Scientific paper

Crystal Structure of Ionic Compound Between Antiviral Drug Acyclovir and Complex Ruthenate(II)

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Dedicated to the memory of Professor Ljubo Golič

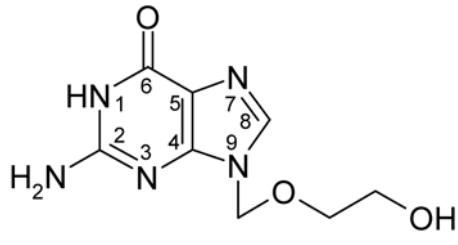
Abstract

Novel compound, (acvH)[trans-$RuCl_4$(dmso-O)NO] (**1**) (dmso-O is dimethylsulfoxide coordinated through oxygen atom), was isolated from the reaction between antiviral drug acyclovir (acv) and ruthenium precursor ($(dmso)_2$H)[trans-$RuCl_4$(dmso-O)NO] (**2**). Crystal structure revealed that compound **1** is of ionic type, containing N(7) protonated acyclovir (acvH) which is not coordinated to the metal center. There is a distorted octahedral coordination around ruthenium(II) center in **1**. Four chlorido ligands are lying in a plane, whereas dmso molecule and nitrosyl group (coordinated through nitrogen atom) are bonded in trans axial positions. In spite the fact that acv (which is nucleoside analogue) is protonated, a glycoside bond between N(9) and side chain remained intact.

Keywords: Bioinorganic chemistry; nucleoside analogues; acyclovir; ruthenium complexes; nitrosyl; X-ray diffraction

1. Introduction

A purine family member, acyclovir (9-(2-hydroxyethoxymethyl)guanine, acv) is a well known, clinically used antiviral drug (Scheme).[1] We have previously studied the interactions of purines and metal ions (copper(II), ruthenium(III)) and structurally characterized a range of metal complexes.[2–8] It is known that nitrogen atom N(9) is the most probable site of coordination in purines but when N(9) is blocked, N(7) is the site of coordination and there are only few exceptions that violate these general guidelines.[9] In acv an acyclic chain is bonded to N(9) and coordination to the metal occurs in most cases through N(7). Oxygen atom O(6) is not directly involved in the bonding but it normally participates in hydrogen bonds to small molecule (e.g. water) that is coordinated to the metal. 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.[4]



Scheme acv

The antitumor properties of ruthenium complexes have been discovered over 30 years ago.[10–12] Phase I. clinical trials have recently been completed for ruthenium compound NAMI-A, [ImH] [trans-$RuCl_4$(dmso-S)Im] (Im= imidazole) and also for KP 1019 ((IndH)trans-[Ru $Cl_4(Ind)_2$] (Ind=Indazole).[13–15] This is an important step before compound is finally approved as an official drug.

Nitric oxide has many important biological functions and amongst other it was also discovered that it is involved in a key step in the formation of metastases.[16] Ruthenium has high affinity for NO and can in one hand act as NO scavenger but on the other hand, ruthenium nitrosyl complexes are studied as controlled NO-releasing agents.[17] These properties are interesting for medical applications- therefore ruthenium nitrosyl complexes are studied also as potential anticancer agents.[18]

In this paper we describe the synthesis and structure determination of a new ruthenium(II) complex, (acvH)[trans-$RuCl_4$(dmso-O)NO] (**1**) that contains an unusual, protonated form of acyclovir.

2. Experimental

2. 1. Synthesis

A ruthenium precursor ($(dmso)_2H$)(trans-[$RuCl_4$(dmso-O)NO] (**2**) was prepared as reported elsewhere.[19–20] Compound **2** (0.0515 g, 0.101 mmol) was dissolved in 30.0 mL of ethanol. Addition of acv (0.0228 g, 0.101 mmol) to the clear violet solution resulted in the formation of suspension that was refluxed for two hours (pH 4). After few days pink needle like crystals suitable for X-ray determination have grown from clear solution. FTIR (cm^{-1} (selected vibrations), Nujol; m-medium, s-strong, v-very): ν_{NO}1873 (vs), $\nu_{C=O}$ 1687 (s) (acv), ν_{SO} 911 (m) (dmso-O), $\nu_{Ru–Cl}$ 330 (s).

2. 2. Analyses

Infrared spectroscopy

Infrared spectrum (Nujol) was recorded on a Perkin-Elmer FT-1720X spectrometer.

2. 3. X-Ray Structure Analysis

X-ray diffraction data for compound **1** were collected on a Nonius Kappa CCD diffractometer at 20(1) °C using graphite monochromated Mo$K\alpha$ radiation. They were processed using DENZO program.[21] The structure was solved by direct methods using SIR97.[22] A full-matrix least-squares refinement on F magnitudes with anisotropic displacement factors for all non-hydrogen atoms using Xtal3.4 was employed.[23] The positions of hydrogen atoms were obtained from the difference Fourier map. The exceptions were hydrogen atoms attached to Csp^3 atoms in the acyclic group from the acvH cation, whose positions were calculated. The parameters of hydrogen atoms were not refined. The end of acyclic group from the acvH cation is disordered (C(92), C(93) and (O93) atoms), which can be seen from the relatively large displacement parameters of these atoms and corresponding bond distances $O(sp^3)$-$C(sp^3)$ and $C(sp^3)$-$C(sp^3)$ which deviate from expected values (see Discussion section). There is also the largest maximum (3.03 e/Å^3) in the final difference Fourier map (1.326(4), 1.534(4) and 1.691(5) Å away from C(91), O(91) and C(92), respectively). Otherwise the structure refinement was successful- in the final cycle of the refinement we used 4327 reflections (included were those "less than" reflections for which F_C was larger than F_O) and 244 parameters and obtained R and R_w values of 0.049 and 0.038, respectively. The resulting crystal data and details concerning data collection and refinement are quoted in Table 1. The crystallographic data for the title compound have also been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition number: CCDC 685725. Copies of the data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/const/retrieving.html

Table 1. Crystal data, data collection and structure refinement of **1**.

Formula	$C_{10}H_{18}Cl_4N_6O_5RuS$
Relative formula weight	577.24
Crystal System	Triclinic
Space group	*P-1*, No. 2
a (Å)	9.4743(2)
b (Å)	10.8443(2)
c (Å)	10.8913(2)
α (°)	96.7270(10)
β (°)	112.7750(10)
γ (°)	93.2780(10)
V (Å^3)	1018.20(4)
Z	2
ρ (Mg m^{-3})	1.883
μ (mm^{-1})	1.432
Color and shape of crystal	Pink needle
Dimensions (mm)	$0.35 \times 0.07 \times 0.02$
T (K)	293(1)
Diffractometer	Nonius Kappa CCD
Type of radiation	MoKα
γ(Å)	0.71073
θ_{max} (°)	27.45
Type of scan	φ and ω
No. of integrated reflections	17567
No. of independent reflections	4622
R_{int}	0.037
No. of observed reflections	3826
Cut-off criterion	$F^2 > 2.0\sigma(F^2)$
No. of contributed reflections	4327
No. of parameters	244
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	3.03,–1.60
$(\Delta/\rho)_{max}$	0.00003
Final R and R_w	0.049, 0.038

3. Results and Discussion

3. 1. Synthesis

In contrast to our previous reactions between acv and ruthenium precursors acv has not coordinated to ruthenium but only exchange of cations (protonated dmso and protonated acyclovir (acvH)) occurred.[7–8] We have realized before that the most common coordination of metal to N(7) atom of acv takes place around neutral conditions. In all such complexes acyclic side chain of acv was not affected after coordination. Not surprisingly, in highly acidic medium hydrolysis of glycosidic bond occurred which was followed by coordination of metal to N(9) of guaninium ion (guaH) protonated at N(7). A typical example of this effect is formation of [trans-$RuCl_4$(guaH)(dmso-S)]·$2H_2O$.[7]

Solution from which title complex crystals have grown was slightly acidic (pH 4) and was obviously not acidic enough that hydrolysis of glycosidic bond was taking place. Acyclovir was protonated at N(7) but acyclic chain remains bonded to N(9) which was not observed for acv before. However, similar observation was also found with some other nucleobase ligands.[24]

3. 2. Description of the Structure of Compound 1

The crystal structure of compound **1** is of ionic type. The asymmetric unit, which is presented in ORTEP[25] Figure 1, consists of protonated, non-coordinated acyclovir and $[RuCl_4(dmso\text{-}O)(NO)]^-$ complex anion. This is the first example of the crystal structure containing protonated form of acyclovir, while there is already known structure containing $[RuCl_4(dmso\text{-}O)(NO)]^-$ anion, with $[(dmso)_2H]^+$ cation in **2**.[19] Hydrogen bonding represents the main difference between these two structures. In compound **1** complex anion is hydrogen bonded through three different intermolecular hydrogen bonds to acvH cations (Figure 2), while in **2** hydrogen bonds are present only within $((dmso)_2H)^+$ cations. In both compounds, Ru(II) is approximately octahedraly coordinated by four chlorido ligands lying in a plane, whereas dmso molecule (coordinated through oxygen atom) and nitrosyl group (coordinated through nitrogen atom) are bonded in trans axial positions. This is in agreement with the fact that in ruthenium complexes a strong -acceptor ligand (like NO) favors coordination through oxygen for opposing dmso ligand.[19] In compound **1** Ru is displaced by 0.118(1) Å from the equatorial mean plane toward nitrosyl group. Bond lengths in **1** (Table 2), Ru–N(11) (1.718(3) Å) and N(11)–O(11) (1.139(5) Å) are similar to the corresponding bond lengths (1.712(5) and 1.134(5) Å) in **2** and to the values in other ruthenium nitrosyl complexes, which is in an agreement with strong $d_{\pi\rightarrow\pi^*}$ NO back-bonding.[19, 26] NO is a highly reactive radical and can coordinate also as nitrosyl cation as present in **2** and also **1**.[19,27] This ligand can form complexes with linear metal–N–O group (angle 165–180°) or bent metal–N–O group (angle 120–140°).[27] In title compound **1** the angle Ru–N (11)–O(11) is close to the linear (176.7(3)°). The stereochemistry of bonded dmso ligand in compound **1** is also similar to the related complex, where S atom is oriented toward the midpoint of chlorines Cl(1) and Cl(3).[19] The fact that three chlorine atoms (Cl(1), Cl(2) and Cl(4)) are acceptors of N–H…Cl hydrogen bonds, donated by acvH cations results in slightly longer Ru–Cl distances (2.3707(8), 2.3701(9) and 2.3857(10) Å) for this chlorine atoms in comparison to Cl(3) atom which is not involved in hydrogen bonding (Ru–Cl(3)= 2.3640(9) Å). Hydrogen bonding geometry is given in Table 3. Each acvH cation, which is protonated at N(7) (the usual site of coordination of acv), is a donor of four intermolecular hydrogen bonds. It is hydrogen bonded through H atom of N(1) and one of two H atoms of amino group to one complex anion and through the other of the two H atoms of amino group to another complex anion. N(7) atom is a donor of intermolecular hydrogen bond (through its H atom) to the O(6) atom of neighboring, symmetry related (-x,1-y,2-z) acvH cation. The crystal packing is additionally stabilized by π...π and π...σ interactions among parallel, symmetry related (*1-x,1-y,2-z*) six membered heteroaromatic rings (N(1), C(2), N(3),

Table 2. Bond distances (Å) and bond angles (°) with e.s.d.'s in parentheses in **1**.

Ru–N11	1.718(3)	N1–C6	1.386(5)
Ru–Cl3	2.3640(9)	N1–C2	1.364(4)
Ru–Cl1	2.3707(8)	N2–C2	1.340(5)
Ru–Cl2	2.3701(9)	N3–C4	1.341(4)
Ru–Cl4	2.3857(10)	N3–C2	1.326(4)
Ru–O1	2.043(2)	N7–C8	1.316(5)
S–O1	1.554(3)	N7–C5	1.377(5)
S–C12	1.783(5)	N9–C91	1.465(5)
S–C11	1.779(4)	N9–C8	1.344(5)
O6–C6	1.242(5)	N9–C4	1.385(4)
O91–C91	1.445(5)	C4–C5	1.374(5)
O91–C92	1.364(7)	C5–C6	1.419(5)
O93–C93	1.506(9)	C92–C93	1.475(9)
O11–N11	1.139(5)		
Cl2–Ru–N11	92.95(10)	C5–N7–C8	107.6(3)
Cl3–Ru–Cl4	173.51(3)	C4–N9–C8	107.6(3)
Cl3–Ru–O1	86.95(9)	C4–N9–C91	126.6(3)
Cl3–Ru–N11	95.16(11)	C8–N9–C91	125.4(3)
Cl4–Ru–O1	86.60(9)	Ru–N11–O11	176.7(3)
Cl4–Ru–N11	91.31(11)	N2–C2–N3	118.7(3)
O1–Ru–N11	177.80(14)	N1–C2–N2	117.4(3)
Cl2–Ru–Cl4	90.88(3)	N1–C2–N3	123.9(3)
Cl1–Ru–Cl2	175.07(3)	N9–C4–C5	106.1(3)
Cl1–Ru–Cl3	89.91(3)	N3–C4–C5	128.5(3)
Cl1–Ru–Cl4	89.23(3)	N3–C4–N9	125.4(3)
Cl1–Ru–O1	88.68(9)	N7–C5–C6	132.7(4)
Cl1–Ru–N11	91.97(10)	C4–C5–C6	119.0(3)
Cl2–Ru–Cl3	89.43(3)	N7–C5–C4	108.2(3)
Cl2–Ru–O1	86.41(9)	O6–C6–C5	128.4(3)
O1–S–C11	102.74(19)	N1–C6–C5	111.3(3)
O1–S–C12	103.05(19)	O6–C6–N1	120.4(3)
C11–S–C12	99.3(2)	N7–C8–N9	110.6(3)
C91–O91–C92	115.4(4)	O91–C91–N9	109.3(3)
Ru–O1–S	121.92(17)	O91–C92–C93	124.0(5)
C2–N1–C6	125.2(3)	O93–C93–C92	102.1(5)
C2–N3–C4	111.9(3)		

Table 3. Hydrogen bond contact distances D...A (Å) and D–H...A angles(°) in **1**.

Donor (D)	Acceptor (A)	D...A	D–H...A
N1	$Cl1^{(x,1+y,z)}$	3.200(3)	169
N2	$Cl2^{(1-x,-y,1-z)}$	3.354(4)	167
N2	$Cl4^{(x,1+y,z)}$	3.352(4)	158
N7	$O6^{(-x,1-y,2-z)}$	2.646(5)	161

C(4), C(5) and C(6)) of acvH cations. Distance among ring centroids is 3.716(2) Å. The normal of ring planes has a direction (3.7, 5.5, 5.0) in fractional units. The angle between centroid vector and normal to ring plane is 27.11°.

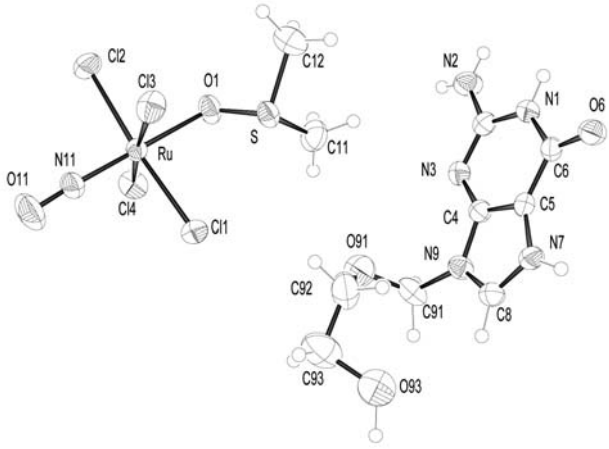


Figure 1. ORTEP view of the asymmetric unit of compound **1** with labeling of nonhydrogen atoms.[25] (Ellipsoids are drawn at 50% probability level.)

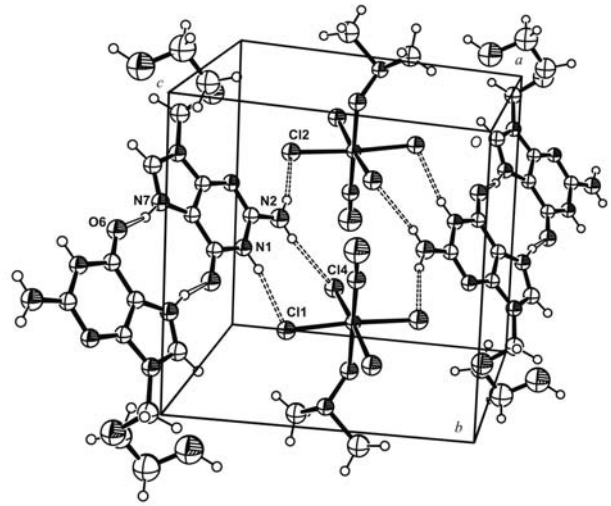


Figure 2. ORTEP view of crystal packing of compound **1**. Dashed lines represent hydrogen bonds.[25]

Bond lengths and angles within the acvH aromatic rings are close to the values in the molecule of free acv and those in ruthenium acv complexes.[7–8, 28] As in all structures containing acv the acyclic group is turned completely out of plane of aromatic rings (always roughly at right angle). Similarly to the complex of acv and Pt(II) the end of acyclic group (C(92), C(93) and (O93) atoms) is slightly disordered which is reflected also in bond lengths O(91)-C(92) 1.364(7), O(93)-C(93) 1.506(9) and C(92)-C(93) 1.475(9)Å which deviate from the expected values $C(sp^3)$-O 1.426(19) and $C(sp^3)$-$C(sp^3)$ 1.530(15), respectively.[29–30]

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Povzetek

Sintetizirali smo novo spojino, (acvH)[trans-$RuCl_4$(dmso-O)NO] (**1**) (dmso-O je oznaka molekule dimetilsulfoksida koordiniranega preko kisikovega atoma), ki je nastala pri reakciji med protivirusnim zdravilom acyclovirjem (acv) in rutenijevim prekurzorjem ($(dmso)_2$H)[trans-$RuCl_4$(dmso-O)NO] (**2**). Kristalna struktura je razkrila, da je spojina **1** ionska in vsebuje na N(7) atomu protonirano molekulo acyclovirja (acvH), ki se ni koordinirala na kovinski center. V spojini **1** je okrog rutenijevega(II) centra popačena oktaedrična razporeditev ligandov. Štirje klorido ligandi ležijo v ravnini, medtem ko sta molekula dmso in nitrozilna skupina (koordinirana preko dušikovega atoma) vezani v trans aksialnih legah. Čeprav je molekula acv (ki je nukleozidni analog) protonirana, je ostala glikozidna vez med N(9) in stransko verigo nespremenjena.