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Ruthenium–carbon bond formation *via* cyclometallation of a nucleobase

Clayton Price,[a] **Michelle A. Shipman,**[a] **Sarah L. Gummerson,**[a] **Andrew Houlton,***[a] **William Clegg**[b] **and Mark R. J. Elsegood**[b]

[a] *Department of Chemistry, University of Newcastle upon Tyne, Newcastle upon Tyne, UK NE1 7RU. E-mail: andrew.houlton@newcastle.ac.uk*
[b] *Crystallography Lab., Department of Chemistry, University of Newcastle upon Tyne, Newcastle upon Tyne, UK NE1 7RU*

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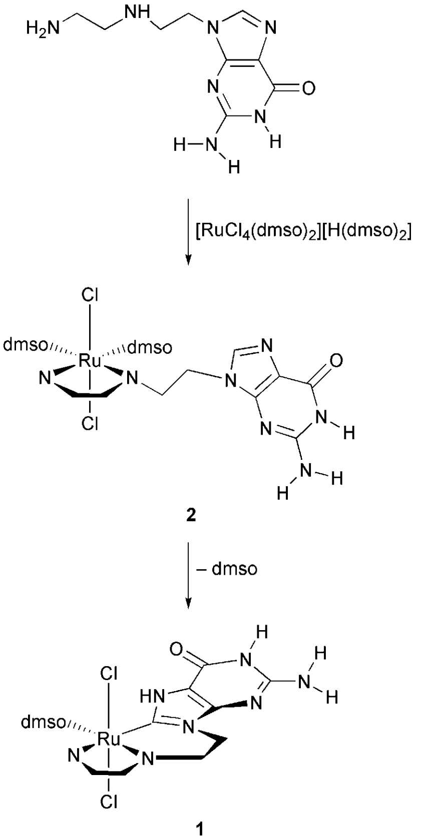
The presence of a chelating tether attached to ethylguanine leads to the formation of a metal–carbon bond at C8 of the nucleobase when reacted with *trans*-[RuCl$_4$(dmso)$_2$]$^-$, in contrast, more typical co-ordination at N7 is seen in the absence of the tether.

Examples of metal complexes that contain metal–carbon bonds to nucleobases are not extensive.[1–10] In fact, for some considerable time, with the exception of Hg,[1–3] these have been restricted to those based on pyrimidine.[4–7] However, we have recently extended the range of organometallic–nucleobase complexes to include adenine[8] with the synthesis of a C8-bound complex.[9] This, along with other examples of unusual metal–nucleobase complexes, was prepared by introducing a chelating tether to the N9-position.[10–12] The equivalent C8–H bond in guanine is more acidic than that in adenine and hence may be expected to more readily undergo metallation possibly without the need for a tethered chelating group. In an effort to investigate this we report on the reaction of ruthenium with 9-[2-(2-aminoethylamino)ethyl]guanine and compare this with the simple alkylated analogue, 9-ethylguanine.

Reaction of *trans*-[RuCl$_4$(dmso)$_2$][H(dmso)$_2$][13] with 9-[2-(2-aminoethylamino)ethyl]guanine hydrochloride[12] in refluxing methanol (12 h) gave, on cooling, a solid precipitate. Column chromatography of the filtrate on silica yielded **1** and a small quantity of a second product, **2**. The ^{1}H NMR spectrum (d$_6$-dmso) of **1** indicated the loss of the resonance associated with C8-H (δ 7.7 in the free ligand) and a new downfield resonance was observed at δ 13.05. This latter feature exchanged on addition of D$_2$O. The ^{13}C{^{1}H} NMR spectra of the complex exhibited a downfield resonance at δ 184.62. By contrast, a resonance corresponding to C8-H is observed (δ 7.7) in the ^{1}H NMR spectrum of **2** and neither the resonance at δ 13.05 nor that at δ 184.62 in the ^{1}H and ^{13}C{^{1}H} spectra is apparent. By comparison with earlier studies on the adenine derived complex[8] it is suggested that **1** contains a cyclometallated guanine residue while in **2** the nucleobase is pendant (Scheme 1). Furthermore **2** interconverts to **1** on further reaction as indicated by NMR and TLC.

Confirmation of metal–carbon bond formation was obtained from a single crystal X-ray analysis,† which identified **1** as *trans*-[RuCl$_2$(en-9-Et-C8-G)(dmso)] (Fig. 1). The central metal ion adopts an octahedral co-ordination geometry and the guanine-diamine acts as a tridentate ligand. Donor atoms are provided by the ethylenediamine function and C8 of the guanine thus generating five- and six-membered chelate rings. Bond lengths (Å) around the metal are Ru–Cl1 2.4105(8), Ru–Cl2 2.4375(8), Ru–S1 2.2139(8), Ru–C8 1.994(3), Ru–N15 2.189(3), Ru–N12 2.139(2). The N7 site bears a proton which modifies the Hoogsteen face of the guanine with respect to hydrogen bonding capability. This N–H proton is involved in an intramolecular interaction with the dmso oxygen (O · · · N distance 2.764 Å). Based upon simple electron counting the guaninyl residue is required to act as a two-electron donor for the complex to be described as a diamagnetic 18-electron species as is indicated by the NMR studies.



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Scheme 1 Formation of a Ru-bonded guanine through cyclometallation *via* a pendant nucleobase intermediate.

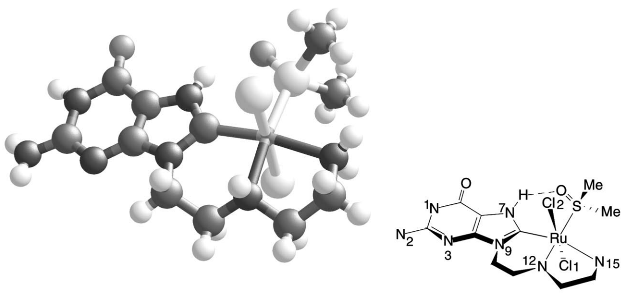

Fig. 1 Molecular structure of the cyclometallated guanine derivative **1**.

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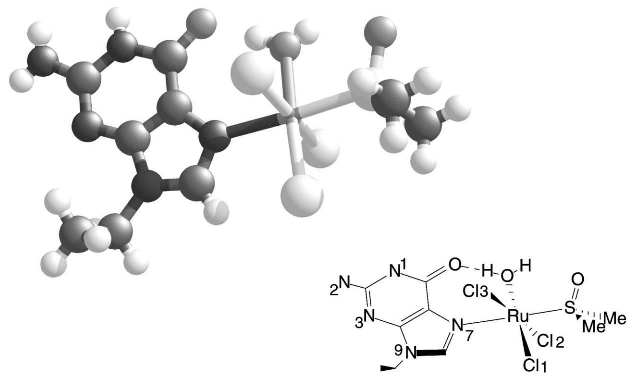

Fig. 2 Molecular structure of N7-co-ordinated ruthenium 9-ethylguanine, **3**.

In contrast, the product isolated from reaction of *trans*-$[RuCl_4(dmso)_2][H(dmso)_2]$ with 9-ethylguanine,‡ **3**, exhibited the more typical N7-co-ordination, with confirmation again obtained from a single crystal X-ray analysis. Fig. 2 shows the molecular structure of **3**, $[RuCl_3(N7\text{-}9EtG)(H_2O)(dmso)]$. Here too the central metal ion adopts an octahedral co-ordination geometry with metal–ligand bond lengths (Å) Ru–Cl1 2.3175(12), Ru–Cl2 2.3100(14), Ru–Cl3 2.3562(12), Ru–S1 2.2567(11), Ru–O1 2.042(4), Ru–N7 2.148(3). The co-ordinated water molecule is involved in intramolecular hydrogen bonding with both guanine O6 (O1 ··· O6 2.416 Å, ∠ O1–H1a–O6 161°) and O2 of dmso (O1 ··· O2, 2.774 Å, ∠ O1–H1b–O2 115°).

Despite the different site of metal ion binding in **1** and **3** the intermolecular interactions are quite similar. In both compounds there are no direct hydrogen bonding interactions between the guanine residues however dimers are formed through N1–H ··· Cl hydrogen bonds (**1** = 3.297 Å; **2** = 3.257 Å). In **1** these involve stacking of the G-residues with a separation of ~3.25 Å. In **3** this interaction is absent as a consequence of co-ordination at N7 which ensures that Cl–Ru–N1–H do not lie in a plane.

In summary, the data reported highlight the unusual co-ordination chemistry that can be induced at nucleobases by the presence of a chelating tether. Furthermore, compound **1** extends the relatively small class of nucleobase complexes that contain a metal–carbon bond to the nucleobase.

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Notes and references

† To a refluxing solution of *trans*-$[RuCl_4(dmso)_2][H(dmso)_2]$ (0.26 g, 0.55 mmol) in methanol (30 ml) was added dropwise a methanolic solution (20 ml) of 9-[2-(2-aminoethylamino)ethyl]guanine hydrochloride (0.15 g, 0.55 mmol), the mixture was refluxed for 12 h. On cooling a solid precipitate formed (**1**) which was collected by filtration and washed with methanol (0.058 g, 22%). Work-up and chromatography of the filtrate (matrix 60 silica, elution with methanol) yielded a small quantity of **2**. Crystals of **1**, suitable for single crystal X-ray diffraction studies, were grown by the controlled cooling of a hot aqueous solution.

1 ^{1}H NMR (d$_6$-dmso, 500 MHz), δ 2.50 (m, 1H, H14^1), 2.83 (m, 1H, H13^1), 2.87 (m, 1H, H13), 2.95 (m, 1H, H14), 3.16 (s, 3H, H17), 3.17 (s, 3H, H16), 3.35 (m, 1H, H11^1), 3.40 (m, 1H, H11), 3.41 (m, 1H, H15^1), 3.88 (m, 1H, H10^1), 4.35 (m, 1H, H15), 4.64 (m, 1H, H10), 4.84 (m, 1H, H12), 6.61 (s, 2H, H2), 10.87 (s, 1H, H1), 13.05 (s, 1H, H7); $^{13}C\{^1H\}$ NMR (d$_6$-dmso, 125 MHz), δ 41.18 (C14), 42.45 (C10), 43.79 (C16), 48.57 (C17), 48.82 (C11), 53.02 (C13), 107.48 (C5), 150.39 (C4), 153.19 (C2), 154.06 (C6), 184.62 (C8). Found: C, 25.83; H, 4.58; N, 18.74. Calc. for $C_{11}H_{25}Cl_2N_7O_4RuS$: C, 25.52; H, 4.81; N, 18.73%; MS $[M - Cl]^+$ at *m*/*z* 452.

2 ^{1}H NMR (d$_6$-dmso), δ 2.33 (m, 1H, H13^1), 2.80 (m, 1H, H14^1), 2.93 (m, 1H, H13), 3.07, 3.08, 3.10, 3.16 (s, 3H, H16, H17, H18, H19), 3.19 (m, 1H, H11^1), 3.72 (m, 1H, H11), 4.16 (m, 1H, H15^1), 4.26 (m, 1H, H15), 4.53 (m, 1H, H12), 4.54 (m, 1H, H10^1), 4.55 (m, 1H, H10), 6.52 (s, 2H, H2), 7.67 (s, 1H, H8), 10.76 (s, 1H, H1); ^{13}C NMR (d$_6$-dmso), δ 41.16 (C10), 42.34 (C14), 43.72, 44.09, 45.04, 45.67 (C16, C17, C18, C19), 48.99 (C13), 50.55 (C11), 116.54 (C5), 137.41 (C8), 151.32 (C4), 153.60 (C2), 156.78 (C6).

Crystal data for **2**: $[C_{11}H_{25}Cl_2N_7O_4RuS]$, $M_r = 523.41$, orthorhombic, space group *Pbca*, $a = 16.4932(10)$, $b = 11.5769(8)$, $c = 19.8969(13)$ Å, $V = 3799.1(4)$ Å^3, $Z = 8$, $D_{calc.} = 1.830$ g cm^{-3}; Mo-Kα radiation, $\lambda = 0.71073$ Å, $\mu = 1.25$ mm^{-1}, $T = 160$ K. Of 22124 measured reflections, corrected for absorption, 4535 were unique ($R_{int} = 0.0326$, $\theta \le 28.6°$); $R = 0.0359$ (F values, $F^2 > 2\sigma$), $R_w = 0.0795$ (F^2 values, all data), GOF = 1.134 for 256 parameters, final difference map extremes +0.60 and −0.84 e Å^{-3}. The structure was solved by direct methods.

‡ For compound **3**, the reactions conditions were as for **1** except 9-[2-(2-aminoethylamino)ethyl]guanine ethylguanine was replaced with 9-ethylguanine. Found: C, 22.36; H, 3.28; N, 14.29. Calc. for $C_9H_{17}Cl_3N_5O_3RuS$: C, 22.39; H, 3.54; N, 14.51%; MS $[M - dmso - Cl]^+$ at *m*/*z* 369.

Crystal data for **3**: $[C_9H_{17}Cl_3N_5O_3RuS]$, $M_r = 482.76$, monoclinic, space group $P2_1/c$, $a = 8.5032(7)$, $b = 24.3211(19)$, $c = 8.1957(6)$ Å, $\beta = 91.942(2)°$, $V = 1694.0(2)$ Å^3, $Z = 4$, $D_{calc.} = 1.893$ g cm^{-3}; Mo-Kα radiation, $\lambda = 0.71073$ Å, $\mu = 1.54$ mm^{-1}, $T = 160$ K. Of 14609 measured reflections, corrected for absorption, 4060 were unique ($R_{int} = 0.0539$, $\theta \le 28.7°$); $R = 0.0473$ (F values, $F^2 > 2\sigma$), $R_w = 0.1226$ (F^2 values, all data), GOF = 1.052 for 218 parameters, final difference map extremes +1.36 and −1.43 e Å^{-3}. The structure was solved by direct methods.

CCDC reference numbers 154228 and 154229. See http://www.rsc.org/suppdata/dt/b0/b009766g/ for crystallographic data in CIF or other electronic format.

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