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Bioorganometallic chemistry: synthesis, structure, and molecular recognition chemistry of (η^5-pentamethylcyclopentadienyl)-rhodium–DNA/RNA complexes in water

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Abstract

A review of the aqueous bioorganometallic chemisty of DNA/RNA nucleobases and of the co-factor, nicotinamide adenine dinucleotide, with an (η^5-pentamethylcyclopentadienyl)rhodium aqua complex, $[Cp^*Rh(H_2O)_3](OTf)_2$, at various pH values, will be presented. The unique structures of the Cp*Rh complexes with adenine, guanine, cytosine, thymine, and nicotinamide adenine dinucleotide bioligands were determined by a combination of ^{1}H- and ^{31}P-NMR, ESI/MS, and single crystal X-ray crystallography. Competitive reactivity studies, principally with the more reactive adenine and guanine derivatives, showed the important bonding characteristics with these nucleobases, while a novel cyclic trimer structure with 9-substituted adenine derivatives provided a new supramolecular receptor for molecular recognition studies with a variety of biologically important guests.

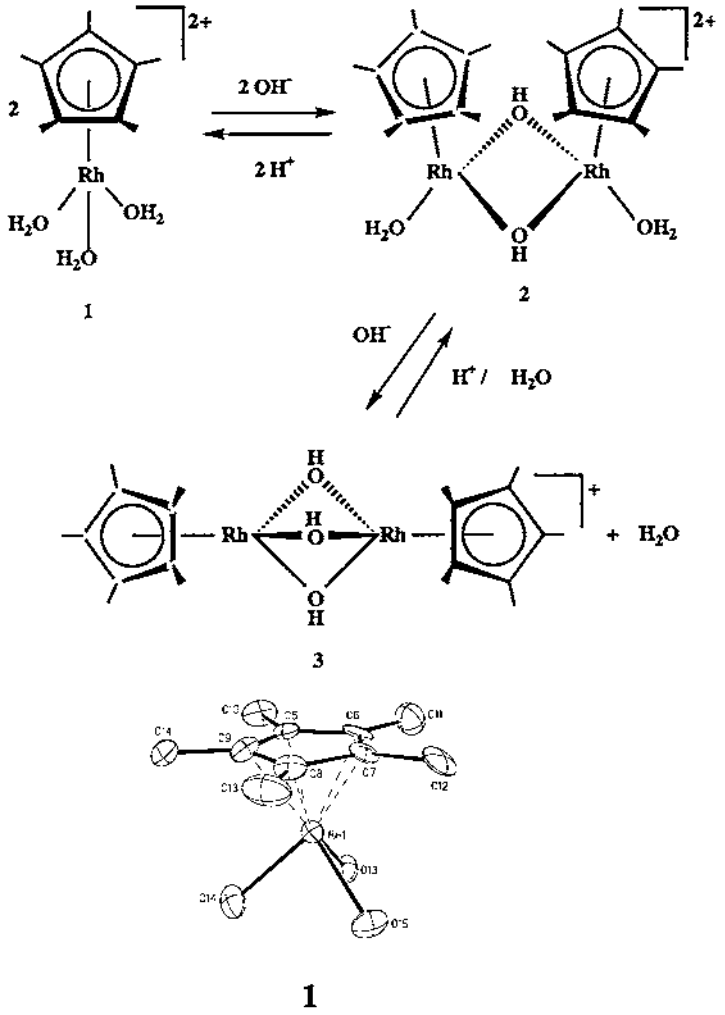
Keywords: Cp*Rh aqua complexes; Cp*Rh–DNA/RNA complexes; Molecular recognition

1. Introduction

Bioorganometallic chemistry is a relatively new aspect of metal–carbon bond compound reactivity that focuses on reactions of organometallic complexes with biological substrates in mainly aqueous solution [1–17]. Surprisingly, we found, about 8 years ago, that no studies of DNA/RNA nucleobases, nucleosides, nucleotides, or oligonucleotides had been reported in *aqueous solution* with (η^5-pentamethylcyclopentadienyl)rhodium (Cp*Rh) aqua complexes. Thus, in this review, we will demonstrate the rich and diverse structural chemistry uncovered via reaction of $[Cp^*Rh(H_2O)_3](OTf)_2$ with these biological ligands in aqueous solution at various pH values [18–27]. We will also discuss the structure and equilibrium of the starting Cp*Rh aqua complexes [28], as a function of pH, and as well, will demonstrate the interesting use of the novel cyclic trimer structure, [Cp*Rh-2-deoxyadenosine]$_3$(OTF)$_3$, as a molecular recognition host for non-covalent interactions with a variety of biological guests [26].

2. Equilibrium studies of Cp*Rh aqua complexes as a function of pH

It was apparent, at the time, that we needed to determine the structures of the Cp*Rh aqua complexes formed, as a function of pH, in order to understand their reactions with the DNA/RNA ligands we wanted to study. Therefore, we reported on an indepth NMR/FAB/MS/potentiometric titration study to show that from pH 2–5 a monomeric Cp*Rh aqua complex, $[Cp^*Rh(H_2O)_3](OTf)_2$, **1**, (pK_1 3.6) was present, which was characterized by X-ray crystallography. However, as the pH was raised to 5–7, a rapid equilibrium existed between this monomer and several [Cp*Rh(μ-OH)] dimers (**2**, pK_2 5.4 and **3**) and, as well, over pH 7 only one dimer was present, $[(Cp^*Rh)_2(\mu\text{-}OH)_3](OTf)$, **3**. Scheme 1 summarizes the Cp*Rh aqua chemistry we discovered along with the X-ray structure of **1** [28].



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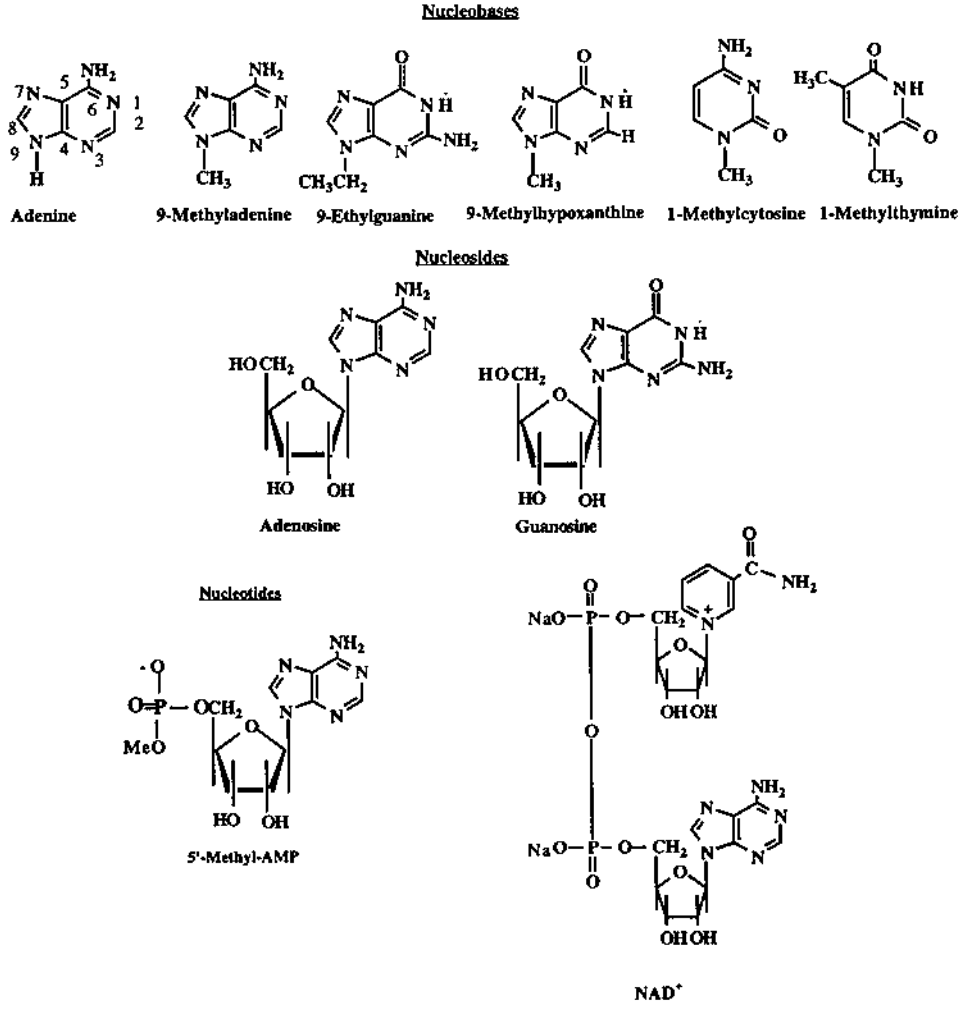
Scheme 1.

3. Reactions of the Cp*Rh aqua complexes with nucleobases, nucleosides, nucleotides, and nicotinamide adenine dinucleotide

*3.1. Cp*Rh cyclic trimers complexes of 9-substituted adenine compounds*

The chart provides the name and structures of many of the DNA/RNA bases utilized in these studies, as well as nicotnamide adenine dinucleotide (NAD^+), an important co-factor in biological redox reactions containing an adenine nucleus. We initiated the reactivity of the various nucleobases with 9-methyladenine (**9-MA**) and $[Cp^*Rh(H_2O)_3](OTf)_2$. The reaction of **9-MA** in D_2O at pD 7.2 provided, by

^{1}H-NMR spectroscopy, evidence for the formation of a Cp*Rh-9-MA complex with dramatic chemical shifts for H2 and H8 in comparison to free **9-MA** at 8.83 and 7.67 ppm, respectively. By utilizing **9-MA-*d*** that is selectively deuterated at H8, we were able to unequivocally assign the chemical shifts to each proton and show that H8 was shifted 0.75 ppm downfield from free **9-MA**, while H2 was shifted 0.47 ppm upfield. We later found that these dramatic chemical shifts were *a diagnostic characteristic for a Cp*Rh cyclic trimer structure*, and was verified by X-ray crystallography [18].



The above-mentioned cyclic trimer product was isolated and purified by recrystallization to yield an orange solid (26%) and then characterized by ^{1}H-NMR, FAB/MS ($m/z = 1456.7$; M–OTf), and single-crystal X-ray crystallography, to

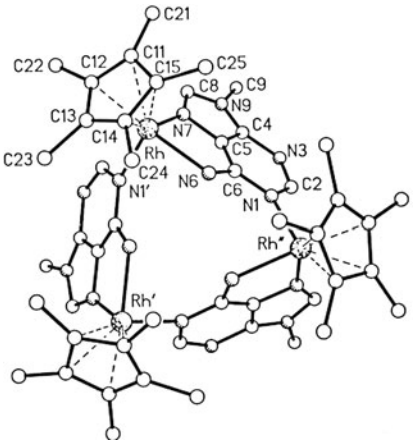


Fig. 1. X-Ray Structure of $[Cp^*Rh(\mu\text{-}\eta^1(N1):\eta^2(N6, N7)\text{-}9\text{-}MA]_3(OTf)_3$.

have, at the time, an unusual and unprecedented organometallic–nucleobase structure (Fig. 1). The single-crystal X-ray structure of an enantiomer, $[Cp^*Rh(\mu\text{-}\eta^1(N1):\eta^2(N6, N7)\text{-}9\text{-}MA]_3(OTf)_3$, was reported previously [18] and showed that it has a triangular dome-like supramolecular structure, with three Cp* groups stretching out from the top of the dome, three Me groups pointing to the bottom, three adenine planes forming the surrounding shell, and three Rh atoms embedded in the top of the dome. This molecule also possesses a C_3 axis, which passes from the top of the dome to the bottom. The distance between the adjacent methyl groups at the bottom of the dome; i.e. at the opening of this potential molecular receptor, is about 7.5 Å, while the cavity depth is a consequence of the substituent on N9 of the nucleobase, nucleoside, or nucleotide and is in the range of ca. 4 Å.

As well, both adenosine and the phosphate methyl ester of 5′-AMP, as further examples, also formed the cyclic trimer structures, $[Cp^*Rh(\mu\text{-}\eta^1(N1):\eta^2(N6, N7)\text{-}Ado/methyl\text{-}5'\text{-}AMP)]_3$ [18,21]. This was primarily determined by ^{1}H-NMR experiments of the Cp*Rh aqua complex, **1**; for example, with the nucleobase, adenosine (**Ado**), in D_2O at pD 7.1 that provided, by ^{1}H-NMR spectroscopy, similar dramatic chemical shifts for H8 (8.92 ppm) and H2 (7.62) that were observed for the unequivocally identified cyclic trimer, $[Cp^*Rh(\mu\text{-}\eta^1(N1):\eta^2(N6, N7)\text{-}9\text{-}MA]_3(OTF)_3$ (Fig. 2).

More recently, it came to our attention that no organometallic complexes of an important co-factor, nicotinamide adenine dinucleotide (NAD^+), containing the adenosine monophosphate group, have been assigned a definitive structure, although Ryabov and co-worker had attempted the reaction of NAD^+ with several Cp*Rh synthons [9,29]. Therefore, we reinvestigated this interesting reaction with co-factor NAD^+ and Cp*Rh aqua complex, **1**, using ^{1}H-NMR spectroscopy from pH 3 to 9.5 to show the presence of the definitive diastereomeric, cyclic trimer complex, $[Cp^*Rh(NAD)]_3(OTf)_3$, with an extremely narrow range of stability; i.e. pH 6.0. Again, the ^{1}H-NMR spectrum provided clear evidence for the cyclic trimer

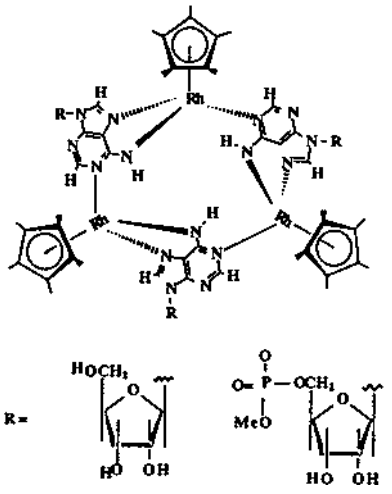


Fig. 2. $[Cp^*Rh(\mu\text{-}\eta^1(N1):\eta^2(N6, N7)\text{-Ado/methyl-5}'\text{-AMP})]_3$.

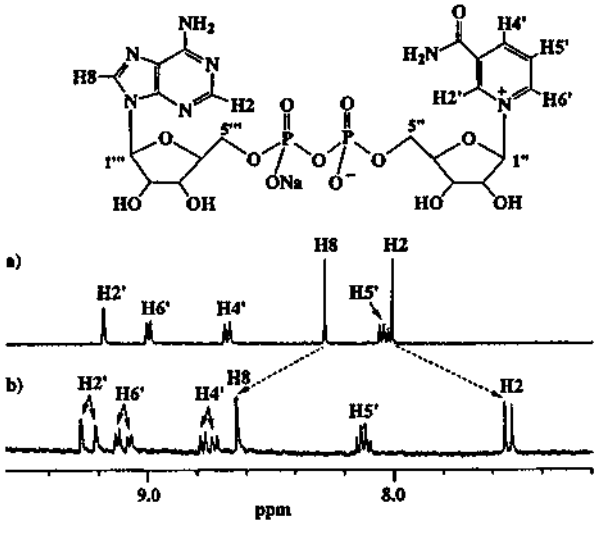


Fig. 3. ^{1}H-NMR spectrum of (a) NAD^+ and (b) $[Cp^*Rh(NAD)]_3(OTf)_3$, **3**. Both spectrum obtained at pH 6.0.

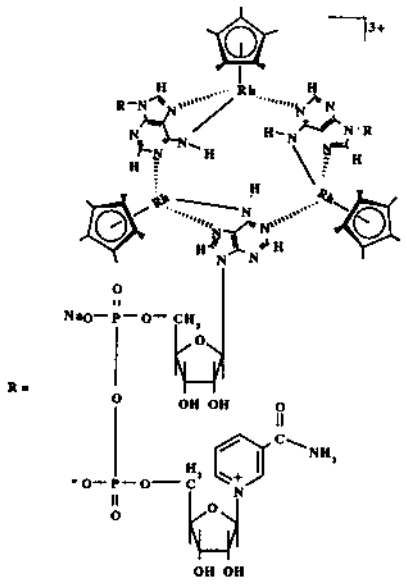


Fig. 4. $[Cp^*Rh(NAD)]_3(OTf)_3$.

structure with the dramatic downfield shift for H8 (in comparison to free NAD^+) of $\Delta\delta = 0.35$ ppm and the upfield shifted H2 of $\Delta\delta = 0.48$ ppm (Figs. 3 and 4) [30].

3.2. Cp*Rh–guanine and hypoxanthine complexes

In contrast to cyclic trimer formation for 9-substituted adenine compounds, it was found that the nucleoside, guanosine (**Guo**), reacted with the Cp*Rh aqua complex, **1**, at pH 5.4 to provide an isolated product that by elemental analysis and FAB-MS ($m/z = 670.1$, [Cp*Rh(Guo)(OTf)]; 556.1, [Cp*Rh(Guo)(OH)]), was a monomer with the formula [Cp*Rh(Guo)(OH)](OTf). The tentative structure was

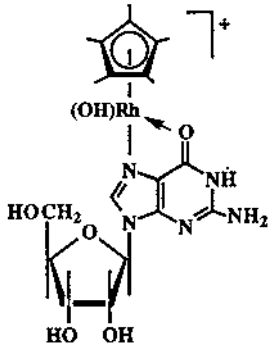


Fig. 5. [Cp*Rh(Guo)(OH)].

elucidated by 500 MHz ^{1}H-NMR spectroscopy in DMSO-d_6 to show a substantial downfield shift for H8 at 8.93 ppm ($\Delta\delta = 1.01$ ppm), which is consistent with N7 binding to the **Guo** nucleus. The NH1 group was also shifted downfield ($\Delta\delta = 0.53$ ppm) and this may be indicative of the 6-C=O group interacting with the Cp*Rh metal center as shown (Fig. 5) [18].

Moreover, an ^{1}H-NMR study was performed with 9-methylhypoxanthine (**9-MH**) and the ethyl anaolgue, since it would also allow us to determine the steric role, if any, of the NH_2 group at C2 of the guanine nucleus (**Guo**, 9-ethylguanine [**9-EG**]) and the bonding mode of NH1. The pH profile of Cp*Rh complex of **9-MH** was studied by

^{1}H-NMR in D_2O [23]. At pD 2.45–5.13, the downfield chemical shifts for both H8 (8.48 ppm, $\Delta\delta = 0.44$ ppm) and H2 (8.35 ppm, $\Delta\delta = 0.17$ ppm) compared to free **9-MH** (H8, 8.04 ppm and H2, 8.18 ppm) are consistent with exclusive N7 binding. However, at pD 6.45, the Cp*Rh-9-MH complex provides the dramatic chemical shifts we have found to be diagnostic for cyclic trimer formation, especially for H8 (downfield shift) and H2 (upfield shift) at 8.60 (H8, $\Delta\delta = 0.56$ ppm) and 7.78 ppm (H2, $\Delta\delta = 0.40$ ppm) as well at 3.73 ppm (9-CH_3, $\Delta\delta = 0.09$ ppm), and 1.84 ppm (Cp*) and strongly suggested the presence, at that time, of the unusual and unprecedented structure, [Cp*Rh-μ-η^1(N1):(η^2(O6, N7)-9- methylhypoxanthyl)]$_3^{3+}$, as unequivocally determined by single crystal X-ray analysis of the ethyl analogue (Fig. 6) [23].

Two structural features of the ethyl analogue, [Cp*Rh-9-ethylhypoxanthyl)]$_3^{3+}$, merit comment. First, the cationic portion had the similar triangular dome-like cavity, with three Cp* groups stretching out from the top of the dome, three ethyl groups pointing to the bottom, three hypoxanthine planes forming the surrounding shell, and three Rh atoms embedded on the top of the dome. The cation also possesses a C_3 axis, which passes from the top of the dome to the bottom. Secondly, the C6–O6 bond distance of 1.296(24) Å falls between the single bond distance of 1.42 Å, found in an alcohol, and the double bond distance of 1.233(4) and 1.230(7) Å, which were observed in inosine. This result suggests that a significant amount of multiple bond character still exists in the C6–O6 bond.

It is important to note that when 9-ethylguanine (**9-EG**) was also studied from pD 2.45 to 6.45, only N7 binding was evident, with no diagnostic chemical shifts for a cyclic trimer structure.

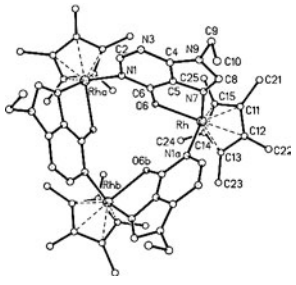


Fig. 6. [Cp*Rh-9-ethylhypoxanthyl)]$_3^{3+}$.

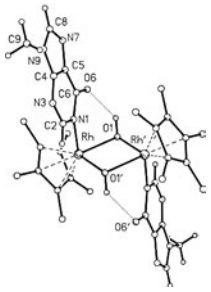


Fig. 7. $[(Cp^*Rh)(\eta^1(N1)\text{-}9\text{-}MH)(\mu\text{-}OH)]_2$.

Interestingly, at pD 10.50, a new Cp*Rh complex of **9-MH** was formed with significant upfield shifts of H8 and H2 that were reminiscent of a $[Cp^*Rh(\mu\text{-}OH)(L)]_2$ dimer complex, where L = 1-methylcytosine [19]. The single crystal X-ray structure of the orange dimer, $[(Cp^*Rh)(\eta^1(N1)\text{-}9\text{-}MH)(\mu\text{-}OH)]_2$, isolated from its aqueous reaction mixture at pH 10.2, is shown in Fig. 7. The main structural features of interest are the unique η^1(N1), rather than η^1(N7) or η^2(N7,O6) binding mode of **9-MH**, and the intramolecular H-bonding between the μ-OH groups and the O6 of this nucleobase.

The above-mentioned result suggests that the NH_2 group at C2 on the guanine nucleus (**9-EG**), whose steric and electronic effects have not been previously well defined during the metal coordination process, *plays a significant steric role*, in this instance, in preventing cyclic trimer formation at pD 6.45; steric rather than electronic due to NH1 pK_a similarities for **9-EG** and **9-MH**.

*3.3. Cp*Rh–cytosine complex*

In order to further establish the reactivity of an exocyclic NH_2 group (in comparison to C6–NH_2–adenine derivatives), we studied the reaction of **1** with 1-methylcytosine (**1-MC**) at pH 5.4 and was found to provide by ^{1}H-NMR, FAB/MS, elemental analysis, and single-crystal X-ray crystallography, a *trans*-μ-hydroxy dimer, with the formula *trans*-$[Cp^*Rh(1\text{-}methylcytosine)(\mu\text{-}OH)]_2(OTf)_2$ (Fig. 8). The 1-methylcytosine binds at N3 and forms intramolecular hydrogen bonds to the μ-OH with the NH_2 group and the μ-OH with the C=O group, but does not form a 4-membered chelate with N3/NH_2; clearly the extensive intramolecular hydrogen bonding of the donor and acceptor μ-OH groups with the NH_2 groups and the the C=O groups overrides any 4-membered chelate, and infact this complex was insoluble in and crystallized from water [19].

*3.4. Cp*Rh–thymine complex*

Reaction of **1** and 1-methylthymine at pH 10 provided one of the most surprisingly unusual and novel structures we discovered in all of our bioorganometallic studies [24]. Fig. 9 shows the reported X-ray crystal structure of the anionic and

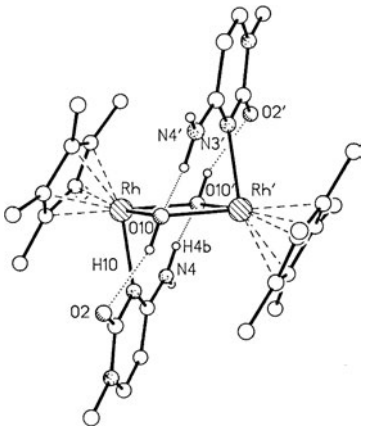


Fig. 8. *trans*-[Cp*Rh(η^1(N3)-1-methylcytosine)(μ-OH)]$_2$(OTf)$_2$.

cationic components, and *a key feature was the linear*, *N*1–*Rh*4–*N*3 *grouping* ([*Rh*(η^1, *N*3-1-*MT*)$_2$]$^-$), *with a bond angle of* 178.2(3)°, *and a near staggered* (98.8°) *configuration of two thymine planes with respect to one another*. Indeed, the two thymine planes are eclipsed, as required by its inversion symmetry. As well, the perpendicular geometry of the two thymine rings gave rise to an interesting stacking arrangement where the two thymine planes are π-stacked to either a Cp* ring of (Cp*Rh)$_2$(μ-OH)$_3$]$^+$ (three such interactions) or to a centrosymmetrically related thymine ring of another anion, which allows the Rh4 center to be shielded by a hydrophobic cavity generated from the five Cp* methyl hydrogens (Rh4–H distances range from 2.93 to 3.16 Å).

Shielding by the carbonyl oxygen lone pair electrons of the 1-MT ligands may also be of some importance; however, the four carbonyl oxygen atoms are hydrogen-bonded to H_2O molecules and none of these interactions are near the Rh4 atom. Moreover, the distances between the least-squared adjacent planes of the Cp* groups and the 1-MT ligands range from 3.45 to 3.58 Å, and the angles, from 0.0 to 2.9°, which agrees well with reported π–π aromatic ring molecular recognition interactions [24].

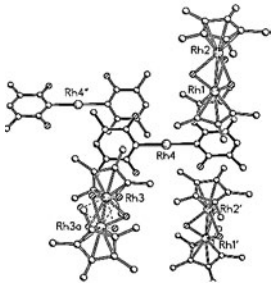
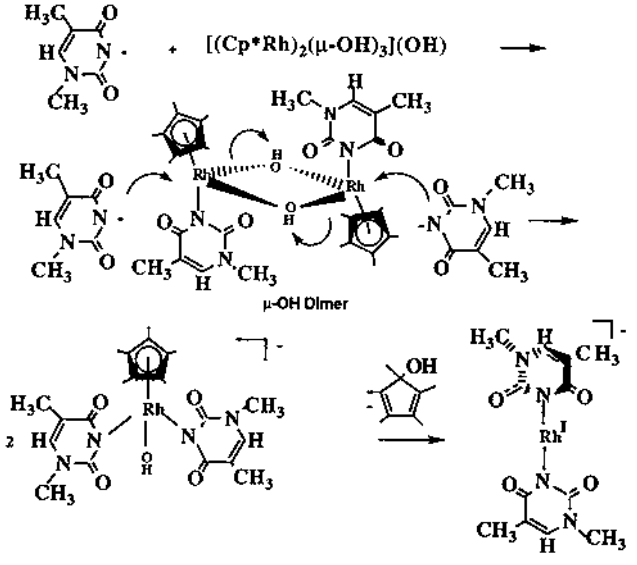


Fig. 9. 2[Rh(η^1, *N*3-1-MT)$_2$]$^-$ · 3[(Cp*Rh)$_2$(μ-OH)$_3$](OH).

The plausible mechanism for formation of the unique complex, [Rh(η^1, N3-1-MT)$_2$]$^-$, is shown in the Scheme 2. The mechanism can be tentatively rationalized by the following observations: The distillate of the reaction mixture was analyzed by GC/MS techniques and provided information that Cp*OH was formed (m/z = 151 and 135, for [M–H]$^+$ and [M–OH]$^+$) during the reaction; clear evidence for the loss of the Cp* ligand from Rh^{3+}. Thus, we speculate that reductive elimination, of Cp*OH from the putative mononuclear [Cp*Rh(1-MT)$_2$(OH)]$^-$ complex provided [Rh(η^1, N3-1-MT)$_2$]$^-$. This former complex, [Cp*Rh(1-MT)$_2$(OH)]$^-$, was thought to form via nucleophilic substitution of 1-MT$^-$ (pK_a 9.7) on the plausible and similarly precedented intermediate, *trans*-[Cp*Rh(μ-OH)(η^1, *N3*-1-MT)]$_2$, the presumed initial product from the reaction of 1-MT$^-$ with [(Cp*Rh)$_2$(μ-OH)$_3$](OH).

3.5. Cp*Rh–Adenine Complex

The recent report of the reaction of an η^6-aromatic ruthenium complex, [(*p*-cymene)RuCl$_2$]$_2$ with adenine in water (no pH was mentioned) with AgOTf, which gave an unusual tetramer, [(*p*-cymene)Ru(μ-η^1(N9):η^2(N6, N7)-adenine]$_4$(OTF)$_4$, as characterized by X-ray analysis [14], prompted us to study the reaction of **1** with adenine at pH ca. 9. Although we have not as yet been able to obtain an X-ray structure of this new Cp*Rh–adenine complex with a reliable *R* value, we are able to assign, from initial X-ray, ^{1}H-NMR, and electrospray ionization mass spectrometry analysis, the new Cp*Rh–nucleobase structure, [(μ-Cp*Rh)$_2$(μ-OH)$_2$(μ-η^1(N1):η^1(N7):η^1(N9)-adenine)]$_3$(OTf)$_4$. We tentatively believe that at pH ca. 9 we deprotonate adenine at N9, which then reacts with the insitu formed [(Cp*Rh)$_2$(μ-



Scheme 2.

$OH)_3$](OTf) to provide the self-assembled product observed. Basically, we envision the structure as two adenine nuclei that are parallel to each other, with each N1, N7, and N9 atom binding the $(Cp^*Rh)_2(\mu\text{-}OH)_2$ group orthogonal to the adenine plane (Fig. 10) [31]. This structure is an obvious candidate for molecular recognition studies and we intend to pursue this goal in the future.

4. Binding and competition experiments: nucleotides and nucleosides

In several binding studies, ^1H and ^{31}P-NMR experiments were conducted with Cp*Rh aqua complex, **1**, and nucleotides, 5′-guanosine monophosphate (**GMP**), 5′-cytidine monophosphate (**CMP**), and 5′-thymidine monophosphate (**TMP**) at pD 7.2 [32]. The ^1H and ^{31}P-NMR spectra show broadened and shifted signals at pD 7.2 for **GMP**, but only broadened ^{31}P-NMR spectra for **CMP** and **TMP**, and no shifts in the ^1H-NMR spectra. The broadened and only slightly shifted ^{31}P-NMR spectra may be consistent with a weak interaction of the $P-O^-$ group with a Cp*Rh complexed H_2O molecule during a fluxional process. Alternatively, **GMP** shows a ^1H-NMR spectrum with a downfield shift for H8 of $\Delta\delta = 0.6$ ppm, indicative of N7 bonding, as well as a broadened, slightly shifted ^{31}P-NMR signal for a similar weak interaction of a complexed H_2O molecule with the $P-O^-$ group as observed for **AMP**.

In attempts to define nucleotide and nucleoside selectivity for the Cp*Rh aqua complex, we carried out several competitive experiments via ^1H-NMR spectroscopy. Thus, competitive reactions of the Cp*Rh–AMP complex with free **GMP** (1:1 mmol) shows displacement of **AMP** and formation of the Cp*Rh–GMP complex, while **CMP** or **TMP** do not alter the ^1H-NMR spectrum of the Cp*Rh–AMP complex. Clearly, the Cp*Rh aqua complex prefers the following selectivity

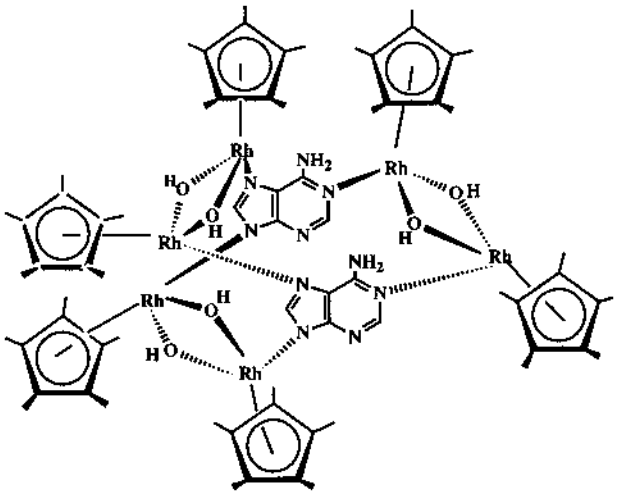


Fig. 10. $[(\mu\text{-}Cp^*Rh)_3(\mu\text{-}OH)_3(\mu\text{-}\eta^1(N1):\eta^1(N7):\eta^1(N9)\text{-adenine})]_2(OTf)_4$.

order: **GMP** > **AMP** > > > **CMP** ca. **TMP**. Moreover, the reaction of [Cp*Rh(Guo)(OH)](OTf), with one equivalent of **Ado** in D_2O at pD 7.3, provides the **Ado** cyclic trimer complex and displacement of the **Guo** ligand; a result opposite to that found with **AMP** and **GMP**. Therefore, we tentatively conclude that the differences between **AMP** and **Ado** in reactivity with **GMP** and **Guo**, respectively, must involve the absence of the phosphate group and the favorable formation of the very stable **Ado** cyclic trimer [32].

5. Molecular recognition of biological guests with the host, $[Cp^*Rh(2\text{-deoxyadenosine})]_3(OTf)_3$

When we discovered the cyclic trimer, 9-substituted adenine structures, having C_3 symmetry, we found that the X-ray/computer generated molecular models conveyed a supramolecular, bowl structure to this host and thought about the possibilities of non-covalent π–π, hydrophobic, and subtle hydrogen bonding interactions with biologically important guest molecules [26]. Indeed this was the case and; moreover, we found that the $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3$ complex was the best host available (Fig. 11 shows on the left, the Dreiding model, while on the right, the CPK model).

Therefore, a variety of guest aromatic and aliphatic amino acids, substituted aromatic carboxylic acids, and aliphatic carboxylic acids including examples such as L-phenylalanine, L-tryptophan (**L-Trp**), phenylacetic and cyclohexylacetic (**CAA**) acids were studied by ^{1}H-NMR spectroscopy (association constants [K_a] and free energies of complexation [$\Delta G°$]) for their non-covalent interactions with host, $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3$ [26]. Apparently, the aromatic groups interact by a classical π–π mechanism, while the aliphatic guests by classical hydrophobic interactions. The computer generated molecular recognition process of **L-Trp** with $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3$ was shown in the energy minimized, space-filling host and the docking of **L-Trp** (Fig. 12) [26]. These overall results suggest that the molecular recognition of **L-Trp** with $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3$ can be

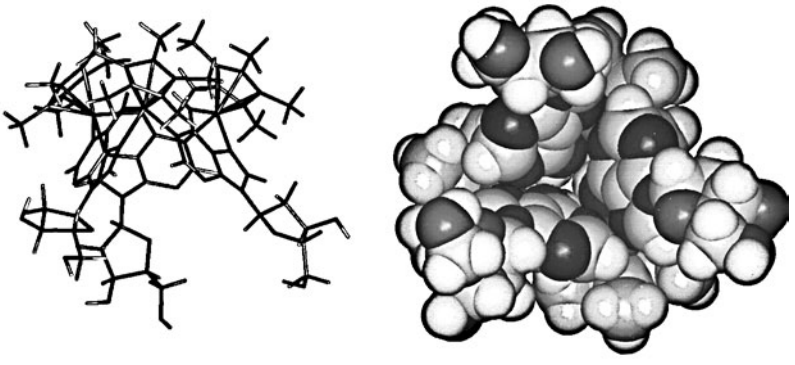


Fig. 11. $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTF)_3$.

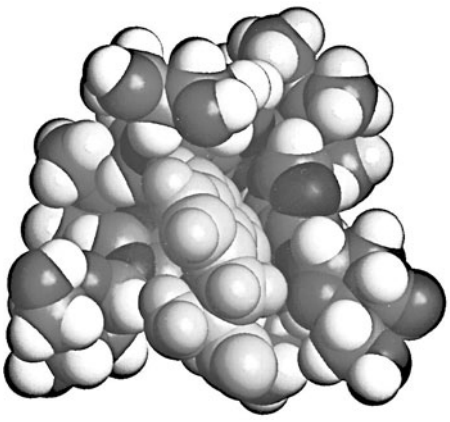


Fig. 12. Host–guest, $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3$·L-Trp.

described in a way that places the **L-Trp** aromatic rings inside of the host cavity with the aromatic plane, or more specifically, the line which bisects the C–H(a) and C–H(a′) bonds parallel to the C_3 axis of the host. Similar Dreiding and CPK models for the $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3$ hydrophobic interaction with **CAA** are shown in Fig. 13.

6. Conclusion

In this paper, we have reviewed our results concerning the new area of bio-organometallic chemistry of DNA/RNA bases/NAD^+ co-factor with Cp*Rh aqua complexes, as a function of pH. Since all of this organometallic chemistry occurs in H_2O, the relevance to biological systems is paramount. The structures we identified by single-crystal X-ray and by NMR/FAB/ESI-MS analysis, that occur as a

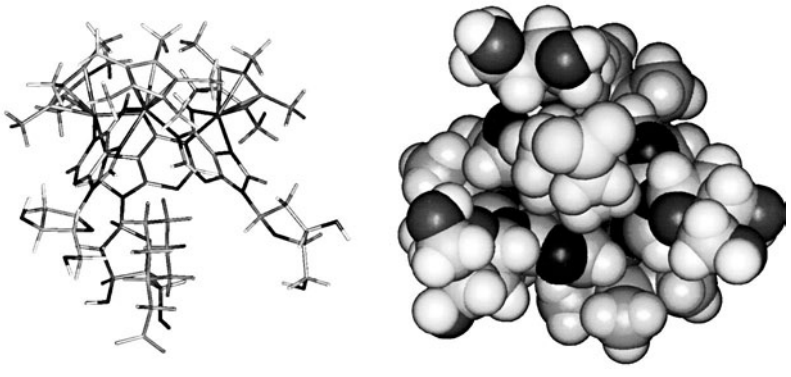


Fig. 13. Host–guest, $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3$·CAA.

function of pH, are unique and represent new vistas for aqueous organometallic chemistry. Finally, the ability of the [Cp*Rh(2′-deoxyadenosine)]$_3$(OTF)$_3$ cyclic trimer complex to act as a molecular receptor for biologically important compounds paves the way for the future utilization of this cyclic trimer as a new class of cyclodextrin mimics for potential prodrug delivery and as possible catalysts for phosphate ester hydrolysis [33]. As well, this molecular receptor, [Cp*Rh(2′-deoxyadenosine)]$_3$(OTF)$_3$, has been shown to have applications as an aqueous NMR shift reagent for a variety of aromatic and aliphatic carboxylic acids, as well as peptides [34].

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