# Synthesis and NMR Studies of Ruthenium(II) Mercaptopurine Riboside Complexes. X-Ray Structure of Bis(9-β-D-ribofuranosyl-6-mercaptopurine)bis-(triphenylphosphine)ruthenium(II) Chloride

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The first X-ray structure of a ruthenium-nucleoside compound and the first structure of a 6-mercaptopurine riboside complex with any metal was obtained with one of several $Ru^{II}$-6-mercaptopurine nucleoside complexes prepared from $[Ru^{II}Cl_2(PPh_3)_3]$; namely, bis(9-β-D-ribofuranosyl-6-mercaptopurine)bis(triphenylphosphine)ruthenium(II) chloride ($C_{56}H_{59.5}Cl_2N_8O_{10.75}P_2RuS_2$).

The synthesis and structural characterization of platinum group metal complexes containing nucleobases are important in view of the anticancer and antibacterial activity exhibited by some $Pt^{II}$, $Ru^{II}$, $Rh^{II}$ and $Rh^{III}$ compounds (for a brief survey see Refs. 1 and 2). Such activity is usually associated with direct attack of the metal species on DNA nucleobases, which leads in many cases to C(2′)-*endo* to C(3′)-*endo*[3] or, rarely, *anti* to *syn*[4] conformational changes. Furthermore, $Ru^{II}$ and $Rh^{III}$ complexes are valuable probes in investigating nucleic acid structures.[5]

$H_2MP$ (6-mercaptopurine) and some of its analogues are of particular interest as ligands since they are themselves active against some types of human cancers.[6] On the other hand, it must be noted that, of the building blocks of nucleic acids, nucleobases and nucleoside monophosphates form complexes which crystallize more readily when compared with nucleoside complexes. Crystal structures of approximately 80 metal-nucleotide complexes have appeared, whereas fewer than 20 metal-nucleoside species have been characterized with single crystal X-ray diffraction (Ref. 7). Crystalline metal-nucleoside compounds reported usually contain $Pt^{II}$, $Pd^{II}$ or $Hg^{II}$ ions, and, less frequently contain first row transition metal ions.[7] Although after $Pt^{II}$, $Ru^{II}/Ru^{III}$ species offer the most promise as anticancer drugs,[8] no $Ru^{II}$-nucleoside or -nucleotide crystal structures have been reported to our knowledge.

Since the anticancer, antimetastatic agents *cis*- and *trans*-

$[RuCl_2(Me_2SO)_4]$ probably target DNA with preferential attack at purine bases (namely guanines) both *in vivo* and *in vitro*, $Ru^{II}$-nucleoside complexes are of considerable interest.[2,8] Here, we report the preparation and characterization of $[Ru^{II}(HMPR)_2(PPh_3)_2]Cl_2 \cdot 2.75\ H_2O$ **1** and $[Ru^{II}(HMGUO)_2(PPh_3)_2]Cl_2 \cdot 3H_2O$ **2** (HMGUO = 6-mercaptoguanosine, HMPR = 9-β-D-ribofuranosyl-6-mercaptopurine). The most important features of the crystal and molecular structure of **1** are also reported. A mixture of $[Ru^{II}Cl_2(PPh_3)_3]$ (1 mmol) and the nucleoside (2 mmol) in refluxing EtOH (20 $cm^3$) under dry $N_2$ afforded golden-yellow crystalline powders on cooling to room temp. The crude products were recrystallized twice from EtOH. Yield, 60%. The compounds are stable in air at room temp. in both the solid and solution (EtOH) phases. Single crystals (triangle-shaped prisms) of **1** were obtained from ethanol.

The crystal lattice of **1**† contains two independent complex cations, uncoordinated water molecules and chloride ions. The structures of the cations (Fig. 1) are very similar; the metal centres in both have a pseudo-octahedral geometry. The coordination spheres consist of two *cis* $PPh_3$ ligands and of two thiopurines chelated through S(6) and N(7). The S donors are *trans* to each other, whereas the N donors are *trans* to the P atoms. As a consequence, the two nucleoside moieties of each complex molecule are chemically equivalent (pseudo-$C_2$ symmetry axis bisecting the P–Ru–P, S–Ru–S and N–Ru–N bond angles).

No interaction exists between the metal centres and the N(1) or N(3) atoms. The four purine (PU) systems do not show any large deviations from planarity. The C–S bond distances average 1.69(2) Å, in agreement with a high percentage of double-bond character of C=S and with protonation of N(1). The values of the C(2)–N(1)–C(6) bond angles [average 122(2)°] are also in agreement with a N(1) protonated atom, on the basis of the Singh rule.[11]

The conformation of the ribose group can be described[12] as C(2′)-*endo*, C(2′)-*endo*, C(2′)-*endo*, C(2′)-*endo*/C(3′)-*exo*, for R(1) (R = ribose), R(2), R(3) and R(4), respectively. The conformation around C(4′)–C(5′) can be described[12] as +*sc* for $\gamma_{OC}$ [O(5′)–C(5′)–C(4′)–C(3′); 60(4), 48(4), 63(4), and 56(4)°]. The R(1) and R(3) groups show statistical disorder around the C(4′)–C(5′) axis. Two distinct positions for O(5′) have been refined. From the second set of coordinates for O(5R1) [namely O(5R1B)] and O(5R3) [namely O(5R3B)], the conformation around C(4′)-C(5′) can be described[12] as -*ac* [$\gamma_{OC} = -113(6)°$] and-*ac*/-*sc* [$\gamma_{OC} = -91(5)°$], respectively.

The conformation of the glycosidic bond χ[C(4)–N(9)–C(1′)–O(4′)] is *anti* for the four ribose moieties [−134(3), −111(2), −138(3), −110(2)° for R(1), R(2), R(3) and R(4), respectively]. This finding is in contrast to the *syn* conformation shown by the two independent molecules of the orthorhombic lattice of the free HMPR nucleoside.[13]

Intramolecular stacking interactions involve PU and Ph rings. No appreciable intermolecular PU···PU or PU···Ph stacking interaction could be detected. Chloride ions and water molecules present in the lattice are not directly linked to the metal centre but are involved in the network of H-bonds.

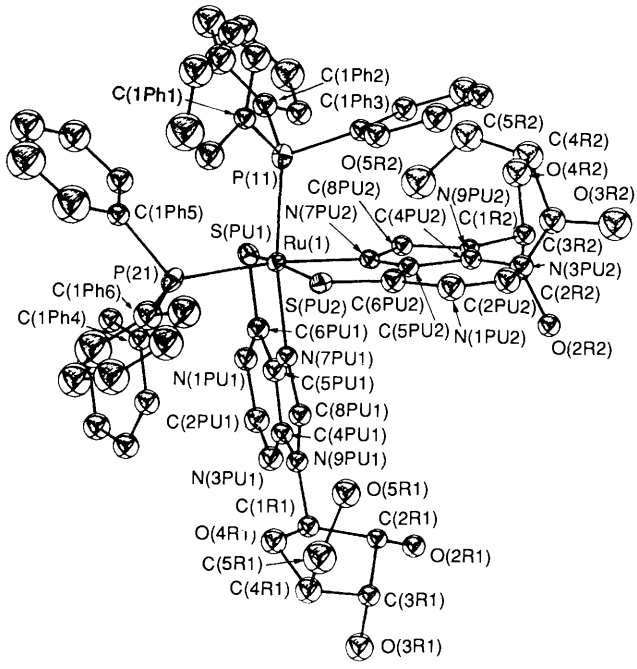


**Fig. 1** ORTEP drawing of one of the complex cations found in the asymmetric unit of **1**. Ellipsoids enclose 30% probability. The labelling scheme of the coordination sphere and the nucleoside atoms is also reported. Selected bond distances for the two complex molecules of the asymmetric unit (Å): Ru(1)–S(PU1) 2.440(8), Ru(1)–S(PU2) 2.424(8), Ru(1)–N(7PU1) 2.10(2), Ru(1)–N(7PU2) 2.11(1), Ru(1)–P(11) 2.337(9), Ru(1)–P(21) 2.336(6), Ru(2)–S(PU3) 2.404(7), Ru(2)–S(PU4) 2.431(8), Ru(2)–N(7PU3) 2.16(2), Ru(2)–N(7PU4) 2.17(2), Ru(2)–P(12) 2.343(6), Ru(2)–P(22) 2.347(9). Selected bond angles (°): S(PU1)–Ru(1)–S(PU2) 168.6(3), S(PU1)–Ru(1)–N(7PU1) 84.5(6), S(PU1)–Ru(1)–N(7PU2) 87.8(6), S(PU1)–Ru(1)–P(11) 96.5(3), S(PU1)–Ru(1)–P(21) 89.2(3), S(PU2)–Ru(1)–N(7PU1) 87.4(6), S(PU2)–Ru(1)–N(7PU2) 83.3(6), S(PU2)–Ru(1)–P(11) 90.3(3), S(PU2)–Ru(1)–P(21) 98.6(3), S(PU3)–Ru(2)–S(PU4) 167.9(3), S(PU3)–Ru(2)–N(7PU3) 83.2(6), S(PU3)–Ru(2)–N(7PU4) 85.5(6), S(PU3)–Ru(2)–P(12) 96.2(2), S(PU3)–Ru(2)–P(22) 89.2(3), S(PU4)–Ru(2)–N(7PU3) 88.7(6), S(PU4)–Ru(2)–N(7PU4) 84.6(6), S(PU4)–Ru(2)–P(12) 90.2(2), S(PU4)–Ru(2)–P(22) 99.6(3).

The $^1H$ NMR spectrum of **1** in $(CD_3)_2SO$ has signals at δ 8.92 [H(8)], 8.45 and 8.47 [H(2)], and 5.76 and 5.64 [H(1′)]. The respective signals for the free HMPR ligand occur at δ 8.56, 8.23, and 5.90. The $^{31}P$ NMR spectrum of **1** shows two peaks at δ 41.82 and 41.55, whereas that of a solution of the HMPR and $PPh_3$ ligands has a signal at δ −9.2. The NMR data suggest the presence of $C_2$ diastereoisomers in a *ca.* 1 : 1 molar ratio. In addition, the $^3J_{1'2'}$ values (4.9 and 2.5 Hz) for the diastereoisomers with H(1′) signals at δ 5.76 and 5.64 suggest that on average the riboses prefer the C(2′)-*endo* and C(3′)-*endo* conformation, respectively, in the two diastereoisomers.[14] The $^1H$ NMR spectrum of **2** in $(CD_3)_2SO$ is also consistent with the presence of the two $C_2$ diastereoisomers in a 1 : 1 molar ratio. The $^3J_{1'2'}$ values (5.2 and 2.7 Hz) also suggest that for one diastereoisomer a C(2′)-*endo* conformation is slightly more favoured, whereas for the other, C(3′)-*endo* is considerably favoured.[14] The $^{31}P$ NMR spectrum of **2** shows one peak at δ 40.5, consistent with coordinated $PPh_3$. For both **1** and **2**, signals are observed at *ca.* δ 14 in the $^1H$ NMR spectra, consistent with a proton at N(1) as suggested by the X-ray structure.

It must be noted that the X-ray analysis of **1** reveals the presence of just one diastereoisomer in the lattice. The X-ray structure reveals no reason that the other diastereoisomer would be less stable. Chelation by N(7) and S(6) makes interconversion of the diastereoisomers unlikely. The NMR

† *Crystal data* for **1**: $[Ru^{II}(HMPR)_2(PPh_3)_2]Cl_2 \cdot 2.75H_2O \equiv C_{56}H_{59.5}Cl_2N_8O_{10.75}P_2RuS_2$, $M$ = 1314.7. Monoclinic, space group $P2_1$ (No. 4), $a$ = 18.735(26), $b$ = 16.553(4), $c$ = 22.401(22) Å, β = 114.91(5)°, $V$ = 6301(5) Å$^3$, $Z$ = 4, $D_c$ = 1.386 g cm$^{-3}$. Data were collected on a Delft Instruments FAST TV area detector diffractometer following previously described procedures.[9] From the range scanned, 19486 data were recorded to give 4610 observed [$F_o > 3\sigma(F_o)$] reflections. The structure was solved *via* direct methods and refined by least-squares analysis. A correction for absorption was made by using DIFABS.[10] The final $R$ and $R_w$ were 0.065 and 0.064 for 613 parameters. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1. Details of the treatment of the disorder [present in the positions of three $Cl^-$ ions and three water molecules, and of two O(5′) atoms] is available as supplementary material from one of the authors (R. C.).

spectra are consistent with equal amounts of the two diastereoisomers. Examination of the solid reveals the presence of many much smaller crystals with different morphology; these undoubtedly contain the other diastereoisomer. In this species, the ribose may have the C(3')-*endo* conformation. The N(7) binding interaction is consistent with suggestions concerning the interaction of guanine sites with $Ru^{II}$ anticancer drugs.[2] The C(2')-*endo* conformation demonstrates that, for species such as **1**, a ribose conformational change does not necessarily occur.

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