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Binding of 9-Methylguanine to [*cis*-Ru(2,2′-bpy)$_2$]$^{2+}$: First X-ray Structure of a *cis*-Bis Purine Complex of Ruthenium

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Reaction of [*cis*-Ru(2,2′-bpy)$_2$(O$_3$SCF$_3$)$_2$] (**1**) with 9-methylguanine (9-MeG) affords the *cis*-[Ru(2,2′-bpy)$_2$(9-MeG)$_2$]$^{2+}$ complex (**2**) in good yield. Two bases bind to the metal center via the N7 atoms. X-ray structure analysis of **2**(SO$_3$CF$_3$)$_2$ (monoclinic, $P2_1/n$, a = 12.5159(6) Å, b = 20.0904(13) Å, c = 17.1202(9) Å, β = 98.981(6)°, V = 4252.1(4) Å^3, Z = 4) reveals that the two bases are in a head-to-tail (HT) orientation with base–base dihedral angle of 60.4°. NMR studies confirm that the complex is stable in water for hours, and no evidence for guanine substitution by solvent molecules was found.

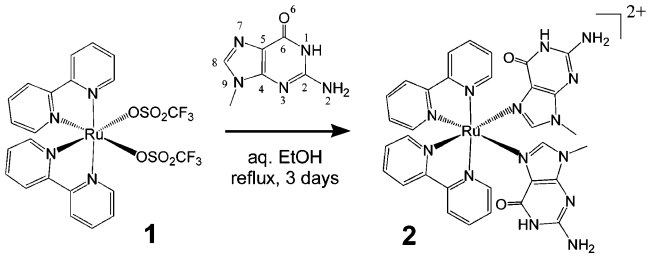
Different ruthenium-based metal complexes are currently being investigated for their antitumor properties. Although the mode of actions of these complexes is not yet well understood, there is evidence that DNA is the target for these compounds similar to the well-established platinum drugs.[1−11] Barton and Lolis,[1] and subsequently Thorp and co-workers,[2] have reported the enantiomeric selectivity for the Λ isomer of *cis*-[RuCl$_2$(phen)$_2$] and *cis*-[Ru(bpy)$_2$(H$_2$O)$_2$]$^{2+}$ (phen = 1,10-phenanthroline; bpy = 2,2′-bipyridine) type complexes in covalent binding to B-DNA. A direct correlation between cytotoxicity and DNA binding was observed by Clarke and co-workers for the representative *cis*-[Ru^{III}Cl$_2$(NH$_3$)$_4$]Cl and *trans*-[Ru^{III}Cl$_4$(Im)$_2$]$^-$ (Im = imidazole) type compounds in cell cultures,[3] and it was shown that DNA binding of [Ru(H$_2$O)(NH$_3$)$_5$]$^{2+}$ occurs preferentially at G.[4,5] Brabec and co-workers showed similar results.[6] Furthermore, compounds such as *mer*-[RuCl$_3$(terpy)] (terpy = 2,2′:6′, 2″-terpyridine), *mer*-[RuCl$_3$(Me$_2$SO)$_3$], and *trans*-[RuCl$_4$(Me$_2$SO)$_2$]$^-$ have all been shown to from interstrand cross-links in DNA and to bind guanine derivatives in a *trans* configuration while *trans*-[RuCl$_2$(Me$_2$SO)$_4$] forms a stable d(GpG) adduct.[7−10]

To our knowledge, there is no structurally characterized ruthenium complex with two DNA bases covalently bound to the metal center.

Reedijk and co-workers have shown that *cis*-[Ru(bpy)$_2$Cl$_2$] forms only a mono adduct with 9-ethylguanine (9-EtG). Even under strong conditions and precipitation of the halides, no bis-guanine complex could be observed.[12] We found under comparable conditions quantitative coordination of two guanines and present in this Communication the first example of a structurally characterized *cis*-bis purine complex of ruthenium.

Complex **2** was obtained by refluxing **1** with 2.4 equiv of 9-MeG in aqueous ethanol (Scheme 1).[13] Diffraction-quality crystals were grown from ethanol and CH_2Cl_2, and an ORTEP presentation of Δ-**2** is given in Figure 1.[14] The complex crystallizes in the monoclinic $P2_1/n$ space group, and the Λ and Δ isomers are both present in the unit cell. The guanines coordinate through N7 with the two bases in a head-to-tail (HT) orientation and with a base−base dihedral

Scheme 1



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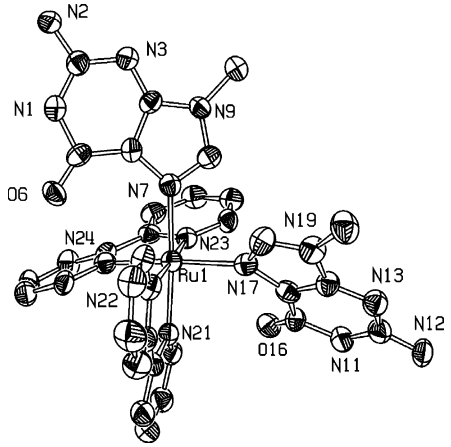

Figure 1. ORTEP view of Δ-[Ru(bpy)$_2$(9-MeG)$_2$]$^{2+}$ (**2**) with 50% probability for thermal ellipsoids. Selected bond distances (Å) and angles (deg) are the following: Ru(1)−N(7) 2.122(5), Ru(1)−N(17) 2.131(4), Ru(1)−N(21) 2.044(5), Ru(1)−N(22) 2.053(5), Ru(1)−N(23) 2.047(4), Ru(1)−N(24) 2.050(4); N(7)−Ru(1)−N(17) 89.12(16), N(7)−Ru(1)−N(21) 175.26(16), N(7)−Ru(1)−N(22) 97.20(19), N(7)−Ru(1)−N(23) 83.77(17), N(7)−Ru(1)−N(24) 95.74(17), N(17)−Ru(1)−N(21) 93.30(16), N(17)−Ru(1)−N(22) 86.50(17), N(17)−Ru(1)−N(23) 97.36(17), N(17)−Ru(1)−N(24) 173.49(17), N(21)−Ru(1)−N(22) 78.90(19), N(21)−Ru(1)−N(23) 99.95(17), N(21)−Ru(1)−N(24) 82.17(18), N(22)−Ru(1)−N(23) 176.05(18), N(22)−Ru(1)−N(24) 97.17(17), N(23)−Ru(1)−N(24) 78.92(17).

angle of 60.4°. The purine moieties are situated with the keto groups pointing between the pyridyl rings of the bpy ligands. In both bases, the carbonyl groups are slightly bent out of plane with O6−C6−N3 and O16−C16−N13 angles of 171.2(4)° and 170.8(5)°, respectively. All bond distances and angles are in good agreement with the closely related *cis*-[RuCl(bpy)$_2$(9-EtG)]$^+$ structure[12] although we find that Ru1−N(bpy) distances are on average 0.017(2) Å longer in **2**. Furthermore, the bpy ligands are not planar. In the bpy ligand with labels N23 and N24 in Figure 1, the two pyridine rings are twisted with respect to each other by an angle of 16.4°, while in the other bpy ligand (with labels N21 and N22) the two pyridine rings are twisted by 11.6°. Bond distances and twist angles might be taken together as an indication of the steric hindrance imposed by the need of accommodating two guanines around the metal center.

(13) Complex **1** was obtained by reacting Ru(bpy)$_2$Cl$_2$ (50 mg, 0.1 mmol, prepared by standard methods) with $AgSO_3CF_3$ (55 mg, 0.22 mmol) in aqueous ethanol (10 mL). After filtration of AgCl, 9-MeG (40 mg, 0.24 mmol) was added, and the solution refluxed for 3 days. The reaction mixture was cooled to room temperature and filtered again. CH_2Cl_2 was then allowed to slowly diffuse into the solution depositing X-ray quality crystals of **2**$(SO_3CF_3)_2$ after 2 days. Yield: 90 mg, 84%. MS data ESI+: 289.2 $m/2z$ = [Ru(bpy)$_2$(9-MeG)]$^{2+}$. UV−vis, H_2O, nm (ϵ, $\times 10^{-4}$ M^{-1} cm^{-1}): 290 (6.37), 331 (1.04), 475 (1.01).

(14) Crystal data: $C_{35}H_{32}Cl_2F_6N_{14}O_8Ru_1S_2$, fw = 1126.84, red block, monoclinic, $P2_1/n$, a = 12.5159(6) Å, b = 20.0904(13) Å, c = 17.1202(9) Å, β = 98.981(6)°, V = 4252.1(4) Å^3, Z = 4, ρ_{calcd} = 1.76 Mg/m^3, μ(Mo Kα) = 4.62 mm^{-1}, Stoe IPDS diffractometer, Mo Kα radiation (λ = 0.71073 Å), 8711 reflections, 3692 with $I > 2\sigma(I)$ used for refinement (R = 0.0486, wR2 = 0.1044, hydrogens calculated).

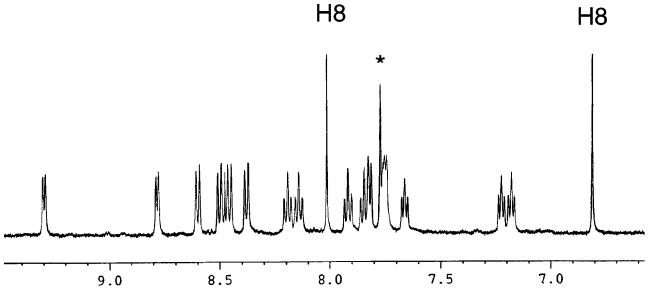

Figure 2. Aromatic region (ppm) of the ^{1}H NMR spectrum of (**2**) in D_2O. The star indicates H8 proton of free 9-MeG.

As previously shown, the guanine ligands cannot freely rotate about the Ru−N7/17 bond.[12] Due to this hindered rotation, the two H8 protons differ significantly in chemical shifts. Indeed, when crystals of **2**$(SO_3CF_3)_2$ are dissolved in water, two distinct sharp singlets separated by about 1.2 ppm are observed. The aromatic region of the ^{1}H NMR spectrum of **2** is shown in Figure 2. No relevant change in the spectrum was found during a 4 h period at 298 K. However, after 3 days the peak of free 9-MeG grows by about 40% indicating that very slow base dissociation took place. Compared to the *cis*-bis guanine complex of the *fac*-[Re(CO)$_3$]$^+$ core, which remains the focus of our current research, complex **2** seems to be more stable as also indicated by the shorter M−N7 distance (on average Re−N7 bond distance = 2.199(9) Å).[15] Although the H8 protons are separated by 2.619(5) Å in the crystal structure, we could not detect a NOESY cross-exchange signal in 2D NMR experiments.

In conclusion, we have presented the first structurally characterized *cis*-bis purine complex of ruthenium. The two guanine bases are in an HT orientation which is the most common solid-state conformation of *cis*-bis ligand complexes of purines with Pt^{II}, Co^{III}, Cu^{II}, and Zn^{II}.[16] The complex is stable in water for hours showing a slow off rate of base dissociation. Our results, in agreement with the experimental evidence mentioned above, confirm that DNA is a possible target of ruthenium-based metal drugs.

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Supporting Information Available: Crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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