Bidentate Sulfoxide Complexes of Ruthenium(II) and Their Preliminary Biological Assessment *in Vitro*

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Received May 30, 1996[⊗]

The complexes *trans*-$RuCl_2(BMSE)_2$ (**1**), *cis*-$RuCl_2(BESE)_2$ (**2**), *trans*-$RuCl_2(BPSE)_2$ (**3**), and *cis*-$RuCl_2(BMSP)_2$ (**4**) have been synthesized and characterized, including X-ray analyses [BMSE = 1,2-bis(methylsulfinyl)ethane, BESE = 1,2-bis(ethylsulfinyl)ethane, BPSE = 1,2-bis(propylsulfinyl)ethane, and BMSP = 1,3-bis(methylsulfinyl)-propane]. Crystal data are as follows: **1**·H_2O, triclinic, $P1$, $a = 8.863(1)$ Å, $b = 14.462(3)$ Å, $c = 7.543(1)$ Å, $\alpha = 103.39(1)°$, $\beta = 113.31(1)°$, $\gamma = 77.23(1)°$, $Z = 2$; **2**·MeOH, triclinic, $P\bar{1}$, $a = 14.858(2)$ Å, $b = 16.732(3)$ Å, $c = 10.609(2)$ Å, $\alpha = 105.14(2)°$, $\beta = 93.34(2)°$, $\gamma = 115.91(1)°$, $Z = 4$; **3**, orthorhombic, *Aba*2, $a = 14.894(1)$ Å, $b = 7.501(1)$ Å, $c = 21.911(2)$ Å, $Z = 4$; **4**, orthorhombic, *Pcab*, $a = 15.257(3)$ Å, $b = 18.138(2)$ Å, $c = 13.395(2)$ Å, $Z = 8$. The structures were solved by the Patterson method and were refined by full-matrix least-squares procedures to $R = 0.026$, 0.026, 0.029, and 0.031 for 10461, 8952, 1594, and 5694 reflections with $I > 3\sigma(I)$, for **1**−**4**, respectively. Preliminary *in vitro* experiments with Chinese hamster ovary cells indicate that the *trans*-complexes accumulate in the cells and bind to DNA to a greater degree than the *cis*-complexes.

Introduction

The potential for using new sulfoxide complexes of Ru as anticancer agents is an intriguing one, following reports on the antitumor activity of *cis*- and *trans*-$RuCl_2(DMSO)_4$,[1,2] and other Ru(III)−DMSO species[3] (DMSO = dimethyl sulfoxide). Our group has been interested in ruthenium−sulfoxide complexes, initially as catalysts for homogeneous hydrogenations of olefins[4] and later as precursors to transition metal-based radiosensitizers,[5] the goal being to synthesize Ru−sulfoxide−nitroimidazole complexes. We have shown that the radiosensitizing abilities of certain 2- and 4-nitroimidazoles are improved upon coordination to Ru(II)[6] using *cis*-$RuCl_2(DMSO)_4$ and *cis*-$RuCl_2(TMSO)_4$ as precursors[5] (TMSO = tetramethylene sulfoxide). The configurations of some resulting $RuCl_2(sulfoxide)_2(L)_2$ complexes (L = a nitroimidazole) were not definitely resolved because no crystal structures were determined, and there are many possible isomers within such complexes, particularly when the ambidentate nature of the sulfoxide (*S*- or *O*-bonding) is considered.

The coordination chemistry of Ru(II)− and Ru(III)−DMSO complexes containing just halogen and the sulfoxide ligands (within neutral, cationic, or anionic species) is rich and diverse,[2,4,7−9] and there have also been problems in repeating some literature syntheses, in part because of the redox properties of sulfoxide ligands.[10] For example, *mer*-$RuCl_3(Me_2S)_3$ has been isolated from reactions of $RuCl_3$ with DMSO;[7] similarly, the thioether complex *mer*-$RuCl_3(THT)_3$ (THT = tetrahydrothiophene) was isolated during attempts to make TMSO complexes,[11] while TMSO complexes of Ru(II)[12−14] and Ru(III)[12] are also well characterized. We have reported the remarkable structure of $[Br_6(TMSO)_2Ru(\mu_2\text{-}TMSO)_2(\mu_3\text{-}TMSO)_2Li_2(TMSO)_2]$, which incorporates a four-membered central Li_2O_2 ring as well as all four possible bonding modes of a sulfoxide moiety.[13] We have also recently characterized crystallographically *trans*-$RuBr_2(TMSO)_4$, containing only *S*-bonded sulfox-

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⊗ Abstract published in *Advance ACS Abstracts,* November 1, 1997.

(1) (a) Mestroni, G.; Alessio, E.; Sava, G.; Pacor, S.; Coluccia, M. In *Metal Complexes in Cancer Chemotherapy*; Keppler, B. K., Ed.; VCH: Weinheim, Germany, 1993; p 157. (b) Sava, G.; Pacor, G.; Zorzet, S.; Alessio, E.; Mestroni, G. *Pharm. Res.* **1989**, *21*, 617. (c) Sava, G.; Zorzet, S.; Giraldi, T.; Mestroni, G.; Zassinovich, G. *Eur. J. Cancer Clin. Oncol.* **1984**, *20*, 841. (d) Monti-Bragadin, C.; Ramani, L.; Samer, L.; Mestroni, G.; Zassinovich, G. *Antimicrob. Agents Chemother*. **1975**, *7*, 825.
(2) Alessio, E.; Mestroni, G.; Nardin, G.; Attia, W. M.; Calligaris, M.; Sava, G.; Zorzet, S. *Inorg. Chem.* **1988**, *27*, 4099.
(3) (a) Sava, G.; Pacor, S.; Bergamo, A.; Cocchietto, M.; Mestroni, G.; Alessio, E. *Chem.-Biol. Interact.* **1995**, *95*, 109. (b) Mestroni, G.; Alessio, E.; Sava, G.; Pacor, S.; Colluccia, M., Boccarelli, A. *Met.-Based Drugs* **1994**, *1*, 41.
(4) (a) James, B. R.; McMillan, R. S. *Can. J. Chem*. **1977**, *55*, 3927. (b) James, B. R.; McMillan, R. S.; Reimer, K. J. *J. Mol. Catal*. **1976**, 439. (c) McMillan, R. S.; Mercer, A.; James, B. R.; Trotter, J. *J. Chem. Soc., Dalton Trans*. **1975**, 1006. (d) Davies, A. R.; Einstein, F. W. B.; Farrell, N. P.; James, B. R.; McMillan, R. S. *Inorg. Chem*. **1978**, *17*, 1965. (e) James, B. R.; McMillan, R. S.; Morris, R. H.; Wang, D. K. W. In *Transition Metal Hydrides;* Bau, R., Ed.; ACS Symposium Series 167; American Chemical Society: Washington, DC, 1978; p 122.
(5) (a) Chan, P. K. L.; Chan, P. K. H.; Hu, H-L.; Frost, D. C.; James, B. R.; Skov, K. A. *Can. J. Chem*. **1989**, *67*, 508. (b) Chan, P. K. L.; Chan, P. K. H.; Frost, D. C.; James, B. R.; Skov, K. A. *Can. J. Chem*. **1988**, *66*, 117. (c) Chan, P. K. L.; Skov, K. A.; James, B. R.; Farrell, N. P. *Chem.-Biol Interact*. **1986**, *59*, 247.
(6) (a) Chan, P. K. L.; Skov, K. A.; James, B. R.; Farrell, N. P. *Int. J. Radiat. Oncol. Biol. Phys*. **1986**, *11*, 937. (b) Chan, P. K. L.; Skov. K. A.; James, B. R. *Int. J. Radiat. Biol*. **1987**, *52*, 49.
(7) Jaswal, J.; Rettig, S. J.; James, B. R. *Can. J. Chem.* **1990**, *68*, 1808.
(8) (a) Alessio, E.; Milani, B.; Calligaris, M.; Bresciani-Pahor, N. *Inorg. Chim. Acta* **1992**, *194*, 85. (b) Henn, M.; Alessio, E.; Mestroni, G.; Calligaris, M.; Faleschini, P.; Attia, W. M. *Inorg. Chim. Acta* **1991**, *187*, 39.
(9) Alessio, E.; Balducci, G.; Calligaris, M.; Costa, G.; Attia, W. H.; Mestroni, G. *Inorg. Chem.* **1991**, *20*, 609.
(10) Kukushkin, V. Y. *Coord. Chem. Rev.* **1995**, *134*, 375.
(11) Yapp, D. T. T.; Jaswal, J.; Rettig, S. J.; James, B. R.; Skov, K. A. *Inorg. Chim. Acta* **1990**, *177*, 199.
(12) Alessio, E.; Milani, B.; Mestroni, G.; Calligaris, M.; Faleschini, P.; Attia, W. M. *Inorg. Chim. Acta* **1990**, *177*, 255.
(13) (a) Jaswal, J.; Yapp, D. T. T.; Rettig, S. J.; James, B. R.; Skov, K. A. *Inorg. Chim. Acta* **1993**, *207*, 97. (b) Jaswal, J.; Yapp, D. T. T.; Rettig, S. J.; James, B. R.; Skov, K. A. *J. Chem. Soc., Chem. Commun*. **1992**, 1528.
(14) Jaswal, J.; Yapp, D. T. T.; Rettig, S. J.; James, B. R.; Skov, K. A. Unpublished results.

S0020-1669(96)00648-9 CCC: $14.00

ides,[14] a complex that has been isolated previously by the Trieste group.[12] The structurally characterized [H(sulfoxide)$_n$][*trans*-$RuCl_4$(sulfoxide)$_2$] complexes are also of interest because of the nature of the cations which contain strongly H-bonded O···H moieties, where sulfoxide = DMSO,[7,9] TMSO,[12] or ^{n}Pr$_2$SO[15] and $n = 1$ or 2.

We decided to extend the range of sulfoxides to include bidentate ligands of the type RS(O)$(CH_2)_n$S(O)R, where $n = 2$ with R = Me, Et, and ^{n}Pr and $n = 3$ with R = Me. The aims were to reduce the number of possible isomers in the preparation of nitroimidazole complexes and to augment the database for antitumor activity of Ru−sulfoxide complexes. In this paper, we report on the synthesis and characterization (including X-ray structural data) of some bidentate sulfoxide complexes of Ru(II), *trans*-dichlorobis(1,2-bis(methylsulfinyl)ethane)ruthenium(II) (**1**), *cis*-dichlorobis(1,2-bis(ethylsulfinyl)ethane)ruthenium(II) (**2**), *trans*-dichlorobis(1,2-bis(propylsulfinyl)ethane)ruthenium(II) (**3**), and *cis*-dichlorobis(1,2-bis(methylsulfinyl)propane)ruthenium(II) (**4**). In addition, the results of experiments investigating the ability of these complexes to traverse a cell membrane and bind to DNA are reported.

Experimental Section

The thioethers (K & K Laboratories), DMSO (BDH), and all other solvents were used as supplied without further purification. The syntheses of the Ru complexes were carried out using standard Schlenk tube techniques under an atmosphere of dry, oxygen-free Ar. The MeOH used was refluxed over Mg powder for 2 h prior to distillation.

Electronic spectra (reported as λ_{max} nm (log ϵ)) were recorded in aqueous solution on a Perkin-Elmer 552A spectrometer, IR spectra (Nujol, KBr plates, in cm^{-1}) on a Nicolet 5DXFT spectrometer, and room-temperature ^{1}H NMR (CD_2Cl_2, $CDCl_3$, CD_3OD, or D_2O) spectra on a Varian XL-300 or a Bruker WH-400 (both in FT mode) with δ shifts in ppm referenced to TMS (s = singlet, d = doublet, t = triplet, m = multiplet). Conductivity measurements (reported in Ω^{-1} mol^{-1} cm^2) were made at room temperature (rt) at 10^{-2}−10^{-3} M concentrations in water using a Thomas Serfass conductivity bridge and a cell from Yellow Springs Instrument Company. The EI mass spectra (reported as *m/z* (relative intensity)) were done on a Kratos MS 50 mass spectrometer, 70 eV. Elemental analyses were performed by P. Borda of the Chemistry Department at UBC.

Sulfoxides and Ru(II)−Sulfoxide Complexes. The sulfoxides were synthesized by the HCl-catalyzed, DMSO oxidations of the corresponding thioethers, according to the literature procedure.[16] Thus, for example, the precursor to 1,2-bis(methylsulfinyl)ethane was 1,2-bis(methylthio)ethane. The sulfoxides were initially isolated as a mixture of diastereomers (*RS* pair and *meso*); recrystallizations (BMSE, 3 times from EtOH; BESE, twice from EtOH; BPSE, twice from benzene; BMSP, 3 times from THF) were used to isolate one isomer.[16] The analytical data for the sulfoxides were satisfactory, and the IR data (see below) agree well with the published values;[16] the ^{1}H NMR data for the sulfoxides have not been previously reported and are given below:

1,2-Bis(methylsulfinyl)ethane (BMSE). ^{1}H NMR (300 MHz, D_2O): δ 2.68 (s, 3H, CH_3), 3.15 (m, 2H, CH_2). IR (ν_{SO}): 1018. Anal. Calcd for $C_4H_{10}O_2S_2$: C, 31.16; H, 6.49. Found: C, 31.06; H, 6.42.

1,2-Bis(ethylsulfinyl)ethane (BESE). ^{1}H NMR (300 MHz, CD_3OD): δ 1.33 (t, 3H, CH_3), 2.78 (m, 2H, CH_3CH_2), 3.02 (m, 2H, CH_2S(O)). IR (ν_{SO}): 1015. Anal. Calcd for $C_6H_{14}O_2S_2$: C, 39.56; H, 7.69. Found: C, 39.69; H, 7.59.

1,2-Bis(propylsulfinyl)ethane (BPSE). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.10 (t, 3H, CH_3), 1.85 (m, 2H, CH_3CH_2), 2.80 (AB qt, 2H, $CH_3CH_2CH_2$), 3.20 (AB qt, 2H, CH_2S(O)). IR (ν_{SO}): 1010. Anal. Calcd for $C_8H_{18}O_2S_2$: C, 45.71; H, 8.57. Found: C, 45.55; H, 8.50.

1,2-Bis(methylsulfinyl)propane (BMSP). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (m, 1H, $CH_2CH_2CH_2$), 2.60 (s, 3H, CH_3), 2.89 (m, 2H, CH_2S(O)). IR (ν_{SO}): 1050. Anal. Calcd for $C_5H_{12}O_2S_2$: C, 35.71; H, 7.14. Found: C, 35.78; H, 7.16.

***trans*-Dichlorobis(1,2-bis(methylsulfinyl)ethane)ruthenium(II), $RuCl_2$(BMSE)$_2$ (1).** $RuCl_3$·$3H_2O$ (0.27 g, 1.0 mmol) was refluxed in MeOH (20 mL) in an atmosphere of H_2 until the solution became dark blue (4 h). BMSE (0.38 g, 2.5 mmol), previously dissolved in MeOH (10 mL), was then added to the "ruthenium-blue" solution, and refluxing was continued under H_2 for a further 4 h. The complex started to form after 1 h and precipitated as a fine, light-green powder. The reaction mixture was filtered while hot, and the precipitate dried *in vacuo* at 70 °C (yield: 80%). ^{1}H NMR (300 MHz, D_2O): δ 3.25 (s, 12H, CH_3), 3.85 (s, 8H, CH_2CH_2). MS: 480 (3.9) [M$^+$], 326 (1.9) [M − $(CH_3SOCH_2)_2]^+$, 63 (100) $[CH_3SO]^+$. IR (ν_{SO}): 1109. UV/vis: 376 (2.94); 301 (3.28). Λ_M: 60.4. Anal. Calcd for $C_8H_{20}Cl_2O_4RuS_4$: C, 19.99; H, 4.17. Found: C, 20.15; H, 4.26. Yellow crystals (as **1**·H_2O) suitable for X-ray analysis were obtained from a saturated aqueous solution of the complex which was left uncovered at rt for a few days.

***cis*-Dichlorobis(1,2-bis(ethylsulfinyl)ethane)ruthenium(II), $RuCl_2$(BESE)$_2$ (2).** Complex **2** was synthesized as for **1**, except the refluxing procedure was continued for 6 h after the addition of the sulfoxide (yield: 55%). Pale yellow crystals (as **2**·MeOH) suitable for X-ray analysis formed in the filtrate after 1 h at rt. ^{1}H NMR (400 MHz, D_2O): δ 1.36, 1.55 (t, 12H, CH_3); 3.30 (td, 2H, C*H* H′C*H*H′; 3.45 (m, 2H, CH_3CH_2); 3.63 (m, 2H, C*H*H′C*H*H′); 3.70 (m, 4H, CH_3CH_2); 3.87 (m, 2H, CH*H*′CH*H*′); 3.93 (m, 2H, CH_3CH_2); 4.09 (dt, 2H, CH*H*-′CH*H*′). MS: 536 (5.0) [M]$^+$, 354 (1.9) [M − $(CH_3CH_2S(O)CH_2)_2]^+$, 77 (100) $[CH_3CH_2SO]^+$. IR (ν_{SO}): 1128. UV/vis: 398 (3.06); 320 (3.23). Λ_M: 33.9. Anal. Calcd for $C_{12}H_{28}Cl_2O_4RuS_4$ (for a powdered sample): C, 26.86; H, 5.22; S, 23.80. Found: C, 26.85; H, 5.22; S, 23.66.

***trans*-Dichlorobis(1,2-bis(propylsulfinyl)ethane)ruthenium(II), $RuCl_2$(BPSE)$_2$ (3).** The procedure was as described for **1**, except that the "ruthenium-blue" solution turned green within a few minutes after addition of the sulfoxide, and the complex precipitated completely within 1 h. The hot solution was filtered and the light yellow precipitate collected. The filtrate was kept at O °C, and more complex precipitated after a few days (yield: 47%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.10 (t, 12H, CH_3); 1.83, 2.20 (m, 4H each, 2 × $CH_3CH_2CH_2$S(O)); 3.40, 3.70 (m, 8H each, 2 × CH_2S(O)CH_2). [A similar spectrum was measured in D_2O but was less clear because of the presence of a broad OH peak.] M.S: 592 (2.2) [M]$^+$; 382 (0.6) [M − $(CH_3CH_2CH_2S(O)CH_2)_2]^+$; 41 (100) $[CH_2CHCH_2]^+$. IR (ν_{SO}): 1128. UV/vis: 395 (3.04); 320 (3.26). Λ_M: 42.7. Anal. Calcd for $C_{16}H_{36}Cl_2O_4RuS_4$: C, 32.43; H, 6.08; S, 21.62. Found: C, 32.41; H, 6.09; S, 21.53. Bright yellow crystals suitable for X-ray analysis were grown overnight in a saturated solution of the complex in MeOH.

***cis*-Dichlorobis(1,3-bis(methylsulfinyl)propane)ruthenium(II), $RuCl_2$(BMSP)$_2$ (4).** The procedure was as described for **1**, except that the "ruthenium-blue" solutions turned green within a few minutes of addition of the sulfoxide, and the complex precipitated within 1 h. The hot solution was filtered and the light yellow precipitate collected (yield: 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20, 2.29 (m, 1H each, $CH_2CH_2CH_2$); 3.41, 3.45 (s, 3H each, CH_3); 3.68, 4.05 (m, 2H each, $CH_2CH_2CH_2$). [A similar spectrum was measured in D_2O−see above.] MS: 508 (0.5) [M]$^+$, 153 (8.4) $[CH_3S(O)(CH_2)_3S(O)CH_3]^+$, 41 (100) $[CH_2CHCH_2]^+$. IR (ν_{SO}): 1085. UV/vis: 336 (2.97); 298 (2.90). Λ_M: 12.6. Anal. Calcd for $C_{10}H_{24}Cl_2O_4RuS_4$: C, 23.62; H, 4.72; Cl, 13.97. Found: C, 23.81; H, 4.78; Cl, 13.69. Crystals suitable for X-ray analysis were grown in a saturated solution of the complex in MeOH.

X-ray Crystallographic Analyses of 1−**4.** Selected crystallographic data appear in Table 1. The final unit-cell parameters were obtained by least squares on the setting angles for 25 reflections with 2θ = 57.5−59.2° for **1**·H_2O, 48.4−54.8° for **2**·MeOH, 26.8−42.0° for **3**, and 54.3−54.9° for **4**. The intensities of three standard reflections, measured every 200 reflections throughout the data collections, decayed uniformly by 2.3 and 2.6% for **1** and **2**, respectively, and were essentially constant for **3** and **4**. The data were processed[17] and corrected for Lorentz and polarization effects, decay (for **1** and **2**), and absorption (empirical, based on azimuthal scans).

(15) Yapp, D. T. T.; Rettig, S. J.; James, B. R.; Skov, K. A. Manuscript in preparation.

(16) Hull, M.; Bargar, T. *J. Org. Chem.* **1975**, *40*, 3152.

(17) *TEXSAN: Crystal structure analysis package;* Molecular Structure Corp.: The Woodlands, TX, 1985.

Table 1. Crystallographic Data[a]

compd	**1**·H_2O	**2**·MeOH	**3**	**4**
formula	$C_8H_{22}Cl_2O_5RuS_4$	$C_{13}H_{32}Cl_2O_5RuS_4$	$C_{16}H_{36}Cl_2O_4RuS_4$	$C_{10}H_{24}Cl_2O_4RuS_4$
fw	498.47	568.61	592.67	508.51
cryst system	triclinic	triclinic	orthorhombic	orthorhombic
space group	*P*1 (No. 1)	$P\bar{1}$ (No. 2)	*Aba*2 (No. 41)	*Pcab* (No. 61)
a, Å	8.863(1)	14.858(2)	14.894(1)	15.257(3)
b, Å	14.462(3)	16.732(3)	7.501(1)	18.138(2)
c, Å	7.543(1)	10.609(2)	21.911(2)	13.395(2)
α, deg	103.39(1)	105.14(2)	90	90
β, deg	113.31(1)	93.34(2)	90	90
γ, deg	77.23(1)	115.91(1)	90	90
V, Å^3	854.6(2)	2244(2)	2448.0(9)	3706.7(7)
Z	2	4	4	8
ρ_{calc}, g/cm^3	1.937	1.683	1.608	1.822
T, °C	21	21	21	21
radiation	Mo	Mo	Mo	Mo
λ, Å	0.710 69	0.710 69	0.710 69	0.710 69
μ(Mo *K*α), cm^{-1}	16.97	13.03	11.95	15.63
$R(F)$	0.026	0.026	0.029	0.031
$R_w(F)$	0.034	0.032	0.030	0.037

[a] $R = \sum||F_o| - |F_c||/\sum|F_o|$, $R_w = (\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2)^{1/2}$.

The structures were solved by conventional heavy atom methods, the coordinates of the Ru, Cl, and S atoms being determined from the Patterson functions and those of the remaining non-hydrogen atoms from subsequent difference Fourier syntheses. The structure analyses of **1** and **2** were initiated in the centrosymmetric space group *P*, this choice being confirmed for the latter by the subsequent successful solution and refinement of the structure. In the case of **1**, a disordered structure resulted in the centrosymmetric space group. The structure of **1** was successfully refined in the noncentrosymmetric space group *P*1, the asymmetric unit containing two ordered, crystallographically independent, molecules of the complex **1** and two water molecules. The structure of **3** was initially solved in the centrosymmetric space group *Cmca*. Disorder of the chelate ring carbon and the *n*-propyl carbon atoms prompted the refinement of the structure in the lower symmetry noncentrosymmetric space group *Aba*2. The asymmetric unit of **2** contains two methanol solvate molecules in addition to two complex molecules (which differ only in the orientation of one ethyl group), while the complex **3** has crystallographically imposed C_2 symmetry. Each of the methanol solvate molecules in the structure of **2**·MeOH showed 2-fold disordered oxygen atoms. The site occupancy factors for the higher-occupancy methanol oxygen atoms were refined, the total occupancy being constrained to sum to 1.00 for each methanol molecule. In compound **3**, the terminal atoms of the *n*-propyl groups on both of the two independent sulfur atoms exhibited a high degree of thermal motion, indicative of probable disordering. A 2-fold disordered model was refined for C(8) (as described above for **2**), but no satisfactory disordered model could be successfully refined for C(5). As a result of both thermal motion and possible unresolved disordering, some geometrical parameters involving the propyl groups deviate significantly from the expected values. All non-hydrogen atoms were refined with anisotropic thermal parameters. Carbon-bound hydrogen atoms were fixed in idealized positions ($d_{C-H} = 0.98$ Å, $B_H = 1.2B_{bonded\ atom}$). The water hydrogen atoms in **1**·H_2O and the higher-occupancy methanol OH protons in **2**·MeOH were included in difference map positions but were not refined. Neutral atom scattering factors and anomalous dispersion corrections for the non-hydrogen atoms were taken from ref 18. For both of the noncentrosymmetric structures, parallel refinements of the mirror-image structures were carried out to determine the absolute configuration of **1**·H_2O and the polarity of **3**. The residuals for the mirror-image structures were slightly higher in both cases. Selected bond lengths and bond angles appear in Table 2. A complete table of crystallographic data, final atomic coordinates and equivalent isotropic thermal parameters, hydrogen atom parameters, anisotropic thermal parameters, complete listings of bond lengths and angles, torsion angles, intermolecular contacts, and least-squares planes are included as Supporting Information.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for *trans*-$RuCl_2$(BMSE)$_2$ (**1**), *cis*-$RuCl_2$(BESE)$_2$ (**2**), *trans*-$RuCl_2$(BPSE)$_2$ (**3**), and *cis*-$RuCl_2$(BMSP)$_2$ (**4**)

bond	**1**·H_2O	**2**·MeOH	**3**	**4**
Ru−Cl	[2.39−2.41][a]	[2.42−2.45][b]	2.41[a]	2.44[b]
Ru−S	[2.31−2.32][b]	[2.26−2.27][a] [2.30−2.31][b]	[2.30, 2.32][b]	2.27[a] [2.35, 2.36][b]
S−O	1.45−1.50	1.47−1.48	1.44, 1.47	1.47, 1.48
C−S	1.72−1.86	1.79−1.81	1.74−1.91	1.77−1.80
Ru−S−O	118.3−120.4	116.3−120.4	118.1, 120.6	113.9−116.5
C−S−O	103.4−111.3	106.3−109.3	99.5−114.8	104.9−107.1
C−S−C	98.1−106.3	100.0−102.8	89.3, 112.1	98.9−100.6
S−C−C[c]	107.1−112.5	106.5−111.3	108.3, 109.0	114.4−115.6[d]
S−C−C[e]		111.3−113.3	109.0, 116.2	
Ru−S−C[c]	102.0−107.2	103.0−105.0	100.4, 106.5	115.1−115.8
Ru−S−C[e]	113.9−115.7	114.4−117.3	114.5, 117.8	111.2−113.6

[a] Trans to Cl. [b] Trans to S. [c] Bonds involving backbone (ring) carbons. [d] The backbone C−C−C angles are 113.1 and 113.4°. [e] The C atom is that of an alkyl substituent.

Biological Assessment. The experimental methods generally have been described in detail for some corresponding studies using cisplatin[19] and are given only in outline here.

Cell Lines. Chinese hamster ovary (CHO) cells were used in all cell accumluation and toxicity experiments. The CHO cells were routinely grown in spinner culture flasks in α-medium (alpha modification of Eagle's minimum essential media with Penstrep antibiotic (1%) and fetal bovine serum (10%); all media and additives were obtained from Gibco). Cell concentrations (cells/mL) were determined using a Coulter cell counter (Coulter Electronics Inc., Hialeah, FL).

Cell Accumulation Studies. These were performed to quantitate the amount of complex in the cells as a function of time and to determine whether there was preferential accumulation in cells incubated under hypoxia (produced by N_2 flow). In a typical experiment, CHO cells were incubated (in air or N_2) in a solution of the complex in α-medium for a specific time; 2×10^6 cells were then removed, pelleted by centrifugation, and washed with phosphate buffer saline (PBS, 10 mL, 0 °C) to remove unbound complex. The final cell concentration was determined, and the cells were pelleted and dried by evaporation. Concentrated HNO_3 was added to the cell pellet, and the solution was agitated overnight at 37 °C to digest the cells. The resulting cell−acid mixture was then analyzed for Ru using atomic absorption spectroscopy (AAS, Varian SpectrAA 300 fitted with a graphite furnace) following calibration with Ru standards supplied by Sigma. The analytical results were expressed as ng of Ru/10^6 cells. Nuclei were also isolated from CHO cells incubated with complexes and analyzed for the presence of Ru to determine if the complexes penetrated the

(18) *International Tables for X-Ray Crystallography;* Kynoch Press: Birmingham, U.K., 1974; Vol. IV, pp 99−102 and 149.

(19) Matthews, J. B.; Adomat, H.; Skov, K. A. *Anti-Cancer Drugs* **1993**, *4*, 463.

nuclear membrane. Approximately 6×10^6 cells were removed from test solutions and lysed mechanically in a Dounce homogenizer (B-type pestle) after two washes in PBS. The whole nuclei, released by rupturing the cell membranes, were collected by high speed centrifugation, dried, and digested overnight with concentrated HNO_3 before being analyzed for the presence of Ru by AAS. Finally, DNA was extracted from cells using a previously described phenol extraction procedure[19] and then was also analyzed for Ru.

Toxicities. The toxicities of the complexes toward CHO cells in air and in N_2 were measured by comparing the plating efficiency (PE) of cells incubated in solutions of the complexes with controls as a function of time.[19,20] Briefly, at given times, aliquots of cells were removed from the incubation vessels (air or in N_2), washed, and diluted 10-fold. A known number of cells (typically 200−300) were then plated into Petri dishes containing α-medium and incubated for 7 days in a cell incubator to allow colonies (defined as >50 cells)[21] to form. After 7 days, the colonies were stained and counted, and the PE was expressed as the ratio of number of colonies over the number of cells plated.

Damaged DNA Affinity Precipitation Assay (DDAP). This was first used to identify proteins that recognized X-ray-induced damage[22] and later to examine proteins that recognized cisplatin-damaged DNA. The latter proteins were purified and identified as high mobility group (HMG) proteins[23] and were found to bind specifically to DNA damaged by cisplatin.[24] A modification of the assay was used to investigate the nature of the interactions between Pt complexes and DNA[24b,25] and by us to study the binding of complexes **1**−**4** to DNA. The procedures have been published elsewhere[25a] and are described briefly here. Calf thymus, double-stranded DNA attached to cellulose beads (Sigma) was incubated with a solution of the complex in PBS. The DNA was then washed rigorously to remove unbound complexes and incubated with the HMG proteins. The DNA was pelleted and washed again to remove unbound protein; following the final wash, the DNA was boiled in buffer to dislodge bound protein. The DNA/protein mixture was then spun to pellet the DNA, and the supernatant was analyzed for the presence of HMG proteins by gel electrophoresis.

Results and Discussion

Characterization of Complexes 1−4. Some ruthenium(II) complexes with bidentate sulfoxide ligands (chiral and nonchiral) were evaluated as potential catalysts for homogenous hydrogenation of olefinic substrates by this group in the mid-70s, although no structural data were reported on the catalyst precursor complexes which included bis(methylsulfinyl) and bis(benzylsulfinyl) ligands analogues of diop (i.e. with the PPh_2 replaced by S(O)R).[4] Reports on other chelating sulfoxide complexes of other transition metals have also appeared.[26,27] Complexes of the first-row transition metals (Mn−Zn) and Cd have the general formula $[M(sulfoxide)_3]^{2+}[ClO_4^-]_2$, where sulfoxide = the entirely *O*-bonded, bidentate sulfoxides RS(O)$(CH_2)_n$S(O)R, for R = Me and Et when $n = 2$ and for R = Me when $n = 3$ or 4; complexes of Pd^{2+} and Pt^{2+} were square planar, of the type $M(MeS(O)(CH_2)_2S(O)Me)Cl_2$, and contained, in contrast, only one, exclusively *S*-bonded chelating sulfoxide ligand. No structural data were reported, and formulation of the complexes was based on elemental analysis and infrared data.[26,27]

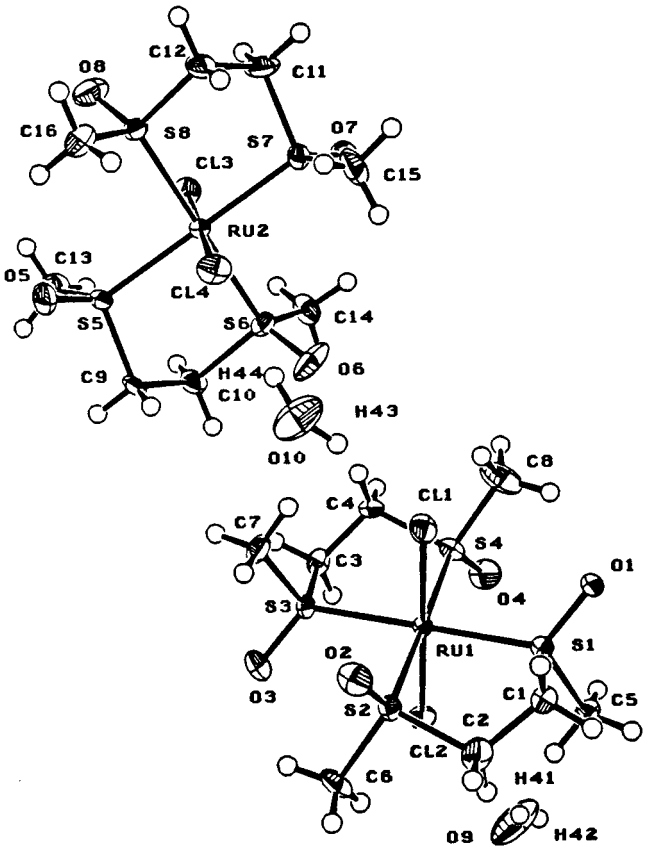

Figure 1. Molecular structure of *trans*-$RuCl_2(BMSE)_2$ (**1**), showing 50% probability thermal ellipsoids for the non-hydrogen atoms. The unit cell contains a water molecule H-bonded to chlorides of two molecules of the complex.

The structures of the four chelating sulfoxide complexes of ruthenium(II) reported here have the general formula $RuCl_2$(sulfoxide)$_2$ with solely S-bonded sulfoxides, and the compounds, which precipitated in nonpredictable *cis* or *trans* forms (Figures 1−4), are generally similar to one another. The complexes are air-stable in the solid state and in water for several hours, but over days decomposition occurs with precipitation of a black solid.

The infrared spectra show that the ν_{SO} values of the free sulfoxides increase upon coordination to Ru (1018 to 1109, 1019 to 1128, 1012 to 1128, and 1050 to 1085 cm^{-1} for complexes **1**−**4**, respectively) consistent with bonding via sulfur.[28] The solution ^1H NMR spectra of all four complexes in D_2O, CD_2Cl_2, or $CDCl_3$ generally reveal small downfield coordination shifts, again consistent with S-bonding;[28] no resonances due to free sulfoxide ligand or the more labile *O*-bonded sulfoxides were observed, again implying the presence of only *S*-bonded sulfoxides in the solution structures.[28]

The ^1H NMR spectra show that the solid-state *cis* or *trans* dichloro structures are retained in solution. In a *cis* structure, the two sets of methyl groups of the alkyl substituents are inequivalent; in a *trans* structure, the corresponding methyl groups are equivalent. The *trans*-**1** and -**3** complexes show a singlet at δ 3.25 and a triplet at δ 1.10, respectively, due to

(20) Moore, B. A.; Palcic, B.; Skarsgard, L. D. *Radiat. Res.* **1977**, *67*, 459.
(21) Alper, T. *Cellular Radiobiology*; Cambridge University Press: Cambridge, U. K., 1979.
(22) Boothman, D. A.; Bouvard, I.; Hughes, E. N. *Cancer Res.* **1989**, *49*, 2871.
(23) Hughes, E. N.; Engelsberg, B.; Billings, P. C. *J. Biol. Chem.* **1992**, *267*, 13520.
(24) (a) Hayes, J. J.; Scovell, W. M. *Biochem. Biophys. Acta* **1991**, *1088*, 413. (b) Scovell, W. M.; Muirhead, N.; Kroos, L. R. *Biochem. Biophys. Res. Commun.*, **1987**, *142*, 826. (c) Marples, B.; Adomat, H.; Skov, K. A.; Farrell, N. P. Unpublished results.
(25) (a) Marples, B.; Adomat, H.; Billings, P. C.; Farrell, N. P.; Koch, C. J.; Skov, K. A. *Anti-Cancer Drug Des.* **1994**, *9*, 389. (b) Billings, P. C.; Davis, R. J.; Engelsberg, B. N.; Skov, K. A.; Hughes, E. N. *Biochem. Biophys. Res. Commun.* **1992**, *188*, 1286.
(26) (a) Madan, S. K.; Hull, C. M.; Herman, L. J. *Inorg. Chem.* **1968**, *7*, 491. (b) Zipp, A. P.; Madan, S. K. *Inorg. Chim. Acta* **1977**, *22*, 49.
(27) Musgrave, T. R.; Kent, G. D. *J. Coord. Chem.* **1972**, *2*, 23.
(28) (a) Rochon, F. D.; Kong, P.; Girad, L. *Can. J. Chem.* **1986**, *64*, 1897. (b) James, B. R.; Morris, R. H. *Can. J. Chem.* **1980**, *58*, 399. (c) James, B. R.; Morris, R. H.; Reimer, K. J. *Can. J. Chem.* **1977**, *55*, 2353.

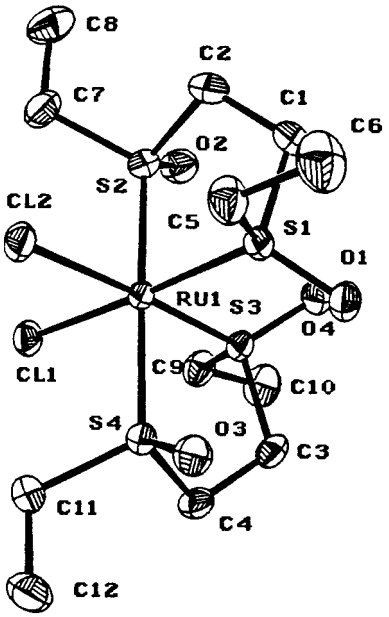

Figure 2. Molecular structure of *cis*-$RuCl_2(BESE)_2$ (**2**), showing 50% probability thermal ellipsoids for the non-hydrogen atoms.

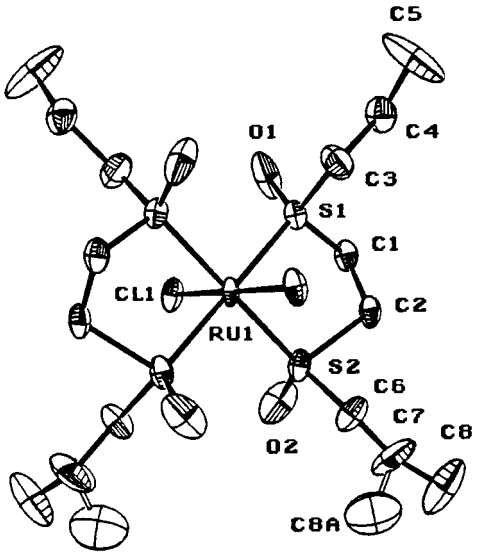

Figure 3. Molecular structure of *trans*-$RuCl_2(BPSE)_2$ (**3**), showing 50% probability thermal ellipsoids for the non-hydrogen atoms.

the methyl groups, while *cis*-**2** and -**4** each give two triplets at δ 1.36 and 1.55 and two singlets at δ 3.41 and 3.45, respectively.

In addition to the singlet due to the methyl group, the ^{1}H NMR of **1** has one other singlet at δ 3.85 assigned to the methylene groups of the coordinated ligand. The ^{1}H NMR spectrum of **2** in D_2O is more complex, and some of the assignments are somewhat tentative; as well as the two triplets, there is a complex series of overlapping multiplets in the region δ 3.3−4.1 due to the various methylene protons of the two inequivalent ligands. While it is not possible to differentiate between the peaks due to each ligand, selective decoupling experiments and a 2D COSY experiment were useful in determining if the peaks were due to the backbone methylenes or those in the ethyl chain. The triplet of doublets centered at δ 3.30 is due to two of the diastereomeric methylenes within the backbone of one ligand ($2 \times H_a$ or H_b), while the multiplet at δ 3.45 (which is simplified when the triplets at δ 1.36 or 1.55 due to the methyls are decoupled) is assigned to the methylenes of the ethyl group.

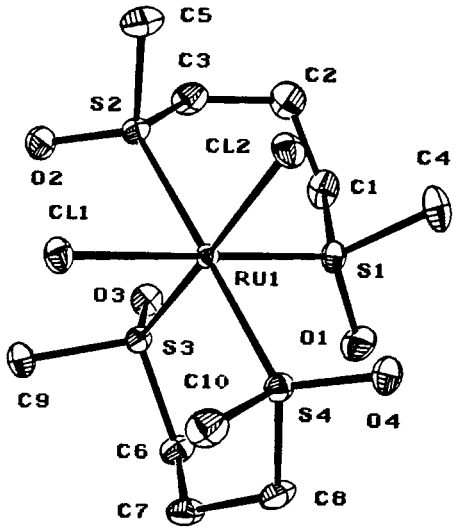

Figure 4. Molecular structure of *cis*-$RuCl_2(BMSP)_2$ (**4**), showing 50% probability thermal ellipsoids for the non-hydrogen atoms.

The multiplet centered at δ 3.67 is simplified by decoupling of the methyls and consists of two overlapping multiplets (δ 3.63 and 3.70) which are due to two backbone methylene protons and four protons from the ethyl groups, respectively. Similarly, the two overlapping multiplets, centered at δ 3.87 and 3.93, correspond to two protons each from the backbone methylenes of a ligand and the methylene of an ethyl group, respectively. The approximate doublet of triplets centered at δ 4.09 is assigned to two protons from the backbone of a ligand.

The ^{1}H NMR spectrum of complex **3** in CD_2Cl_2 indicates that the resonances of the bound ligand are generally shifted downfield (vs the free ligand) and that the protons become more inequivalent as expected for *S*-bonded sulfoxides.[29] The two sets of multiplets centered at around δ 2 and 3.5 have an integration ratio of 1:2. The multiplets at δ 3.5 are assigned to the two sets of methylenes (backbone and propyl chain) adjacent to the S atom, while the remaining set of multiplets centered at δ 2 is due to the β-protons in the propyl chain which, of some interest, become inequivalent upon coordination to the metal. The inequivalence of the α-protons (backbone carbons and propyl chain) increases as expected for *S*-bonded sulfoxides,[29] but the inequivalence within the β-protons is not usually detected.

For complex **4**, the resonance of the central methylene in the ligand backbone is shifted slightly upfield and split into two multiplets (δ 2.37 to 2.20 and 2.29) upon coordination. The methylenes adjacent to S, however, shift downfield and are also split into two multiplets found at δ 3.68 and 4.05, respectively. It is not clear why the central methylene shifts upfield even when the sulfoxide is *S*-bonded.

Conductivity data obtained for complexes **1**−**4** in fresh, aqueous solutions (Λ_M: 60.4, 33.9, 42.7, and 12.6, respectively) indicate that the complexes undergo some dissociation in aqueous solution which is probably due to replacement of the chloride by water; the Λ_M values were constant for several hours. No free sulfoxides were detected in D_2O using ^{1}H NMR.

All four complexes are essentially octahedral with *trans* angles ranging from 174.2 to 179.8° and *cis* angles ranging from 83.4 to 94.1°. Each molecular structure shows two bidentate sulfoxides coordinated exclusively through S; complexes **1** and **3** are *trans*, while **2** and **4** are *cis*. The chelating ligands in all

(29) Kitching, W.; Moore, C. J.; Doddrell, D. *Inorg. Chem.* **1970**, *9*, 541.

four structures have opposite chiralities at the two optically active S-atoms. The *trans* complexes are approximately (**1**) or exactly (**3**) centrosymmetric with mutually trans S-atoms having opposite configurations and are therefore nonchiral. The two *cis* complexes, **2** and **4**, have approximate C_2 symmetry with the pair of mutually trans S-atoms having the same chirality. The *cis* complexes are chiral, but in both cases the crystal structures contain equal numbers of the two isomers. Figures 2 and 4 both depict the Λ isomers in which the trans S-atoms both have the *S* configuration.

The Ru−Cl bond lengths (see Table 2) within the *cis* complexes are slightly longer than those within the *trans* complexes due to the stronger *trans* influence of S but are typical of those found in other Ru(II)−Cl complexes (e.g. 2.42 Å in the Ru(II)/Cl/DMSO systems).[2,7,30] The same pattern is seen with the Ru−S distances where the mutually *trans* bond distances in the *cis*-complexes are longer than those *trans* to Cl. These bond distances are again similar to those found in other Ru(II) complexes (e.g. the DMSO[2,7,30] and TMSO systems).[11,12]

The S−O bond lengths of the four complexes (see Table 2) fall in the range 1.45−1.49 Å and are comparable to those found in S-bonded DMSO[2,7,30] and TMSO.[11,12] In accordance with data for other *S*-bonded sulfoxides, these bond distances are probably shorter than those in the free ligand; no structural data for the free ligands have been found in the literature, but it is likely that the S−O bond distances within the free ligands are probably similar to those found in free DMSO[31] and TMSO[32] and are likely to be about 1.5−1.6 Å.

The C−S bond lengths and bond angles for the ligands within complexes **1**−**4** are similar to those found within free sulfoxides (e.g. DMSO,[31] TMSO,[32] and Ph_2SO[33]), indicating that the structures of the free sulfoxides are generally little changed by coordination. The structures of the coordinated ligand can probably be used as approximations for the structures of the free ligand. The average S−C−C_{ring} bond angle (109°) found within the coordinated ligands of **1**−**3** is that of tetrahedral carbon, indicating again that the geometry of these ligands is essentially unchanged upon coordination. In addition, the internal bond angles are typical of those found within five-membered rings such as cyclopentane (108°).

The average S−C−C (115.0°) and C−C−C (113.3°) bond angles found within the coordinated sulfoxide ligand in **4** are necessarily smaller than those expected for planar six-membered rings (120°) due to puckering of the ring, the deviation from typical tetrahedral angles being due to the ring strain effects. As expected, these angles are larger than those found within the five-membered rings formed with the $RS(O)(CH_2)_2S(O)R$ sulfoxides.

Of some interest, the unit cell for *trans*-$RuCl_2(BMSE)_2$ contains a water molecule hydrogen-bonded to two chlorides from two different molecules of the complex. The average H−Cl distance is 2.38 Å, which is 0.87 Å shorter than the sum of the van der Waals radii of Cl and O (3.25 Å) and is indicative of strong hydrogen bonding.[34] Previous crystal data reported for other Cl···H−O systems do not meet the requirements for strong hydrogen bonding.[35]

Biological Data. Preliminary investigations into the biological characteristics were carried out with aqueous solutions of these complexes *in vitro* in Chinese hamster ovary (CHO) cells. The results indicate that all 4 complexes accumulate in CHO cells but without hypoxic selectivity, not surprising in view of the lack of a "bioreducible" moiety—the use of the corresponding Ru(III) complexes would be of interest in this regard. The accumulations for **1** after a 4 h incubation time were 89 and 95 ng of Ru/10^6 cells for oxic (in air) and hypoxic (under N_2) conditions, respectively; corresponding numbers were 6 and 11 for **2**, 202 and 149 for **3**, and 17 and 11 for **4**. All nuclei samples were positive for Ru. For comparison, cisplatin produced 5 and 8 ng of Pt/10^6 cells after aerobic and hypoxic incubations, respectively. The DNA extracted from the cells also analyzed for the presence of Ru (expressed as ng of Ru/mg of DNA): For complexes **1**−**4,** the numbers were 1.34, 0.18, 0.10, and 0.11, respectively. The cell membranes and cytoplasm obtained from the lysis of whole CHO cells also showed the presence of Ru, although the relative proportions in the different cell components (proteins, cellular structures, etc.) were not determined. Thus the complexes do traverse the nuclear membrane and are bound to DNA and possibly nuclear components. The strength of the binding, indicated by the fact that the Ru remained attached to the DNA throughout the vigorous extraction procedure,[19] argues for the presence of a covalent interaction. [The amount of **3** associated with DNA (0.10 ng of Ru/mg of DNA) is surprisingly low in view of the fact that the complex accumulates the most in CHO cells (202 or 149 ng of Ru/10^6 cells) and causes damage which is the most recognized by HMG proteins (see below); the low Ru levels in this case could possibly result from removal of the complex during the isolation procedures.]

Experiments on protein recognition of DNA damage (DDAP) also indicate that complexes **1**−**4** all interact with DNA in some manner and that the interaction is recognized by the HMG nuclear proteins; the intensity of the protein band on the gel is related to the number of adducts formed with the DNA and the strength of the protein binding to the adduct and so can be used as a qualitative measure of the amount of complex present on the DNA. The intensities of the stains were "strong" for **1**, "medium" for **2**, "strong" for **3**, and "weak" for **4**, and on this basis, the *trans*-complexes **1** and **3** appear to bind more strongly to DNA than the *cis*-complexes **2** and **4**. The results indicate that the binding mode of the *trans*-Ru complexes may be finally "cisplatin-like" (e.g., cis interactions of the metal with two N-bases of DNA), even though the "precursor drugs" are of very different structures (octahedral Ru(II) and square-planar Pt(II)). Of note, the Trieste group has demonstrated that interaction of *trans*-$RuCl_2(DMSO)_4$ with DNA forms a "cisplatin-like" kink.[36] Although more studies are required to confirm these preliminary findings, they appear qualitatively consistent with the studies of the Trieste group.

The complexes were examined for their effects on clonogenic survival in both aerobic and hypoxic conditions. However, the plating efficiences remained indistinguishable from those in control experiments, for up to 4 h at the conditions tested: With and without 1.0 mM **4**, the PE values were in the range 0.4−0.5 in air and under N_2, and corresponding data for **1** (1.0 mM), **2** (0.05 mM), and **3** (0.05 mM) gave PE values in the ranges of 0.2−0.3, 0.2−0.4, and 0.2−0.3, respectively, with no significant hypoxic selectivity. Dose−response curves for **1** and **4** (up to 3 mM) and for **2** and **3** (limited by solubility to 0.7 mM) also revealed no toxicity even at the highest concentrations. Thus

(30) Mercer, A.; Trotter, J. *J. Chem. Soc., Dalton Trans.* **1975**, 2480.
(31) Thomas, R.; Shoemaker, C. B.; Eriks, K. *Acta Crystallogr.* **1966**, *21*, 12.
(32) Dodge, R.; Johnson, Q.; Selig, W. *Cryst. Struct. Commun.*, **1972**, *1*, 181.
(33) Abrahams, S. C. *Acta Crystallogr.* **1957**, *10*, 417.
(34) Elmsley, J. *Chem. Soc. Rev.* **1980**, *9*, 91.
(35) Clark, J. R. *Rev. Pure Appl. Chem.* **1963**, *13*, 50.
(36) Esposito, G.; Cauci, S.; Fogolari, F.; Alessio, E.; Scocchi, M.; Quadrifoglio, F.; Viglino, P. *Biochemistry* **1992**, *31*, 7094.

the complexes are nontoxic either in air or under N_2, despite their binding to DNA, while cisplatin does exhibit enhanced cytotoxicity in hypoxic CHO cells.[19]

The lack of toxicity of the Ru complexes is thus surprising; more definitive information on the relative binding modes of the Ru and Pt to the protein is needed. The interaction of HMG proteins to the Ru may be much weaker than to cisplatin which is strong,[25b] and in any case, factors other than binding to DNA may be responsible for toxicity.[19] The Trieste group suggest that the most probable binding site of *cis*-$RuCl_2(DMSO)_4$ to DNA is via the N-7 of guanine.[37] The *trans* species chelates via the N-7 and α-oxygen of a phosphate of 2′-deoxyguanosine monophosphate, while *cis*-coordination to two guanine N-7 atoms has also been demonstrated,[38] and this latter type is known for *cis*-Pt(II) complexes. The nature of the interaction of our *cis*- and *trans*-chelated sulfoxide complexes with purine and pyrimidine bases remains to be studied.

Acknowledgment. We thank the Natural Sciences and Engineering research Council of Canada and the Medical Research Council of Canada for financial support and Johnson Matthey Ltd. and Colonial Metals Inc. for the loan of $RuCl_3 \cdot 3H_2O$. Dr. B. Marples provided invaluable assistance with the DDAP assay, and H. Adomat with the accumulation and toxicity studies.

Supporting Information Available: Complete tables of crystallographic data, final atomic coordinates and equivalent isotropic parameters, hydrogen atom parameters, anisotropic thermal parameters, bond lengths, bond angles, torsion angles, intermolecular contacts, and least-square planes for **1**−**4** (20 pages). Ordering information is given on any current masthead page.

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(37) Cauci, S.; Alessio, E.; Mestroni, G.; Quadrifoglio, F. *Inorg. Chim. Acta* **1987**, *137*, 19.

(38) (a) Cauci, S.; Viglino, P.; Esposito, G.; Quadrifoglio, F. *J. Inorg. Biochem.* **1991**, *43*, 739. (b) Alessio, E.; Xu, Y.; Cauci, S.; Mestroni, G.; Quadrifoglio, F.; Viglino, P.; Marzilli, L. G. *J. Am. Chem. Soc.* **1989**, *111*, 7068.