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Synthesis and Infrared and Magnetic Resonance Studies of Organorhodium Complexes of Guanosine, Inosine, 1-Methylinosine, Purine, Adenine, and Adenosine

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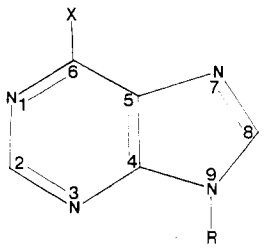
Solid complexes of the type $[Rh(PPh_3)_2(CO)L]PF_6$ (L = guanosine, inosine, 1-methylinosine, purine, adenine, adenosine) have been prepared by the reaction of nucleic base derivatives and $[Rh(PPh_3)_2(CO)_3]PF_6$ in a 1:1 ratio in CH_2Cl_2/CH_3OH. The complexes have been characterized by ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectroscopy and infrared spectroscopy in $(CD_3)_2SO$ and CH_2Cl_2. Data that support binding at O_6 of guanosine, inosine, and 1-methylinosine are presented. The binding preferences of the electrophile $[Rh(PPh_3)_2(CO)]^+$ are discussed in terms of possible steric interactions.

Introduction

The interaction of nucleic acid constituents with transition-metal complexes has become an area of considerable investigation in recent years.[1,2] The basis for this interest is growing evidence that the toxicity of some heavy metals and the antineoplastic activity of certain metal ions and complexes might involve interaction of the metal ions or complexes with DNA.

Nucleic acid constituents offer a variety of possible coordination sites for transition-metal complexation. In addition to nitrogen donor atoms in the purine and pyrimidine rings, several nucleic acid constituents and many of their important derivatives possess exocyclic donor atoms. The ribose and ribophosphate groups of nucleosides and nucleotides also possess potential binding sites. The ability of the various donor atoms to act as sites of complexation has generally been found to depend on the following factors: (a) the relative basicity of the individual donor atoms, (b) steric interactions between exocyclic groups on the nucleic base or nucleoside and other ligands in the coordination sphere, and (c) attractive or repulsive forces acting between the exocyclic groups on the nucleic base or nucleoside and other coordinated ligands.[1-6] Due to these factors and the possibility of delocalization of electron density in the heterocyclic rings, it is generally difficult to predict which site will indeed be the binding site for a given metal complex.

This study was undertaken in order to examine additional factors affecting the interactions of heavy metals with nucleic acid constituents. In this investigation we have used the unifunctional electrophile carbonylbis(triphenylphosphine)rhodium(I) cation, $[Rh(PPh_3)_2(CO)]^+$, to study the binding properties of the following nucleic acid constituents: purine (**1**, X = R = H), adenine (**1**, X = NH_2, R = H), adenosine



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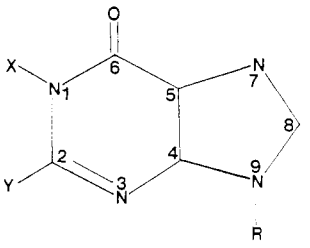

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(**1**, X = NH_2, R = ribose), guanosine (**2**, X = H, Y = NH_2, R = ribose), inosine (**2**, X = H, Y = H, R = ribose), 1-methylinosine (**2**, X = CH_3, Y = H, R = ribose). It was thought that the bulkiness of the triphenylphosphine ligands could create steric restraints that might lead to coordination at sites different from those observed for simple metal ions or less sterically demanding metal complexes.

Experimental Section

Materials. Guanosine (Guo), inosine (Ino), 1-methylinosine (1-MeIno), purine (Pur), adenine (Ade), and adenosine (Ado) were obtained from Sigma Chemical Corp. and were used without further purification. $[Rh(PPh_3)_2(CO)_3]PF_6$ was prepared according to the procedure of Schrock and Osborn.[7]

Methods. ^1H NMR and ^{31}P NMR spectra were measured on a JEOL FX90Q Fourier transform (FT) spectrometer. ^1H NMR spectra were recorded at 89.55 MHz, with $(CH_3)_4Si$ as an internal standard. ^{31}P NMR spectra were obtained at 36.19 MHz, with 85% H_3PO_4 as the external standard. ^{13}C NMR spectra were measured at 22.51 MHz by using a JEOL FX90Q FT spectrometer or at 15.09 MHz by using a Nicolet TT-14 FT spectrometer. $(CH_3)_4Si$ was used as the internal standard for all ^{13}C NMR spectra. All spectra were obtained at room temperature with 0.15 M solutions. Infrared (IR) spectra were measured with use of a Digilab FTS-20 C/V FT IR spectrometer. IR liquid cells equipped with NaCl or KBr plates were used to obtain $(CD_3)_2SO$ and CH_2Cl_2 solution spectra. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Preparation of Complexes. All rhodium(I) complexes of nucleic bases and their derivatives were prepared by the same procedures. To a solution of 0.500 g of $[Rh(PPh_3)_2(CO)_3]PF_6$ in 5 mL of dichloromethane in a 250-mL flask was added an equimolar amount of the appropriate ligand suspended in 25 mL of methanol. The mixture was stirred for 5–12 h. After the ligand dissolved and no further evolution of CO was observed, the solution was taken to dryness on a rotary evaporator, yielding a yellow solid. After the yellow solid was dissolved in dichloromethane, the volume of the solution was reduced. The product, which precipitated upon addition of ether, was recrystallized from dichloromethane/ether. Yields were 80–90%.

Results and Discussion

Preparation of Complexes. Earlier work by Shrock and Osborn[7] with rhodium(I) and rhodium(II) complexes pointed out the ease of formation of complexes of the type $[Rh(PPh_3)_2(CO)L]PF_6$ (where L is a neutral base) from $[Rh(PPh_3)_2(CO)_3]PF_6$. Monocarbonyl complexes can be prepared with bases as weak as acetone and acetonitrile. The monocarbonyl complexes have square-planar geometries with the triphenylphosphine ligands in a trans disposition.

The fact that nucleic acid constituents contain several possible sites of complexation led us to believe that solid monocarbonylrhodium(I) complexes of nucleic acid constituents could be isolated and characterized. Several of these complexes have indeed been prepared according to eq 1. The

$$[Rh(PPh_3)_2(CO)_3]PF_6 \xrightarrow[CH_2Cl_2,CH_3OH]{L} [Rh(PPh_3)_2(CO)L]PF_6 \quad (1)$$

(1) Marzilli, L. G. *Adv. Inorg. Biochem.* **1981**, *3*, 47.
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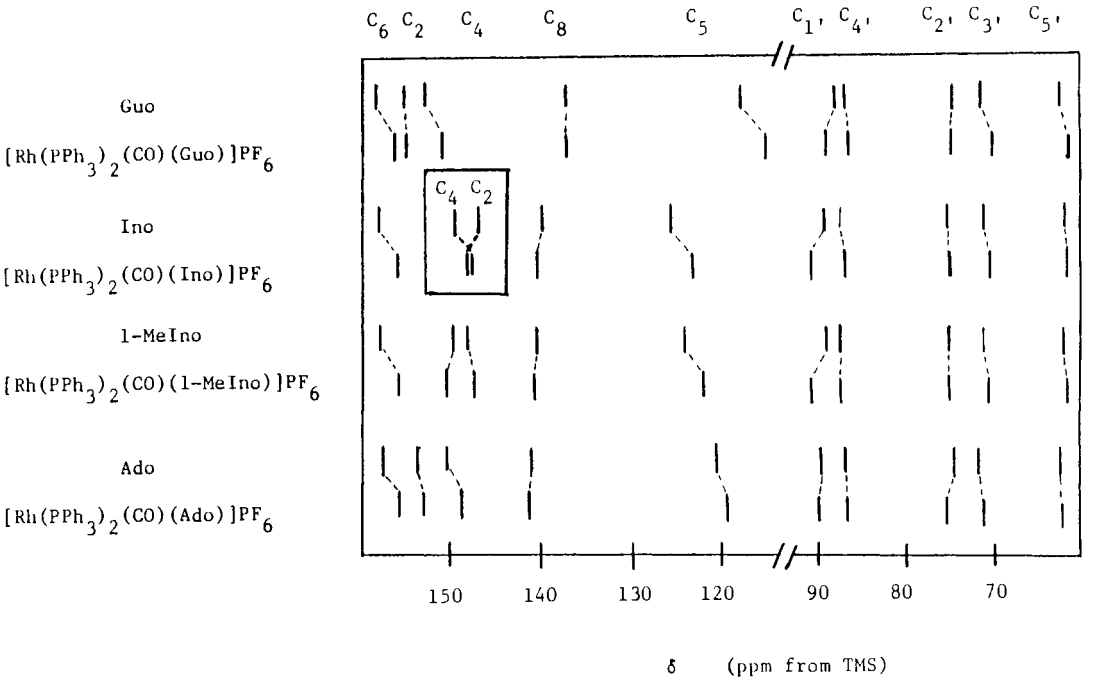

Figure 1. ^{13}C NMR spectral chart for Rh(I)–nucleoside complexes.

Table I. Elemental Analysis of Rh(I) Complexes

compd		%C	%H	%N
$[Rh(PPh_3)_2(CO)(Guo)]PF_6$	calcd	52.04	4.00	6.46
	found	51.72	4.34	6.31
$[Rh(PPh_3)_2(CO)(Ino)]PF_6$	calcd	52.82	3.87	5.24
	found	52.26	4.36	5.07
$[Rh(PPh_3)_2(CO)(1\text{-MeIno})]PF_6$	calcd	53.25	4.10	5.17
	found	52.15	4.37	5.05
$[Rh(PPh_3)_2(CO)(Ado)]PF_6$	calcd	52.87	4.15	6.56
	found	51.80	4.61	6.33
$[Rh(PPh_3)_2(CO)(Pur)]PF_6$	calcd	54.80	3.72	6.09
	found	54.43	4.11	6.07
$[Rh(PPh_3)_2(CO)(Ade)]PF_6$	calcd	53.32	3.82	7.58
	found	53.87	3.98	7.39
$[Rh(PPh_3)_2(CO)(cyclohexanone]PF_6$	calcd	56.16	4.49	
	found	56.78	4.41	

analytical data for the complexes are given in Table I. The complexes have a characteristic yellow color and are readily isolated and recrystallized from CH_2Cl_2.

Guanosine, Inosine, and 1-Methylinosine Complexes. Infrared studies[8-10] have shown that in neutral solution the keto form is predominant for Guo and Ino and exclusive for 1-MeIno. In neutral solution, N_1 of the keto tautomer is not a likely binding site due to protonation in Guo and Ino and methylation in 1-MeIno, while N_3 is not a probable binding site because of its weak basicity and relative inaccessibility due to the presence of the ribose moiety. Therefore, N_7 and O_6 are the most probable sites of complexation by a metal ion. Past investigations of the interactions of Guo and Ino with various transition metals have shown N_7 to be the preferred binding site since it is the most basic site available in neutral solution.[1-4,11,12] There appears to be little evidence of metals binding exclusively at O_6 of Guo and Ino in neutral solution, though Marzilli and co-workers[13] have recently reported evidence for metal ions binding at O_6 under basic conditions in $(CD_3)_2SO$. Earlier reports of transition-metal interaction at O_6 via chelate ring formation are largely unsubstantiated.[2,3]

In this study we have used ^1H NMR, ^{13}C NMR, ^{31}P NMR, and infrared spectroscopy to determine the nature of rhodium(I) complexes of nucleosides in $(CD_3)_2SO$. The solvent $(CD_3)_2SO$ is one of the few solvents in which both ligands and complexes are sufficiently soluble to yield ^{13}C NMR spectra. Also, $(CD_3)_2SO$ has been shown to minimize the nucleic base stacking effects, which occur in aqueous solution.[14] Proton exchange between solvent and base is precluded in $(CD_3)_2SO$, although $(CD_3)_2SO$ can participate in hydrogen bonding with the nucleic base derivatives.[15] The reference state is taken to be the one in which the base is hydrogen bonded to the solvent, and further changes in the spectra of the base are attributed to interactions with the metal ions.

The use of ^{13}C NMR chemical shift data has been shown to be a valuable tool in identifying binding sites in nucleic bases.[11-13] Caution must be exercised in assigning binding sites exclusively on the basis of ^{13}C chemical shift data. However, in general, the proximity of a given atom to the site of coordination is indicated by the magnitude of the change in its chemical shift. Table II summarizes the ^{13}C chemical shift data for the Guo, Ino, and 1-MeIno ligands and their rhodium(I) complexes. Spectral comparisons are presented in Figure 1. The NMR peak assignments are based on previous work.[16,17]

The absence of complexation to the ribose moiety in the nucleosides is demonstrated by the relatively small shifts of the ribose carbon resonances. For the Guo complex, the largest shift occurs for C_5 (2.7 ppm upfield). An almost equally large shift is observed for C_6 (2.1 ppm upfield). Buncel and coworkers[11] reported that, in complexes of $MeHg^{II}$ with Guo and Ino, coordination of the positively charged mercury species

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Table II. ^{13}C NMR Chemical Shifts for Rh(I)-Nucleoside Complexes

		δ^a									
		base carbon atoms					ribose carbon atoms				
compd	solvent	C_6	C_2	C_4	C_8	C_5	C_1'	C_4'	C_2'	C_3'	C_5'
Guo	Me_2SO-d_6	156.9	153.7	151.4	135.7	116.8	86.6	85.3	73.8	70.5	61.5
$[Rh(PPh_3)_2(CO)(Guo)]PF_6$	Me_2SO-d_6	154.8	153.5	149.7	136.1	114.1	87.2	84.9	73.5	69.3	60.8
	CH_2Cl_2	154.8	153.6	148.9	136.8	116.5	91.4	87.5	74.9	71.7	62.9
Ino	Me_2SO-d_6	156.6	145.8	148.2	138.7	124.5	87.6	85.6	74.1	70.3	61.3
$[Rh(PPh_3)_2(CO)(Ino)]PF_6$	Me_2SO-d_6	154.5	146.7	146.3	139.0	121.7	88.3	85.3	73.8	69.4	60.8
	CH_2Cl_2	154.4	146.9	146.5	139.1	123.5	91.3	87.5	75.1	71.2	62.5
1-MeIno	Me_2SO-d_6	156.3	148.7	147.5	139.1	122.9	87.3	85.5	74.0	70.2	61.2
$[Rh(PPh_3)_2(CO)(1\text{-MeIno})]PF_6$	Me_2SO-d_6	154.4	149.1	146.3	139.3	120.8	88.2	85.4	73.8	69.6	60.9
Ado	Me_2SO-d_6	156.2	152.4	149.1	139.9	119.4	88.0	85.9	73.5	70.7	61.7
$[Rh(PPh_3)_2(CO)(Ado)]PF_6$	Me_2SO-d_6	153.9	151.4	147.3	139.9	118.1	88.1	85.3	73.8	69.8	61.1

[a] Chemical shifts are measured from $(CH_3)_4Si$ internal standard at 15.09 MHz.

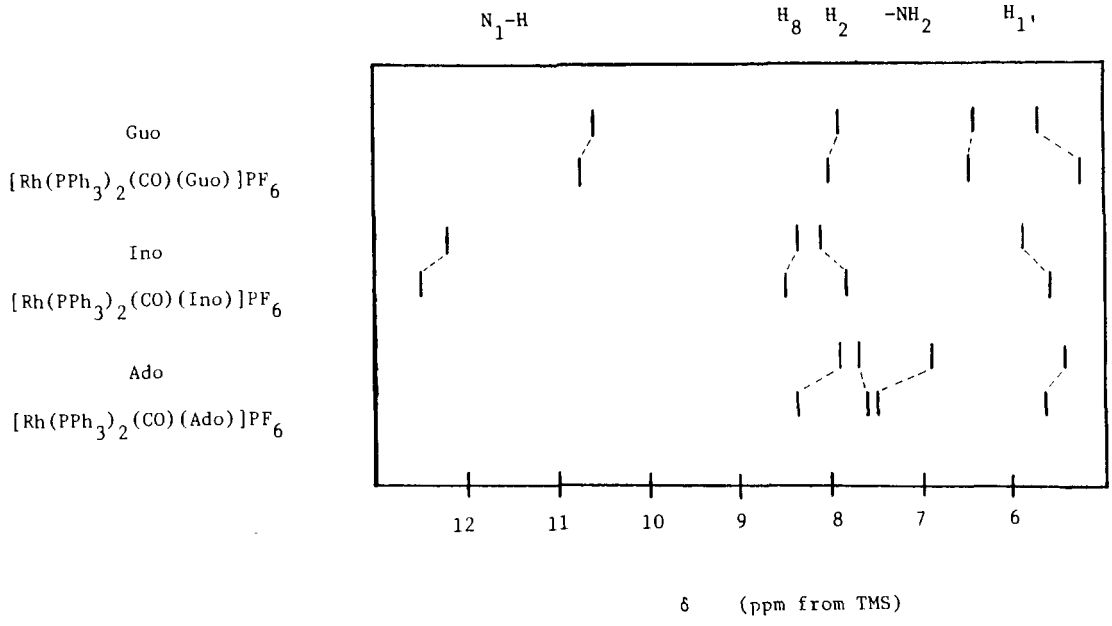

Figure 2. ^1H NMR spectral chart for Rh(I)–nucleoside complexes.

at N_7 results in relatively large shifts for C_8 (3 ppm downfield), while the other carbon resonances are affected to a lesser extent. When the $MeHg^{II}$ coordinates to N_1, after removal of H_1, large shifts in C_6 and C_2 are observed. Since the C_8 and C_2 resonances in the Rh(I)–Guo complex shift by only 0.4 and 0.2 ppm, respectively, neither N_7 nor N_1 (with removal of H_1) is implicated as the binding site. Because of possible steric interaction with the ribose group it is highly unlikely that N_3 is the binding site. The negligible shift in the C_2 resonance is consistent with the lack of coordination at N_3. The only remaining potential binding site is O_6. Binding at O_6 in Guo could explain the large shifts in the C_6 and C_5 resonances since these carbons are closest to the proposed binding site and would therefore be expected to show the largest resonance shifts. The lack of shift in the C_2 and C_8 resonances confirms their remoteness to the binding site in Guo.

For the Ino system, the largest shifts also occur at C_5 (2.8 ppm upfield) and C_6 (2.1 ppm upfield). The lack of an appreciable shift in C_8 rules out N_7 as the binding site for Ino. As in the case of the Guo system, the ^{13}C NMR data implicate O_6 as the binding site on Ino.

Binding at N_1, accompanied by loss or shift of the N_1 proton, cannot be completely ruled out on the basis of the ^{13}C data. So that the possibility of binding at N_1 via proton shift could be explored, the 1-MeIno complex was investigated since methyl migration would seem to be less likely than proton shift. The 1-MeIno complex, like the Guo and Ino complexes, exhibits the largest shifts for C_5 (2.1 ppm upfield) and C_6 (1.9 ppm upfield), with C_2 being essentially unaffected. The fact that C_8 in the 1-MeIno does not shift upon complexation virtually eliminates N_7 as the binding site. The similarities in the shifts of C_5 and C_6 for Ino and 1-MeIno suggest that the binding sites in the Ino and 1-MeIno complexes are the same, O_6.

Complementary ^1H NMR data are given in Table III, and comparisons of spectral shifts are shown in Figure 2. Buncel and co-workers[11] report that coordination at N_7 by $MeHg^{II}$ results in large downfield shifts of the H_8 and the N_1–H resonances of Guo and Ino and the exocyclic NH_2 resonance of Guo. These shifts are believed to result from changes in electron density in the ring system that occur as a result of alkylation or metalation at N_7.[11,18,19] Shifts in the proton resonances of the Guo, Ino, and 1-MeIno rhodium(I) complexes examined in this study are not comparable to those observed for the $MeHg^{II}$ complexes. This observation is consistent with the lack of coordination at N_7 for the rhodium(I) complexes. The Rh(I)–Guo system shows the greatest shift in the N_1–H resonance (0.11 ppm). In the Ino system, N_1–H and H_2 show identical shifts of 0.27 ppm, whereas H_8 only changes by 0.01 ppm. The H_8 and H_2 resonances for the

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Table III. ^{1}H NMR Chemical Shifts for Rh(I)–Nucleoside Complexes

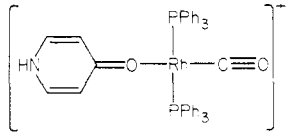
compd	$\delta^{a,b}$ N_1-H	NH_2	H_8	H_2	$H_{1'}$
Guo	10.61[c]	6.44	7.93		5.73 (d)
$[Rh(PPh_3)_2(CO)(Guo)]PF_6$	10.72[c]	6.47	7.99		5.26 (d)
Ino	12.23[c]		8.36	8.10	5.90 (d)
$[Rh(PPh_3)_2(CO)(Ino)]PF_6$	12.50[c]		8.46	7.83	5.61 (d)
Ado		6.92	7.91	7.71	5.45 (d)
$[Rh(PPh_3)_2(CO)(Ado)]PF_6$		7.50	8.35	7.60	5.62 (d)

[a] Chemical shifts are measured in Me_2SO-d_6 from $(CH_3)_4Si$ internal standard at 89.55 MHz. [b] All resonances are singlets unless otherwise indicated; d = doublet. [c] Very broad peaks.

1-MeIno complex cannot be assigned with certainty due to their proximity to the intense resonances of the triphenylphosphine groups. Even though the proton shifts are smaller and less definitive than the ^{13}C shifts, the available proton NMR data are suggestive of binding at a site other than N_7.

If the nucleosides are complexing through O_6 in the Guo, Ino, and 1-MeIno systems, it is expected that such binding will manifest itself in the carbonyl stretching region of the IR spectra of the complexes. Although some changes between the free and complexed ligands are evident in the solid-state spectra, these changes are inconclusive since Guo has been shown to exist in at least two crystalline forms with quite different spectra in the 1000–1500-cm^{-1} region.[20] Canty and co-workers[20] have shown that the spectrum of Guo in this region is highly sensitive to hydrogen-bonding effects. Schrock and Osborn[7] have prepared complexes of the type $[Rh(PPh_3)_2(CO)L]PF_6$, where L = acetone, dimethylformamide, and dimethylacetamide, in which coordination through the oxygen lone pairs leads to a lowering of ν(C=O) by only 25–50 cm^{-1} upon complexation. Surprisingly, the solution IR spectra of the Guo, Ino, and 1-MeIno system in $(CD_3)_2SO$ exhibit little difference between ν(C=O) of the free ligands and those of the complexed ligands.

For further exploration of the likelihood of a negligible change in ν(C=O) upon complexation with rhodium(I) species, two additional complexes, $[Rh(PPh_3)_2(CO)$(cyclohexanone)$]PF_6$ and $[Rh(PPh_3)_2$(4-hydroxypyridine)$]PF_6$, were studied. No significant change in ν(C=O) (1710–1706 cm^{-1}) of cyclohexanone in $(CD_3)_2SO$ is observed upon complexation with $[Rh(PPh_3)_2(CO)]^+$. When 4-hydroxypyridine is coordinated to $[Rh(PPh_3)_2(CO)]^+$, two complexes are formed, one of which is the pyridone complex.[21]



The pyridone form of 4-hydroxypyridine has been shown to be the dominant form in solution.[22] The stretching frequency ν(C=O) occurs at 1638 cm^{-1} for the free pyridone ligand in $CHCl_3$[23] and also at 1638 cm^{-1} for the pyridone ligand in the complex in $CHCl_3$.[21] Since coordination occurs at the oxygen for the cyclohexanone and pyridone ligands, the negligible shifts in ν(C=O) when these ligands are complexed give credence to the conclusion that the electrophile $[Rh(PPh_3)_2(CO)]^+$ can coordinate to the exocyclic oxygen of Guo, Ino, and 1-MeIno without causing significant change in the carbon–oxygen stretching frequency.

Table IV. ^{31}P NMR Chemical Shifts and Coupling Constants of Rh(I) Complexes

compd	solvent	δ^a	J(Rh-P), Hz
$[Rh(PPh_3)_2(CO)(Guo)]PF_6$	Me_2SO-d_6	31.20	126.98
	CH_2Cl_2	31.14	126.95
$[Rh(PPh_3)_2(CO)(Ino)]PF_6$	Me_2SO-d_6	30.90	126.39
$[Rh(PPh_3)_2(CO)(1\text{-MeIno})]PF_6$	Me_2SO-d_6	30.87	131.83
$[Rh(PPh_3)_2(CO)(Ado)]PF_6$	Me_2SO-d_6	30.36	121.39
$[Rh(PPh_3)_2(CO)(Pur)]PF_6$	Me_2SO-d_6	32.21	126.96
	CH_2Cl_2	30.94	126.95
$[Rh(PPh_3)_2(CO)(Ade)]PF_6$	Me_2SO-d_6	32.20	126.96
$[Rh(PPh_3)_2(CO)((CD_3)_2SO)]PF_6$	Me_2SO-d_6	28.65	126.95

[a] Chemical shifts are reported in ppm from 85% H_3PO_4 external standard at 36.19 MHz.

One possible reason for the lack of shift in ν(C=O) of Guo, Ino, and 1-MeIno is replacement of the coordinated ligands with solvent molecules. If rapid solvent–ligand exchange were occurring, the observed ^{13}C NMR and ^{1}H NMR chemical shifts would be time-averaged values of the free and complexed ligands. So that the possibility of solvent–ligand exchange could be examined, NMR spectra were obtained for the rhodium(I) complexes dissolved in CH_2Cl_2. The nucleosides are insoluble in CH_2Cl_2, although the complexes are soluble. Since CH_2Cl_2 is generally considered to be a poor coordinating ligand, it is not expected that CH_2Cl_2 will displace the nucleosides from the complexes. Spectral data summarized in Table II allow comparisons of ^{13}C NMR chemical shifts of the Guo and Ino complexes in $(CD_3)_2SO$ and CH_2Cl_2. The small differences that are observed can probably be attributed to solvent effects caused by differences in polarity and solvating properties of the two solvents rather than solvent–ligand exchange. For comparison purposes, IR spectra were also obtained on the CH_2Cl_2 solutions of the nucleoside complexes. Small differences in $\nu(C_6{=}O)$ were observed for the different solvents, but these differences are conceivably due to solvent effects.

For further investigation of the possibility of solvent exchange, the complex $[Rh(PPh_3)_2(CO)((CD_3)_2SO)]PF_6$ was investigated. The ^{31}P NMR data given in Table IV show noticeable differences in the ^{31}P chemical shift of the $(CD_3)_2SO$ complex and the nucleoside or nucleic base complexes. The absence of the ^{31}P resonances attributable to $[Rh(PPh_3)_2(CO)((CD_3)_2SO)]PF_6$ in $(CD_3)_2SO$ solutions of the nucleic base complexes indicates that the solvent has not replaced the nucleic bases. If rapid solvent–ligand exchange were occurring, the ^{31}P NMR chemical shifts would be time-averaged values of the $(CD_3)_2SO$ and the nucleic base complexes. A time-averaged ^{31}P chemical shift of the nucleic base complex in $(CD_3)_2SO$ would be expected to occur upfield of the chemical shift measured in CH_2Cl_2 under conditions of no exchange. The results in Table IV show that the ^{31}P chemical shifts for the Guo and Pur complexes in $(CD_3)_2SO$ are not averaged values. In fact, the chemical shifts in $(CD_3)_2SO$ are slightly downfield from the values in CH_2Cl_2; thus, substitution of the nucleic base is not occurring in $(CD_3)_2SO$.

Adenosine, Purine, and Adenine Complexes. In many cases, transition-metal binding to adenosine has been shown to occur through N_7 even though N_1 is more basic and might be expected to be the binding site.[1-4,24-26] Binding at N_7 may be enhanced when other ligands in the coordination sphere of the metal can engage in hydrogen bonding with the exocyclic amine group.[27-29] There is less evidence that implicates the

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Table V. ^{13}C Chemical Shifts for Rh(I) Complexes of Purine and Adenine

compd	δ[a]				
	C_4	C_2	C_8	C_6	C_5
Pur	154.8	152.1	146.2	145.6	130.4
$[Rh(PPh_3)_2(CO)(Pur)]PF_6$	153.9	152.0	147.6	142.5	132.0
Ade	151.3	152.4	139.3	155.3	
$[Rh(PPh_3)_2(CO)(Ade)]PF_6$		151.3	142.0		

[a] Chemical shifts were measured in Me_2SO-d_6 at 15.09 MHz with $(CH_3)_4Si$ as the internal standard.

exocyclic amine in Ado as the exclusive binding site. The electron pair on the NH_2 is not readily available for donation since it is delocalized into the ring.[2] It has been proposed, however, that the exocyclic amine in conjunction with N_7 can be used in chelate formation with certain transition metals.[14]

The ^{13}C NMR data (Table II) for $[Rh(PPh_3)_2(CO)(Ado)]PF_6$ suggest that coordination occurs at N_1. The largest shift is observed for C_6 (2.3 ppm upfield). Upfield shifts of 1.0, 1.8, and 1.3 ppm are observed for C_2, C_4, and C_5, respectively. The fact that C_8 does not shift virtually eliminates N_7 as the binding site. Again, N_3 is not considered to be a likely site of complexation because of steric factors and the low basicity of the site. The ^1H NMR data for the Ado system show that the largest proton shift occurs for the exocyclic NH_2 resonances (0.58 ppm downfield). A downfield shift of 0.44 ppm is observed for H_8, and an upfield shift of 0.11 ppm is observed for H_2. Because of the small shifts involved, the ^1H NMR results are not conclusive, yet they cannot be interpreted as being contradictory to the conclusions based on the ^{13}C NMR data.

In view of the observations that $[Rh(PPh_3)_2(CO)_3]PF_6$ readily reacts with very weak bases and that coordination to Ado has been observed at N_7 for some metals, it was of interest to see whether alkylation of Ado at N_1 would lead to coordination at N_7. All attempts to synthesize the 1-MeAdo complex were unsuccessful. The lack of formation of a 1-MeAdo complex supports the conclusion that binding occurs at N_1 in the Ado complex and that steric hindrance might be a factor in the lack of coordination at N_7.

Since purine and adenine do not present the same potential steric problems as adenosine, the Pur and Ade complexes were investigated. The absence of the ribose group makes N_3, even though weakly basic, a possible coordination site. The absence of an exocyclic group at C_6 in purine virtually eliminates the steric differences between N_1 and N_7.[6] It is therefore expected that the most basic sites of Pur, N_7 or N_9, are the favored sites for complexation.

The ^{13}C NMR peak assignments[30] and chemical shift data are presented in Table V. These results reveal that in the case of Pur the largest resonance shifts occur for C_6 (3.1 ppm upfield), C_5 (1.6 ppm downfield), and C_8 (1.4 ppm downfield). The shifts in C_6 and C_8 are in the same direction and are of comparable magnitude to those observed by Buncel and coworkers[11] for C_6 and C_8 in the $MeHg^{II}$ complexes of Guo and Ino when binding occurs at N_7. The similarity in these results implicates N_7 as the binding site on Pur. The negligible shift in C_2 (0.1 ppm upfield) virtually eliminates N_1 and N_3 since a larger shift in C_2 is expected for coordination at these sites. The ^1H NMR data on the Pur complex are not useful in assigning the binding site since the ligand resonances are masked by the intense triphenylphosphine resonances. However, other work involving transition-metal interactions with nucleic bases suggests that purine and its derivatives preferentially bind through N_9 and/or N_7 rather than N_1.[1-4,26,31,32]

The ^{13}C NMR spectrum of Ade shows four resonances (Table V). These are assigned to C_6, C_2, C_4, and C_8 by comparison with previous results.[16] The spectrum of the rhodium(I) complex shows only two of these four resonances. These two resonances, at 151.3 and 142.0 Hz, are assigned to C_2 and C_8, respectively. On the basis of this assignment, C_8 exhibits a large shift of 2.7 ppm downfield, while C_2 exhibits a smaller shift of 1.1 ppm upfield. The large shift in C_8 implicates a site adjacent to C_8, N_7 or N_9, as the binding site.

For purine derivatives, it appears that N_7 is a possible site of complexation for $[Rh(PPh_3)_2(CO)]^+$ only in the absence of the ribose group. This is true even when N_7 is the most basic available coordination site, as is the case for Guo, Ino, 1-MeIno, and 1-MeAdo. In the absence of the ribose moiety, coordination of $[Rh(PPh_3)_2(CO)]^+$ to the nucleic bases occurs at the most basic site, as expected. As illustrated by the Ado complex, the ribose group does not prevent complexation at N_1.

The stability of the complexes of Pur, Ade, and Ado in $(CD_3)_2SO$ was investigated by the methods discussed earlier. No indication of solvent exchange for these ligands was evident. The ^{31}P NMR resonances of $[Rh(PPh_3)_2(CO)(Pur)]PF_6$ are essentially the same in $(CD_3)_2SO$ as they are in CH_2Cl_2. The small change seen in the ^{31}P chemical shifts between the solvents is in the direction opposite to that expected for ligand–solvent exchange.

It was hoped that the coupling between ^{103}Rh ($I = {}^1/_2$, 100%) and ^{31}P would provide additional insight into the nature of the complexes; however, the ^{31}P chemical shift and the rhodium–phosphorus coupling constant do not appear to be useful diagnostic tools for these types of complexes.

Concluding Remarks. The relative basicity of the various binding sites in nucleic bases has generally been found to be the deciding factor in determining the sites of complexation. Steric factors and other interactions such as hydrogen bonding and chelation can preclude the prediction of the binding site for a given metal complex. The present work provides further evidence that predicting binding sites on nucleic bases is not routine. The IR and ^1H, ^{13}C, and ^{31}P NMR data for $[Rh(PPh_3)_2(CO)(Guo)]PF_6$, $[Rh(PPh_3)_2(CO)(Ino)]PF_6$, and $[Rh(PPh_3)_2(1\text{-MeIno})]PF_6$ are consistent with coordination at O_6. These systems appear to be among the few where binding apparently occurs exclusively at O_6 in neutral solution. Complexation of the bulky $[Rh(PPh_3)_2(CO)]^+$ moiety to Ado occurs at N_1, the most basic site, but apparently cannot be forced to bind at N_7 when N_1 is alkylated. This behavior, and the O_6 binding in Guo, Ino, and 1-MeIno, is probably due, in part, to steric interactions between the bulky triphenylphosphine groups and the ribose moiety.

The O_6 interaction for Guo is of particular interest since it is thought that the antitumor behavior of many substances is a result of their interaction at O_6 of the guanine constituent of DNA.[33] The work presented here suggests that O_6 is a feasible binding site if there are factors that preclude binding to the heteroatoms in the ring. Further studies in our laboratory are being directed toward characterizing other rhodium–nucleoside complexes and evaluating their potential as antitumor agents.

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Registry No. $[Rh(PPh_3)_2(CO)(Guo)]PF_6$, 84049-95-6; $[Rh(PPh_3)_2(CO)(Ino)]PF_6$, 84049-97-8; $[Rh(PPh_3)_2(CO)(1\text{-MeIno})]PF_6$, 84056-86-0; $[Rh(PPh_3)_2(CO)(Ado)]PF_6$, 84049-99-0; $[Rh(PPh_3)_2(CO)(Pur)]PF_6$, 84050-01-1; $[Rh(PPh_3)_2(CO)(Ade)]PF_6$, 84050-03-3; $[Rh(PPh_3)_2(CO)(cyclohexanone)]PF_6$, 84050-05-5; $[Rh(PPh_3)_2(CO)_3]PF_6$, 53433-43-5.

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Chemistry of Ruthenium. 7.[1] Aquo Complexes of Isomeric Bis[2-(arylazo)pyridine]ruthenium(II) Moieties and Their Reactions: Solvolysis, Protic Equilibria, and Electrochemistry

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The two blue isomers of $RuCl_2L_2$ are trans,cis (**2**) and cis,cis (**3**) in the following sequence: N(pyridine), N(pyridine); N(azo), N(azo) [L = 2-(phenylazo)pyridine (pap) or 2-(*m*-tolylazo)pyridine (tap)]. Both **2** and **3** undergo facile and stereoretentive displacement of Cl^- by H_2O in the presence of aqueous Ag^+, affording the corresponding isomers **5** and **6** of $Ru(OH_2)_2L_2^{2+}$ (isolated as the perchlorate hydrate). Conversely, **5** and **6** regenerate **2** and **3**, respectively, in chloride media. Deprotonation of **5** (L = pap; $pK_1 = 6.80$, $pK_2 = 8.66$) affords $Ru(OH)(OH_2)(pap)_2^+$ (**8**) and $Ru(OH)_2(pap)_2$ (**9**), both of which have been isolated in the pure form (the former as a perchlorate salt). The $t_{2g} \rightarrow \pi^*(L)$ MLCT transition energies as well as the N=N stretching frequencies decrease on deprotonation (**5** > **8** > **9**) due to t_{2g}–$p(OH^-)$ and t_{2g}–$\pi^*(L)$ interactions. Both **5** and **6** (but not **8** and **9**) undergo stereoretentive solvolysis in donor solvents (S), furnishing $RuS_2L_2^{2+}$, of which one, viz., $Ru(PhCN)_2(tap)_2^{2+}$, is isolated as a crystalline perchlorate. Reaction of **5** (L = pap) with pyridine (py) and subsequent acidification and processing furnishes the perchlorate salt of the monobasic acid ($pK_1 = 6.80$) $Ru(OH_2)(py)(pap)_2^{2+}$ (**7**). The p*K* values of **5** and **7** reflect the strong π acidity of L. The consequent stability of the t_{2g} level in turn leads to high redox potentials in Ru–L complexes. Complexes **8** (in MeCN) and **9** (in CH_2Cl_2) display quasi-reversible Ru(IV)/Ru(III) and Ru(III)/Ru(II) couples: $\mathbf{8}^{2+} + e^- \rightleftharpoons \mathbf{8}^+$, $\mathbf{8}^+ + e^- \rightleftharpoons \mathbf{8}$; $\mathbf{9}^{2+} + e^- \rightleftharpoons \mathbf{9}^+$, $\mathbf{9}^+ + e^- \rightleftharpoons \mathbf{9}$. The respective $E°_{298}$ values are as follows: 1.18, 1.89 V; 1.07, 1.53 V (vs. SCE). For **7** (in MeCN) the couple $\mathbf{7}^+ + e^- \rightleftharpoons \mathbf{7}$ is observed ($E°_{298} = 1.5$ V) initially but it is rapidly replaced by a couple with $E°_{298}$ of 1.88 V due to solvolysis. In acidic (pH 1–4) aqueous media the $2e^-$–$2H^+$ couple $Ru^{IV}(O)(py)(pap)_2^{2+} + 2e^- + 2H^+ \rightleftharpoons \mathbf{7}$ occurs ($E°_{298} = 1.20$ V).

Introduction

Well-characterized aquo complexes of ruthenium(II) that have been isolated in the crystalline state are relatively uncommon.[2-8] Such species are potential starting materials for making a variety of ruthenium–ligand bonds by the nucleophilic displacement reactions (1) and (2), where D and D^- are

$$(Ru—OH_2)^{2+} + D \rightarrow (Ru—D)^{2+} + H_2O \quad (1)$$

$$(Ru—OH_2)^{2+} + D^- \rightarrow (Ru—D)^{+} + H_2O \quad (2)$$

respectively neutral or anionic ligands. Simple deprotonation, straightforward electron loss, and a coupling of the two in oxidative proton loss constitute yet other reaction possibilities (eq 3–6).

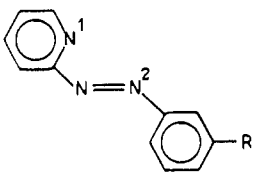
$$(Ru—OH_2)^{2+} \rightarrow (Ru—OH)^{+} + H^+ \quad (3)$$

$$(Ru—OH_2)^{2+} \rightarrow (Ru^{III}—OH_2)^{3+} + e^- \quad (4)$$

$$(Ru—OH_2)^{2+} \rightarrow (Ru^{III}—OH)^{2+} + H^+ + e^- \quad (5)$$

$$(Ru—OH_2)^{2+} \rightarrow (Ru^{IV}=O)^{2+} + 2H^+ + 2e^- \quad (6)$$

We have shown[9,10] that the bidentate azopyridine ligand L (**1**) imparts excellent stability to ruthenium(II). It was



R = H; L = pap
R = Me; L = tap

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therefore considered logical that the mixed species with L and H_2O as coligands should be stable enough for ready isolation in the pure state. Herein we report the synthesis and characterization of two isomeric forms of the diaquo species $[Ru(OH_2)_2L_2](ClO_4)_2 \cdot H_2O$ and of the monoaquo complex $[Ru(OH_2)(py)L_2](ClO_4)_2 \cdot H_2O$ (py = pyridine). Selected reactions belonging to types 1–6 are described for one of the diaquo isomers as well as for the monoaquo complex. Where appropriate, the results are compared with those of Ru–bpy species (bpy = 2,2′-bipyridine).

While L is the general abbreviation for the azopyridine ligands, the two specific ligands concerning us here, viz., 2-(phenylazo)pyridine and 2-(*m*-tolylazo)pyridine are respectively abbreviated as pap and tap.

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