Novel Ru^{III}-DMSO Complexes of the Antiherpes Drug Acyclovir

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Treatment of the anionic Ru^{III} precursor X[*trans*-$RuCl_4$(DMSO-*S*)$_2$] (X = protonated DMSO, Na^+, NH_4^+) and acyclovir (acv) in various solvents yields two new products *mer*-[$RuCl_3$(acv)(DMSO-*S*)(CH_3OH)]·0.5CH_3OH (**1**) and *mer*-[$RuCl_3$(acv)(DMSO-*S*)(H_2O)]·H_2O (**2**) in which hydrogen bonds between the acv purine oxygen and coordinated methanol or water, respectively, play an important role.

The antitumor properties of simple ruthenium(III) coordination compounds were discovered over 30 years ago,[1] and since then several tumor-inhibiting ruthenium complexes have been isolated and characterized,[2] with DMSO-ruthenium-N donor ligand ternary complexes being amongst the most promising. The typical example of the group, NAMI-A, [ImH] [*trans*-$RuCl_4$(DMSO-*S*)Im] (Im = imidazole), has already entered clinical phase I trials.[3] The main advantages of ruthenium-DMSO complexes are the selectivity for solid tumor metastases and the lack of significant host toxicity.

Acyclovir [9-(2-hydroxyethoxymethyl)guanine, acv] is a well-known antiviral drug used in clinical practice. The crystal structures of acv complexes with Cu,[4] Pt,[5] Ni, Co, Cd and Zn,[6] have appeared in the literature. It was found that the coordination of acv to the metal occurs in most cases through N(7) only, whereas O(6) is not directly involved in the bonding. The sole exception is [$Cu(acv)_2(H_2O)_2$](NO_3)$_2$, in which a pseudo-chelate N(7)/O(6) bonding of a purine to the metal was found.[4c]

Recently, the interactions of two Ru^{II}-DMSO precursors, *cis*- and *trans*-[$RuCl_2$(DMSO)$_4$], with acv were studied by NMR spectroscopy in aqueous solution. The authors proposed the formation of mono and bis adducts with N(7) as the preferred binding site.[7]

Our basic idea was to prepare an NAMI-A type compound of acv with the formula [*trans*-$RuCl_4$(acv)(DMSO-*S*)]$^-$. The main chemical feature of the Ru^{III} anionic precursor of NAMI-A type complexes, X[*trans*-$RuCl_4$(DMSO-*S*)$_2$] (X = protonated DMSO, Na^+, NH_4^+), is the facile dissociation of one of the two *trans* S-bonded DMSOs, attributed to the relatively large *trans* effect of this ligand.[8] The coordination position set free by DMSO is easily replaced by a nitrogen donor ligand (L) and through this synthetic procedure a wide class of derivatives with the general formula X[*trans*-$RuCl_4$(DMSO-*S*)L] (NAMI-A type complexes) have been prepared from acetone or DMSO/acetone mixtures. In these reactions it has never been observed that chloride ions were substituted; nevertheless, stepwise chloride hydrolysis occurs after dissolution of these products at physiological pH and it is thus relevant for their in vivo mechanism of action.

The generally poor solubility of acv limits the choice of solvents in which the reaction with the Ru^{III} precursor could be performed. Surprisingly, we realized that, regardless of the solvent used, coordination of acv trans to DMSO-S was always accompanied by replacement of one chloride with a molecule of a hydrogen bond donor, either H_2O (adventitious or solvent) or methanol (solvent), to give neutral species. In this paper we report the synthesis and solid-state structures of two Ru^{III}-DMSO complexes of acv:

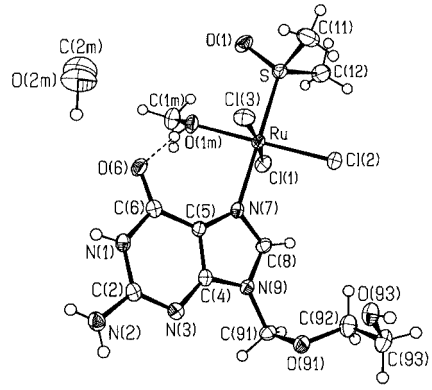

Figure 1. View of the asymmetric unit of **1**; selected bond lengths (Å): Ru−Cl(1) 2.309(2), Ru−Cl(2) 2.326(2), Ru−Cl(3) 2.362(2), Ru−S 2.270(2), Ru−O(1m) 2.072(6), Ru−N(7) 2.127(5), O(6)−C(6) 1.245(8)

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mer-[$RuCl_3$(acv)(DMSO-*S*)(CH_3OH)]·0.5CH_3OH (**1**) and *mer*-[$RuCl_3$(acv)(DMSO-*S*)(H_2O)]·H_2O (**2**), which provide a new insight into the reactivity of the [*trans*-$RuCl_4(DMSO)_2]^-$ precursor and, in particular, show the important role of H bonds in these reactions.

Treatment of X[*trans*-$RuCl_4$(DMSO-*S*)$_2$] with acv in methanol yielded brown-red crystals of **1**; when the same reaction was performed in water or various nondried solvents (such as ethanol, propanol, acetone/DMSO mixtures, nitromethane) crystals of **2** were isolated instead. The structures of compounds **1** and **2** were determined by X-ray diffraction analysis; the asymmetric unit and selected bond lengths for each compound are reported in Figure 1 and 2, respectively, and the crystallographic data in Table 1.

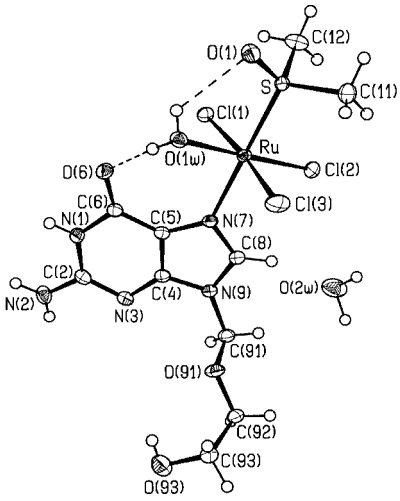

Figure 2. View of the asymmetric unit of **2**; selected bond lengths (Å): Ru−Cl(1) 2.3686(4), Ru−Cl(2) 2.3187(5), Ru−Cl(3) 2.3210(6), Ru−S 2.2677(5), Ru−O(1w) 2.077(1), Ru−N(7) 2.132(2), O(6)−C(6) 1.247(3)

In both complexes **1** and **2** the geometry about the Ru^{III} ion is distorted octahedral, as expected, with three chloride ions in a *mer*-configuration and DMSO (coordinated through S) *trans* to acv. An oxygen atom from methanol (in **1**) or water (in **2**) is additionally coordinated to ruthenium. The ruthenium-oxygen distances in both compounds are similar and are also similar to those found in the literature.[9] In both complexes one Ru−Cl bond is significantly longer than the remaining two since only that chloride ion is an acceptor of an intermolecular hydrogen bond. In **1**, Cl(3) is hydrogen bonded to an amino group of the symmetry related complex [contact distance N(2)···Cl(3) 3.298(6) Å], whereas in **2**, Cl(1) is hydrogen bonded to a noncoordinated water molecule [contact distance O(2w)···Cl(1) 3.291(2) Å] and to an amino group of the symmetry related complex [contact distance N(2)···Cl(1) 3.445(2) Å]. The shortening of the Ru−S bond in these complexes relative to the precursor (above 2.34 Å) has already been interpreted as being due to an increased π-back-bonding contribution from Ru^{III}.[8,10] All other bond lengths and angles in both compounds are also in an agreement with the corresponding data cited in the literature.[11]

Table 1. Crystallographic data for **1** and **2**

	1	**2**
Formula	$C_{11.5}H_{23}Cl_3N_5O_{5.5}RuS$	$C_{10}H_{21}Cl_3N_5O_6RuS$
Molecular weight	558.84	546.8
Crystal system	monoclinic	monoclinic
Space group	*C*2/*c*, No. 15	$P2_1/c$, No. 14
a (Å)	23.3032(4)	10.5096(1)
b (Å)	14.4930(3)	13.5455(1)
c (Å)	13.0879(3)	13.9131(1)
β (°)	110.7292(8)	104.331(1)
V (Å^3)	4134.07(15)	1919.00(3)
Z	8	4
Crystal size (mm)	0.20 × 0.10 × 0.03	0.32 × 0.30 × 0.25
Crystal description	plate	prism
Crystal colour	brown-red	brown-red
D_x (Mg m^{-3})	1.795	1.892
μ (mm^{-1})	1.283	1.381
T (K)	150(1)	150(1)
Wavelength (Å)	0.71073 (Mo-K_α)	0.71073 (Mo-K_α)
Data-collection mode	ω scans	ω scans
θ_{max} (°)	27.5	27.5
No. of integrated refl.	29217	36309
R_{int}	0.040	0.023
No. of unique refl.	4724	4393
No. of observed refl.	3948	4047
Threshold criterion	$F^2 > 2\sigma(F^2)$	$F^2 > 2\sigma(F^2)$
Final *R* and R_w	0.037, 0.034	0.026, 0.025
No. of contributing. refl.	4409	4211
No. of parameters	249	299
$(\Delta/\sigma)_{max}$	0.0005	0.004
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.98, −1.13	0.69, −1.20

Whereas the replacement of one DMSO-S molecule in the precursor with the N-donor ligand acv is to be expected, further replacement of one of the four chloride ions by the oxygen-bearing ligand is rare. We have tried to prevent the dissociation of the chloride ion from ruthenium by increasing the concentration of chloride in solution [by addition of $(CH_3)_4NCl$ or NaCl]. However one of the four chloride ions attached to ruthenium in the precursor was again substituted by water and the final product of this reaction was **2**. To date, syntheses performed in anhydrous solvents under inert atmosphere did not result in the isolation of the NAMI-A type acv analogue, which is another proof that such a reaction is not favourable in the case of acv.

Inspection of the crystal structures of both compounds suggests that the replacement of chloride with methanol (in **1**) or water (in **2**) is induced by the formation of intramolecular hydrogen bonds (marked with dashed lines in Figure 1 and 2). The oxygen atom O(6) from acv is hydrogen bonded to either coordinated methanol (**1**) or water (**2**). Both hydrogen bonds are strong: contact distance O(1m)···O(6) 2.517(7) Å in **1** and O(1w)···O(6) 2.573(2) Å in **2**. In **2**, the second hydrogen atom of water is additionally involved in hydrogen bonding to the oxygen atom of DMSO [contact distance O(1w)···O(1) 2.918(2) Å]. (In both structures there are additional intermolecular hydrogen bonds which are described in the CIF supplementary material deposited with the CCDC).

The neutral species **1** and **2**, which still maintain some solubility in aqueous solution, are thus good models for the first intermediate species that is expected to form upon stepwise chloride hydrolysis from NAMI-A type complexes in physiological solution. We are aware of only two examples where a similar chloride replacement was reported. The complex *mer*-[$RuCl_3(H_2O)$(DMSO-*S*)(dmtp)]·H_2O[12] was prepared by the dissolution of dmtpH[*trans*-$RuCl_4$(dmtp)(DMSO-*S*)] (dmtp = 5,7-dimethyl[1,2,4]triazolo[1,5-*a*] pyrimidine) in water, and strong hydrogen bonds between coordinated dmtp and coordinated water were also found in this case. Just recently it was reported that treatment of [$(dmso)_2H$][*trans*-$RuCl_4$(DMSO-*S*)$_2$] with 9-ethylguanine (9EtG) in methanol yielded *mer*-[$RuCl_3$(9EtG)(H_2O)(DMSO-*S*)] (**3**), in which the coordination sphere of ruthenium is very similar to that of **2**; the X-ray structure showed that the coordinated water molecule is involved in strong intramolecular hydrogen bonding with the oxygen atoms of guanine and DMSO-S.[13] The chemical difference between **3** and **2** is in the group bonded to N(9); instead of the ethyl group of **3** there is a 2-hydroxyethoxymethyl in **2** which, besides being bulkier, also acts as a donor and acceptor of intermolecular H bonds. Additionally, the crystals of **2** also contain noncoordinated water molecules and the consequence of this is that the packing of **3** and that of **2** are substantially different. In the structure of **3** there are N(1)−H···Cl(3) and N(2)−H···O(2) intermolecular H bonds, while in the structure of **2** intermolecular H bonds N(1)−H···O(1), N(2)−H···O(93), N(2)−H···Cl(1), O(93)−H···O(2w), O(2w)−H···N(3) and O(2w)−H···Cl(1) are present. Furthermore, in **3** the stacking of guanine residues was not observed. In contrast, in the structures of **1** and **2** we have observed pairs of symmetry-related acv residues for which the planes through their aromatic rings are nearly parallel. The distances between such planes are 3.25 Å in **1** and 3.50 Å in **2**, so the interactions between π electronic systems are possible.

The IR spectra of compounds **1** and **2** are very similar. In free acv the carbonyl stretching band is found at 1715 cm^{-1} whereas the bending frequency of the amino group falls at 1631 cm^{-1}.[4] Four bands are found in the spectra of both complexes in the range 1657−1630 cm^{-1}. According to the crystal structures, we assume that these absorptions can be ascribed to the stretching of the hydrogen bonded carbonyl group and to the bending of the hydrogen bonded amino group. A similar trend was previously observed in other N(7) metal-bonded complexes of acv.[4a,6]

The UV/Vis spectra of **1** and **2** were assigned according to the data of similar complexes reported in the literature.[8,12,14] The highest energy band found at 278 nm in both complexes was attributed to π-π* transitions of the ligand,[14] whereas the remaining absorptions are typical charge-transfer bands from three chlorides in a *mer*-geometry on Ru^{III}.[15]

Experiments to assess the possible cytotoxic and antiviral activity of compounds **1** and **2** are currently being planned in collaboration with other groups.

Experimental Section

***mer*-[$RuCl_3$(acv)(DMSO-*S*)(CH_3OH)]·$0.5CH_3OH$ (1):** X[*trans*-$RuCl_4$(DMSO-*S*)$_2$] (0.235 mmol) was dissolved in absolute methanol (30.0 mL) and acv (0.235 mmol) was added whilst stirring. The solution was heated at 50 °C until all acv had dissolved. The colour of the solution changed from orange to brown-yellow. Brown-red crystals appeared in the solution after one day of isothermal evaporation of the solvent in air (0.0723 g, 55.2% yield). The crystals were filtered off, washed with diethyl ether and dried in air. $C_{11.5}H_{23}Cl_3N_5O_{5.5}RuS$ (558.8): calcd. C 24.71, H 4.15, N 12.53; found C 24.61, H 4.08, N 12.59. Selected IR bands (Nujol): $\tilde{\nu}$ = 1657 cm^{-1} (s, sh), 1650 (s, sh), 1640 (vs), 1634 (vs), 1608 (s); 1082 (m, S=O for DMSO-*S*); 423 (w, Ru−*S*). UV (methanol): λ_{max} (ε) = 278 nm (6889 $dm^3 \cdot mol^{-1} \cdot cm^{-1}$), 374 (3256), 438 (1124).

***mer*-[$RuCl_3$(acv)(DMSO-*S*)(H_2O)]·H_2O (2):** This complex was prepared from several solvents following similar reaction procedures. Initially it was prepared from aqueous solution: X[*trans*-$RuCl_4$(DMSO-*S*)$_2$] (0.235 mmol) was dissolved in distilled water (30.0 mL) and acv (0.235 mmol) was added. The mixture was stirred for two hours until all the acv had dissolved. The colour of the solution changed from orange to dark green. After three days the precipitation of free acv and of a very small amount of brown-red crystals of the product occurred from the solution. These crystals were filtered off, washed with diethyl ether and dried in air. It was later found that the yield was much higher if ethanol was used as solvent (the same procedure as for compound **1**, yield 43.5%). It was also realized that this product can be isolated from many other nondried solvents such as propanol, acetone/DMSO mixtures, nitromethane. $C_{10}H_{21}Cl_3N_5O_6RuS$ (546.8): calcd. C 21.97, H 3.87, N 12.80; found C 22.27, H 3.60, N 12.63. Selected IR bands

(Nujol): $\tilde{\nu}$ = 1657 cm^{-1} (s, sh), 1650 (s, sh), 1640 (vs), 1633 (vs), 1602 (s); 1081 (m, S=O for DMSO-*S*); 426 (w, Ru−S). UV (methanol): λ_{max} (ε) = 278 nm (7182 $dm^3 \cdot mol^{-1} \cdot cm^{-1}$), 376 (3346), 438 (1138).

X-ray Crystallographic Study: X-ray diffraction data for compounds **1** and **2** were collected on a Nonius Kappa CCD diffractometer using graphite monochromated Mo-K_α radiation. Data were processed using DENZO-SMN program.[16] Both structures were solved by direct methods using SIR-97.[17] The positions of the hydrogen atoms were obtained from the difference Fourier map. Atom C(2m) from the noncoordinated methanol molecule in **1** lies on a twofold axis. The positions of three hydrogen atoms bonded to C(2m) were not determined. For both compounds we employed full-matrix least-squares refinement on *F* with anisotropic displacement factors for all non-hydrogen atoms using the Xtal3.4 program.[18] All observed and those "less than" reflections for which F_c was greater than F_0 were included in the final refinement. The hydrogen atom parameters of **1** were not refined. In the case of **2** only the coordinates of hydrogen atoms were refined while their displacement parameters were not. The resulting crystal data and details concerning data collection and refinement for both compounds are quoted in Table 1. ORTEP[19] was used for the preparation of the figures.

CCDC-178936 and CCDC-178937 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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