Interactions of the Rh_2^{4+} formamidinate complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ (form = *N, N'*-di-*p*-tolylformamidinate anion) with nucleobases and nucleosides

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Abstract

The Rh_2^{4+} formamidinate complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ (form = *N, N'*-di-*p*-tolylformamidinate anion) reacts with adenine and N^6,N^6-dimethyladenine in molar ratio 1:1 and 1:2 giving mono- and bis-axial adducts $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(L)_n$ (L = adenine, N^6,N^6-dimethyladenine; $n = 1, 2$) with the adenine ligands coordinated through the N(3) atoms. In contrast when both the N(3) and N(9) atoms are blocked, the complex reacts in a different way. Adenosine (ado) in fact coordinates through the dimetal core leading to the Rh_2^{5+} complex $Rh_2(\mu\text{-form})_2(O_2CCF_3)(\mu\text{-ado})_2$ which has been characterized by EPR spectroscopy. In this complex adenosine behaves as a bidentate mono-anionic ligand coordinated at the equatorial positions through N(1) and the deprotonated amino nitrogen. Similarly the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ reacts with cytosine, 1-methylcytosine and cytidine via a mono-electron oxidation leading to the paramagnetic complexes $Rh_2(\mu\text{-form})_2(O_2CCF_3)(\mu\text{-L})_2$ (L = cytosine, 1-methylcytosine, cytidine) with the cytidinic ligands equatorially coordinated through N(3) and the deprotonated amino nitrogen atoms.

Introduction

Complexes containing the Rh_2^{4+} core represent a unique example of compounds which exhibit both interesting catalytic [1] and biological activity [2]. The latter properties were exploited in 1972 when it was reported that the complex $Rh_2(O_2CCH_3)_4$ exhibits antitumoral activity against some malignancies. This report, associated with the subsequent studies leading to ascertain the biological target of these complexes and their mode of action as antitumor agent [3], showed that the Rh_2^{4+} complexes with the lantern structure possess the right structural and electronic properties to interact with biological molecules.

Recently we reported the synthesis of the complexes $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ and $Rh_2(\mu\text{-form})_4$ (form = *N,N'*-di-*p*-tolylformamidinate anion) bearing basically the same structure of the dirhodium(II,II) carboxylate derivatives [4]. Both the complexes were evaluated for their toxicity on the rat and for their efficacy against some tumors of this animal [5]. While the homoleptic complex $Rh_2(form)_4$ does not show any appreciable biological activity, the mixed-ligand complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ exhibits equal antitumoral activity and fewer toxic effects than the well known *cis*-$Pt(NH_3)_2Cl_2$ and other dirhodium(II,II) derivatives. The different antitumoral activity between the two complexes was ascribed to steric factors which in the tetrakisformamidinate derivative do not allow access to the axial positions which are the primary targets of any Lewis bases when reacted with this class of compounds. On the contrary the mixed-ligand derivative exhibits virtually free axial coordination sites so that it can potentially form mono- and bis-adducts with biological molecules. Furthermore this complex, due to the presence of the labile trifluoroacetate groups, exhibits equatorial reactivity too, allowing the introduction of mono- and bidentate neutral ligands in the equatorial positions [6].

The interesting biological activity of the above-named complex led us to explore more deeply its biological activity following two routes; one involves the investigation of its activity against tumoral lines more similar to the human ones; the other one involves the investigation of its reactivity towards biological molecules in order to obtain a better understanding of their antitumor properties. In this paper we report on the reactivity of the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ with nucleic acid bases and some nucleosides.

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Results and discussion

The complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ reacts with adenine and N^6, N^6-dimethyladenine in molar ratio 1:1 and 1:2 leading to green solutions from which the mono- and bis-adducts $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(L)_n$ (L = adenine, $n=1$ (**1**), $n=2$ (**2**); L = dimethyladenine, $n=1$ (**3**), $n=2$ (**4**)) were easily recovered in 80% yields. Complexes **1–4**, which exhibit similar IR, ^1H NMR and conductivity features, are very stable compounds, soluble in a large variety of solvents where they behave as non-electrolytes. The assignment of the structure and the coordination mode of the nucleobases was not straightforward and was deduced by a combination of spectroscopic data and the results of the reactions with adenosine and N^6,N^6-dimethyladenosine. IR and ^1H NMR spectroscopy were not much help in detecting the coordination mode of the nucleobases; the former because a great number of absorptions fall in the region ranging from 1500 to 1700 cm^{-1} due to ν(C–C), δ(C–N) and $\delta(NH_2)$ of the ligand and $\nu_{asym}(CO_2)$ of the trifluoroacetate groups, the latter because complexes **1–4** give rise to broad signals indicative of dynamic processes. While we have not succeeded in spectroscopically characterizing these species, the following considerations enabled us to draw some conclusions on the attachment mode of the ligands and the structure of **1–4**.

The solid IR spectrum of **1** and **2** shows, in the 3000–3500 cm^{-1} region, two medium intensity absorptions. These bands, assigned to the stretching of the exocyclic NH_2 groups, are shifted towards lower frequencies with respect to the free nucleobase suggesting its involvement in hydrogen bond formation. On the other hand the broad bands exhibited in the ^1H NMR spectrum from **1–4**, which are diamagnetic, are indicative of a dynamic process suggesting that **1–4** are partially dissociated and that there is rapid exchange between bound and dissociated adenine according to the well known properties of the dirhodium(II,II) axial adducts [7]. Furthermore previous studies showed that when bidentate ligands coordinate at the equatorial position of the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ the displaced CF_3COO groups became mono-coordinated at the axial positions. These axially mono-ligated groups are easily ionizable in coordinating solvents leading to ionic species [6]. Conductivity measurements carried out in dichloromethane or $CH_3C\,N$ show that complexes **1–4** are non-electrolytes pointing out that the reaction proceeds without disruption of the original 'lantern' structure. Very likely the adenine ligands, reacting with the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$, behave as a monodentate N-donor base coordinating at the axial positions.

Concerning the coordination sites of adenine, previous studies with various transition metals have shown N(1) and N(7) to be the preferred binding sites. In dimethyladenine these atoms are unavailable as coordination sites because of steric hindrance of the two methyl groups attached to the exocyclic nitrogen atom so that in complexes **3** and **4** only N(3) and N(9) may participate in bonding with the rhodium atoms. This suggestion is further supported by the reaction of N^6,N^6-dimethyladenosine with $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$. This nucleoside does not react since the steric hindrance due to the methyl and ribose groups hinders N(1) and N(7), and N(3) and N(9), respectively. Both the former nitrogen atoms were suggested to be involved in bonding with the complex $Rh_2(O_2CCH_3)_4$ leading to a polymeric compound in which the base bridges two Rh_2^{4+} units through the N(1) and N(7) atoms [3e]. Space-filling molecular models show that when the adenine is coordinated to the metal through N(3) the proton attached to N(9) may be involved in hydrogen bonds with the oxygen atoms of the trifluoroacetate groups. Interligand hydrogen bonding has been found to significantly affect the coordination mode of nucleic acid bases so that the N(3) coordination is rationalizable from electronic and intraligand hydrogen bonding considerations. On this basis, although we have no spectroscopic evidence, we suggest that complexes **1** and **2** and **3** and **4**, which are expected to be isostructural, display the structure depicted in Fig. 1 with the adenine axially coordinated through the N(3) atoms.

This binding mode is no longer possible for adenosine because N(3) is sterically unavailable and N(9) is blocked by the ribose fragment. Adenosine (ado), whose coordination sites are then restricted to N(1), N(6) and N(7), reacts with the parent complex in a very different way giving a green solution which becomes royal blue. From this solution a compound analyzing as $Rh_2(\mu\text{-form})_2(O_2CCF_3)(\mu\text{-ado})_2$ (**5**) was recovered in 60% yield. The color of this complex makes the attachment mode of the ligand as well as its structure even more intriguing. Blue colored compounds suggest in fact the presence of the Rh_2^{5+} core indicating that the reaction

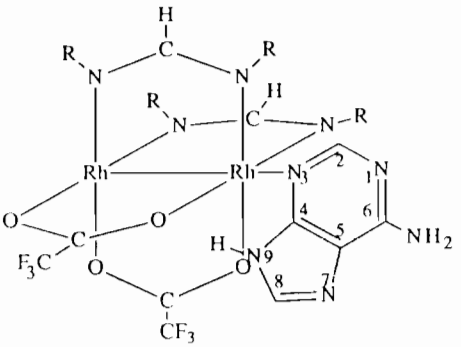

Fig. 1. Structure of complexes **1–4** showing the adenine axially coordinated through the N(3) atom.

proceeds via a mono-electron oxidation. According to this suggestion the EPR spectrum of **5** in frozen solution shows two signals (Fig. 2): the low-field one is unresolved while that at high-field is splitted into three resonances with 1:2:1 intensities. This hyperfine structure is easily interpreted on the basis of the hyperfine magnetic interaction between one unpaired electron delocalized over two equivalent ^{103}Rh nuclei ($I = 1/2$). Conductivity measurements show that complex **5** is non-conducting in dichloromethane while in acetonitrile it exhibits conductance values that one would expect for a 1:1 electrolyte due to the dissociation of a CF_3COO group. The presence of a ionizable trifluoroacetate group is significant because it suggests, as previously found, that in complex **5** the CF_3COO group is axially mono-coordinated. From these data, it may be deduced that the equatorial positions in complex **5** are occupied by two formamidinate and two adenosinate groups which then behave as bidentate mono-anionic ligands. Concerning the coordination sites of adenosine, we suggest that it uses N(1) in combination with the deprotonated amino nitrogen (Fig. 3) because the N(1)–C(6)–N(6) fragment possesses the right electronic and geometric requirements to act as a bridge between the two rhodium atoms better than the N(6)–C(6)–N(7) fragment.

Cytosine, 1-methylcytosine and cytidine exhibit a similar behaviour. Cytosine (cyto) in fact reacts with the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ in molar ratio 1:2 leading to a green solution that becomes royal blue indicating that this reaction also occurs via a mono-electron oxidation. The resultant compound was characterized by IR, EPR spectroscopy and elemental analysis. The latter showed that the reaction proceeds with elimination of trifluoroacetic acid and formation of a

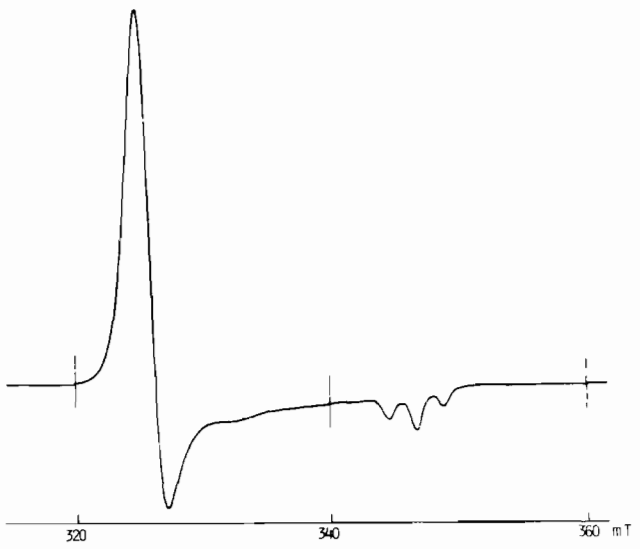

Fig. 2. EPR spectrum of the complex $Rh_2(\mu\text{-form})_2(O_2CCF_3)(\mu\text{-ado})_2$ (**5**) detected at 100 K using dichloromethane as solvent.

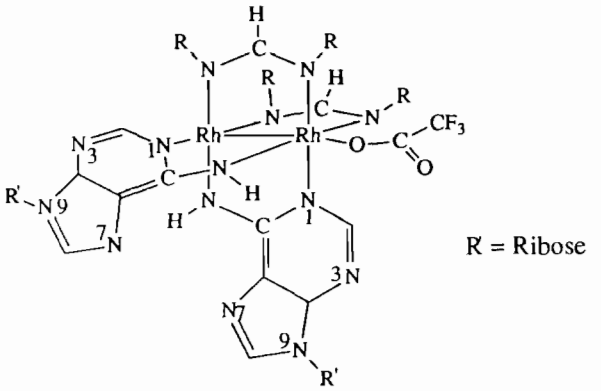

Fig. 3. Coordination sites of adenosine in complex **5**.

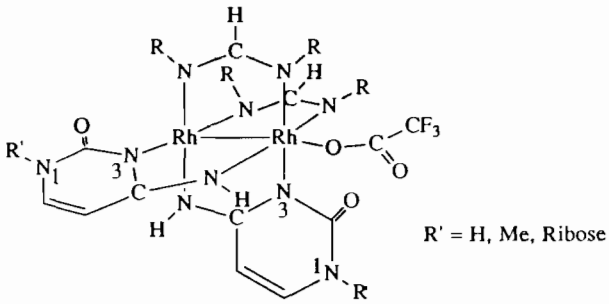

Fig. 4. Structure of complex **6**.

compound corresponding to the formula $Rh_2(\mu\text{-form})_2(O_2CCF_3)(\mu\text{-cyto})_2$ (**6**) with the two cytosinato fragments acting as bridging ligands (Fig. 4). The existence of the paramagnetic unit Rh_2^{5+} is reflected by the EPR spectra recorded in dichloromethane at room temperature and 100 K. For complex **6** the high-field pattern also displays a resolved hyperfine structure because of the large value of the hyperfine component A_3 in the spin Hamiltonian of the Rh...Rh system. The IR spectrum of **6**, which in CH_3CN behaves as 1:1 electrolyte, consists of strong absorptions at 1662, 1624 and 1526 cm^{-1}. The absorption at 1526 cm^{-1}, assigned to the stretching $\nu_{asym}(NCN)$, is typical of a formamidinate group bonded to a Rh_2^{5+} core [8] while the absorption at 1662 cm^{-1}, assigned to the $\nu(CO)$, suggests that the carbonyl is not involved in coordination so that the base may be coordinated to the rhodium atoms through N(3) and N(4). The successive reactions with 1-methylcytosine and cytidine confirm this suggestion.

1-Methylcytosine and cytidine react with the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ in molar ratio 1:2 affording the complexes $Rh_2(\mu\text{-form})_2(O_2CCF_3)(\mu\text{-L})_2$ (L = 1-methylcytosine (**7**), cytidine (**8**)) which exhibit similar IR and EPR features. The presence of the methyl group coordinated to N(1), on one hand, does not allow it to be coordinated, on the other hand it disfavors the carbonyl as a coordinating site. Conse-

quently the only coordinating sites available for this ligand are the N(3) and the exocyclic nitrogen N(4). The same considerations apply to cytidine for the presence of the ribose fragment attached to N(1).

The formation of complexes **6–8** may be rationalized in terms of an initial formation of axial adducts through the more basic N(3) atom. Accordingly the initial green color of the reaction mixtures is typical of axial adducts of the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ with azotate ligands. Further equatorial isomerization [6] and ring closure through th exocyclic nitrogen may occur. Coordination of a second pyrimidine base followed or very likely preceded by the oxidation of the Rh_2^{4+} fragment, whose potential in the meantime is reduced by the substitution of one trifluoroacetate group with the azotate ligand, leads to the formation of species **6–8**.

The reactivity pattern of cytosine and its derivatives with the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ is significantly different from that exhibited by the tetracarboxylate derivative $Rh_2(O_2CCH_3)_4$. This species in fact, while reacting with adenine and polyadenylic acids, does not react with cytosine and polycytidylic acid. This failure of reactivity has been explained in terms of interligand steric constraint between the acetate oxygens and the carbonyl and the exocyclic amino nitrogen when the cytosine is coordinated at the dimetal core through N(3). The results here reported suggest that coordination of rhodium at N(3) of cytosine is possible when subsequent metallation of the deprotonated exocyclic amine nitrogen also occurs.

As already found for $Rh_2(O_2CCH_3)_4$, the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ does not react with guanine, guanosine, and uracil but it reacts very slowly with thymine giving a green compound which we could not characterize.

Conclusions

The reactivity of the complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ with nucleobases and nucleosides allows us to draw some conclusions. The Rh_2^{4+} complexes, if supported by the appropriate ligands, may exert their antitumoral activity through: (i) axial coordination; (ii) equatorial coordination; (iii) redox processes. The latter processes, previously never observed in reactions of transition metal complexes with the constituents of the nucleic acids, may occur when good σ-donor groups, such as the formamidinate ligands, are present in the 'lantern' structure. The presence of these groups reduces the oxidation potential of the corresponding Rh_2^{4+} derivatives allowing thermodynamic access to mixed-valent complexes containing the Rh_2^{5+} core. On the contrary equatorial coordination is favored by the presence of good leaving groups such as the trifluoroacetate ligands.

Experimental

The complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ was prepared according to the literature procedure [4a]. Other reagents and solvents were used as received. IR spectra were recorded on a Perkin-Elmer FT 43 instrument. EPR spectra were recorded by using a Bruker SR 200D spectrometer. Elemental analyses were performed by the Microanalytical Laboratory of the Organic Chemistry Institute of Milan and Analitische Laboratorien Malissa and Reuter, Elbach, Germany. The reactions were carried out either under a purified N_2 atmosphere or in air.

$Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(ade)$ (1)

To an acetate solution of $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ (115.6 mg, 0.12 mmol) was added 17.1 mg (0.12 mmol) of adenine dissolved in water 1 (ml) and the mixture thus formed was stirred at room temperature for 24 h. During this time the solution changes from red–brown to a green color. The mixture was filtered and taken to dryness, and the residue was washed twice with water. Crystallization from diethyl ether gave complex **1** as a green powder. Yield 90%. *Anal.* Calc. for $C_{39}H_{35}N_9O_4F_6Rh_2$: C, 46.21; H, 3.48; N, 12.43; F, 11.2. Found: C, 46.19; H, 3.26; N, 12.32; F, 9.92%. IR absorptions (KBr pellet, cm^{-1}); 3270(w, br), 3170(w, br), 1663(s, br), 1583(s).

The complexes $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(ade)_2$, $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(N^6,N^6\text{-dimethyladenine})$ and $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(N^6,N^6\text{-dimethyladenine})_2$ were obtained in exactly the same way as the analogous complex **1** by using the appropriate molar ratio.

$Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(ade)_2$ (2)

Green. Yield 55%. *Anal.* Calc. for $C_{44}H_{40}N_{14}F_6O_4Rh_2$: C, 46.00; H, 3.5; N, 17.03; F, 9.92. Found: C, 45.55; H, 3.57; N, 16.72; F, 8.6%. IR absorptions (KBr pellet, cm^{-1}); 3254(w), 3161(3), 1668(s, br), 1619(m), 1593(s).

$Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(N^6,N^6\text{-dimethyladenine})$ (3)

Green. Yield 55%. *Anal.* Calc. for $C_{41}H_{35}N_9F_6O_4Rh$: C, 47.95; H, 4.05; N, 11.97; F, 10.50. Found: C, 47.27; H, 3.73; N, 12.10; F, 10.94%. IR absorptions (KBr pellet, cm^{-1}): 1650(s, br), 1630(m), 1620(s), 1570(s).

$Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(N^6,N^6\text{-dimethyladenine})_2$ (4)

Green. Yield 60%. *Anal.* for $C_{48}H_{48}N_{14}F_6O_4Rh_2$: C, 47.85; H, 4.01; N, 16.27; F, 9.46. Found: C, 47.95; H,

4.43; N, 15.08; F, 8.4%. IR absorptions (KBr pellet, cm^{-1}); 1664(s, br), 1619(s), 1587(s).

$Rh_2(\mu$-form$)_2(O_2CCF_3)(\mu$-adenosine$)_2$ (5)

The complex was prepared by reacting an acetone solution of $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ (99.2 mg, 0.1 mmol) with 58.2 mg (0.2 mmol) of adenosine dissolved in the minimal amount of water. The reaction mixture was stirred at room temperature for 6 h during which time the red–brown solution turned green and finally blue. The solvent was evaporated and the residue repeatedly washed with water. Crystallization from CH_2Cl_2/hexane gave complex **5** in 60% yield. *Anal.* Calc. for $C_{54}H_{56}N_{14}O_{12}F_6Rh_2$: C, 45.90; H, 3.99; N, 13.87; F, 8.06. Found: C, 45.64; H, 4.01; N, 13.30; F, 7.95%. IR absorptions (KBr pellet, cm^{-1}); 1504(s), 1638(w). EPR spectrum (CH_2Cl_2, 100 K): $g_\perp = 2.07$; $g_\parallel = 1.950$; $A_\parallel = 20\times10^4$ cm^{-1}. Molar conductivity (Ω^{-1} cm^2 M^{-1}): λ (CH_3CN, 10^{-3} M) 106.

$Rh_2(\mu$-form$)_2(O_2CCF_3)(\mu$-cytosine$)_2$ (6)

The complex $Rh_2(\mu\text{-form})_2(\mu\text{-}O_2CCF_3)_2(H_2O)_2$ (82.2 mg, 0.08 mmol) was dissolved in acetone and stirred with 19.97 mg (0.16 mmol) of cytosine dissolved in water. The resultant green mixture was allowed to stir for about 4 h, during which time the color changed from green to blue–violet. After evaporation of the solvent the residue was washed with water and crystallized from benzene/heptane. Yield 70%. *Anal.* Calc. for $C_{42}H_{40}N_{10}F_6O_6Rh_2$: C, 45.83; H, 3.66; N, 12.72; F, 10.35. Found: C, 45.73; H, 4.16; N, 13.06; F, 10.15%. IR absorptions (KBr pellet, cm^{-1}); 1559(w), 1624(m). EPR spectrum (CH_2Cl_2, 100 K): $g_\perp = 2.08$; $g_\parallel = 1.985$; $A_\parallel = 18\times10^4$ cm^{-1}. Molar conductivity (Ω^{-1} cm^2 M^{-1}): λ (CH_3CN, 10^{-3} M) 106.

$Rh_2(\mu$-form$)_2(O_2CCF_3)(\mu$-1-methylcytosine$)_2$ (7)

A procedure similar to that for complex **6** was followed using 1-methylcytosine. Blue color. Yield 55%. *Anal.* Calc. for $C_{44}H_{44}N_6O_4F_6Rh_2$: C, 46.82; H, 3.92; N, 12.40; F, 10.10. Found: C, 47.1; H, 4.2; N, 13.1; F, 10.0%. IR absorptions (KBr pellet, cm^{-1}); 1576(m), 1615(w), 1678(m). Molar conductivity (Ω^{-1} cm^2 M^{-1}): λ (CH_3CN, 10^{-3} M) 90.

$Rh_2(\mu$-form$)_2(O_2CCF_3)(\mu$-cytidine$)_2$ (8)

62.02 mg (0.25 mmol) of cytidine dissolved in water were added to an acetone solution of $Rh_2(form)_2(O_2CCF_3)_2(H_2O)_2$ (93.3 mg, 0.1 mmol). After 20 h the resultant blue solution was filtered and the volatiles removed *in vacuo*. The residue was washed with water and extracted with diethyl ether, and crystallized from $CHCl_3$/heptane giving complex **8** as black needles. Yield 60%. *Anal.* Calc. for $C_{42}H_{40}N_{10}F_6O_6Rh_2$: C, 45.76; H, 4.13; N, 10.26; F, 8.35. Found: C, 45.32; H, 4.50; N, 10.80; F, 7.92%. IR absorptions (KBr pellet, cm^{-1}): 1559(w), 1636(s). EPR spectrum (CH_2Cl_2, 100 K): $g_\perp = 2.069$; $g_\parallel = 1.558$; $A_\parallel = 22\times10^4$ cm^{-1}. Molar conductivity (Ω^{-1} cm^2 M^{-1}): λ (CH_3CN, 10^{-3} M) 100.

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