ciation of the ion pair will result in an apparent decrease of ΔV^*. Such an effect is significant in those solvents with larger dielectric constants, e.g., PC. No information is available, however, concerning the pressure effect on the ion pair formation in organic solvents.

DMF with the largest DN gives a negative ΔV^*. The molecule is not as large as PC and can go deep into the coordination sphere to overcompensate the increase in volume at the transition state caused by the break of one end of the ligands. The complex undergoes solvolysis in this solvent. However, since the solvolysis proceeds more slowly than the decrease in CD strength by a factor of more than 10, the encountered experimental error will remain less than ca. 10%. If one of the $acac^-$ ligands leaves the coordination sphere to give bis(acetylacetonato)bis(dimethylformamide)germanium(IV) ion on solvolysis, the product can be of either cis or trans isomerism. If the trans isomer were formed, it cannot be optically active and the experimental error comes only from the apparent molar extinction coefficient ϵ, whenever the ratio $\Delta\epsilon_{305}/\epsilon_{287}$ is used in place of the CD strength itself for the first-order kinetic plot. If *cis*-$[Ge(acac)_2(DMF)_2]^+$ were formed with retention of the configuration, the product could contribute to the CD strength at 305 nm. However, bis(β-diketonato) complexes of metal ions have UV absorption maxima due to the exciton band at a lower wavenumber region than the tris-type complexes do.[17] The CD strength at the negative exciton peak of this bis(β-diketonato) complex should shift to the lower wavenumber region for the present Δ isomer, which has a negative CD peak at a lower wavenumber side. The $\Delta\epsilon$ decreases more steeply than the molar extinction coefficient does at the higher wavenumber side of the peaks. Therefore, the contribution of *cis*-$[Ge(acac)_2(DMF)_2]^+$ to the $\Delta\epsilon_{305}/\epsilon_{287}$ ratio cannot be large. The ln $(\Delta\epsilon_{305}/\epsilon_{287})$ vs. time plots, in fact, remained linear until 70% of the initial $[Ge(acac)_3]^+$ racemized. This fact supports indirectly the legitimacy of our kinetic treatment.

Conformity of the racemization mechanism in donating and less donating solvents was also discussed on the basis of the rather continuous change of ΔH^* and ΔS^* values.[8] The present results support that the racemization proceeds via an intermediate with one unidentate ligand that was formed by a solvent-assisted bond break. However, a less donating solvent assists the bond break to only a very small extent.

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Registry No. $(-)_{589}$-$[Ge(acac)_3]ClO_4$, 76370-51-9.

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Cyclic Voltammetry Studies of Metalloflavin Complexes in Aqueous Solution

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Electrochemical studies of stable tetraammineruthenium(II) complexes of 10-methylisoalloxazine, 3,10-dimethylisoalloxazine, and riboflavin are reported. While approximating metal-stabilized flavosemiquinones in some of their properties, these complexes are best formulated as Ru^{II}-Fl_{ox} rather than Ru^{III}-Fl·. The reduction of the flavin ligand is shown to proceed through two successive single-electron steps rather than by the apparent two-electron process exhibited by the free flavins under similar conditions. This appears to be largely due to destabilization of the fully reduced flavin. Measurements of the pK_a values were determined spectrophotometrically and are used to extrapolate from experimental reduction potential data as a function of pH. Coordination of the metal to the N-5 and O-4 positions of the isoalloxazine ring modulates the acid–base behavior of the flavin so that distinct pH regions emerge where electron transfer occurs without simultaneous proton transfer. A minimum separation between the two one-electron flavin reduction potentials occurs when the flavosemiquinone complex is 50% protonated at the N-1 position. An unusually high oxidation potential for the Ru(II) indicates substantial donation of electron density from the metal onto the isoalloxazine ring. Several types of absorption phenomena are present owing to time-dependent adsorptions of the complex and interactions of the free flavin following dissociation of the reduced complex. Such processes are identified and discerned form bulk solution redox couples. The results are discussed in terms of possible mechanisms for protein control of flavin redox behavior.

Introduction

Flavin coenzymes occur in a variety of oxidoreductase proteins to interface between organic oxidations (and reductions) occurring by two-electron processes and electron transfer to (or from) metal centers requiring single electrons.[1-3] Only molybdenum, which occurs relatively rarely in biological systems, also performs this interface function. In addition to being able to operate by one- or two-electron steps, flavins exhibit electrochemical potentials which are modulated over a range of 600 mV by the effects of protein binding.[3]

Since flavins engage in electron transfer with a variety of metal centers in proteins, it has long been speculated that metal coordination of these coenzymes may take place.[1,2,4-6] However, only in one case have flavin and metal sites been shown to be in a proximity close enough to allow a strong interaction evident in EPR spectra.[7] For this reason a lower limit of 10–15 Å is usually placed on the distance between flavin and metal sites in proteins. While separations of this

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magnitude make direct metal–flavin interaction unlikely, fluctuations in protein conformation may still allow for this possibility. Steric requirements around the iron or molybdenum centers involved further restrict metal coordination of the flavin; however, only very transient binding would be necessary for electron transfer to occur.

In the model proposed by Fritchie for interaction with iron–sulfur sites, it is suggested that coordination of the flavin through the N-5 and O-4 sites could lead to an intermediate of distorted octahedral geometry around the iron. This would place the iron in a relatively strong ligand field (formed by the flavin and four anionic sulfurs) and cause it to become low spin. Malin has shown that Fe(II) in a strong field environment provided by anionic ligands approximates the isoelectronic Ru(II) in its bonding properties.[8] Since Ru(II) is well-known for its ability to form stable complexes with readily reducible organic heterocycles,[9] it provides a convenient system for probing metal–flavin interactions.

Aside from the possibility of metal–flavin complexation in proteins, it is clear that coordination of a Lewis acid at various points on the electrochemically active isoalloxazine ring has a substantial effect on both the electrochemical potential and the propensity of the flavin toward one- or two-electron oxidations or reductions.[2,10-12] The polarity and donor–acceptor characteristics of the environment also affect these properties.[12,13] Thus, an integrated study on the electrochemical effects of flavin coordination, pH, and aqueous vs. nonaqueous environments should reveal much about the methods open to proteins in controlling the reactivity of these coenzymes.

Work reported earlier on a series of metalloflavin complexes derived from *cis*-$(H_2O)_2(NH_3)_4Ru^{II}$ showed that these complexes retain their integrity under a variety of solvent and pH conditions.[14,15] A complete structure determination showed that the metal ion is tightly bound to the N-5 position and is less strongly chelated by the O-4 site. Owing to the slow exchange rates of most nitrogen ligands on Ru(II),[9] the complexes studied in solution involve the same firm metal coordination as is evident in the solid state. Structural, chemical, and spectroscopic measurements suggest that the flavin is in a partially reduced form when coordinated to this metal ion.[14,15] This results from substantial back-donation of electron density from a fully populated d_π orbital on the metal to the lowest unoccupied π orbital on the ligand, so that these compounds simulate metal-stabilized flavosemiquinones.[15] However, for reasons treated at length elsewhere[15] and also addressed in the Discussion, it is preferable to regard these compounds as Ru(II) complexes of fully oxidized flavins.

Finally, while a great deal is now known about the effects of various ligand environments on the reduction potentials of metal ions, relatively little is known concerning the effects of metal ions on the electrochemical behavior of organic heterocycles. Since Ru(II) complexes of aromatic heterocyclic ligands are now being intensely studied with regard to solar energy transduction,[16] it is important to begin systematically delineating the electrochemical effects of metal coordination on molecules with extensive π-acceptor systems.

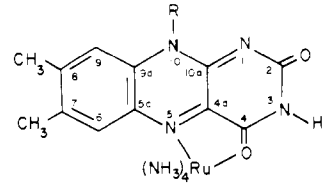

Figure 1. Structure and numbering system for Ru-Fl_{ox}.

The electrochemical properties of several Ru^{II}–flavin complexes have now been studied in aqueous solution by cyclic voltammetric techniques. The effect of pH on the reduction potentials of these metalloflavins is of particular interest since it illustrates how protonation at various sites affects the separation between the two one-electron addition processes of a flavin strongly ligated at the N-5 site.

Abbreviations. The flavin ligands employed in this work are riboflavin (Rib), 10-methylisoalloxazine (10-MeIAlo), and 3,10-dimethylisoalloxazine (3,10-Me_2IAlo). Flavin ligands as a class are referred to as: fully oxidized flavin (Fl_{ox}), flavosemiquinone (Fl·), and fully reduced flavin (Fl_{red}). Tetraammineruthenium(II) complexes of the various flavins are referred to as Ru-Fl. Reduction potentials as determined by cyclic voltammetry are termed E_{cv}, while reduction current peak potentials are denoted as E_c and anodic wave peak potentials as E_a.

Experimental Section

Synthesis. The compounds $[(10\text{-MeIAlo})(NH_3)_4Ru](PF_6)_2\cdot H_2O$ and $[(3,10\text{-}Me_2IAlo)(NH_3)_4Ru](PF_6)_2\cdot H_2O$ were synthesized according to a previously reported method.[15] The compound $[(Rib)(NH_3)_4Ru]Cl_2\cdot H_2O$ was similarly prepared and purified. Separation of the riboflavin complex was performed by sequential ion-exchange chromatography on Biorex-70 and Sephadex CM-25 columns eluted with 0.4 M ammonium formate. Following repetitive rotary evaporation to remove the buffer, a solid was obtained by dissolution of the residue in a minimum volume of methanol and addition of methanol saturated with tetrabutylammonium chloride. The precipitate was filtered, washed with acetone, and stored in a vacuum desiccator. Yields were typically 10–15%. Anal. Calcd for $[(Rib)(NH_3)_4Ru]Cl_2\cdot 2.5H_2O$: H, 5.64; C, 30.86; N, 16.94; Ru, 15.3. Found: H, 5.18; C, 30.81; N, 16.50; Ru, 15.1.

Electrochemistry. Cyclic voltammetry scans were taken on an electrochemical apparatus constructed in this laboratory and described elsewhere[17] or with a Bioanalytical Systems Model CV-1A using the same recording instrumentation. The instrument was daily calibrated relative to the $(NH_3)_6Ru^{III/II}$ couple. Concentrations of the complex ion under study were typically in the millimolar range with scan rates of 125 mV/s unless otherwise noted. Working electrodes employed were platinum-disk (Beckmann), a Brinkmann hanging-mercury-drop electrode (HMDE), and carbon-paste electrodes from Bioanalytical Systems. All measurements were made relative to a standard calomel electrode (SCE) but are reported relative to the standard hydrogen electrode (SHE) by subtracting 242 mV from the experimental value.

Values for the reduction potentials (E_{cv}) were taken at a point midway between the cathodic and anodic peaks of a chemically reversible couple. Reversibility was determined on the basis of approximately equal cathodic and anodic peaks and a separation between these peaks comparable to that noted for the $(NH_3)_6Ru^{III/II}$ couple (60–90 mV) under the same conditions. In cases where a relatively slow chemical reaction was noted, the scan rate was increased until the cathodic and anodic peak currents were nearly equal and the reduction potential was determined as before. If this was not possible, no value of E_{cv} is reported. Where adsorption effects interfered with E_{cv} measurements, a small concentration of Triton X-100 was added to eliminate the interference.

Measurements of pH were made with a Fisher microcombination pH electrode using a Markson Model 90 digital pH meter. Buffer systems and the pH ranges employed were as follows: HCl, pH 0–2; glycine/HCl, pH 2–4; acetic acid/sodium acetate, pH 4–6; phosphate, pH 6–8; Tris HCl, pH 8–9; glycine/LiOH, pH 9–11; LiOH, pH

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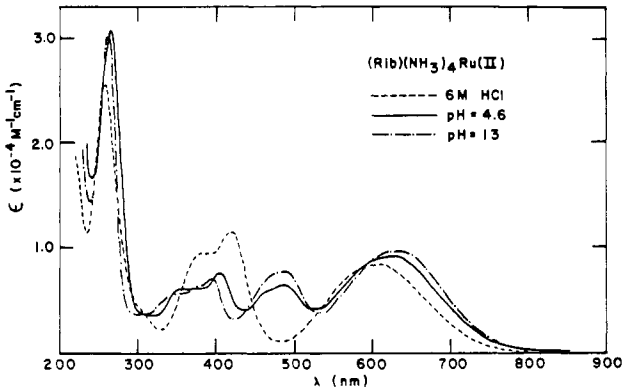

Figure 2. Spectra of $(Rib)(NH_3)_4Ru^{II}$.

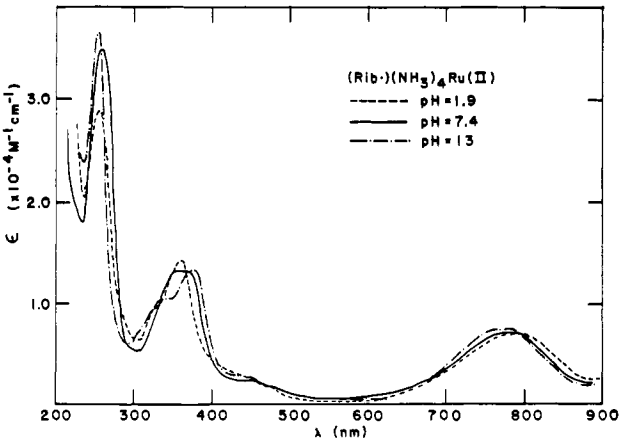

Figure 3. Spectra of $(Rib\cdot)(NH_3)_4Ru^{II}$.

11–14. Buffers were adjusted to an ionic strength of 0.1 with a standard LiCl solution.

Spectroscopy. Spectra were recorded on a Perkin-Elmer Model 575 spectrophotometer which was thermostated at 25 °C. Values of pK_a and molar absorptivities for the $Ru\text{–}Fl_{ox}$ complexes were determined spectrophotometrically with the use of previously described methods.[15] Values of pK_a and molar absorptivities for the Ru-Fl complexes were similarly determined with the use of an argon-purged cuvette. Reduction to the semiquinone form above pH 9 was affected by addition of a 50% excess of an approximately 2 mM solution of sodium dithionite, which had been freshly prepared in a 0.01 M phosphate buffer adjusted to pH 7.6 and deaerated by argon bubbling. Below pH 9, a 3 mM solution of Eu(II) was used to reduce the flavin complex. Isosbestic points were present in all spectrophotometric titrations.

Results

Spectra and pK_a Values. Electronic spectra of the three protonation forms of $(Rib)(NH_3)_4Ru^{II}$ are shown in Figure 2. Analogous spectra for the three protonation forms of the flavosemiquinone complex $(Rib)(NH_3)_4Ru^{II}$ are given in Figure 3. Spectra for the corresponding forms of the 10-MeIAlo and 3,10-Me_2IAlo complexes are similar and tabulations of E_{max} and λ_{max} for these complexes are given in Supplementary Table I. Spectrophotometrically determined pK_a values for these complexes are given in Table I. Values of pK_a determined from spectrophotometric titration and those estimated from discontinuities in the graphs of E_{cv} vs. pH for the individual complexes (cf. Table I and Figures 4 and 5) agree well within experimental error.

Cyclic Voltammetry Studies. A typical cyclic voltammetry scan over the entire region of interest is shown Figure 6 for $(Rib)(NH_3)_4Ru^{II}$. Earlier work has shown that wave I corresponds to the Ru(II)/Ru(III) couple, wave II is for the addition of a single electron to the flavin ligand to form a coordinated radical (Ru-Fl·) species, and wave III pertains to the second one-electron reduction of the flavin to yield $Ru\text{-}Fl_{red}$.[14] This has since been verified by direct coulometric titration which yielded values of $n_{II} = 1.09$ and $n_{III} = 1.06$ at pH 8.5.[18] For convenience, the flavin reductions will be treated first and then the ruthenium couple.

Prewaves and Postwaves. Adsorption phenomena were often evident in the cyclic votammetry of these complexes, particularly when the HMDE was employed as the working electrode. While these effects have been the subject of consid-

Table I

pK_a for $Ru\text{-}Fl_{ox}$ and Ru-Fl· Complexes[a]

ligand	Fl_{ox}-H⁺ (N-1)	Fl_{ox} (N-3)	Fl· (N-1)	Fl· (N-3)
3,10-Me_2IAlo	0.47 ± 0.06[b]		4.3 ± 0.1	
10-MeIAlo	0.60 ± 0.03[b,c]	7.37 ± 0.09[c]	4.1 ± 0.1	11.3 ± 0.2
Rib	0.7 ± 0.1[b]	7.4 ± 0.1	3.98 ± 0.09	10.9 ± 0.2

pK_a for Rib

free Rib	0.25	10.0	8.3 (N-5)
Rib_{red}		6.7 (N-1)	

[a] pK_a values determined spectrophotometrically at 25 °C in 0.1 M LiCl. Unless otherwise noted. Deprotonation sites are given in parentheses throughout. [b] Determined in HCl/LiCl; $\mu = 1.0$. [c] Taken from ref 15. [d] Taken from ref 23.

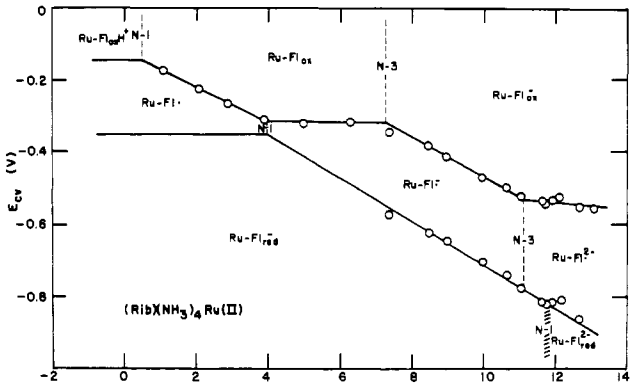

Figure 4. E_{cv} vs. pH diagram for $(Rib)(NH_3)_4Ru^{II}$ showing experimental points and extrapolations from experimental data with use of spectrophotometrically determined pK_a values. Crossing a solid horizontal line in this diagram indicates a one-electron oxidation or reduction of the flavin ligand. Crossing a vertical dashed line indicates a single-proton equilibrium at the specified site on the flavin ring. Crossing a diagonal solid line pertains to a one-electron redox process accompanied by a single-proton equilibrium. The hatched line for pK_a of $Ru\text{-}Fl_{red}^-$ indicates area where data suggest an additional proton equilibrium (see text).

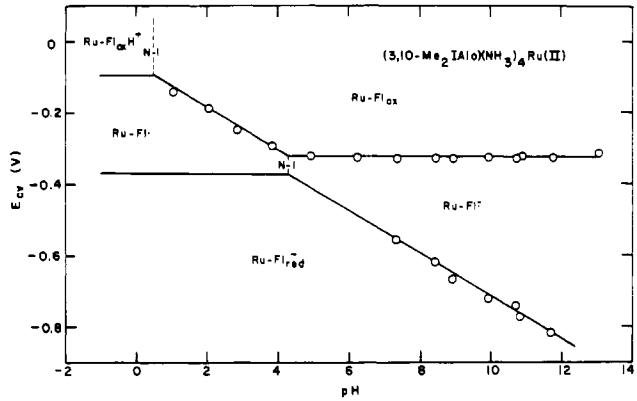

Figure 5. E_{cv} vs. pH plot for $(3,10\text{-}Me_2IAlo)(NH_3)_4Ru^{II}$ (refer to legend for Figure 4).

(18) Condit, D.; Stankovich, M., personal communication.

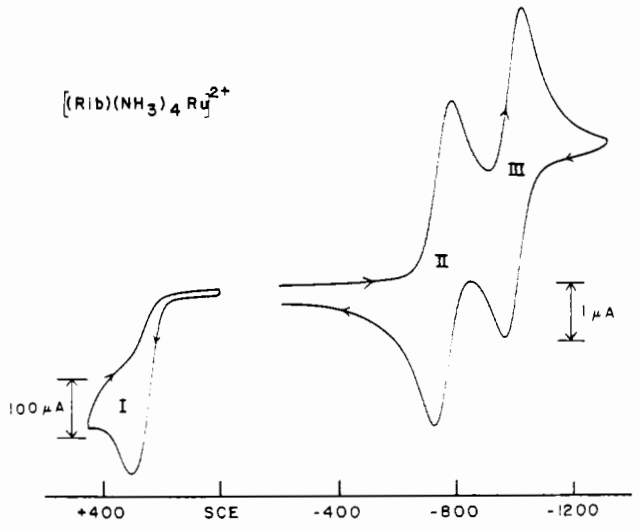

Figure 6. Cyclic voltammetry scan of $(Rib)(NH_3)_4Ru^{II}$ on HMDE at pH 11.0. Scan rate is 125 mV/s; concentration is approximately 5 mM.

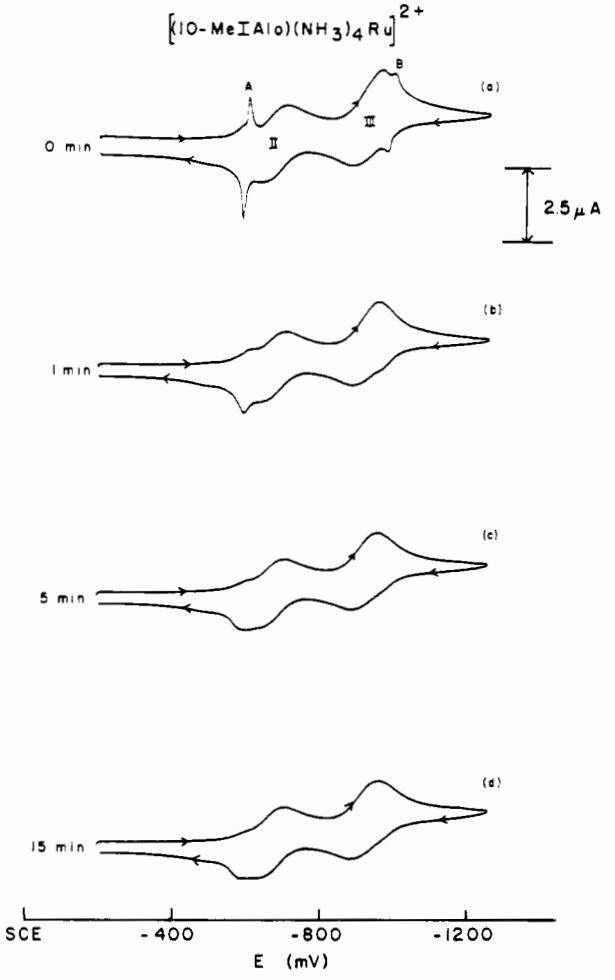

Figure 7. Cyclic voltammetry scans of time-dependent adsorption waves evident with $(10\text{-MeIAlo})(NH_3)_4Ru^{II}$ on HMDE at pH 7–9.

erable interest,[10] they are relevant to the present work only in that they be differentiated from bulk solution phenomena. For these reasons adsorption peaks are described in sufficient detail to identify them but are discussed only summarily.

Figure 7 shows a time-dependent prewave (A) occurring at a potential positive of wave II and a similar postwave (B) at a potential negative of wave III. Both waves were evident for all three complexes when studied with the use of an HMDE

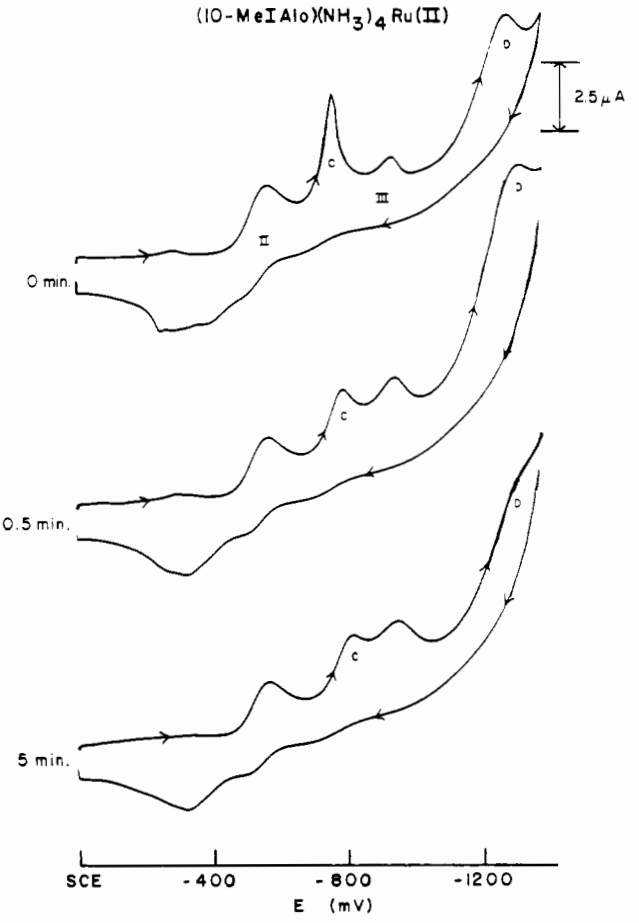

Figure 8. Cyclic voltammetry scans of time-dependent waves evident with $(10\text{-MeIAlo})(NH_3)_4Ru^{II}$ on HMDE at pH 4.6. Scans were taken on new Hg drops after times indicated.

in aqueous solution but were not present on other types of electrodes or in nonaqueous solvents. These adsorption waves altered their behavior in concert with time and under changing solution conditions. Allowing the mercury drop to age in solution for several minutes prior to scanning yielded a decrease in these current peaks which continued to diminish with time and change in potential to eventually converge with the nearby oxidation or reduction waves for the complex ion in solution. The potential of these adsorption waves followed that of the material in solution as the pH was varied. Below pH 7, these peaks were usually not in evidence and they disappeared more rapidly with increasing pH so that maximum currents were obtained in the pH 7–9 range.

These peaks are similar to those observed by Hartley and Wilson in studying the cyclic voltammetric behavior of FMN on a HMDE.[19] Prewaves are normally taken as evidence that the reduced species is more strongly adsorbed than the oxidized form and postwaves as the reverse.[10] Adsorption wave A in Figure 7 indicates that Ru-Fl· is more strongly adsorbed than $Ru\text{-}F_{ox}$. The adsorption currents (B) negative of wave III suggest that the semiquinone form is also more strongly adsorbed than the fully reduced species. The time-dependent behavior may be due to a pH-dependent conformational change eventually yielding a stable film on the electrode surface.[19]

Below pH 7, several time-dependent reduction peaks appeared in the region negative of wave II that were not accompanied by corresponding oxidation peaks. The 10-MeIAlo and $3,10\text{-}Me_2IAlo$ complexes exhibited three peaks in this

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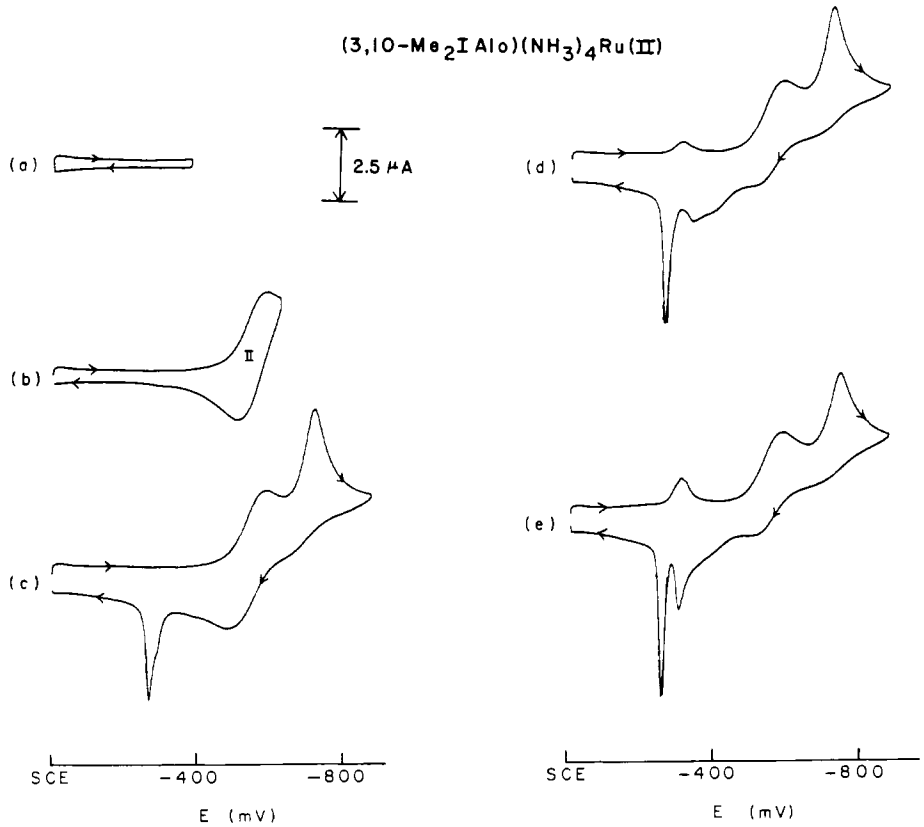

Figure 9. Repetitive cyclic voltammetry scans showing the occurrence of waves pertaining to oxidation and reduction of free and adsorbed flavin ligands following dissociations of reduced complex.

region (labeled C, III, and D in Figure 8) when scanned immediately with the use of a new mercury surface. The relative currents of C and III varied as a function of time with greater rates of change occurring at lower pH. Scans on new mercury drops of increasing age depict a broadening in peak C with a concomitant decrease in its maximum current and a movement toward progressively more negative potentials. Eventually peak C merges into the more cathodic peak III which gradually increases in current. At pH 2.0 this process was observed to be complete within 1 min while at pH 4.9 it was still incomplete after 15 min. The most negative peak, D, was evident for all complexes but was often poorly resolved and eventually blended into the background current tail. Peak III was not initially observed for the riboflavin complex. Scans taken on carbon-paste electrodes revealed a single well-resolved peak at potentials similar to those noted for the single peak remaining after long periods of time on the HMDE. A second poorly resolved shoulder was also usually present on the background current tail.

The initial shape of peak C and its occurrence when new mercury drops (held at the potential of the reference electrode) were employed suggest that this reduction process arises from the adsorption of Ru-Fl onto the electrode surface. Furthermore, this peak appears only when the previously described time-dependent adsorption peaks (cf. Figure 7) do not. It is additionally distinguished in that it is broader and its rate of merging with the nearby reduction wave (III) is more strongly pH dependent. The time-dependent nature of this reduction and its slow approach to an equilibrium position at neutral pH make it difficult to assign potentials for the addition of the second electron to the flavin ligand below pH 7. When equilibrium was approached, the potential of the resultant reduction peak maximum was often more negative than might be expected on the basis of any simple pH behavior for the free complex. The oxidation peak corresponding to that for reduction wave III disappears more rapidly with decreasing pH. Thus the shift in the apparent position of wave III away from the value expected for a simple protonation is probably due to both the dependence of the peak position on the kinetic parameter[20] and the overlapping of the time-dependent peak C.

It has long been known that catalytic hydrogen waves occur with adsorbed Fl_{red} on mercury surfaces up to pH 8.[10] This suggests that peak D in Figure 8, which invariably occurred on the hydrogen reduction current tail, is due to the reduction of H^+ catalyzed by Ru-Fl_{red} or Fl_{red} adsorbed onto the surface of the electrode.

Dissociation of Reduced Complexes. A series of time-independent prewaves, which occurred only below pH 7 on both HMDE and carbon-paste electrodes, is indicated in Figure 9. In the pH range 4–7, this anodic prewave normally occurred only when potentials negative of the second reduction potential for the flavin ligand had been reached. However, below pH 4 this new wave was also noticeable when only the first reduction potential for the coordinated flavin had been scanned over. Upon subsequent scans, a second anodic prewave grew in at a potential approximately 75 mV positive of the initial prewave. Upon further scanning, the first peak diminished and broadened to merge with the second peak. Subsequent scans also revealed a cathodic peak which appeared to pertain to the reduction of the original anodic prewave. Similar behavior was evident for all the complexes under study. Comparison of cyclic voltammograms for the corresponding free ligands revealed a close correlation between the behavior of these prepeaks and the peaks evident in initial scans of the free flavins under identical conditions. Later scans on the free ligands revealed a reversible two-electron process in this region. These peaks are clearly due to the presence of free flavin following dissociation of the reduced complexes in acid media.

(20) Bard, A. J.; Faulkner, L. R. "Electrochemical Methods"; Wiley: New York, 1980; pp 213–248.

Reduction Potentials. The pH dependence of the values of E_{cv} for the two ligand reduction potentials of the 3,10-Me_2IAlo and riboflavin complexes are shown in Figures 4 and 5, respectively. These figures clearly show the ranges over which reversible waves and valid E_{cv} values were obtained (as determined by the criteria stated in the Experimental Section). Reduction potentials are extrapolated beyond these points on the basis of spectrophotometrically determined pK_a values. The corresponding graph for the 10-MeIAlo complex is similar to that for the riboflavin species and is given as Supplementary Figure 1 on microfilm. The complexes exhibited reversible or nearly reversible behavior over the ranges plotted on these graphs. The 3,10-Me_2IAlo complex underwent marked irreversible spectral changes at pH 12, and wave II also exhibited irreversible behavior above this pH. Below pH 7 wave II appeared as an irreversible couple for all three complexes.

The values of E_{cv} for wave II were identical within experimental error when taken on carbon-paste, glassy-carbon, platinum-disk, or hanging mercury drop electrodes. Similar results were obtained for wave I on both carbon-paste and Pt-disk electrodes; however, owing to the adsorption phenomena discussed earlier, there was some variation in the position of the cathodic peak for wave III between carbon paste and the HMDE, with the latter yielding slightly more positive potentials.

Due to proton-assisted dissociation of the reduced forms of the complex below pH 7 and the presence of multiple adsorption phenomena, experimental E_{cv} values for the Ru-Fl·/Ru-Fl_{red} couple could not be obtained in this region. Above pH 12, base-catalyzed decomposition of the 3,10-Me_2IAlo complex limited the data on this ion as well. The transient nature of the Ru-Fl_{red} species also prevented their study by conventional spectroscopic techniques. As a result, no value for the proton ionization constant could be directly determined for any Ru-Fl_{red} complex. Nevertheless, the lack of a change in the slope of the E_{cv} vs. pH line for wave III in the region of the pK_a of Ru-Fl· suggests that the pK_a for dissociation of the proton at N-1 of Ru-Fl_{red} is not resolved from that for N-3 of the former ion, so that it may also be around 11.5. So that pK_a values could be discerned in plots of this type, the difference between the pK_a of the oxidized and reduced forms must be greater than 1–2 units.

Metal Oxidation. In all but very low pH solutions, wave I for the Ru(III)/Ru(II) couple was irreversible and did not exhibit a cathodic wave above pH 4. Only in the pH range below 3 were the cathodic and anodic peak currents approximately equal. Under these conditions the peak separations (75–105 mV) approached that for the reversible $(NH_3)_6Ru^{III/II}$ couple when scanned at 125 mV/s. This allows good estimations of E_{cv} between pH 1 and 3. Between pH 1 and 2, values of E_{cv} remained constant for all complexes and were determined to be 0.94, 0.95, and 0.89 V for the 10-MeIAlo, 3,10-Me_2IAlo, and riboflavin complexes, respectively. Above pH 2.0 for the 10-MeIAlo complex and pH 2.3 for the riboflavin complex, values of E_{cv} decreased with a slope of approximately −60 mV/pH unit while the value for the 3,10-Me_2IAlo ion remained constant. This indicates a pK_a of approximately 2.1 for the loss of a proton from the N-3 site of Ru^{III}-Fl_{ox}. Due to the instability of these oxidized ions, this value could not be independently verified.

Discussion

Spectra. The spectra of the Ru-Fl_{ox} complexes differ from those of the free ligands in that a new band centered around 620 nm becomes evident upon coordination of the Ru(II) ion. In addition, large bathochromic shifts occur in the flavin bands originally centered around 345 and 435 nm. These changes result in spectra which are similar to those for neutral flavosemiquinones (Fl·) having a Lewis acid coordinated at the N-5 position.[5,21-23] In harmony with this are previously reported structural data on the 10-MeIAlo complex which indicate the geometry of the coordinated ligand to be midway between that of fully oxidized (Fl_{ox}) and fully reduced (Fl_{red}) flavins.[15] The amount of back-donation of electron density from the metal to the ligand is so substantial that these complexes simulate metal-stabilized flavosemiquinones. The similarity between the spectra of the various Ru-Fl· and Ru-Fl_{ox} complexes further supports this contention.

The appearance of a band in the 600–800-nm region upon partial population of the lowest unoccupied molecular orbital suggests that this band may be sensitive to the net electronic population of this molecular orbital and so to the amount of π-electron density on the flavin ligand. The bathochromic shift in this feature upon deprotonation or reduction of the Ru-Fl_{ox} complexes appears to correlate with increasing π-electron density on the flavin.

Assignment of Cyclic Voltammetric Waves. The dilemna of assigning simple valence-bond structures to these complexes is not unlike that encountered concerning the oxidation state of iron in oxyhemoglobin and has been addressed previously.[15] While the electronic spectra and structural parameters approximate those expected for metal-stabilized flavosemiquinones, i.e., Ru^{III}-Fl·, it must be emphasized that these ions are diamagnetic and their NMR spectra are most easily interpreted on the basis of retrodative bonding from Ru(II) increasing the electron density in the π system of the flavin ring.

Since the reduction potential (0.10 V) of *cis*-$(H_2O)_2(NH_3)_4Ru^{III}$ is considerably higher than that of the free flavins, it is more reasonable to assign the metal the lower oxidation state. Also, absurdities result from attempting to interpret the electrochemical data by using Ru^{III}-Fl· as the preferred valence structure. This would require wave I to arise from the oxidation of a flavosemiquinone and wave II to involve the Ru(II)/Ru(III) couple and so yield potentials far out of the normal range for either species. It is considerably more consistent with the large amount of electrochemical data available for both flavins[10] and ruthenium ammine complexes[24] to interpret the results presented here starting from the even-electron formalism. In addition (as described in Results) adequate care was taken to discriminate between adsorption currents and those due to complexes in the bulk solution. For these reasons, wave I is assigned to the Ru(II)/Ru(III) couple, wave II to coordinated Fl_{ox}-Fl·, and wave III to coordinated Fl·-Fl_{red}.

Proton Equilibria. The equilibria between the various forms of the Ru-Fl complexes are summarized in Figure 10. Reference should also be made to the graphical representations in Figures 4 and 5. Chelation of the metal to the N-5 and O-4 sites of the flavin causes significant modifications of the acid–base behavior of the flavin in all three oxidation states. In contrast to the electrochemical behavior of the free flavins, which is pH dependent over the entire range,[25] these complexes exhibit pH regions where electron transfer is not accompanied by proton transfer. Coordination of the metal prevents protonation at N-5 and (in most cases) causes the flavin to be more acidic than the corresponding form the free ligand. This prevents the ionization equilibrium for the neutral semiquinone from overlapping with that for the fully oxidized and reduced

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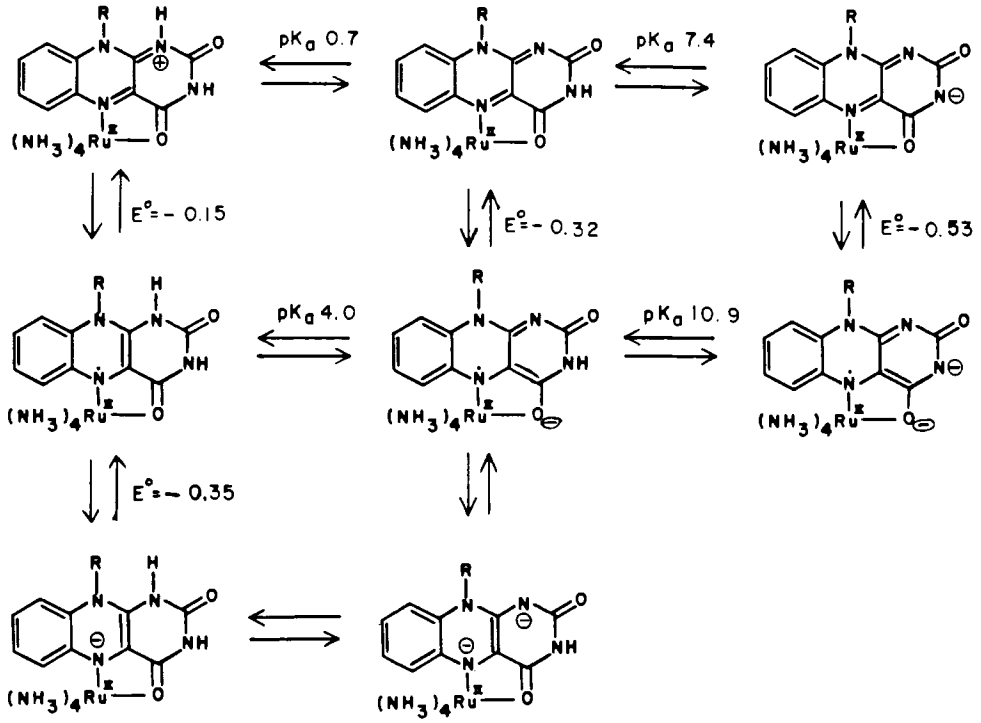

Figure 10. Summary of structures, pK_a, and E_{cv} values of the various Ru-Fl complexes.

forms as occurs with the free flavins. Eliminating this overlap results in the areas of constant potential as the pH is varied.

In general, flavosemiquinone complexes are unstable at low pH due to the competition for the N-5 site by protons, and fully reduced flavin complexes are known to be unstable at any pH.[1,5,12,13] In fact, the reversible couple noted for the addition of the second electron to the flavin ligand at high pH is the first evidence to be reported for the existence of any metal-Fl_{red} species. The Ru-Fl_{red} complexes dissociate quickly below pH 7 and the Ru-Fl· complexes rapidly yield free flavins below pH 4. Earlier spectroelectrochemical studies on the 10-MeIAlo complex yielded spectroscopic evidence for this dissociation at low pH[15] and the spectrophotometric titrations of the Ru-Fl complexes in this work further verify that the rate of decomposition increases with decreasing pH. The formation of the Ru-Fl_{red} complexes is most likely due to the substitution-inert character of Ru(II) rather than to any high affinity between this metal ion and the flavin ligand in preference to protonation at the N-5.

The pK_a values for the Ru-$Fl_{ox}H^+$ complexes are similar to those for the corresponding free ligands (cf. values in Table I). The similarity in spectra of the Ru-$Fl_{ox}H^+$ complexes, coupled with the correspondence in their pK_a values, indicates a common ionization site. Since the chelaton of a divalent metal ion between N-5 and O-4 should hinder protonation at these sites, the only positions readily available for proton addition are N-1 and O-2. After consideration of the preference for the keto form in the free ligand,[26,27] the most likely site for the additional proton in Ru-$Fl_{ox}H^+$ is N-1. Similar arguments suggest the deprotonation site in the neutral ligand Ru-Fl· series of complexes to also be N-1.

Coordination of Ru(II) to aromatic heterocyclic ligands often increases their *basicity* through back-donation of electron density.[9] However, this effect can be more than offset by electrostatic interactions due to the charge on the metal, particularly if the protonation site in question is not in conjugation with the coordination site. ESR studies have shown that little of the spin density of an electron added to the lowest lying flavin π orbital resides at the N-1 site.[6,28] Also, since electrostatic effects of this type usually decrease as the inverse square of the distance,[29] these should not strongly affect the N-1 site. As a result it is not surprising that there is only a slight decrease in the acidity of N-1 upon coordination of the metal ion at N-5.

The correspondence in spectra among the three Ru-Fl_{ox} complexes and between the deprotonated riboflavin and 10-MeIAlo complexes indicate a common neutral ligand form for the Ru-Fl_{ox} ions and a common deprotonation site. Since the 3,10-Me_2IAlo complex does not exhibit a second deprotonation equilibrium, ionization in the riboflavin and 10-MeIAlo complexes must occur from the N-3 site to yield the monoanionic ligand complexes. Analogous logic also allows the assignment of N-3 as the deprotonation site in the Ru-Fl· complexes. Since these pK_a values are sufficiently widely separated, the E_{cv} vs. pH plots for each of the three complexes exhibit a clear slope of approximately 60 mV/pH unit in the region between the pK_a's of the Ru-Fl_{ox} and the corresponding semiquinone species and so indicate a single proton equilibrium.

The neutral Fl_{ox} ligands become approximately 2.6 orders of magnitude more acidic at the N-3 position upon coordination of the metal ion. This increase is probably due to electrostatic effects arising from the cationic metal being situated relatively close to this site.

The neutral Fl· ligands are 4–4.5 orders of magnitude more acidic than the free flavosemiquinones. Since protonation occurs at N-1, this increase is most likely due to the presence of this higher energy tautomeric form which is forced by the presence of the metal ion at N-5. It is the N-5 tautomer which is favored in free HFl·.[26,27] Owing to the change in acidity, the semiquinone pK_a no longer occurs between those for the neutral Fl_{ox} and Fl_{red} and the first reduction potential remains constant in the midrange of pH.

The coordinated semiquinones exhibit a second deprotona-

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Table II. Selected Flavin and Ru-Fl Reduction Potentials

entry no.	half-reaction	redn potential, V	ref
1	$Rib_{ox} + 2H^+ + 2e \rightarrow H_2Rib_{red}$	−0.21[a]	25
2	$Rib_{ox} + H^+ + e^- \rightarrow HRib\cdot$	−0.24[b]	25, 30
3	$HRib + H^+ + e^- \rightarrow H_2Rib_{red}\cdot$	−0.17[b]	25
4	$Rib_{ox} + e^- \rightarrow Rib^-\cdot$	−0.33[c]	25, 30
5	$HRib\cdot + e^- \rightarrow Rib_{red}^-$	−0.15[c]	25
6	$1\text{-Et-}Fl_{ox}^+ + e^- \rightarrow 1\text{-Et-}Fl\cdot$	−0.01[d]	11
7	$5\text{-Et-}Fl_{ox}^+ + e^- \rightarrow 5\text{-Et-}Fl\cdot$	0.43[e]	11
8	$1\text{-Et-5-}HFl^{+}\cdot + e^- \rightarrow 1\text{-Et-5-}HFl_{red}$	0.175	11
9	$5\text{-Et-}Fl\cdot + e^- \rightarrow 5\text{-Et-}Fl_{red}$	−0.01	11
10	$Ru\text{-}(1\text{-}HFl_{ox}^+) + e^- \rightarrow Ru\text{-}(1\text{-}HFl\cdot)$	−0.15	this work
11	$Ru\text{-}(1\text{-}HFl\cdot) + e^- \rightarrow Ru\text{-}(1\text{-}HFl_{red})$	−0.35	this work
12	$Ru\text{-}Fl_{ox} + e^- \rightarrow Ru\text{-}Fl^-\cdot$	−0.32	this work

[a] Value at pH 7. [b] Mathematically resolved with the use of first entry; see ref 25. [c] Estimated from graphical presentation of data in ref 25. [d] Flavin is 1,10-ethylene-bridged lumichrome. [e] Flavin is 5-ethyl-7,8,10-trimethylisoalloxazine.

tion around pH 11 not evident with the free ligands. This arises from the loss of the N-3 proton and yields a new class of $Fl\cdot^{2-}$ complexes. Lowering the proton affinity at this site also eliminates the addition of a proton upon reduction of $Ru\text{-}Fl_{ox}$ at high pH.

Since the metal ion prevents protonation at N-5, the Fl_{red} ligand must always be at least monoanionic (with the possible exception of transient complexes formed in strongly acidic media). Preliminary results in nonaqueous systems also indicate the formation of $Ru\text{-}Fl_{red}^{2-}$ which presumably results from deprotonation at the N-1 position. The data presented here suggests that the pK_a for this process in water is approximately 11.5.

Metal Ion Effects on Flavin Reduction Potentials. The reduction potentials of the flavin complexes reflect the relative affinities of the three ligand oxidation states for the metal ion. Since the synthetic reactions are kinetically slow and also yield side products, it is difficult to directly measure the ligand–metal association constants. (However, once isolated, the individual $Ru\text{-}Fl_{ox}$ complexes remain quite stable so that single species or simple equilibria were in fact investigated.)

Valid comparisons with the free flavin reduction potentials can be made as long as truly analogous values are selected for consideration. The flavin reduction potentials at pH 7 ($E^{\circ\prime}$ values), which are usually cited, are pH dependent[25] and so are not well suited for comparison with those of other species having altered protonation equilibria. However, since these are the most familiar and biologically relevant quantities, they should be addressed. Reduction of riboflavin at pH 7 occurs by an apparent two electron transfer. However, reference to entries 2 and 3 of Table II shows that this is due to the reduction potential for addition of the second electron being greater than that for the addition of the first.[25] The corresponding $E^{\circ\prime}$ values for the Ru-riboflavin complexes are −0.32 and −0.51 V for the addition of the first and second electrons, respectively.

Coordination of the metal ion destabilizes the reduced forms at pH 7. This is particularly evident for the lower couple which is shifted negatively by 0.34 V. A portion of this destabilization can be attributed to a net negative charge residing on the coordinated flavin following reduction. While the Ru(II) has a higher formal charge than a proton, this is largely dispersed over the ammine ligands so that the effect on the flavin is not as great. Ruthenium(II) ammines also tend to donate electron density onto aromatic heterocycles[9] and so may cause the ligand to become more difficult to reduce. The relatively greater destabilization of the fully reduced form can be at least partly attributed to the formation of a higher energy tautomer of the Fl_{red} ligand with the proton bound at N-1 rather than N-5.

More valid comparisons can be made between the potentials for adding a single electron to the flavin without simultaneous proton accompaniment. Consideration of entries 6 and 10 of Table II reveals that coordination of Ru(II) causes the addition of the first electron to the flavin to occur at a potential 0.14 V more negative than that for the free flavin in the same tautomeric state. This difference can be attributed to the substantial transfer of electron density from the metal to the flavin in the $Ru\text{-}Fl_{ox}$ form so that further electronic addition becomes substantially more difficult.

While retrodative bonding has been postulated for other metalloflavin complexes, only Ru(II) forms stable adducts with neutral Fl_{ox} ligands and only in this set of compounds is there unequivocal evidence for back-bonding. On the other hand, complexes with $Fl^-\cdot$ are known with several divalent metal ions. This appears to be due to the substantial electron density localized at N-5 of the flavosemiquinone radical anion so that it serves as a much better Lewis base than the quinone form. Comparison of entries 4 and 12 in Table II shows that addition of the first electron occurs at a similar potential for both free and coordinated riboflavin. This reasonably suggests that the affinity of Ru(II) for Fl_{ox} due to retrodative bonding approximately equals its affinity for $Fl^-\cdot$ resulting from simple dative coordination.

A different result emerges in the case of the lower couple. Unfortunately, the reduction potential for the neutral flavosemiquinone in the same tautomeric form as that of $Ru\text{-}HFl\cdot$ is not available so that a strictly analogous comparison is not possible. Nevertheless, consideration of entries 5, 8, or 9 vs. entry 11 of Table II shows that metal coordination significantly destabilizes Fl_{red} relative to $Fl\cdot$. Hemmerich[2] and Schug[11] have shown that different tautomeric forms of the flavin yield greatly different reduction potentials and so different propensities for proceeding by single- or double-electron transfers. In comparison with the potential estimated for the reduction of $HRib\cdot$ (entry 5, which presumably involves at least some N-1 tautomer but with the majority in the N-5 form), the destabilization owing to the metal ion amounts to −0.2 V. Relative to having protons at both the N-5 and N-1 positions (the case approximated by entry 8), the difference amounts to over 0.5 V. Compared to the reduction potential for the pure N-5 tautomer, the metal-induced destabilization of the fully reduced form is −0.34 V.

This destabilization of Fl_{red} is in contrast to what might be expected upon coordination of a dipositive metal ion, which could be thought to favor the fully reduced form on the basis of charge neutralization of the added electron. (Unlike the case for the addition of the first electron, back-bonding considerations do not play a role here since the π orbital utilized is already partially populated and so is unable to accept significant electron density from the metal.) However, these electrostatic effects are probably minimized by dispersion of the cationic charge over the ammine ligands. More importantly, fully reduced flavins are known to have very small affinities for metal ions relative to the semiquinone form,[1,5] so that the ratio of association constants strongly favors the semiquinone. Finally, a portion of the destabilization relative to the free flavin can be attributed to formation of the higher energy tautomer involving protonation at N-1 rather than N-5.

Conclusion. Direct coordination of a flavin coenzyme to an iron–sulfur core in a protein to yield hexacoordination around the iron, as suggested by Fritchie,[4] should cause this iron to become low spin. Flavin complexes of Ru(II) provide a convenient and stable system for determining the effects of such a low-spin, d^6 metal ion on the redox properties of flavins. The high affinity and kinetic inertness of Ru(II) when coordinated

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to nitrogen ligands allows the formation of several previously inaccessible metalloflavin complexes involving the neutral quinone, dianionic semiquinone, and fully reduced flavins. Apart from the possibility of direct metal-flavin ligation, which has yet to be established in a metalloflavoprotein, aspects of the studies reported here can be extended to the general case of the coordination of a Lewis acid to the N-5 site of a flavin, for which spectroscopic evidence does exist in a number of flavoproteins.[2]

The most obvious effect of coordination at the N-5 site is the wide separation (266 mV at pH 7) between what are overlapping reduction potentials in the free flavin. This causes the flavin to undergo oxidation and reduction in discrete one-electron steps and prevents disproportionation of the flavosemiquinone.

The studies of E_{cv} vs. pH for the Ru-Fl complexes provide the only such data available for metalloflavin complexes with quantitatively characterized proton equilibria and so illustrate how flavin redox potentials can be adjusted by affecting proton availability at the N-1 and N-3 sites of a N-5 ligated coenzyme. Reference to Figure 4 indicates how the accessibility of the lower redox couple can be controlled by the availability of a proton at the N-1 site. The separation between the first and second flavin reduction potentials is minimized when a proton is of such availability as to not protonate Fl_{ox}, to partially protonate Fl·, and to fully protonate Fl_{red}. The small separation (40 mV) between the couples in this pH region may even cause the electron transfer to occur by an apparent two-electron process. If the proton is forced onto the Ru-Fl_{ox} form, then the first reduction becomes more facile and diverges from the lower redox process. If a proton is totally unavailable to add at the N-1 position, then the two potentials are widely separated. Proton loss resulting from the presence of a base at the N-3 site does not affect the separation between the two redox processes of an N-5 ligated flavin but does cause the first to decrease in potential with increasing pH at the same rate as the second. When a proton is unavailable to bind the N-3 site of either the Fl_{ox} or Fl· complexes, the couples again diverge.

Control of the availability of a proton or a base at a particular site on a substrate molecule is a property which is very well-handled by proteins. A better approximation of an average environment on the interior of a protein, as opposed to the exterior aqueous environment approximated in this work, would be provided by similar studies in an amide solvent. These investigations are now under way.

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Registry No. $[(Rib)(NH_3)_4Ru]Cl_2$, 78591-56-7; $[(3,10\text{-}Me_2Alo_{ox})(NH_3)_4Ru]^{2+}$, 69290-19-3; $[(10\text{-}MeAlo_{ox})(NH_3)_4Ru]^{2+}$, 69290-17-1; $[(Rib_{ox})(NH_3)_4Ru]^{2+}$, 78591-57-8; $[(3,10\text{-}Me_2IAlo\cdot)(NH_3)_4Ru]^{2+}$, 78591-58-9; $[(10\text{-}MeIAlo\cdot)(NH_3)_4Ru]^{2+}$, 78591-59-0; $[(Rib\cdot)(NH_3)_4Ru]^{2+}$, 78591-60-3; $[(3,10\text{-}Me_2IAloH_{ox})(NH_3)_4Ru]^{3+}$, 78591-61-4; $[(10\text{-}MeIAloH_{ox})(NH_3)_4Ru]^{3+}$, 78591-62-5; $[(RibH_{ox})(NH_3)_4Ru]^{3+}$, 78609-76-4; $[(10\text{-}MeIAlo_{ox}^-)(NH_3)_4Ru]^+$, 78591-63-6; $[(Rib_{ox}^-)(NH_3)_4Ru]^+$, 78591-64-7; $[(3,10\text{-}Me_2IAlo^-\cdot)(NH_3)_4Ru]^+$, 78591-65-8; $[(10\text{-}MeIAlo^-\cdot)(NH_3)_4Ru]^+$, 78591-66-9; $[(Rib^-\cdot)(NH_3)_4Ru]^+$, 78591-67-0; $(10\text{-}MeIAlo^{2-}\cdot)(NH_3)_4Ru$, 78591-68-1; $(Rib^{2-}\cdot)(NH_3)_4Ru$, 78609-77-5; $[(10\text{-}MeIAlo_{ox})(NH_3)_4Ru]^{3+}$, 78591-69-2; $[(3,10\text{-}Me_2IAlo_{ox})(NH_3)_4Ru]^{3+}$, 78591-70-5; $[(Rib_{ox})(NH_3)_4Ru]^{3+}$, 78591-71-6; $[(3,10\text{-}Me_2Alo_{red}^-)(NH_3)_4Ru]^+$, 78591-72-7; $[(10\text{-}MeAlo_{red}^-)(NH_3)_4Ru]^+$, 78591-73-8; $[(Rib_{red}^-)(NH_3)_4Ru]^+$, 78591-74-9.

Supplementary Material Available: A figure of the E_{cv} vs. pH plot for $(10\text{-}MeIAlo)(NH_3)_4Ru^{II}$ and tables of E_{max} and λ_{max} for Ru-Fl_{ox} and Ru-Fl complexes in various protonation states and cyclic voltammetry data used in E_{cv} vs. pH plots (8 pages). Ordering information is given on any current masthead page.

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Fluxionality of Uranyl β-Diketonate–Base Complexes. Behavior of Uranyl Trifluoroacetylacetonate–Dimethyl Sulfoxide

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The F NMR spectral behavior of a mixture of the cis and trans uranyl trifluoroacetylacetonate–dimethyl sulfoxide complexes indicates that base migration rather than anion rotation is the preferred intramolecular rearrangement path. The intramolecular nature of the process is consistent with the lack of correlation between the fluxional rate and the heats of solution of a series of bases which yield rearranging hexafluoroacetylacetonate complexes.

It has recently been found that uranyl hexafluoroacetylacetonate–base complexes of the general formula $UO_2(hfacac)_2 \cdot B$ undergo a rearrangement in aprotic media that is fast on the NMR time scale.[1,2] This results in averaging the ^{19}F NMR spectra of the complexes to a single band which can be resolved by cooling. The tetrahydrofuran complex[3] exhibits a coalescence temperature of about −80 °C which is typical of the behavior of other compounds with relatively small bases like dimethyl sulfoxide and trimethylphosphate.[4]

Under the assumption that the reaction is intramolecular, it was proposed that the fluxionality is due to a gyroscopic path taken by the base as it travels about the chelated uranyl ion. This report is concerned with two mechanistic issues; the validity of an intramolecular rearrangement rather than a unimolecular dissociation being rate determining and the

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