures were solved by standard Patterson and difference Fourier techniques and refined by full-matrix least-squares methods with anisotropic thermal parameters for the non-hydrogen atoms, with the exception of the pyH ring of the structure which, due to disorder, was refined as a rigid group with isotropic temperature factors for individual atoms. All hydrogen atoms were located on stereochemical grounds and included as fixed contributors, with the exception of the H-atoms of the mobile pyH which were not included. Bonded H-atom scattering factors[11] and complex scattering factors[12] were employed for the remaining atoms. Figure 1 was drawn with the ORTEP program[13] with all non-H atoms represented with 50% ellipsoids for the anisotropic thermal parameters.

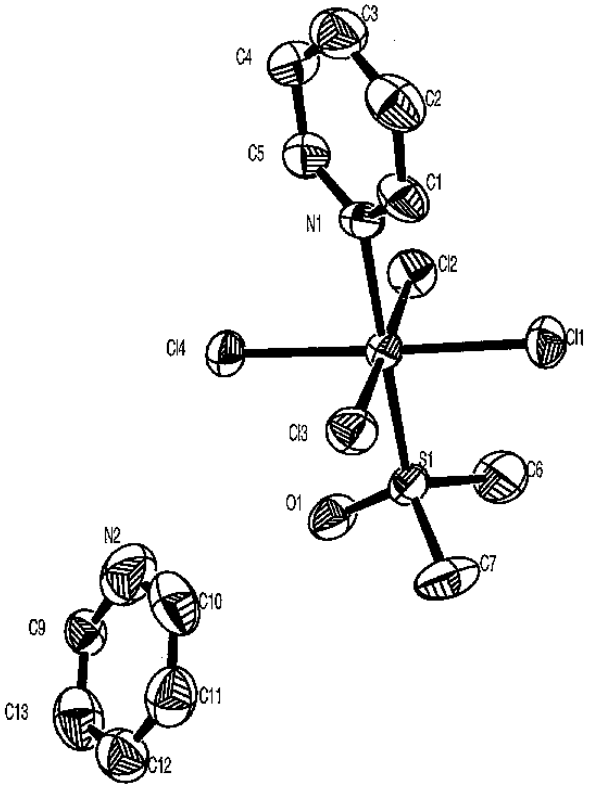


Figure 1. ORTEP drawings of [pyH]*trans*-[$RuCl_4$(DMSO)(py)] at 50% probability level.

Spectroscopic measurements

IR spectra pellets were prepared from crystalline powder samples diluted in CsI. Measurements were performed on a Bomem-Michelson 102 spectrometer in the 4000-200 cm^{-1} region .

EPR spectra were obtained from a polycrystalline powder sample, using a quartz tube, on a Varian E-109 or on a Bruker ESR 300 E spectrometer equipped with X band bridge at -160 °C. Modulation amplitude: 9 gauss. Microwave power: 10 mW.

Cyclic voltammetry was carried out at room temperature in freshly distilled methanol containing 0.1 mol L^{-1} of $Bu_4N^+CO_4^-$ (TBAP), using an EG&G/PARC electrochemical system consisting of a 273 A potentiostat. A three electrode system with resistance compensation was used throughout. The working and auxiliarly electrodes were a stationary platinum foil and a wire, respectively. The reference electrode was Ag/AgCl, a medium in which ferrocene is oxidized at 0.48 V (Fc+/Fc); all potentials are refered to this electrode.

The half-wave potentials for the cyclic voltammetric reversible processes were estimated by the average of the anodic and cathodic peak potential ($E_{1/2} = (E_{pa} + E_{pc})/2$).

Solution electrical conductivities were measured in methanol at 25 °C under anaerobic conditions using a Micronal conductivity bridge.

Results and Discussion

Selected interatomic bond distances and interatomic angles are listed in Table 2. Figure 1 is a drawing of the complex [pyH]*trans*-[$RuCl_4$(DMSO)(py)]. The Ru(III) ion is octahedrally coordinated to four coplanar chlorine atoms and the nitrogen atom of the pyridine ring trans to the dimethyl sulfoxide ligand. A protonated pyridine molecule is electrostatically bound to the negatively charged Ru(III) complex, completing the coordination sphere of the compound.

The Ru-Cl and Ru-N bond lengths in the complex [2.351(2) Å (average) and 2.116(7) Å, respectively] are comparable to those found for similar complexes: [pyH]*trans*-[$RuCl_4(py)_2$] [2.353(2) and 2.082(8) Å][18]; [pyH][$RuCl_4$(CO)(py)] [2.342(4) and 2.14(1) Å][18]; [M-[ImH]*trans*-[$RuCl_4(Im)_2$] [2.349(1) and 2.079(3) Å][26]; [4-M-ImH]*trans*-[$RuCl_4$(4-M-Im)$_2$] [2.364(2) and 2.087(6) Å][26] and [M-ImH]*trans*-[$RuCl_4$(CO)(M-Im)$_2$] [2.348(2) and 2.126(6) Å][17]. In our complex the Ru-S distance is 2.295(2) Å and the S=O distance is 1.478(7) Å, essentially the same obtained for others dimethyl sulfoxide ruthenium(III) complexes, such as [$(DMSO)_2$H]*trans*-[$RuCl_4(DMSO)_2$] and [$RuCl_3(DMSO)_2$(DMSO)][19].

Only one S=O strong absorption band is observed in the IR spectrum at 1076 cm^{-1} (S-bonded DMSO)[19,20] for the [NH_4]*trans*-[$RuCl_4(DMSO)_2$] suggesting a *trans* configuration. The molar conductivity data obtained from fresh solutions of this complex and of the [pyH]*trans*-[$RuCl_4$(DMSO)(py)] in methanol, are close to 120 Ω^{-1} mol^{-1}, consistent with 1:1 electrolytes[28].

Table 2. Selected bond distances (Å) and selected interatomic angles (Å) for [pyH]*trans*-[$RuCl_4$(DMSO)(py)].

Bond distances (Å)		Interatomic angles (Å)	
Ru (1) - N(1)	2.116(7)	N(1) - Ru(1) - S(1)	178.4(2)
Ru (1) - S(1)	2.295(2)	N(1) - Ru(1) - Cl(1)	89.9(2)
Ru (1) - Cl(1)	2.349(2)	S(1) - Ru(1) - Cl(1)	89.98(9)
Ru (1) - Cl(3)	2.350(2)	N(1) - Ru(1) - Cl(3)	89.2(2)
Ru (1) - Cl(2)	2.356(2)	S(1) - Ru(1) - Cl(3)	92.44(8)
Ru (1) - Cl(4)	2.360(2)	Cl(1) -Ru (1) - Cl(3)	90.80(9)
N(1) - C(5)	1.327(1)	N(1) -Ru(1) - Cl(2)	89.4(2)
N(1) - C(1)	1.338(1)	S(1) -Ru(1) - Cl(2)	89.00(9)
C(1) - C(2)	1.387(1)	Cl(1) -Ru(1) - Cl(2)	89.62(9)
C(2) - C(3)	1.41(2)	Cl(3) -Ru (1) - Cl(2)	178.50(8)
C(3) - C(4)	1.35(2)	N(1) - Ru(1) - Cl(4)	88.5(2)
C(4) - C(5)	1.353(1)	S(1) - Ru(1) - Cl(4)	91.59(8)
N(2) - C(8)	1.29(2)	Cl(1) - Ru`(1) - Cl(4)	178.11(7)
N(2) - C(9)	1.39(2)	Cl(3) - Ru(1) - Cl(4)	90.19(9)
C(8) - C(12)	1.27(2)	Cl(2) - Ru(1) - Cl(4)	89.35(9)
C(9) - C(10)	1.36(2)	C(5) - N(1) - C(1)	117.5(8)
C(10) - C(11)	1.35(2)	C(5) - N(1) - Ru(1)	121.8(7)
C(11) - C(12)	1.37(2)	C(1) - N(1) - Ru(1)	120.6(6)
Cl(5) - C(13)[1]	1.43(5)	C(1) - C(2) - C(3)	117.8(1)
Cl(5) - C(13)	1.66(5)	N(1) - C(1) - C(2)	122.4(1)
Cl(5) - Cl(6)	2.30(3)	C(4) - C(3) - C(2)	118.4(1)
Cl(5) - Cl(6)	2.41(3)	C(3) - C(4) - C(5)	119.9(1)
Cl(6) - C(13)	1.36(4)	N(1) - C(5) - C(4)	123.7(1)
Cl(6) - C(5)[1]	2.30(3)	O(1) - S(1) - C(6)	106.8(5)
C(13) - C(13)[1]	1.05(7)	O(1) - S(1) - C(7)	106.1(5)
C(13) - Cl(5)[1]	1.43(5)	C (6) - S(1)- C(7)	98.3(7)

The EPR spectra of the [NH_4]*trans*-[$RuCl_4(DMSO)_2$] complex measured in the solid state (X band, -160 °C) gave a single, very broad line with g = 2.189 (Figure 2). This indicates that in the solid state the compound forms aggregates, probably as shown in Scheme I.

It is interesting to point out that when this [NH_4]*trans*-[$RuCl_4(DMSO)_2$] complex is dissolved in aqueous or methanol solution the EPR spectrum changes completely showing immediate formation of an axial and a rhombic species (Figure 3a). So the time-scale for hydration (or solvation) followed by labilization of a *trans* chloro ligand by another solvent molecule as measured by EPR is about 15 min. The g values for [$RuCl_3(DMSO)(MeOH)_2$] are g_1= 2,43, g_2= 2,31, g_3= 1,85 (Figure 3c). This rhombic product was also detected by Alessio et al.[21]. This complex is formed in solution by rapid dissociation of one DMSO (coordinated *via* the S atom) in the *mer,cis*-[$RuCl_3(DMSO)_2(DMSO)$] through the intermediate [$RuCl_3(DMSO)(DMSO)(solv)$] which slowly loses another DMSO (coordinated *via* the O atom) forming the final product [$RuCl_3(DMSO)(solv)_2$] (solv = H_2O or CH_3OH).

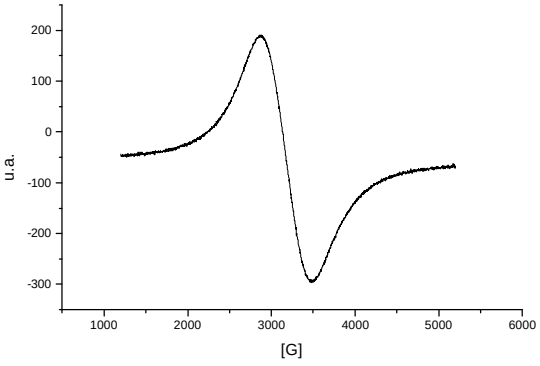


Figure 2. EPR spectrum of [NH_4]*trans*-[$RuCl_4(DMSO)_2$] in the solid state at -160 °C.

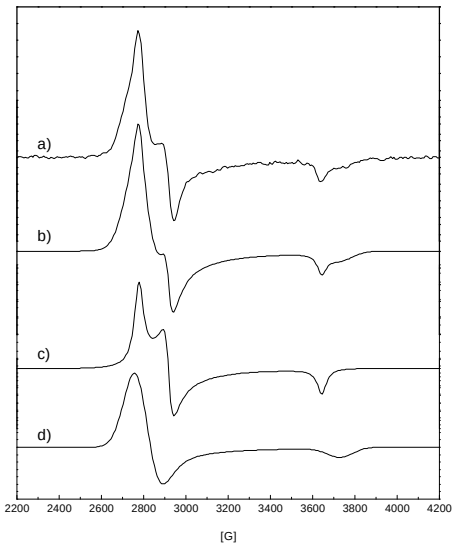
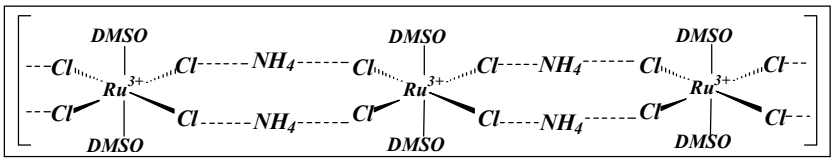


Figure 3. (a) Experimental EPR spectrum at -160 °C, of [NH_4]*trans*-[$RuCl_4$(DMSO)(MeOH)] formed from the precursor [NH_4]*trans*-[$RuCl_4(DMSO)_2$] immediately after dissolution in methanol; (b) Simulated spectrum for, (c + d); (c) Simulated and experimental spectrum of the orthorombic [$RuCl_3(DMSO)(MeOH)_2$] species; (d) Simulated spectrum for the axial [NH_4]*trans*-[$RuCl_4$(DMSO) (MeOH)] species.

The fast displacement of one DMSO in these complexes and the loss of chloride, as shown in Scheme 2, are in agreement with the relatively large trans effect of the S-bonded DMSO[27] and chloride[29]. After 15 h in methanol solution, only [$RuCl_3(DMSO)(MeOH)_2$] was detected by EPR, reproducing experimentally the simulated spectrum shown in Figure 3c.



Scheme 1. Structure of (micro-) aggregates of the [NH_4]*trans*-[$RuCl_4(DMSO)_2$] complex.

The EPR spectrum of the $[(DMSO)_2H]$*trans*-$[RuCl_4(DMSO)_2]$ complex in the solid state, at -160 °C, is shown in Figure 4. This species shows $g_{\perp} = 2.35$ and $g_{//} = 1.87$ which is typical of an axial structure. This complex in a fresh solution of MeOH shows a mixture of compounds where the DMSO is displaced by the solvent and there is also probably a simultaneous dissociation of a chloride forming the $[RuCl_3(DMSO)(MeOH)_2]$ complex. This mixture is detected in the EPR spectrum (Figure 5).

The cyclic voltammogram of $[NH_4]$*trans*-$[Ru^{3+}Cl_4(DMSO)_2]$ in methanol solution is shown in Figure 6. In this voltammogram it is possible to detect three redox processes at the metal center: the first one (A) with $E_{1/2} = -0.21$ V belongs to the reduction of the $[NH_4]$*trans*-$[Ru^{3+}Cl_4(DMSO)(MeOH)]$ since the dissociation of one DMSO molecule from this complex is fast[19]; the second process (B), $E_{1/2} = -0.03$ V, involves the reduction of the $[Ru^{3+}Cl_3(DMSO)(MeOH)_2]$ which is formed slowly in solution as detected by EPR. The third process (C) is electrochemical in contrast with the first two that are chemical processes. In this case, considering that the cathodic wave at 0.0 V decreases and the wave at 0.24 V increases this suggests that the species responsible for this process is generated at the electrode, after the reduction of the $[Ru^{3+}Cl_3(DMSO)(MeOH)_2]$ complex. This compound could be the $[Ru^{2+}Cl_2(DMSO)(MeOH)_3]$($E_{1/2}$ = 0,22 V) as suggest by Costa *et. al.* for the similar complex $[Ru^{2+}Cl_2(DMSO)(H_2O)_3]$[30]. This process is clearly shown in Figure 6 and Scheme 3.

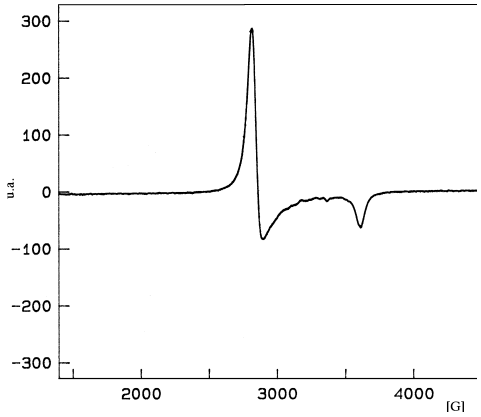


Figure 4. EPR spectrum of $[(DMSO)_2H]$*trans*-$[RuCl_4(DMSO)_2]$ in solid state, at -160 °C.

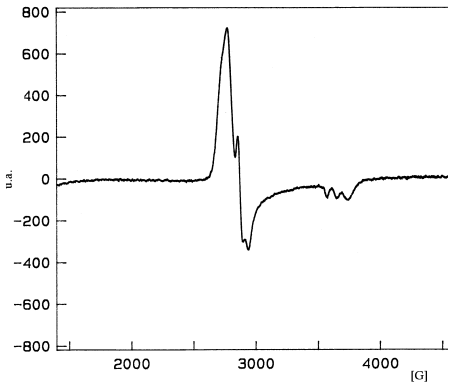
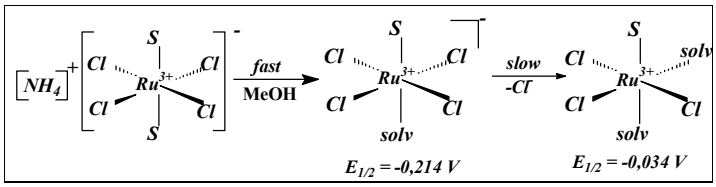


Figure 5. EPR spectrum of $[(DMSO)_2H]$*trans*-$[RuCl_4(DMSO)_2]$ in MeOH, at -160 °C.



Scheme 2. Fast substitution of a DMSO ligand by a methanol molecule and slow labilization of a chloride in the $[NH_4]$*trans*-$[RuCl_4(DMSO)_2]$ complex.

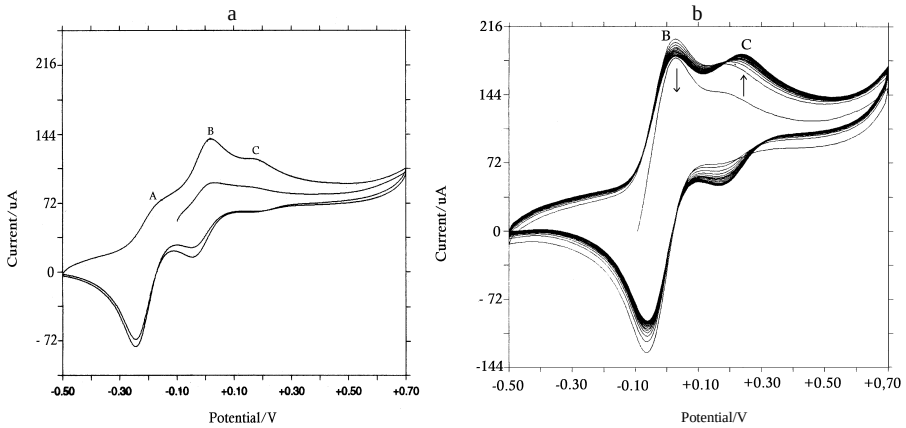
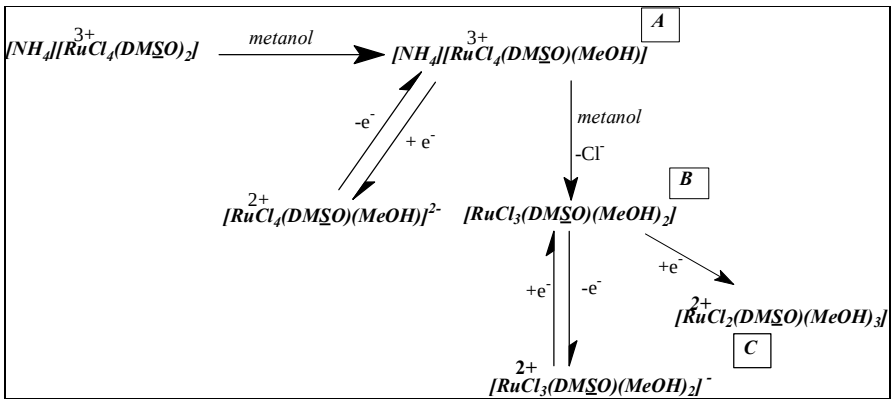


Figure 6. Cyclic voltammogram of $[NH_4]$*trans*-$[RuCl_4(DMSO)_2]$ in MeOH $1.0x10^{-3}$ mol L^{-1}, recorded at 100 V/s, 0.1 mol L^{-1} TBAP (vs. Ag/AgCl). A) $[NH_4]$*trans*-$[RuCl_4(DMSO)(MeOH)]$; B) $[RuCl_3(DMSO)(MeOH)]$; C) $[RuCl_2(DMSO)(MeOH)_3]$. (Notice that the cyclic voltammograms show the convertion of species A to species B).



Scheme 3. Chemical behavior of [NH_4]*trans*-[$RuCl_4(DMSO)_2$] in methanol solution: A) [NH_4]*trans*-[$RuCl_4$(DMSO)(MeOH)]; B) [$RuCl_3$(DMSO)(MeOH)]; C) [$RuCl_2$(DMSO)($MeOH)_3$]; 0.1 M, TBAP (vs. Ag/AgCl).

Conclusions

The Na-*trans*-[$RuCl_4(DMSO)_2$] complex reacts with ammonia or a heterocyclic nitrogen donor ligand (L) to form compounds of the general formula Na-*trans*-[$RuCl_4$-(DMSO)(L)] and *mer*, *cis*-[$RuCl_4$(DMSO)(Im)] (Im = imidazole). These complexes appear to be very promising for cancer therapy[31]. The knowledge of the chemical behaviour of these ruthenium-sulfoxide complexes in solution is very important in order to rationalise their activity as possible drugs. We therefore studied the [NH_4]-*trans*-[$RuCl_4$ (DMSO)(L)] (L=DMSO and py) complexes by EPR and cyclic voltammetry. The first, and perhaps most important, conclusion that can be drawn from our work is that according to the measured electrochemical potentials of the studied complexes a biological reduction process is thermodynamically possible for Ru(III)-DMSO compounds. Thus the ease of reduction of these complexes in aqueous or methanol solution suggests that this process is likely to occur, at least partially, also *in vivo*. In our study the EPR technique was usefull for detecting the species in solution, and provided information about the transformations of the complexes in solution.

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