$$\theta_{aa} = -8.08 \text{ au}$$
$$\theta_{bb} = 3.54 \text{ au}$$
$$\theta_{cc} = 4.54 \text{ au}$$

The electric field gradients at S are of interest since they are so different for SH_2 and SH_4. Actually the difference in $q_{zz}(S)$ values is not surprising since the two axial atoms (lying close to the positive and negative z axes) are not present in SH_2. However, the SH_2 group in SH_4 is similar structurally to that in SH_2 and hence one might expect the $q_{xx}(S) = q_{yy}(S)$ values to be nearly equal.

Finally, the calculated potentials at sulfur reflect the fact, also indicated by the population analyses and S 1s orbital energies, that the S atom is most positively "charged" in SH_6.

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Nitrogen-Bound and Carbon-Bound Xanthine Complexes of Ruthenium Ammines

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Abstract: Complexes of a series of alkylated xanthine derivatives in which ruthenium(II and III) is bound to the N_7 or C_8 sites of the purine are described. The N-bound ruthenium(III) complexes exhibit two ligand-to-metal charge transfer bands, which provide information about the energies of molecular orbitals on the xanthine ligand. The ruthenium(II) complexes exhibit metal-to-ligand charge transfer transitions in the ultraviolet. Reduction potentials for the neutral and deprotonated ligand complexes are reported. Measurements of pK_a values for both N- and C-bound Ru(II and III) complexes are presented. Evidence for a trans labilization effect in the series of C_8-xanthinylideneruthenium(III) complexes is described.

The effect of metal ions on purine bases is of considerable interest for several reasons. Metal ions participate in the biological functions of nucleic acids.[1-3] Heavy-metal adducts of nucleic acids have proved useful in an X-ray structure determination of a tRNA[4] and have been investigated in attempts to sequence nucleic acids by electron microscope techniques.[5] Several platinum compounds have shown antitumor activity believed to be due to their ability to form complexes with nucleic acids.[6]

Xanthines have been studied as models for nucleosides[7] and are attractive as ligands because various methylated derivatives are available. Alkylation of the xanthine ring limits the number of possible metal binding sites and increases the solubility of the ligand. The aquopentaammineruthenium(II) ion exhibits a high degree of selectivity for binding to unsaturated nitrogens.[8] This behavior coupled with the use of methylated xanthines has led to the synthesis of a number of pentaammineruthenium(II and III) xanthine complexes with the metal bound at N_7. These ruthenium complexes are substitution inert in both the 2+ and 3+ oxidation states, a feature which facilitates their isolation and systematic study.

Purine ligands can also bind to the metal ion through the carbon adjacent to the nitrogens on the imidazole ring in a manner analogous to the series of ruthenium–imidazolylidene compounds synthesized in this laboratory by Sundberg.[9] An X-ray structure determination of one of the compounds, whose synthesis is reported here, shows that the ruthenium is indeed bonded to the C_8 site.[10] These compounds can be considered to be complexes of a purine ylide and as such can be included in the growing number of metal-carbene complexes.[11,12] The ruthenium-carbon and equatorial ruthenium-ammonia bonds are substitution inert in both the 2+ and 3+ oxidation states of the metal. Carbon-bound ligands of this type have been observed to exert a trans labilizing effect on saturated ligands in ruthenium(II) complexes.[13] This effect extends to the ruthenium(III) complexes, the C_8-bound xanthine ligands increasing the lability of water or chloride ligands by several orders of magnitude relative to aquo- or chloropentaammineruthenium(III). This trans effect correlates with a substantial trans influence observed in the structure of a C_8 -caffeine-chlorotetraammineruthenium(III) chloride.[10]

Abbreviations

The various methylated xanthine ligands are represented by the abbreviation [*a,b,c*] where *a, b,* and *c* are numbers representing the methylated sites. A superscript minus sign indicates a deprotonated ligand. Nitrogen bound ligands have the prefix N, while carbon-bound ligands have the prefix C. The ligand representation is followed by a number in parentheses denoting the oxidation state of the ruthenium (Figures 1 and 2). It should be noted that, owing to labilization of the position trans to the C-bound ligand, the trans ammonias are replaced by H_2O in the ruthenium(II) complexes and by H_2O or Cl in the ruthenium(III) complexes. The structural formulas when first introduced anticipate evidence to be introduced later bearing on the structures.

Experimental Section

Chemicals and Reagents. Chloropentaammineruthenium(III) chloride was prepared by refluxing hexaammineruthenium(III) chloride, obtained from Matthey Bishop Inc., in 6 *M* HCl for 4 hr followed by crystallization from 0.1 *M* HCl.[14] Caffeine, theophylline, and theobromine were purchased from Matheson Coleman and Bell and were used without further purification. Isocaffeine, 1,9-dimethylxanthine, and 3,9-dimethylxanthine were obtained from FLUKA AG, Buchs, Switzerland, and were used without further purification. Hydrochloric and perchloric acid solutions were standardized against standard NaOH or sodium carbonate. Hydrochloric acid solutions were also made up directly with Titrisol (Brinkmann Instruments Inc.). Lithium chloride and lithium perchlorate standard solutions were prepared by treating lithium carbonate with hydrochloric or perchloric acid and adjusting to neutral pH. Chloride solutions were standardized by potentiometric titration with standard silver nitrate. The ion exchange resin, AG-50 WX-2, 200–400 mesh, was purchased from Bio-Rad Laboratories and purified according to a standard method used in this laboratory.[15] Microanalyses were performed by the Stanford Microanalytical Laboratory, Stanford, Calif.

Equipment. Spectra were recorded on a Cary 15 spectrophotometer. Electrochemical measurements were made on a cyclic voltammetry apparatus constructed in this laboratory using a platinum button (Beckman) or a hanging drop mercury electrode (Brinkmann) as the indicator electrode and a standard calomel reference electrode. Measurements of pH were made with a Metrohm combination glass electrode on a Beckman Expandomatic pH meter standardized with Beckman buffers. Nmr spectra were taken with a Varian A-60 nuclear resonance spectrometer.

Synthesis of Compounds. The nitrogen bound complexes of 3,9-dimethylxanthine, 1,9-dimethylxanthine, and 1,3,9-trimethylxanthine were prepared by allowing an argon purged solution of chloropentaammineruthenium(III) trifluoroacetate to react with a stoichiometric amount of the xanthine ligand at pH 3–4 over zinc amalgam for about 30 min, with occasional warming to dissolve the ligand. The zinc amalgam was then removed and the solution was oxidized by bubbling air through it for at least 1 hr. The products were separated on a 10-cm AG-50 ion exchange column eluted with increasing concentrations of hydrochloric acid. Usually the only significant band was formed by a red complex elutable with 3 *M* HCl. The eluate was roto-evaporated to dryness, filtered, evaporated again, and then dissolved in a minimum amount of 1 *M* HCl. Ethanol was added and crystals formed on cooling. The red crystals were collected and were washed with water–ethanol before storing in a desiccator. *Anal.* Calcd for $[3,9\text{-Me}_2\text{Xan}(\text{NH}_3)_5\text{Ru}]\text{Cl}_3\cdot 2\text{H}_2\text{O}$: C, 16.52; N, 24.78; H, 5.35; Cl, 20.90. Found: C, 16.51; N, 24.66; H, 5.08; Cl, 20.80. *Anal.* Calcd for $[1,9\text{-Me}_2\text{Xan}(\text{NH}_3)_5\text{Ru}]\text{Cl}_3\cdot \text{H}_2\text{O}$: C, 17.13; N, 25.67; H, 5.13; Cl, 21.67. Found: C, 16.94; N, 26.02; H, 5.06; Cl, 21.41. *Anal.* Calcd for $[1,3,9\text{-Me}_3\text{Xan}(\text{NH}_3)_5\text{Ru}]\text{Cl}_3\cdot 2\text{H}_2\text{O}$: C, 18.38; N, 24.11; H, 5.59; Cl, 20.34. Found: C, 18.10; N, 24.56; H, 5.41; Cl, 20.23.

Theophylline was allowed to react with aquopentaammineruthenium(II) in a similar fashion except that after about 30 min the zinc was removed and the solution was diluted about tenfold with water and adjusted to pH 2. This solution was allowed to stand for several hours before it was oxidized with air. Ion exchange on a 10-cm AG-50 column showed three major bands. A purple band determined to be the carbon-bound complex eluted first with 2–3 *M* HCl followed by a red band comprised of the nitrogen-bound complex eluting with 3 *M* HCl and finally a second purple band eluting with 4 *M* HCl. The last band was shown to be composed of a complex having two theophylline ligands per ruthenium. The fractions were roto-evaporated to dryness and redissolved in a small amount of 1 *M* HCl. Any yellow precipitate (chloropentaammineruthenium(III) chloride) present at this time was filtered off and the sample was ion exchanged a second time. Otherwise ethanol was added to induce crystallization on cooling. Crystals were collected, washed with ethanol, and stored in a desiccator. In eluting mixtures of N-[1,3](III) and C-[1,3](III) with trifluoracetic acid, the order of elution was reversed, with complex N-[1,3](III) eluting in 3 *M* acid and complex C-[1,3](III) eluting in 5–6 *M* acid. *Anal.* Calcd for $[1,3\text{-Me}_2\text{Xan}(\text{NH}_3)_5\text{Ru}]\text{Cl}_3\cdot \text{H}_2\text{O}$: C, 17.13; N, 25.67; H, 5.14; Cl, 21.67. Found: C, 17.53; N, 25.85; H, 5.41; Cl, 21.45. *Anal.* Calcd for $[1,3\text{-Me}_2\text{Xan}(\text{NH}_3)_4\text{RuCl}]\text{Cl}_2\cdot \text{H}_2\text{O}$: 17.75; N, 23.65; H, 4.68; Cl, 22.45. Found: C, 17.64; N, 23.75; H, 4.49; Cl, 22.08. *Anal.* Calcd for $[(1,3\text{-Me}_2\text{Xan})_2(\text{NH}_3)_4\text{Ru}]\text{Cl}_3\cdot 3\text{H}_2\text{O}$: C, 24.37; N, 24.36; H, 4.96; Cl, 15.41. Found: C, 23.89; N, 24.46; H, 4.70; Cl, 15.71.

The carbon-bound caffeine complexes were prepared in a manner similar to that described above. Ion exchange chromatography showed two major bands: a red band, determined to contain a complex with a substitution-inert inner-sphere chloride, eluting with 1–2 *M* HCl, and a purple band eluting with 2–3 *M* HCl, comprised of complex C-[1,3,7](III) in equilibrium with chloride ion. These bands were roto-evaporated to dryness and redissolved in 1 *M* HCl. Ethanol was added to induce crystallization on cooling overnight in a refrigerator. *Anal.* Calcd for $[1,3,7\text{-Me}_3\text{Xan}(\text{NH}_3)_3\text{RuCl}_2]\text{Cl}\cdot \text{H}_2\text{O}$: C, 20.41; N, 20.83; H, 4.50; Cl, 22.59. Found: C, 20.24; N, 21.04; H, 4.41; Cl total, 21.53; Cl ionic, 14.58. *Anal.* Calcd for $[1,3,7\text{-Me}_3\text{Xan}(\text{NH}_3)_4\text{RuCl}]\text{Cl}_2\cdot 3\text{H}_2\text{O}$: C, 18.34; N, 21.39; H, 5.39; Cl, 20.31. Found: C, 18.14; N, 21.74; H, 4.89; Cl, 20.33.

Theobromine was allowed to react with aquopentaammineruthenium(II) in 1 *M* trifluoromethylsulfonic acid solution. The ion exchange step revealed several bands, believed to be the products resulting from substitution of ammonia by chloride. The major product eluted as a red band in 2 *M* HCl and was followed by a purple band eluting in 2–3 *M* HCl. The fraction containing the purple band was chromatographed twice more and roto-evaporated to dryness. A purple solid was precipitated by addition of ethanol to a solution of the complex in a minimum of 1 *M* HCl and cooling. *Anal.* Calcd for $[3,7\text{-Me}_2\text{Xan}(\text{NH}_3)_4\text{RuCl}]\text{Cl}_2\cdot 2\text{H}_2\text{O}$: C, 17.10; N, 22.79; H, 4.92; Cl, 21.63. Found: C, 16.82; N, 23.06; H, 4.35; Cl, 21.78.

Determination of Acid Dissociation Constants. The values of pK_a were determined spectrophotometrically for the ruthenium complexes using the relation:

$$pK_a = \text{pH} - \log \frac{A' - A}{A - A''} \qquad (1)$$

where A' is the absorbance of the neutral ligand complex, A'' is the absorbance of the deprotonated ligand complex, and A is the absorbance of a mixture of both species at a given pH. All absorbance readings were made on solutions of the same concentration of the ruthenium complex in 0.1 *M* chloride media for the nitrogen-bound complexes and in 0.1 *M* perchlorate media for the carbon-bound compounds. For the determination of the pK_a values for the Ru(III) species the pH was varied by adding a drop of 0.1 *M* hydrochloric or perchloric acid or 0.1 *M* lithium hydroxide. The pH was determined before and after the absorbance reading. Solutions of ruthenium(II) complexes were prepared by reducing the ruthenium(III) complex in 0.1 M lithium chloride media over zinc amalgam with continuous argon purge or with hydrogen gas over a piece of platinum wire in an all-glass flow-through titration apparatus filled with a 1-cm uv-visible cell.[16] Flow through the cell was maintained by stirring with a magnetic stirrer. The apparatus was fitted with a combination glass electrode and a micrometer syringe filled with argon purged acid or base. The pH was varied by means of the microburet and the solution was allowed to equilibrate for at least 1 min before a spectrum was taken.

Differences in pK_a values for the Ru(II) and Ru(III) species were also determined by applying the relation

$$\Delta pK_a = \frac{\Delta E_f}{59} \tag{2}$$

where ΔpK_a is the difference between the pK_a values of the ruthenium(II) and ruthenium(III) complexes and ΔE_f is the difference in formal potentials (in millivolts) between the neutral ligand and deprotonated ruthenium(III-II) couples. The value of ΔpK_a derived in this fashion agreed well with that determined from spectrophotometrically determined pK_a values.

Electrochemical Measurements. Potentials of the neutral ligand complexes were measured in 0.1 M acid by cyclic voltammetry using a platinum button or hanging drop mercury electrode. Measurements made with either electrode were identical within experimental error. Chloride ion was removed from solutions of the C_8-bound complexes by precipitation with an equivalent amount of silver perchlorate. Formal potentials were measured at half the distance between the anodic and cathodic peaks. Peak separations were generally about 63 mV and were usually no greater than that measured for the hexaammineruthenium(III-II) couple under the same conditions. Formal potentials for the deprotonated ligand complexes were measured in an appropriate buffer solution made up to an ionic strength of 0.1 with a lithium chloride solution at a pH at least one unit greater than the pK_a value of the ruthenium(II) complex (the pK_a value for a Ru(II) complex is always higher than for the corresponding Ru(III) complex).

Spectra. Extinction coefficients of the nitrogen-bound ruthenium(III) complexes were calculated from spectra taken in 0.1 M HCl for the neutral ligand species and in 0.1 M LiCl at a pH adjusted with 0.1 M LiOH to a value at least two units greater than the pK_a value of the complex. The values for the ruthenium(III) C_8-bound species were similarly determined in 0.1 M $HClO_4$ and 0.1 M $LiClO_4$ at a chloride concentration at least five orders of magnitude less than the chloride association constant of the complex. Solutions of the ruthenium(II) complexes were prepared in 0.1 M LiCl purged with argon in a Zwickel flask with zinc amalgam as the reducing agent.

Chloride association constants were determined from the inverse of the slope of a plot of $(A^0 - A)/[Cl]$ *vs.* A, where A^0 is the absorbance at a given wavelength at zero chloride concentration and A is the absorbance at the same wavelength at a given chloride concentration. The ionic strength was adjusted to 1.0 with $LiClO_4$ and, for the series, the concentration of Ru(III) was kept constant at about 10^{-5} M.

Results

Synthesis. The preparation of the nitrogen-bound complexes is similar to that used by Ford, *et al.*,[17] for a series of ruthenium-pyridine species. The formation of the carbene complexes appeared to be acid catalyzed as noted by Sundberg.[9] Caffeine and theobromine formed only carbon-bound complexes, while 9-alkylated xanthines yielded almost exclusively N_7-bound compounds. Reactant solutions of the 9-alkylated ligands allowed to stand for several hours at low pH in the presence of ruthenium(II) yielded only very small amounts of a species having the appearance of a C-bound form of the Ru(III) complex after oxidation. Xanthosine formed a complex with pentaammineruthenium(II) which on oxidation exhibited a spectrum at low pH similar to that of complex N-[1,3,9](III). Theophylline formed both nitrogen- and carbon-bound complexes as well as a bistheophylline combination. The latter compound is believed to be *cis*-bis(1,3-dimethylxanthine)tetraammineruthenium(III) chloride, N-$[1,3]_2$(III), by analogy to a cis imidazole species isolated by Sundberg. An attempt to synthesize this complex from *cis*-dichlorotetraammineruthenium(III) chloride yielded a species with a spectrum similar to that of N-$[1,3]_2$(III). Solutions of N-[1,3](II) when allowed to stand at low pH for several hours yielded complexes N-$[1,3]_2$(III), N-[1,3](III), and C-[1,3](III) which were identified on the basis of their electronic spectra after oxidation and separation by ion exchange chromatography.

Table I. Uv-Visible Spectra of N_7-Bound Complexes in 0.1 M Chloride Media[b]

Ligand	Ru(III)		Ru(II)	
	λ_{max}	$\epsilon_{max} \times 10^{-3}$	λ_{max}	$\epsilon_{max} \times 10^{-3}$
N-[3,9][a]	231	9.4	236	9.2
	268	8.4	264	11.0
	309	1.46	373	1.2
	508	0.30		
N-$[3,9]^-$	216	23.0	265	11.0
	269	9.6	352	1.3
	311	1.64		
	560	0.30		
N-[1,9][a]	263	8.3	233	8.2
	309	1.52	260	12.3
	503	0.31	375	1.75
N-$[1,9]^-$	237	9.2	247	11.1
	282	7.5	265	11.0
	333	1.37	355	2.3
	630	0.66		
N-[1,3][a]	267	8.2	232	8.0
	304 (s)	1.2	261	11.1
	516	0.33	373	1.9
N-$[1,3]^-$	273	8.7	267	11.4
	359	2.6	366	1.8
	594	0.96		
N-[1,3,9]	268	7.9	237	8.3
	309	1.33	264	11.2
	510	0.31	372	1.7

[a] Spectra in 0.1 M HCl, all other spectra in 0.1 M LiCl. [b] (s) Represents a shoulder.

Attempts to synthesize metal-carbene species from 7,9-dimethylxanthine and xanthosine yielded only very small amounts of substances showing a broad absorption around 580 nm. The ruthenium(III)-carbene complexes were observed to undergo photodecomposition and decomposed more rapidly at high pH, but appeared to be stabilized by acid and chloride ion.

Spectra. The spectra of the nitrogen-bound pentaammineruthenium(II and III) complexes are summarized in Table I. The spectra of the dialkylated xanthine ruthenium(III) complexes are remarkably similar to that of the trialkylated-ligand complex N-[1,3,9](III). These spectra exhibit a broad visible absorption centered about 510 nm with a second more intense band at 309 nm in the ultraviolet. Removal of a proton from the xanthine ligand causes shifts in these two bands dependent upon the deprotonation site. In all cases the visible band shifts to lower energy and, with the exception of N-$[3,9]^-$(III), increases in intensity. The ultraviolet band changes little with deprotonation at N_1, changes only in energy on deprotonation at N_3, but shows significant changes in both energy and intensity on loss of a proton at N_9. The other bands in the ultraviolet can be attributed to $\pi \rightarrow \pi^*$ ligand transitions.[18,19] These bands, if affected at all, are usually shifted slightly to higher energy relative to the spectra of the free ligands, with the higher energy transtion occasionally being obscured. A single exception to this is the spectrum of N-$[1,9]^-$(III) where the higher energy band is shifted 11 nm toward higher energy and the lower energy transition is shifted 6 nm toward lower

Table II. Ultraviolet–Visible Spectra of C_8-Bound Complexes at $\mu = 0.1$[a]

	Ru(III)		Ru(II)[d]	
Ligand	λ_{max}	$\epsilon_{max} \times 10^{-3}$	λ_{max}	$\epsilon_{max} \times 10^{-3}$
C-[1,3][b]	239	9.4	258	8.7
	276	10.2	268 (s)	8.5
	315 (s)	2.2	347	9.8
	589	1.40		
C-[1,3]$^-$ [c]	282	8.0		
	329	4.4		
	410 (s)	0.33		
	641	2.5		
C-[3,7][b]	241	9.2		
	274	8.8		
	315	2.4		
	593	1.5		
C-[3,7]$^-$ [c]	282	7.1		
	335	5.1		
	415 (s)	0.32		
	650	2.1		
C-[1,3,7][b]	241	9.0	255	7.5
	273	9.7	275	8.0
	316	2.9	349	10.7
	605	2.0		
C-[1,3,7]$^-$ [c]	278	7.4		
	336	5.1		
	418	0.57		
	663	2.8		
C-[1,3,7][b,e] Cl	244	9.1		
	279	10.1		
	346 (i)	2.12		
	551	0.66		
C-[1,3,7]$^-$ [c,e] Cl	288	10.2		
	336	4.1		
	623	1.2		

[a] (s) represents a shoulder, (i) represents an inflection point. [b] 0.1 *M* $HClO_4$. [c] 0.1 *M* $LiClO_4$. [d] 0.1 *M* LiCl. [e] Substitution inert chloride cis to caffeine ligand.

energy relative to the free ligand. A new band at 216 nm appears in the spectrum of N-[3,9](III) which is not apparent in the spectrum of the free ligand.[18]

The spectra of the ruthenium(II) nitrogen-bound complexes show a broad absorption around 373 nm which shifts somewhat to higher energy on deprotonation of the ligand. The xanthine intraligand transitions are usually shifted toward higher energy relative to the free ligand with a peak appearing at 232 nm in the spectrum of N-[1,3](II) which is not evident in the spectrum of theophylline.[19]

The spectra of the C_8-bound complexes are summarized in Table II. With the exception of the inner sphere chloride complex, the neutral ligand complexes of ruthenium(III) show a broad absorption in the visible region about 600 nm and a second more intense absorption at 315 nm in the ultraviolet. These bands appear at lower energy and increase in intensity on deprotonation of the xanthine ligand. In chloride media the visible band shifts to higher energy with decreased intensity while an ultraviolet absorption appears at lower energy. In the spectrum of compound C-[1,3,7]Cl(III) the visible band occurs at higher energy and is of lower intensity while an ultraviolet band appears at lower energy. The other absorptions in the ultraviolet may be attributed to transitions in the xanthine ligands. The absorption around 274 nm in the neutral ligand complexes is of similar energy and intensity to the usual $\pi \rightarrow \pi^*$ transitions of these ligands. The absorption around 240 nm is not, however, evident in the spectra of the free ligands. Bands of similar energy and intensity do occur in the spectra of other methylated xanthines, particularily in 7,9-dialkylated xanthines.[18]

The spectra of C-[1,3](II) and C-[1,3,7](II) exhibit an intense band around 348 nm. The two other peaks in the ultraviolet are in the range expected for xanthine $\pi \rightarrow \pi^*$ transitions.[18,19]

Table III. pK_a Values for Deprotonation[a]

Ligand	Deprotonation site	pK_a Ru(III)	pK_a Ru(II)	ΔpK_a	ΔpK_a[b]
N-[3,9]	N_1	7.95 ± 0.03	9.55 ± 0.1	1.4	1.5
N-[1,9]	N_3	3.91 ± 0.02	5.50 ± 0.1	1.5	1.5
N-[1,3]	N_9	2.19 ± 0.03	5.81 ± 0.1	3.6	3.7
C-[1,3]	N_9	3.73 ± 0.05	>9.4		
C-[3,7]	N_9	3.07 ± 0.06			
C-[1,3,7]	N_9	3.20 ± 0.05	>9.4		

Free Ligands[c]

Ligand	Deprotonation site	pK_a
3,9-Dimethylxanthine	N_1	10.14
1,9-Dimethylxanthine	N_3	5.99
1,3-Dimethylxanthine	$N_{7,9}$	8.68
3,7-Dimethylxanthine	N_1	10.00

[a] Determined spectrophotometrically using eq 1. [b] Determined electrochemically using eq 2. [c] Reference 18.

Equilibrium Constants. pK_a values for loss of a proton from the various ruthenium(II and III) complexes are presented in Table III. The deprotonation site for the nitrogen-bound complexes is determined by methyl substitution on the xanthine ligand. In all cases the addition of a ruthenium(III) to the xanthine ring markedly increases the acidity of the ligand.[18] For the N-bound complexes the effect is most evident at the N_9 position where the ionization constant is increased by 10^6 over that of free theophylline. At the N_1 and N_3 positions the enhancement of acidity is by a factor of approximately 100. For the ruthenium(II) complexes the increase in acidity is much less.

Addition of a ruthenium(III) to C_8 also considerably enhances the acidity of the xanthine ligand, although it must be pointed out that binding at this site alters the structure of the ligand. It is of interest that the pK_a of N-[1,3](III) is less than that of C-[1,3](III), even though the ruthenium moiety is closer to the ionization site. The measurements of the pK_a of the ruthenium(II) carbon bound species were vitiated by irreversible decomposition of these complexes at high pH although it is possible to place a lower limit on the pK_a values of these complexes. The great difference in the acidity of the ruthenium(III) and ruthenium(II) carbon-bound complexes and the decrease in the acidity of theophylline by addition of the ruthenium(II) moiety at C_8 is notable.

Chloride association constants for C-[1,3](III) and C-[1,3,7](III) in the position trans to the purine ligand were determined to be 14.5 ± 3 and 15.5 ± 3 in 0.1 *M* acid at an ionic strength of 1.0. The range of half-lives for approach to equilibrium in 0.1–1.0 *M* chloride media was 50–10 sec.

Electrochemistry. Formal potentials as measured by cyclic voltammetry are reported in Table IV. The observed separation between the anodic and cathodic peaks indicates that all the couples observed are reversible. A plot of E_f *vs.* pH for N-[1,3](III-II)-N[1,3]$^-$(III-II) showed intersections in the curve at approximately the pK_a values of the ruthenium(III) and ruthenium(II) complexes and a slope of 59 mV/pH unit between these two points. In all cases the changes in potential between the neutral ligand and deprotonated ligand couples were approximately those expected from the difference in pK_a values between the ruthenium(III) and ruthenium(II) species.[20]

Due to rapid decomposition of the carbene complexes at high pH, it was impossible to determine reliable potentials

Table IV. Formal Reduction Potentials of Ruthenium(III-II) Xanthine Complexes $\mu = 0.1$

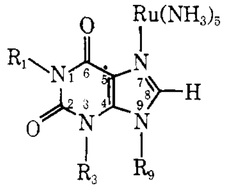
Ligand	Metal binding site	E_f(mV) *vs.* nhe	Media
N-[3,9]	N_7	219	0.1 *M* HCl
N-[3,9]$^-$	N_7	130	Glycine-LiOH-LiCl, pH 10.6
N-[1,9]	N_7	211	0.1 *M* HCl
N-[1,9]$^-$	N_7	117	Tris-LiCl, pH 7.3
N-[1,3]	N_7	206	0.1 *M* HCl
N-[1,3]$^-$	N_7	−10	Phosphate-LiCl, pH 7.0 Tris-LiCl, pH 7.3
N-[1,3,7]	N_7	212	0.1 *M* HCl
C-[1,3]	C_8	442	0.1 *M* $HClO_4$
C-[3,7]	C_8	462	0.1 *M* $HClO_4$
C-[1,3,7]	C_8	461	0.1 *M* $HClO_4$
N-[3,9]	N_7	219	0.1 *M* HCl
N-[3,9]$^-$	N_7	130	Glycine-LiOH-LiCl, pH 10.6

for these deprotonated couples. Measurements made immediately after dissolution of the samples gave values around 80 mV. The reduction potentials for the carbene complexes are notably higher than those of the nitrogen-bound complexes. This trend has been observed for a series of carbon- and nitrogen-bound ruthenium-imidazole complexes.[21] For all the neutral ligand species the values of E_f are significantly greater than the value of 51 mV reported for hexaammineruthenium(III-II).[22] The neutral ligand nitrogen-bound complexes have formal reduction potentials less than that reported for the pyridinepentaammineruthenium(III-II) couple (305 mV)[22] while the potentials for the carbon-bound ruthenium(III-II) complexes are greater.

Nmr. Proton magnetic resonance spectra of N-[1,3](II) taken in 0.1 *M* DCl-D_2O solution showed three theophylline peaks with integrated intensity ratios of 3:3:1 and an unresolved multiplet for the ammonia hydrogens. The spectra of C-[1,3](II) showed only two xanthine proton peaks due to the two methyl groups and a broad symmetric peak in the area expected for coordinated ammonia.

Discussion

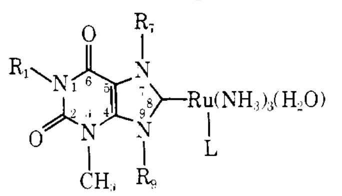
Structure. The N series of compounds is believed to have the ruthenium bound at N_7. Overlap between the πd orbitals on ruthenium(II) and the π-system of an aromatic ligand should provide stability to a ruthenium-nitrogen bond.[8] This overlap together with a kinetic preference for available nitrogens causes pentaammineruthenium(II) to bind selectively to "pyridine" nitrogen sites.[17] Isocaffeine provides only one such site and it is reasonable to assume that the ruthenium binds at N_7 in N-[1,3,9](II and III). If ligation to oxygen were to occur it is unlikely that the metal would discriminate between O_6 and O_2 and both isomers should be present. Only one band was evident in the chromatographic purification of compounds N-[3,9](III), N-[1,9](III), and N-[1,3,9](III) and isosbestic points were observed in the spectrophotometric titrations of N-[3,9](III), N-[1,9](III), and N-[1,3](III) indicating that only one type of complex was present. The similarity of the spectra of the N series of compounds provides good evidence for a common binding site in the series.



Complex				
Ru(III)	Ru(II)	R_1	R_3	R_9
N-[3,9](III)	N-[3,9](II)	H	CH_3	CH_3
N-[3,9]$^-$(III)	N-[3,9]$^-$(II)		CH_3	CH_3
N-[1,9](III)	N-[1,9](II)	CH_3	H	CH_3
N-[1,9]$^-$(III)	N-[1,9]$^-$(II)	CH_3		CH_3
N-[1,3](III)	N-[1,3](II)	CH_3	CH_3	H
N-[1,3]$^-$(III)	N-[1,3]$^-$(II)	CH_3	CH_3	
N-[1,3,9](III)	N-[1,3,9](II)	CH_3	CH_3	CH_3

The broad multiplet in the nmr spectrum of N-[1,3](II) is consistent with a pentaammine metal ion bound at N_7 since there should be three types of ammonia ligands present: two in a position to form hydrogen bonds with O_6,[7] two opposite the first pair, and one trans to the heteroligand. The presence of a methyl group at N_3 appears effectively to block binding of a large metal ion to N_9 as indicated by the isolation of only one type of monoxanthine nitrogen-bound complex when theophylline is allowed to react with pentaammineruthenium(II) and the formation of only carbon-bound species when caffeine and theobromine react under the same conditions.

A molecular structure determination by X-ray crystallography has recently been completed for [C-[1,3,7]Cl_2(III)]Cl · H_2O showing that the ruthenium binds to the caffeine ligand at C_8 and that the two chloride ions bind directly to the ruthenium: one cis and one trans to the xanthine ligand with the trans Ru–Cl bond being about 0.1Å longer than the cis.[10] This indicates that in the crystalline state the C series of compounds contains a chloride ion bound trans to the carbene ligand, when isolated from 1 *M* chloride media. Titration of [C-[1,3,7]Cl_2(III)]Cl with silver ion at low pH revealed that one of the two inner-sphere chloride ligands is substitution labile. Carbene ligands are known to exert strong trans influences, and Isied has shown that the 4,5-dimethylimidazolylidene ligand exhibits a marked trans effect on the lability of the water molecule in (4,5-dimethylimidazolylidene)aquotetraammineruthenium(II).[13] The short half-lives for reaching equilibrium with chloride ion reported here for C-[1,3](III) and C-[1,3,7](III) indicate an anation rate enhancement on the order of 10^3 relative to aquopentaammineruthenium(III). The chloride association constants, which are an order of magnitude less than that reported for chloropentaammineruthenium(III),[23] are consistent with a weakening of the trans ruthenium(III)-chloride bond.



Complex					
Ru(III)	Ru(II)	L	R_1	R_7	R_9
C-[1,3](III)	C-[1,3](II)	NH_3	CH_3	H	H
C-[1,3]$^-$(III)		NH_3	CH_3	H	
C-[3,7](III)	C-[3,7](II)	NH_3	H	CH_3	H
C-[3,7]$^-$(III)		NH_3	H	CH_3	
C-[1,3,7](III)	C-[1,3,7](II)	NH_3	CH_3	CH_3	H
C-[1,3,7]$^-$(III)		NH_3	CH_3	CH_3	
C-[1,3,7]Cl(III)		Cl	CH_3	CH_3	H
C-[1,3,7]$^-$Cl(III)		Cl	CH_3	CH_3	

The proton magnetic resonance of C-[1,3](II) indicates that the four ammonia ligands are nearly equivalent and therefore must be in the plane perpendicular to the carbene ligand. This is consistent with the known structure of (4,5-

dimethylimidazolylidene)tetraammineruthenium(II) carbonyl[9] in which the ammonias are nearly equivalent and in the same plane. The lack of a peak corresponding to a proton on C_8 in the nmr spectra of C-[1,3](II) is also consistent with metal binding to this carbon.

Solutions of N-[1,3](II) at pH 2 were observed to rearrange producing N-$[1,3]_2$(III) and C-[1,3](III) on oxidation; however, solutions of C-[1,3](II) did not isomerize to form nitrogen bound complexes under the same conditions. From this it appears that C-[1,3](II) is thermodynamically favored while, it is evident from varying the reaction times, that N-[1,3](II) is kinetically favored when theophylline is allowed to react with aquopentaammineruthenium(II).

Spectra. The broad visible absorption band in the spectra of the neutral ligand N series of complexes can be attributed to a charge transfer transition from a π-orbital on the xanthine to a partially filled orbital on ruthenium(III). Evidence for this is that deprotonation of the xanthine causes a shift to lower energy and, with the exception of N-$[3,9]^-$(III), an increase in the intensity of this band. The band appearing around 309 nm in the neutral ligand N series can also be assigned as a $\pi \rightarrow$ d ligand to metal charge transfer since this band shifts to lower energy in the spectra of N-$[1,9]^-$(III) and N-$[1,3]^-$(III) and increases in intensity in the spectrum of the latter. These two charge transfer bands are similar to those observed in a series of N_7-guaninepentaammineruthenium(III) complexes previously reported[24] and can be considered as $\pi \rightarrow$ d ligand to metal charge transfers from separate π levels on the ligand.

The shifts in these two bands when the xanthine ligand is deprotonated at N_1, N_3, or N_9 may provide information about the nature of the two π-molecular orbitals. Assuming the energy of the acceptor orbital remains constant, the energy of the L $\rightarrow$ M charge-transfer transition depends only on the energy of the donor LMO. This is a reasonable assumption for the pentaammineruthenium(III) series of complexes since the "t_{2g}" orbital should be essentially nonbonding in the ground state. In the excited state there may be mixing between the π-d orbitals on the metal and the π-system of the ligand, as has been shown for a number of ammineruthenium(II)-pyridine complexes.[25] The extent of this mixing should be similar for the series discussed here, so that the energies of the transitions observed are still meaningful. This assumption is supported by the fact that the charge-transfer transition in the visible region is significantly higher for xanthine ligands (19.6 kK) than for guanine ligands (17.3 kK)[24] as would be expected from the relative ionization potentials of the ligands.[26]

Deprotonation of the xanthine ligand causes the purine π-donor levels to increase in energy. The xanthine donor levels responsible for the visible charge transfer transitions increase in energy on deprotonation at a given site in the order $N_3 > N_9 > N_1$. In the case of the donor levels responsible for the uv charge transfer bands, the corresponding order is $N_9 > N_3 > N_1$.

The spectra of the neutral ligand N series of ruthenium(II) complexes are characterized by a broad absorption centered around 373 nm. This band appears to shift to higher energy on deprotonation of the ligand indicating that it is a metal-to-ligand charge transfer transition. Such transitions are typical of ruthenium(II)-ammine moieties on "pyridine" nitrogens and have been attributed to d $\rightarrow$ π^* transitions.[8,17] These transitions occur at slightly lower energy than those for the corresponding guaninepentaammineruthenium(II) complexes[24] as might be expected in substititing an electron-withdrawing oxo group for an amine at C_2.

The broad absorption in the visible region of the spectra of the ruthenium(III)-carbon-bound complexes can be attributed to a ligand to metal charge transfer, since it shifts to lower energy on deprotonation of the xanthine and to higher energy when the effective charge of the metal ion is reduced by addition of chloride. The band occurring at 315 nm in the aquotetraamine series of C-bound complexes behaves in an analogous fashion on deprotonation of the ligand and may be due to a $\pi \rightarrow$ d ligand to metal transition from a different π level on the ligand. The inflexion point at 346 nm in the spectrum of C-[1,3,7]Cl(III) may be due to the sum of two charge transfer bands, one from the xanthine, which would be expected to be at higher energy relative to C-[1,3](III), and one from the chloride. The band at 336 nm in the spectrum of C-$[1,3,7]^-$Cl(III) is of similar energy to the chloride to ruthenium transition at 327 nm evident in the spectrum of chloropentaammineruthenium(III). With the exception of C-[1,3,7]Cl(III), the neutral ligand C-bound complexes show a peak at 327 nm in 0.1 *M* chloride media which may be due to a combination of xanthine and chloride charge transfer transitions to the ruthenium.

The intense band around 348 nm in the spectra of C-[1,3](II) and C-[1,3,7](II) is believed to be analogous to the metal to ligand charge transfer seen in the nitrogen-bound complexes. The p orbital of a bound carbene should be considerably electron deficient, thereby facilitating the donation of electron density from the filled metal d orbitals.[11,12]

pK_a Values. The presence of ruthenium(III) at N_7 has a profound effect on the acidity of the xanthine ligand. The acidity of the deprotonation site closest to the metal, N_9, is increased by 10^6 while the ionization constants of protons at N_1 and N_3, which are approximately equidistant from the metal, are increased by a factor of 100.

The effects registered here can be compared with those exerted by $Co(NH_3)_5^{3+}$ on carboxylic acids. This group enhances the acidity of acetic acid[27] by *ca.* 2 × 10^5 (this situation is comparable to that for $Ru(NH_3)_5^{3+}$ at N_7 affecting the N_9 position, in the sense that in both cases the metal ion and the proton are three atoms removed) and of $HC_2O_4^-$ by a factor of *ca.* 100[28] (here the metal ion and proton are four atoms removed as is the case for $Ru(NH_3)_5^{3+}$ at N_7 with the proton at N_1 or N_3). The group $Ru(NH_3)_5^{2+}$ at N_7 enhances the acidity at N_9 by approximately 10^3 but those at N_1 and N_3 by a factor of less than 10. The enhancement at N_9 is surprisingly high in view of the small effect which coordination of acetic acid to $Ru(NH_3)_5^{2+}$ has on the acidity of the ligand—a factor of only 30[29] and, unless back-donation is invoked in the case of acetic acid as ligand, leaves little scope for such an effect on the acidity of the purine ligand.

Compound C-[1,3,7](III) can deprotonate only at N_9, and the similarity in the spectra of compounds C-$[1,3]^-$(III), C-$[3,7]^-$(III) and C-$[1,3,7]^-$(III) indicates that this deprotonation site is common to all three complexes. Since the metal is closer to the ionization site, electrostatic considerations might predict that deprotonation at N_9 would be facilitated in the carbon-bound complexes relative to the nitrogen-bound complex N-[1,3](III). However, it appears that other effects overwhelm the simple electrostatic effect and the acidity of the Ru(III) carbene complexes is an order of magnitude less than that of N-[1,3](III). Allowing chloride ions to interact with the C series of complexes in solution lowered the acidity of these complexes, presumably by decreasing the effective charge of the metal center. The great difference between the acidity of the ruthenium(II) and ruthenium(III) carbene complexes is consistent with the back-donation of a considerable amount of electron density from the ruthenium(II) into the π system of the xanthine. An effect similar to this has been described for pyrazinepentaammineruthenium(II) in which the basicity of the pyrazine is increased by conjugation with the divalent ruthenium.[17] The decrease in acidity of C-[1,3](II) and C-[1,3,7](II) relative to C-[1,3,7](III) and C-[1,3,7](III) correlates well with the intense metal to ligand charge transfer band and the stabilization of ruthenium(II) relative to ruthenium(III) evident in the electrochemical measurements.

Electrochemistry. The more positive reduction potentials relative to that for the hexaammineruthenium(III-II) couple for all the neutral ligand nitrogen-bound complexes indicate that the xanthine ligand stabilizes ruthenium(II) relative to ruthenium(III). This is apparently caused by transfer of πd electron density to the ligand in the ruthenium(II) state and has been discussed by Lim[22] for a number of pentaammineruthenium complexes involving heterocyclic ligands. Deprotonation of the xanthine destabilizes ruthenium(II) somewhat since the presence of a negative charge on the ligand decreases its ability to accept electron density from the metal. The degree of this effect is dependent upon the proximity and conjugation of the deprotonation site with regard to the metal binding site. Less positive reduction potentials caused by the deprotonation of the xanthine ligand are also consistent with stabilization of the Ru(III) state by a negatively charged ligand. The effects of backdonation and charge stabilization cannot be separated.

Binding at the C_8 site appears to stabilize ruthenium(II) relative to ruthenium(III) much more than does coordination at N_7. The π orbital of a carbene is expected to be electron deficient and should be a good acceptor of electron density from the metal.[11,12] This property may account for the apparent thermodynamic stability of the C_8 isomer over the N_7 isomer when bound to ruthenium(II).

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A Reexamination of the Metal–Nitrogen Bond in Certain Imidazole and Pyrazole Complexes

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Abstract: The previously reported experimental data, which had been interpreted as evidence of ambidentate metal coordination of the aromatic bases imidazole or pyrazole through either of their nitrogen atoms, has been carefully reexamined. In direct contradiction to the previous report, the true paramagnetic proton magnetic resonance (pmr) shift of the N-1 proton of imidazole is shown to be downfield when this base is coordinated to either Ni(saloph) or Co(saloph) (saloph = *N,N'*-bis(salicylidene)-*o*-phenylenediamino). Pmr and electronic spectral data purported to indicate the existence of two different 1:1 adducts between Co(saloph) and either imidazole or pyrazole are shown to be either erroneous or misinterpreted. Electronic spectral data indicate that pyrrole does not form adducts with either Ni(saloph) or Co(saloph). It is concluded that N-1 of imidazole, N-1 of pyrazole, and the nitrogen of pyrrole do not coordinate Ni(saloph) or Co(saloph).

Imidazole, **1**, and its derivatives frequently occur as the metal binding sites of biologically important macromolecules. Consequently the mode of bonding between metals and imidazole is of considerable importance. Some recent experiments have been interpreted to indicate that imidazole may coordinate metals not only in the well-recognized manner through N-3 but also *via* N-1.[1] Similarly it has been suggested that pyrazole, **2**, may coordinate metals