Contribution from the Department of Chemistry,
University of Pittsburgh, Pittsburgh, Pennsylvania 15260

η^2 Coordination of $Ru^{II}(hedta)^-$ at the C-5–C-6 Bonds of Cytidine and Uridine

Songsheng Zhang, Lori A. Holl, and Rex E. Shepherd*

Received June 12, 1989

$Ru^{II}(hedta)L^-$ complexes ($hedta^{3-}$ = *N*-(hydroxyethyl)ethylenediaminetriacetate) were prepared for a series of ligands related to the uridine and cytidine nucleosides. The ligands studied included L = uracil, uridine (U), 1-methyluracil, 1,3-dimethyluracil (1,3-DMU), 3-methyluridine, thymidine (T), cytosine, cytidine (C), 3-methylcytidine, pyrimidine, pyrazine, and pyridine. The $Ru^{II}(hedta)L^-$ complexes were characterized by ^1H and ^{13}C NMR spectroscopy, cyclic voltammetry, and differential-pulse polarography. A novel coordination mode for $Ru^{II}(hedta)^-$ at the C-5–C-6 olefinic bonds of the uridine- and cytidine-related bases is observed in addition to coordination at the more normal binding site of N-3 (and N-1) in the absence of methyl- or ribose-blocking groups at N-1 or N-3. η^2 coordination at the C-5–C-6 bond is absent for the sterically hindered T nucleobase. When both the N-1 and N-3 positions of pyrimidines are blocked by CH_3 or a ribose unit (1,3-DMU, 3-methyluridine, 3-methylcytidine) only the C-5–C-6 coordination mode is observed; two stereochemical isomers are detected by ^1H and ^{13}C NMR spectroscopy for the 3-methyluridine and 3-methylcytidine olefinically bound complexes in ratios of 3:2 and 1:1, respectively. All other olefinically bound complexes of the uridine/cytidine-related series are present as one stereoisomer. The η^2-coordinated $Ru^{II}(hedta)^-$ complex of 1,3-DMU has a formation constant of 2.0×10^3 M^{-1} (μ = 0.10, T = 22 °C). The C-5–C-6 coordination is characterized by a $Ru^{III/II}$ couple of ca. 0.62 V, upfield ^{13}C shifts of the C-5 and C-6 ring carbons (38–50 ppm), and an upfield ^1H shift of the C-5 H proton (0.66–1.38 ppm), similar to the case for $Ru^{II}(hedta)L^-$ complexes of 1,3-butadiene, styrene, and other simple olefins. Pyrimidine and pyridine bases that have an α-hydroxyl or amino group are observed to form a metal chelate, with ruthenium binding between N-3 and the deprotonated exo donor group; chelation stabilizes Ru^{IV} and Ru^{III} complexes of these ligands. An additional $Ru^{IV/III}$ electrochemical wave at ca. 1.00 V vs NHE is observed for the chelated forms of uridine/cytidine/thymidine-related bases at higher pH; this form is abundant above pH 9.

Introduction

A knowledge of where and how small transition-metal complexes bind to various components of DNA, RNA, or their cleavage fragments is important for a variety of biochemical and medical applications.[1,2] These include the development of antitumor drugs for chemotherapy and heavy-metal labels for use in X-ray crystallography. Studies of the binding of metal complexes to the DNA duplex are also important in understanding the blocking or accelerating influence of metallodrugs on replication and transcription. Extensive studies with Pt^{II} antitumor drugs related to cisplatin have been carried out toward these aims, and many related studies with Pt^{II} drugs are still in progress.[3,4] The focus of metal ion binding to nucleotides has often emphasized the Pt^{II} ammines due to their importance in chemotherapy. It is now understood that the preferential binding site of $Pt^{II}(NH_3)_2$ is at the N-7 donors of adjacent GG sequences; less frequently, AG sequences are labeled.[3,4] Most of our knowledge of metal ion binding for the pyrimidine and purine bases of DNA and RNA has been obtained with softer Pt^{II} and CH_3Hg^+ probe ions (and sometimes with Cu^{2+} or Zn^{2+}) by means of ^1H and ^{13}C NMR, Raman, CD, and X-ray methods.[1-3,5] The studies that we report in this paper reveal a novel, alternative metal ion binding site at the C-5–C-6 bond of the pyrimidine bases C and U for soft metal centers such as Ru^{II} and Os^{II}.

Metal ion association with the phosphate moieties of DNA/RNA or nucleotides and exocyclic oxygen donors of the nucleobases of DNA and RNA are well-known for the harder metal ions (group II cations, 3+ lanthanide ions, Zn^{2+}, Mn^{2+}, Cu^{2+}, etc.).[2] However, coordination via only the exocyclic O donors frequently requires high molarities of the metal ion and nucleobase in order to observe the effects. A greater interest exists for the sites of stronger, and less labile, interactions with the nucleobases for the antitumor drugs and heavy-metal labels. The most common binding sites of the DNA/RNA bases A, G, C, T, and U have been observed to be as follows:[1,3,6,7] adenosine (A), N-7 with minor association at N-1; guanosine (G), N-7 with minor binding at O-6 and N-1 sometimes proposed at high pH; cytidine (C) at N-3; uridine (U) and thymidine (T), at N-3 only above physiological pH (>9).

The coordination sites of U and C are of primary interest for this report. For bases related to C, there are several additional documented coordination modes as well as the prominent case of N-3. The literature has been surveyed by Lippert who references the following monodentate (i–iii), bidentate (iv, v) and bridging (vi, vii) modes:[8,9]

(1) (a) Lippert, B.; Arpalahti, J.; Krizanovic, O.; Micklitz, W.; Schwartz, F.; Trotscher, G. In *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*; Nicolini, M., Ed.; Martinus Nijhoff: Boston, MA, 1987; pp 563–581. (b) Lippard, S. J.; Barton, J. K. In *Nucleic Acid-Metal Ion Interactions*; *Spiro*, T. G., Ed.; Metal ions in Biology, Vol. 1; Wiley-Interscience: New York, 1980; Chapter 2.

(2) (a) Marzilli, L. G.; Kistenmacher, T. J.; Eichhorn, G. L. In *Nucleic Acid-Metal Ion Interactions*; Spiro, T. B., Ed.; Metal Ions in Biology, Vol. 1; Wiley-Interscience: New York, 1980; Chapter 5. (b) Izatt, R. M.; Christensen, J. J.; Rytting, J. H. *Chem. Rev.* **1973**, *71*, 439.

(3) (a) Nicolini, M.; Ed. *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*; Martinus Nijhoff: Boston, MA, 1987. (b) Reedijk, J.; Richtinger-Schepman, A. M.; van Oosterom, A. T.; van de Putte, P. *Struct. Bonding* **1987**, *67*, 53–89. (c) Sherman, S. E.; Lippard, S. J. *Chem. Rev.* **1987**, *87*, 1153. (d) van der Veer, J. L.; Reedijk, J. *Chem. Brit.* **1988**, *24*, 775. (e) Sundquist, W. I.; Bancroft, D. P.; Chassot, L.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 8559.

(4) (a) Sherman, S. E.; Gibson, D.; Wang, A. H.-J.; Lippard, S. J. *Science* **1985**, *230*, 412. (b) Hemelryck, B. V.; Girault, J.-P.; Chottard, G.; Valadon, P.; Laoui, A.; Chottard, J.-C. *Inorg. Chem.* **1987**, *26*, 787. (c) Cohen, G. L.; Ledner, J. A.; Bauer, W. R.; Ushay, H. M.; Caravana, C.; Lippard, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2487. (d) Ushay, H. M.; Tullius, T. D.; Lippard, S. J. *Biochemistry* **1981**, *20*, 3744. (e) Tullius, T. D.; Lippard, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 4620. (f) Caradona, J. P.; Lippard, S. J. In *Platinum Coordination Complexes in Cancer Chemotherapy*; Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds.; Martinus Nijhohff: Boston, MA, 1984; p 14 and references therein. (g) Caradona, J. P.; Lippard, S. J.; Gait, M. J.; Singh, M. *J. Am. Chem. Soc.* **1982**, *104*, 5793. (h) Lippard, S. J.; Ushay, H. M.; Merkel, C. M.; Poirier, M. C. *Biochemistry* **1983**, *22*, 5165.

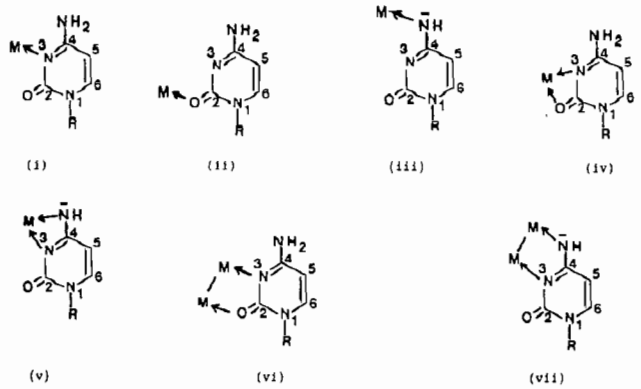
(5) (a) Chu, G. Y. H.; Tobias, R. S. *J. Am. Chem. Soc.* **1976**, *98*, 2641. (b) Mansy, S.; Chu, G. Y. H.; Duncan, R. E.; Tobias, R. S. *J. Am. Chem. Soc.* **1978**, *100*, 607. (c) Chu, G. Y. H.; Duncan, R. E.; Tobias, R. S. *Inorg. Chem.* **1977**, *16*, 2625. (d) Kong, P.-C.; Theophanides, T. *Inorg. Chem.* **1974**, *13*, 1167. (e) Kong, P.-C.; Theophanides, T. *Inorg. Chem.* **1974**, *13*, 1981. (f) Girault, J.-P.; Chottard, G.; Lallemand, J.-Y.; Huguein, F.; Chottard, J.-C. *J. Am. Chem. Soc.* **1984**, *106*, 7227. (g) Miller, S.; Marzilli, L. *Inorg. Chem.* **1985**, *24*, 2421. (h) Winter, J. A.; Lin, F.-T.; Shepherd, R. E. *Inorg. Chim. Acta* **1989**, *155*, 155. (i) Eichhorn, G. L.; Berger, N. A.; Butzow, J. J.; Clark, P.; Rifkind, J. M.; Shin, Y. A.; Tarien, E. *Adv. Chem. Ser.* **1971**, *No. 100*, 135. (j) Eichhorn, G. L. *Nature* **1962**, *194*, 474. (k) Shin, Y. A.; Eichhorn, G. L. *Biochemistry* **1968**, *7*, 1026. (l) Zimmer, C.; Luck, G.; Fritzsche, H.; Triebel *Biopolymers* **1971**, *10*, 441. (m) Clarke, M. J.; Taube, H. *J. Am. Chem. Soc.* **1974**, *96*, 5413.

(6) Graves, B. J.; Hodgson, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 5608 and references therein.

(7) Migrations between the dominant coordination site and other exocyclic donors or ring nitrogen positions are often pH dependent.

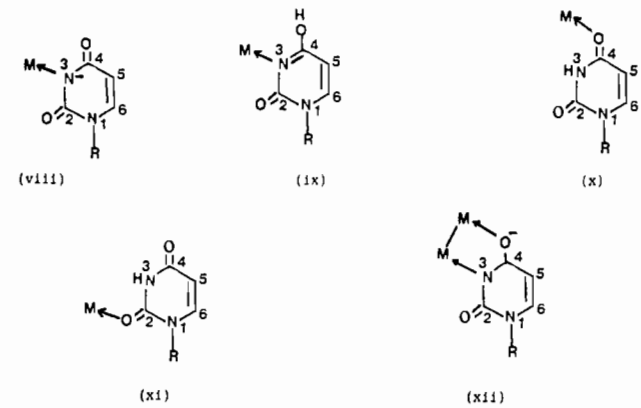
(8) Faggiani, R.; Lippert, B.; Lock, C. J. L.; Speranzini, R. A. *J. Am. Chem. Soc.* **1981**, *103*, 1111.

0020-1669/90/1329-1012$02.50/0

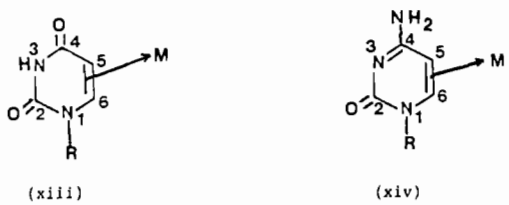


The coordination complexes of uracils have recently been reviewed by Goodgame and Jakubovic.[10] Hard or labile metal ion complexes have been isolated for Mg^{II}, Ca^{II}, Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, and Cu^{II}; these uracil complexes have metal coordination via O-4.[11,12] However, soft metal centers exhibit coordination at the ring nitrogen positions.[10] The Ru^{II} oxygen bonds are labile, and the strong association of Ru^{II} with π-acceptor ligands strongly favors the coordination of Ru^{II} complexes at the nitrogen donors and the olefinic linkages, as shown in this current report. Therefore, no O-4 coordination of uracils is anticipated for Ru^{II} except as a kinetic transient during ligand substitution for binding at other ring positions. Indeed, the NMR evidence and electrochemical data presented in this report substantiate this assumption.

The coordination sites for bases related to U are similarly related to those of C, with the following being most important:[13-15]



No acknowledgement of an η^2-bonding mode, xiii or xiv, is generally given.



The C-5–C-6 double bonds of pyrimidines U and C are the site attack of acetoxymercuration reagents and bis(pyridine)osmium tetroxide.[1] Neither of these reagents yields a metal–olefin complex, but reaction rather occurs with addition across the C-5–C-6 bond for the osmium reagent and with formation of a metal–carbon σ bond at C-5 of U and C with mercuriacetates.[1] The C-5 mercuri derivatives of the pyrimidines are valued intermediates in the synthesis of antiviral agents.[16] Organopalladium reagents have been used in palladium-mediated couplings at C-5 between olefins and organosulfides.[16] Bergstrom et al.[16] have proposed that a Pd(II)/Hg(II) metal exchange at C-5 precedes binding of an olefin or organodisulfide at Pd(II); rearrangement of the σ-bonded pyrimidine–Pd^{II}–substrate system couples the olefin or organosulfide to the C-5 position. Although this chemistry has been known since 1976,[16b] no isolation of the proposed σ-bonded Pd^{II} intermediates has been possible, owing to facile coupling reactions under mild conditions.[16] Only C-5 mercuri–pyrimidine bonds are mentioned in reviews of the literature prior to 1981.[1,2] An extensive search of the 1982–1988 literature revealed no other C-5 metallo-bonded species with uracil, cytosine, dimethyluracil, uridine, or cytidine with typical Ru^{II}, Rh^{I}, Pd^{II}, Au^{I}, or Au^{III} reagents. For example $[(Ph_3P)_2Rh(CO)]^+$, $[Rh(CO)_2L]^+$, and $[Rh(CO)_2Cl]$ are all bonded via N-3 to nucleobases related to C and U and N-7 with purines; G also binds via O-6.[17] Activated rings such as 5-fluoro-6-iodo-1,3-dimethyluracil form σ-bonded Pd^{II} complexes by oxidative addition at the C–I(6) bond.[17e] Lippert et al. have prepared a rare Pt^{III} binuclear complex $[Pt_2(1\text{-MeU})_2(NH_3)_4(1\text{-MeU})]^{3+}$, which contains one 1-methyluracil anion (1-MeU) bonded through C-5 to one of the Pt^{III} centers.[14] Two other 1-MeU anions are coordinated as bridging bidentate donors via the normal N-3, O-4 chelation of uracil derivatives of the "platinum pyrimidine blues".[14,15] No other report of a π metal complex in the olefinic region of C, U, or T appears to have been reported prior to 1990.[18]

In this account we show that $Ru(hedta)^-$ binds at three positions: at N-3 of C and U (normal positions), via a chelate binding mode between N-3 and an exocyclic donor of the pyrimidines at high pH, and via the novel C-5–C-6 olefinic complexation. In a related manuscript we have shown that $Ru(NH_3)_5^{2+}$ and $Os(NH_3)_5^{2+}$ will also associate with the C-5–C-6 bond of 1,3-dimethyluracil (1,3-DMU).[19] The association constant of $Ru(NH_3)_5^{2+}$ for 1,3-DMU is only 8 M^{-1}, which probably accounts for its absence of detection in prior studies of $Ru(NH_3)_5^{3+/2+}$ reagents with nucleobases related to C.[20] Coordination at the nitrogens of 1,3-DMU is severely blocked by methylation in 1,3-DMU. Therefore, only the complex analogous to the C-5–C-6 π-bound isomer of $Ru(hedta)U^-$ is observed in the 1,3-DMU complexes. Unlike the case for the Pt^{III} σ-bonded uracil derivative, both the C-5 H and C-6 H resonances are identifiable in the Ru(hedta)$^-$-derivatized species, which indicates an olefinic coordination mode rather than a σ-bonded structure.

Our interest in the olefinic bonding mode of pyrimidines originates from our former studies of the coordination of $Ru(CN)_5^{3-}$, $Ru(NH_3)_5^{2+}$, $Os(NH_3)_5^{2+}$, and $Ru^{II}(hedta)^-$ with olefinic and N-heterocyclic π acceptors and with imidazole donors.[21-31] The

(9) Beyerle-Pfnur, R.; Schollhorn, H.; Thewalt, U.; Lippert, B. *J. Chem. Commun.* **1985**, 1510.
(10) Goodgame, M.; Jakubovic, D. A. *Coord. Chem. Rev.* **1987**, *79*, 97.
(11) Cartwright, B. A.; Goodgame, M.; Johns, K. W.; Skapski, A. C. *Biochem. J.* **1978**, *175*, 337.
(12) Ghosh, P.; Mukhopadhyay, T. K.; Sarkar, A. R. *Transition Met. Chem.* **1984**, *9*, 46.
(13) (a) Faggiani, R.; Lippert, B.; Lock, C. J. L. *Inorg. Chem.* **1980**, *19*, 295. (b) Lippert, B. *Inorg. Chim. Acta* **1981**, *55*, 5. (c) Lippert, B.; Schollhorn, H.; Thewalt, U. *J. Am. Chem. Soc.* **1986**, *108*, 6616.
(14) Schollhorn, H.; Thewalt, U.; Lippert, B. *J. Chem. Soc., Chem. Commun.* **1986**, 258.
(15) Mascharak, P. K.; Williams, I. D.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 6428 and references therein.
(16) (a) Bergstrom, D.; Beal, P.; Husain, A.; Jenson, J. *J. Am. Chem. Soc.* **1989**, *111*, 374 and references therein. (b) Bergstrom, D. E.; Ruth, J. J. *J. Am. Chem. Soc.* **1976**, *98*, 1587. (c) Hirota, K.; Isobe, Y.; Kitade, Y. Maki, Y. *Synthesis* **1987**, *5*, 495.
(17) (a) Abbott, D. W.; Woods, C. *Inorg. Chem.* **1984**, *23*, 3629. (b) Abbott, D. W.; Woods, C. *Inorg. Chem.* **1983**, *22*, 2918. (c) Pneumatikakis, G.; Markopoulos, J.; Yannopoulis, A. *Inorg. Chim. Acta* **1987**, *136*, L25. (d) Singh, M. M.; Rosopulos, Y.; Beck, W. *Chem. Ber.* **1983**, *116*, 1364. (e) Urata, H.; Tanaka, M.; Fuchikanni, T. *Chem. Lett.* **1987**, 751.
(18) This statement is based on a search of the Chemical Abstract Service (CAS-OnLine) data base.
(19) Zhang, S.; Shepherd, R. E. *Inorg. Chim. Acta* **1989**, *163*, 237.
(20) Clarke, M. J. The Potential of Ruthenium in Anticancer Pharmaceuticals. In *Inorganic Chemistry in Biology and Medicine*; Martell, A. E., Ed.; 1980 American Chemical Society: Washington, DC, 1980; Chapter 10.
(21) (a) Sundberg, R. J.; Shepherd, R. E.; Taube, H. *J. Am. Chem. Soc.* **1972**, *94*, 6558. (b) Shepherd, R. E.; Taube, H. *Inorg. Chem.* **1973**, *12*, 1392. (c) Jones, C. M.; Johnson, C. R.; Asher, S. A.; Shepherd, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3772. (d) Kristine, F. J.; Johnson, C. R.; O'Donnell, S.; Shepherd, R. E. *Inorg. Chem.* **1980**, *19*, 2280.
(22) (a) Johnson, C. R.; Shepherd, R. E. *Inorg. Chem.* **1983**, *22*, 2439. (b) Johnson, C. R.; Shepherd, R. E. *Inorg. Chem.* **1983**, *22*, 1117.

π acceptors that we have most recently examined include linear olefins, such as 1,3-butadiene, styrenes, and acetylenes.[26,27,29,30] The coordination of C and U via the C-5–C-6 olefinic bond to the ruthenium(II) and osmium(II) pentaammine and polyamino polycarboxylate reagents show a clear parallel to the $Ru(NH_3)_5^{2+}$ and $Os(NH_3)_5^{2+}$ η^2-decorated aromatic rings concurrently under study by Harman and Taube.[32-35] The coordination of $Ru(NH_3)_5^{2+}$ to a series of nucleoside bases or their methylated modifications has been carefully studied previously in the laboratories of Taube and Clarke.[36-38,46] In those prior reports, binding of the $(NH_3)_5Ru^{2+/3+}$ reagents was always observed at the normal N-7 or N-3 ring positions or to the exocyclic nitrogen of A and C.[6,20] The unusual complexation of C-2 of imidazoles by $(NH_3)_5Ru^{2+}$ [21] has only been observed for caffeine (at C-8)[37] but not for other purines or xanthines.[20] Therefore, this report represents the first one of metal ion η^2 coordination to the A, G, C, U, or T bases and a new example of an organometallic interaction with nucleobases.

Experimental Section

Reagents. Pyrimidine, pyrazine, 2-methylpyrazine, 5-amino-4,6-dichloro-pyrimidine, 4-methylpyridine, pyridine, cytosine, cytidine, uracil, uridine, thymidine, and α-pyridone were obtained from Aldrich and used as supplied. 1-Methyluracil, 3-methyluridine, 1,3-dimethyluracil, 1-methylcytosine, and 3-methylcytidine methosulfate were obtained from Sigma. All other reagents were analytical grade.

$Na[Ru(hedta)(H_2O)]\cdot 4H_2O$. The synthesis and analysis of this complex were reported previously from our laboratories.[39] The method corresponds to synthesis of the $Ru^{II}(edta)^{2-}$ complexes by Shimizu,[40] Matsubara and Creutz,[41] and Diamantis and Dubrawski.[42]

Table I. Reduction Potentials and MLCT Band Maximum Data for $Ru^{II}(hedta)^-$ Pyrazines and Pyrimidines

			MLCT		
L	ligand no.	$E_{1/2}$	ν, $cm^{-1} \times 10^3$	λ, nm	$10^{-3}\epsilon$
H_2O		0.00			
pym	**2**	0.142	24.7	405	6.69
4-CH_3pym	**1**	0.172	23.8	420	7.42
ADCpym	**3**	0.192	22.9	437	1.10
2-CH_3pz	**4**	0.207	22.2	450	1.24
pz	**5**	0.262	21.1	475	
2-CH_3pzH^+	**6**	0.302	19.1	525	1.03
2-pzCOOH	**7**	0.320	18.3	547	7.57
N-CH_3pz^+		0.542			

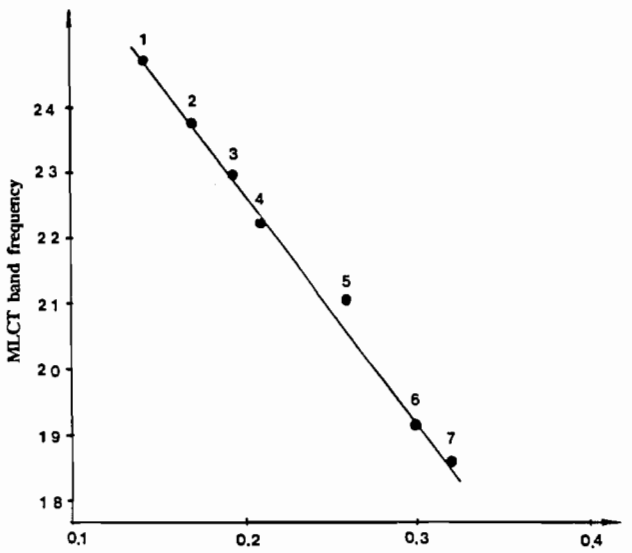


Figure 1. Correlation between $E_{1/2}$ and MLCT-band frequency for Ru(hedta)$^-$–pyrazines and –pyrimidines. Ligand numbers: (1) 4-methylpyrimidine; (2) pyrimidine; (3) 2-methylpyrimidine; (4) 2-methylpyrazine; (5) pyrazine; (6) 2-methylpyrazinium ion; (7) 2-pyrazinecarboxylate.

$Ru^{II}(hedta)L^-$ Complexes. The complex of a desired ligand from the above reagent list was obtained for NMR or electrochemical study by reaction of the $Na[Ru(hedta)(H_2O)]\cdot 4H_2O$ salt in either H_2O or D_2O. The sample was maintained over Zn/Hg under Ar to retain the Ru^{II} oxidation state. Mixing of reagents was achieved by magnetic stirring with rice-sized Teflon-covered stirring bars and by the agitation of the Ar stream. Suitable transfers under Ar between 15.0-mL preparative flasks, NMR tubes, and electrochemical cells were achieved by using gastight-syringe techniques or fluid transfers through Teflon surgical tubing attached to stainless steel needles. Flasks were sealed with rubber septa. Complexes were not isolated as solids because the complexes exist in several isomeric forms at equilibrium with each other or their binding constants are sufficiently small to produce dissociation during efforts at recrystallization, resulting in recontamination. Reactions required ca. 24 h to achieve final equilibrium. Some new evidence with pyrimidine has shown only N-bound complexes at ca. 3 h, while olefinically bound species appear after 24 h.[53]

Instrumentation. Electrochemical studies were performed under Ar on an IBM 225 electrochemical analyzer operating in the cyclic voltammetry and differential-pulse modes. The sweep rates were 50 mV/s for CV and 40 mV/s for DPP. The DPP method used a stepping voltage of 50 mV. A glassy-carbon working electrode, a sodium chloride saturated calomel electrode (SSCE reference), and a Pt-wire auxiliary elec-

(23) Johnson, C. R.; Shepherd, R. E. *Inorg. Chem.* **1983**, *22*, 2439.
(24) (a) Johnson, C. R.; Henderson, W.; Shepherd, R. E. *Inorg. Chem.* **1984**, *23*, 2754. (b) Hoq, M. F.; Shepherd, R. E. *Inorg. Chem.* **1984**, *23*, 1851.
(25) Johnson, C. R.; Shepherd, R. E. *Synth. React. Inorg. Met.-Org. Chem.* **1984**, *14*, 339.
(26) Henderson, W. W.; Bancroft, B. T.; Shepherd, R. E.; Fackler, J. P. *Organometallics* **1986**, *5*, 506.
(27) Shepherd, R. E.; Proctor, A.; Henderson, W. W.; Myser, T. K. *Inorg. Chem.* **1987**, *26*, 2440.
(28) (a) Elliott, M. G.; Shepherd, R. E. *Inorg. Chem.* **1987**, *26*, 2067. (b) Sabo, E. M.; Shepherd, R. E.; Rau, M. S.; Elliott, M. G. *Inorg. Chem.* **1987**, *26*, 2897.
(29) Elliott, M. G.; Shepherd, R. E. *Inorg. Chem.* **1988**, *27*, 3332.
(30) Elliott, M. G.; Zhang, S.; Shepherd, R. E. *Inorg. Chem.* **1989**, *29*, 3036.
(31) (a) Siddiqui, S.; Henderson, W. W.; Shepherd, R. E. *Inorg. Chem.* **1987**, *26*, 3101. (b) Henderson, W. W.; Shepherd, R. E. *Inorg. Chem.* **1985**, *24*, 2398.
(32) (a) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1987**, *109*, 1883. (b) Harman, W. D.; Taube, H. *Inorg. Chem.* **1987**, *26*, 2917.
(33) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 5725.
(34) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 7555.
(35) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 7906.
(36) (a) Clarke, M. J.; Taube, H. *J. Am. Chem. Soc.* **1974**, *96*, 5413. (b) Clarke, M. J.; Taube, H. *J. Am. Chem. Soc.* **1975**, *97*, 1397.
(37) Krentzien, H.; Clarke, M. J.; Taube, H. *Bioinorg. Chem.* **1975**, *4*, 1397.
(38) (a) Clarke, M. J. *J. Am. Chem. Soc.* **1978**, *100*, 5086. (b) Clarke, M. J. *Inorg. Chem.* **1971**, *16*, 738. (c) Clarke, M. J.; Buchbinder, M.; Kelman, A. D. *Inorg. Chim. Acta* **1978**, *27*, 187.
(39) Zhang, S.; Shepherd, R. E. *Inorg. Chem.* **1988**, *27*, 4712.
(40) Shimizu, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2921.
(41) Matsubara, T.; Creutz, C. *Inorg. Chem.* **1979**, *18*, 1956.
(42) Diamantis, A. A.; Dubrawski, J. V. *Inorg. Chem.* **1981**, *20*, 1142.
(43) (a) Ford, P. C. *Coord. Chem. Rev.* **1970**, *5*, 75. (b) Toma, H. P.; Malin, J. M. *Inorg. Chem.* **1973**, *12*, 1039. (c) Hrepic, N. V.; Malin, J. M. *Inorg. Chem.* **1979**, *18*, 409. (d) Taube, H. *Survey of Progress in Chemistry*; Scott, A. F., Ed.; Academic Press: New York, 1973; Vol. 6, Chapter 1.
(44) Ford, P. C.; Rudd, DeF. P.; Gaunder, R.; Taube, H. *J. Am. Chem. Soc.* **1968**, *90*, 1187.
(45) (a) Shepherd, R. E.; Taube, H. *Inorg. Chem.* **1973**, *12*, 1392. (b) Toma, H. E.; Stadler, E. *Inorg. Chem.* **1985**, *24*, 3085.
(46) (a) Kastner, M. E.; Coffey, K. F.; Clarke, M. J.; Edmonds, S. E.; Eriks, K. *J. Am. Chem. Soc.* **1981**, *103*, 5747. (b) Clarke, M. J.; Dowling, M. G.; Garafalo, A.; Brennan, T. F. *J. Am. Chem. Soc.* **1979**, *101*, 223.
(47) $Ru^{II}(hedta)^-$ represents the oxidation state of the Ru complex in bulk solution. Chelation to the metal center influences $E_{1/2}$ of both the $Ru^{III/II}$ and $Ru^{IV/III}$ couples. Ru(hedta)$(H_2O)^-$ exhibits a $Ru^{IV/III}$ wave at 1.15 V.
(48) A chelated complex readily forms with 8-hydroxyquinoline, L. Holl and R. E. Shepherd, unpublished results.
(49) Zhang, S.; Shepherd, R. E. Unpublished results.
(50) No high chelate form is observed with 2-aminopyrimidine; therefore, chelation via N-3, O-2 seems more likely: Zhang, S.; Shepherd, R. E. To be published.
(51) Isied, S.; Taube, H. *Inorg. Chem.* **1976**, *15*, 3070.
(52) Lim, H.; Barclay, D. J.; Anson, F. C. *Inorg. Chem.* **1972**, *11*, 1460.
(53) Zhang, S.; Shepherd, R. E. Work in progress.

trode were employed in the conventional three-electrode assembly. The electrolyte solution was 0.10 M NaCl at 22 °C.

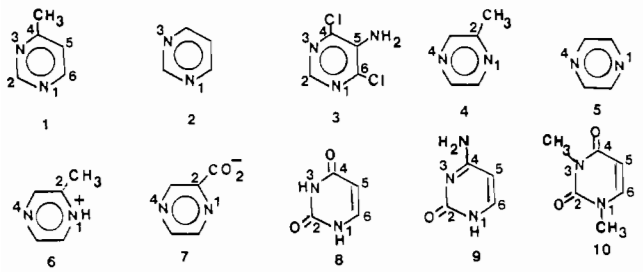
^1H and ^{13}C nuclear magnetic resonances were recorded on a Bruker AF300 NMR or AF500 NMR spectrometer at magnetic fields of 70.46 and 117.44 kG, respectively. ^1H spectra employed frequencies of 300.13 and 500.13 MHz, respectively. ^{13}C spectra were obtained at 125.767 MHz at the 117.44-kG field. All spectra were recorded in D_2O as the solvent; HOD (4.80 ppm) or a free ligand resonance as an internal standard served as the reference for the ^1H spectra. The internal standard for ^{13}C spectra was *p*-dioxane. Assignments for the ^1H spectra were obtained by using standard decoupling procedures. A standard 14-H broad-band decoupling was used for ^{13}C spectra. Visible spectra of the complexes were recorded on a Varian-Cary 118C spectrophotometer in quartz cells.

Results

Coordination of Simple Pyrimidines. $Ru^{II}(hedta)(H_2O)^-$ and its $Ru^{II}(edta)(H_2O)^{2-}$ analogue are known to undergo substitution with N-heterocycles, CO, N_2, and π-acceptor ligands to form 1:1 complexes (eq 1).[16,28-31] $Ru^{II}(NH_3)_5L^{2+}$, $Ru^{II}(edta)L^{2-}$, and

$$Ru^{II}(hedta)(H_2O)^- + L \rightleftarrows Ru^{II}(hedta)L^- + H_2O \quad (1)$$

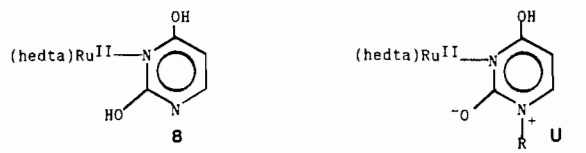
$Ru^{II}(CN)_5L^{3-}$ complexes of π-acceptor N-heterocyclic ligands are known to exhibit a linear correlation between the $Ru^{III/II}$ reduction potentials and the metal-to-ligand charge-transfer transitions (MLCT).[23,41-44] A series of $Ru^{II}(hedta)^-$ complexes of methyl-, chloro-, amino-, and carboxyl-substituted pyrimidines and pyrazines (**1**–**7**) were prepared via reaction 1 with a 20% excess of



ligand present. The $Ru^{II}(hedta)L^-$ complexes were examined spectrophotometrically to determine the position of the long-wavelength MLCT band and by cyclic voltammetry and differential-pulse polarography to obtain III/II $E_{1/2}$ values at $\mu = 0.10$ (NaCl), $T = 22.0$ °C (Table I). An excellent linear correlation is again observed for the $Ru(hedta)L^{-/0}$ simple pyrimidine and pyrazine derivatives (**1**–**7**) when the energies of the MLCT band are plotted against the $E_{1/2}$ values of the respective complexes (Figure 1): slope = $(-35.14 \pm 1.73) \times 10^3$ cm^{-1}/V; intercept = $(29.73 \pm 0.41) \times 10^3$ cm^{-1}. In all cases at $[Ru^{II}(hedta)^-]:[L]$ concentrations at 1:1.20, no evidence for bis-substituted species or any isomer other than the N-base-bound form was observed. In the complexes based on the series **1**–**7**, where the binding sites are not equivalent, steric effects dictate[45] binding at N-1 and N-4 for **1**, **4**, **6**, and **7**. It is known that the heterocyclic N-bound forms of $Ru(NH_3)_5L^{3+/2+}$ exhibit $E_{1/2}$ values that are ca. 0.23 V more positive than those of their respective $Ru(hedta)L^{0/-}$ or $Ru(edta)L^{-/2-}$ complexes.[19,29,30,36-38,41,42,46] For example, the $E_{1/2}$ values for the pyrimidine (**2**) complexes are 0.43 V for the $(NH_3)_5RuL^{3+/2+}$ couple[38] and 0.172 V for the $Ru(hedta)L^{-/0}$ couple (Table I). Furthermore, deprotonated forms of guanine and cytosine bases coordinated to $Ru(NH_3)_5^{2+/3+}$ produce $E_{1/2}$ values that are negative of those of the aqua complex by ca. −0.05 to −0.19 V upon coordination at N-1 of the guanine anion or at N-4 of deprotonated cytosine.[36,38] Therefore the various N coordination sites for **1**–**9** may be assigned with the assistance of the $E_{1/2}$ potential. The predicted $E_{1/2}$ for $Ru(hedta)L^{0/-}$ couples as a function of binding site can be deduced from the literature values for the $Ru(NH_3)_5L^{3+/2+}$ analogues.[38,20]

The CV/DPP method is particularly sensitive to detection of olefinically bound rings[19,29,32-35] with $(NH_3)_5M^{II}$ ($M^{II} = Ru^{II}$, Os^{II}) and $Ru^{II}(hedta)^-$ (see below). η^2-olefin complexes were absent in the electrochemical waves of the $Ru^{II}(hedta)L^-$ complexes of ligands **1**–**7**. Although pyrimidines with exocyclic $-CH_3$, $-NH_2$, and −Cl conors contribute to the linearity of Figure 1, when we attempted to add the uracil (**8**) and cytosine (**9**) $Ru^{II}(hedta)^-$ complexes to these data, widely divergent behavior was observed. No easily assignable MLCT band was apparent for these complexes for either the uracil or cytosine. These complexes exhibited three CV/DPP waves at pH ~7, indicative of an isomer mixture. This prompted a careful examination of the electrochemical and ^1H NMR behavior of the cytidine (C) and uridine (U) complexes, since these have the N-1 position blocked with the ribose sugar moiety. This feature potentially reduces the number of coordination isomers of C and U. Furthermore, C and U possess greater solubility than uracil and cytosine, as well as relating more directly to the binding of metals to these nucleosides in DNA or RNA.

Coordination of Uridine and Cytidine. The $Ru^{III/II}(hedta)(H_2O)^{0/-}$ couple exhibits its $E_{1/2}$ value at 0.00 V vs NHE ($\mu = 0.10$ (NaCl), $T = 22.0$ °C). The cyclic voltammetric and differential-pulse polarographic data of the $Ru^{II}(hedta)U$ complexes are shown in Figure 2 at pH 2.07, 6.97, and 9.15 after ca. 15 h of reaction time. Typical concentrations in the electrochemical studies were 3.0×10^{-3} M in $Ru^{II}(hedta)L^-$ with 20% excess ligand. At pH 2.07 only the wave for the $Ru(hedta)(H_2O)^-$ complex ($E_{1/2}$ ~0.00 V) and another wave at $E_{1/2} \cong 0.62$ V are observed; see Figure 2A. At pH 6.97 three species are observed with $E_{1/2} = -0.078$, +0.622, and ~0.97 V (Figure 2B). The species with $E_{1/2}$ with −0.078 V is compatible with binding of U at N-3.[20] The related uracil complex has an $E_{1/2} = -0.06$ V for this wave. Upon adjustment to pH 9.15 the amount of the uridine species $E_{1/2} \cong 0.94$ V is much increased (Figure 2C). It will be shown that the wave at ca. 0.94 V is that for a $Ru^{IV/III}$ couple. The pH dependence for uridine suggests the following structures for N-3 coordination at lower pH values:



The α-hydroxyl is then available for deprotonation at high pH. A model system using α-pyridone is shown in a later section of this report to provide a similar high pH behavior, yielding a species with $E_{1/2} = 1.01$ V for the $Ru^{IV/III}$ wave compared to 0.97 V for the ionized uridine. We believe the deprotonated form adopts a chelate interaction with $Ru^{II}(hedta)^-$ at high pH.[47] No parallel behavior is observed for any pyrimidine lacking an α-hydroxyl or α-amino unit.[48,50]

For the cytidine complexes at pH 2.02, only two species are detected; these are $Ru(hedta)(H_2O)^-$ and another with $E_{1/2} \cong +0.72$ V (Figure 3A). At pH 6.85 three species with $E_{1/2} = +0.07$, +0.64, and +1.03 V are found (Figure 3B). The species with $E_{1/2} = +0.07$ V is the one anticipated for binding C at N-3. The matching cytosine complex wave is at +0.05 V. At pH 9.05, four species with $E_{1/2}$ values of −0.078, +0.072, 0.64, and 1.01 V are observed. The additional species with $E_{1/2}$ of −0.078 V is anticipated for cytosine bound as an anionic ligand via a deprotonated exo amine (N-4).[20] Again, the one of highest $E_{1/2}$ ($Ru^{IV/III}$ wave) increases in amount quite markedly with higher pH; we assign this species to a chelated form involving N-3 and the exo (N-4)H^- donors. The $Ru^{II}(hedta)L$ species with $E_{1/2} \cong 0.64$ V is much less abundant for C than for U. Thus, a free nitrogen lone pair at N-3 of C competes favorably for coordination vs the form responsible for the 0.64-V wave.

The species with $E_{1/2} = 0.64$ V for C and 0.62 V for U show reduction potentials similar to those of the olefin and styrene complexes of $Ru^{II}(hedta)^-$ and their $Ru(NH_3)_5^{3+/2+}$ analogues (see Table II).[27-30] The cyclic voltammograms of the species responsible for the 0.64- and 0.62-V waves for C and U complexes are only electrochemically quasi-reversible, chemically irreversible due to an EC sequence at the electrode surface.[30] This behavior has been shown previously to involve the competitive, rapid aquation for Ru^{III} olefin complexes that prevents kinetic electrochemical reversibility. The $(NH_3)_5OsL^{3+/2+}$ analogues are slower to aquate, and their cyclic voltammograms are more reversible.[30-32] Coordination of $Ru^{II}(hedta)^-$ to an olefinic chro-

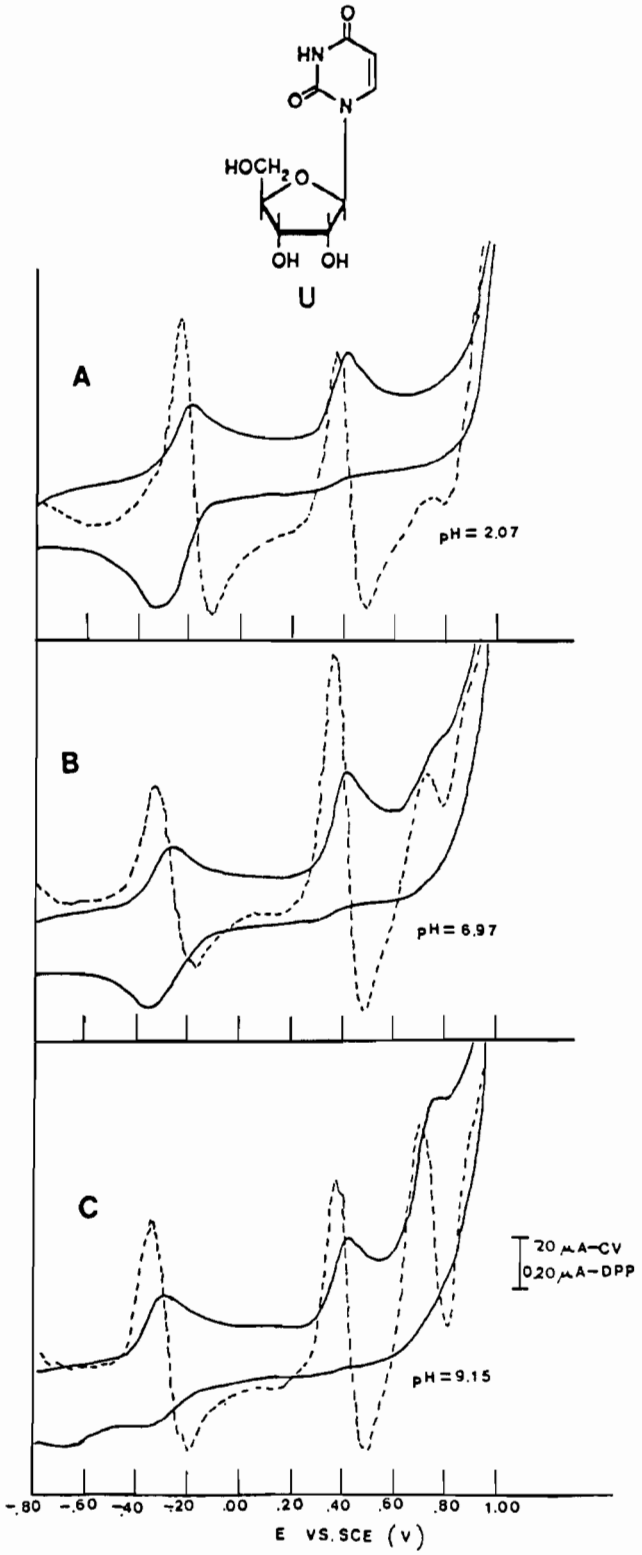


Figure 2. Cyclic voltammetry and differential-pulse polarography data for the Ru(hedta)$^-$–uridine system at 15 h: (A) pH 2.07; (B) pH 6.97; (C) pH 9.15; (broken curve) DPP (current amplitude 100×); (solid curve) CV. Conditions: $[Ru^{II}]_{tot} = 3.0 \times 10^{-3}$ M; $[U]_{tot} = 4.6 \times 10^{-3}$ M; $\mu = 0.10$ (NaCl); $T = 22$ °C.

mophore generates a Ru^{II}(hedta)L complex having an $E_{1/2}$ value close to 0.64 V, which is rather invariant with the nature of nearby groups or substituents.[29,30] The most sterically accessible double bonds of C and U are the C-5–C-6 olefinic bonds. Coordination of Ru^{II}(hedta)$^-$ to this position is confirmed by ^{1}H NMR studies reported in a subsequent section.

Protonation at N-3 for the olefinically bound C produces a 0.08-V shift in $E_{1/2}$ from 0.64 V when the pH ≥6.85 to $E_{1/2}$ = 0.72 V at pH 2.02. A 0.095-V increase in potential is observed

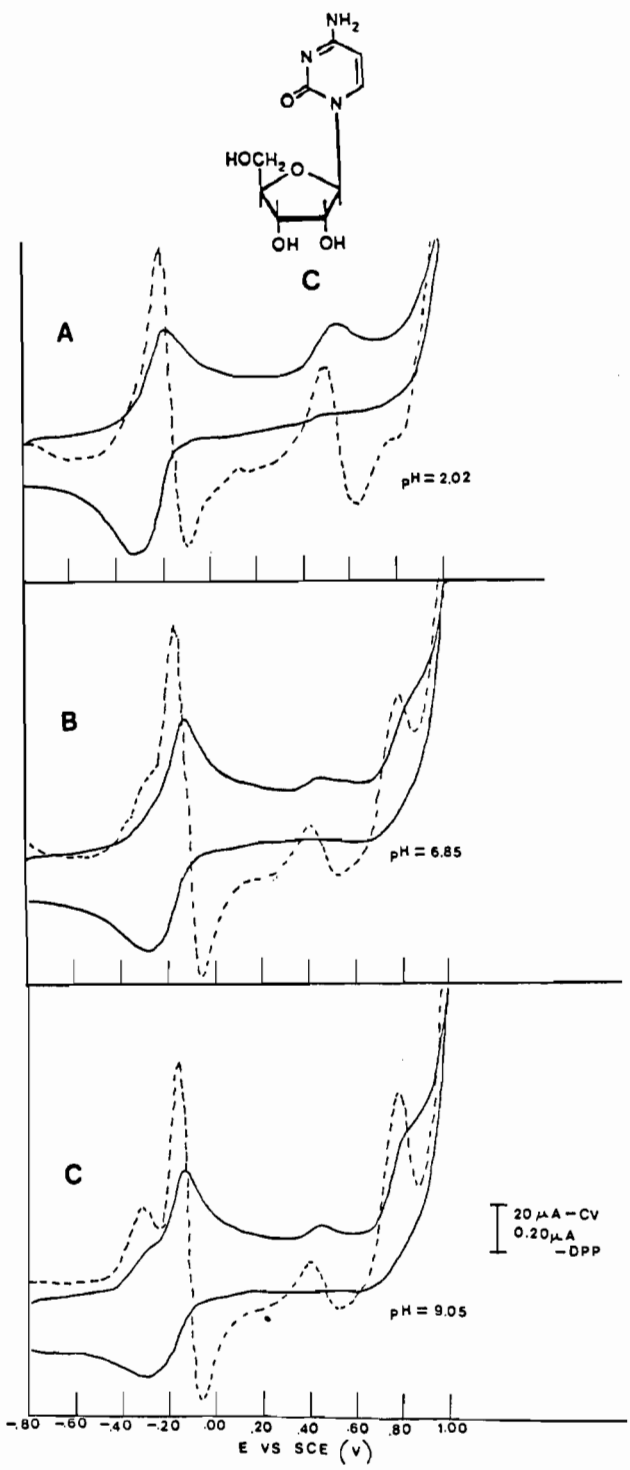


Figure 3. Cyclic voltammetry and differential-pulse polarography data for the Ru(hedta)$^-$–cytidine system at 15 h: (A) pH 2.02; (B) pH 6.85; (C) pH = 9.05; other conditions as in Figure 2.

when Ru(hedta)$(CH_3pz)^{-/0}$ is protonated at the remote nitrogen to 2-methylpyrazine. The influence of the protonation effect on pyrazines has been attributed to the cationic pyrazinium ligands acting as better π acceptors. The influence for the olefinically bound complex of C must be largely electrostatic in origin, since it will be shown that coordination of Ru^{II} or Os^{II} at the C-5–C-6 bond of C or U disrupts the ring conjugation significantly.

Ru^{II}(hedta)(1,3-DMU)$^-$ Complex. 1,3-Dimethyluracil, 1,3-DMU (**10**), was coordinated to Ru^{II}(hedta)$^-$ in order to further reduce the number of coordination isomers and to serve as a probe of olefin coordination at the C-5–C-6 bond. Both N-1 and N-3 are hindered by methylation of **10**. The cyclic voltammogram of the Ru^{II}(hedta)(1,3-DMU)$^-$ complex is shown in Figure 4; only the aqua complex ($E_{1/2} \sim 0.00$ V vs NHE) and the olefinically

Table II. $E_{1/2}$ Values of $(NH_3)_5RuL^{3+/2+}$ and $Ru(hedta)^{0/-}$ Complexes

L[a]	$E_{1/2}$, V: $RuA_5L^{3+/2+}$	$E_{1/2}$, V: $Ru(hedta)L^{0/-}$	ref
styrene	0.95	0.64	30
4-vinylbenzoic acid	1.01 (pH 2.20)	0.64 (pH 2.01)	30
4-vinylbenzoate	1.02 (pH 8.10)	0.62 (pH 7.14)	30
1,3-butadiene	0.94	(0.59)[b]	29, 30
CHDM	0.84	0.45	30
CO	1.40	0.99	30, 51
DMAD	1.00	0.88	26, 30
pyrazine	0.490	0.262	30, 52
pyrimidine	0.40	0.172	30, 38
pyridine	0.305	0.10[c]	41, 52
H_2O	0.051	0.00	30, 52
1,3-DMU	1.01	0.63	19, this work

[a] Abbreviations: CHDM = 3-cyclohexene-1,1-dimethanol; DMAD = dimethylacetylenedicarboxylic acid dimethyl ester; 1,3-DMU = 1,3-dimethyluracil. [b] Value of 1,3-cyclohexadiene complex. [c] Value for the pentadentate $edta^{4-}$ complex; usually the $E_{1/2}$ values of the $edta^{4-}$ complex are ca. 0.04 V more negative of the corresponding value for the $hedta^{3-}$ complex.

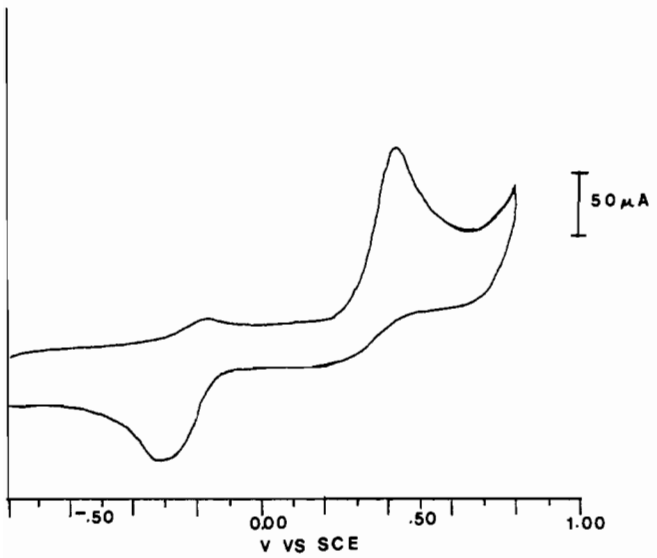


Figure 4. Cyclic voltammetry and differential-pulse polarography data for the $Ru(hedta)^-$–1,3-dimethyluracil system. Conditions: $[Ru^{II}]_{tot}$ = 7.03×10^{-3}; $[1,3\text{-DMU}]_{tot} = 1.44 \times 10^{-2}$ M; pH ~7.0; μ = 0.10 (NaCl); T = 22 °C.

bound 1,3-DMU complex ($E_{1/2}$ = 0.63 V vs NHE) are detected. A formation constant of 2.0×10^3 M^{-1} is calculated from the DPP data. No high pH, "chelate" form with $E_{1/2}$ near 1.0 V is observed as anticipated with blocking CH_3 groups. Parallel studies reported elsewhere also show 1,3-DMU complexation by $(NH_3)_5Ru^{2+}$ and $(NH_3)_5Os^{2+}$ as evidenced by cyclic voltammetry ($E_{1/2}$ values in concert with olefinic $M(NH_3)_5^{2+}$ complexes) and by large upfield ^1H and ^{13}C shifts of both the C-5 and C-6 protons and the C-5 and C-6 carbons of 1,3-DMU in the respective $(NH_3)_5M^{II}(1,3\text{-DMU})^{2+}$ (M^{II} = Ru^{2+}, Os^{2+}) species.[19] Additional conformational isomers have been encountered when $(NH_3)_5Ru^{2+}$ or $(NH_3)_5Os^{2+}$ binds to the C-5–C-6 bond of 3-methyluridine.[49] However, only one isomer is detected for 1,3-DMU with either of these reagents or $Ru^{II}(hedta)^-$. The ^1H NMR spectrum of the $Ru^{II}(hedta)$-(1,3-DMU)$^-$ complex is shown in Figure 5. The presence of free 1,3-DMU serves as an internal reference. The C-5 H is shifted upfield 0.85 ppm, and C-6 H is shifted downfield by 0.20 ppm. This indicates direct Ru^{II} coordination with the C-5–C-6 olefinic bond in 1,3-DMU. Models of the 1,3-DMU complexes of $M(NH_3)_5^{2+}$ (M^{II} = Ru^{II}, Os^{II}) and $Ru^{II}(hedta)^-$ show that both the C-5 H and C-6 H environments are reasonably equivalent when $M(NH_3)_5^{2+}$ is coordinated above the ring, assuming free rotation of the $M(NH_3)_5^{2+}$–olefin bond. The steric effect of the Ru^{II}-(hedta)$^-$ moiety clearly prevents the same free rotation, and the

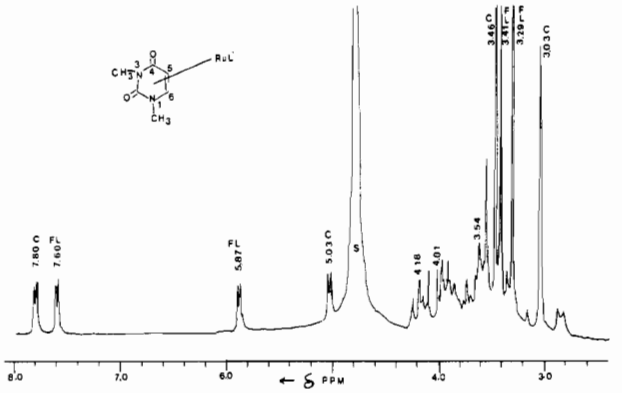


Figure 5. ^1H NMR spectrum of the $Ru(hedta)^-$–1,3-DMU system. Key: FL = free ligand 1,3-DMU; C = olefin-bound complex; S = HOD solvent resonance.

optimal placement of the coordinated C-5–C-6 bond requires the C-5 H to be near the carbonyl of one coordinated glycinato ring of the $hedta^{3-}$ ligand while the C-6 H is near the saturated $-CH_2CH_2OH$ pendant group. This inequivalence accounts for a different shift behavior of C-6 H (downfield) compared to the upfield shifts of both protons of C-6 and C-5 when the $M(NH_3)_5^{2+}$ moiety is coordinated. A disruption of the original planarity of the 1,3-DMU ring must occur with a redistribution of the electron densities and localization of the double bond in the C-5–C-6 region. The methyl groups presumably are turned out of plane. It has been observed for $(NH_3)_5Ru^{2+}$ that the equilibrium constant for formation of the olefinically bound species (ca. 8 M^{-1}) is much smaller for 1,3-DMU than for uridine where N-3 carries a hydrogen and N-1 is bound by ribose.[19] Integration of the ^1H NMR spectrum of a 0.123 M 1:1 $Ru(hedta)(H_2O)^-$–1,3-DMU solution at 60 h indicated a formation constant of 770 M^{-1} for Ru(hedta)(1,3-DMU)$^-$ compared to 2.0×10^3 M^{-1}, obtained at 22 °C for 7.03×10^{-3} M reagents in 0.10 M NaCl by integration of differential-pulse polarographic waves. Equilibrium studies by varying the $Ru^{II}(hedta)^-$:ligand ratio from 1:1 to 1:10 confirm the equilibrium condition and the value of 2.0×10^3 M^{-1}.[53] The agreement between the NMR and electrochemical determinations seems acceptable considering the differing ionic media in the two separate determinations. The $Ru^{II}(hedta)^-$ moiety is a better π donor than $Ru(NH_3)_5^{2+}$ toward 1,3-DMU by a factor of at least 250, as estimated by its larger formation constant.

The presence of a steric effect when N-3 is methylated suggests that the CH_3 or ribose at N-1 turns down below the plane containing the metalated C-5–C-6 bond. The methyl at N-3 presumably could be placed below the metalated plane or above it on the side of the M^{II} complex. The steric effect argues that the N-3 methyl is on the side toward the complexing metal because if it were away from the metal, virtually the same steric repulsion would be observed as for the uridine complex. These orientations of N-1 and N-3 substituents place their lone pairs in the preferred equatorial orientation. In harmony with this view is the fact that for the 1,3-DMU complex the N-1 CH_3 is downfield of the free ligand by 0.05 ppm, while the N-3 CH_3 is upfield by 0.26 ppm. The assignments of the N-1 CH_3 and N-3 CH_3 has been made on the basis of the ^1H NMR spectra for the 3-methyluridine complex, which has only the N-3 CH_3, and the 1-methyluracil complex, which has only the N-1 CH_3 moiety. Confirming data for the $(NH_3)_5M^{II}$ (M^{II} = Ru^{II}, Os^{II}) complexes have been obtained.[49] The N-3 CH_3 of 3-methyluridine experiences the same upfield shift as for N-3 CH_3 in 1,3-DMU; the N-1 CH_3 of 1-methyluracil experiences the downfield shift (Table III).

^1H NMR Spectra of C and U Complexes. Upfield shifts ($\Delta\delta$) of both the C-5 and C-6 protons occur upon $Ru^{II}(hedta)^-$ coordination to uridine and cytosine (see Figures 6 and 7 for cytosine/cytidine and uracil/uridine complexes). The magnitude of the effect (see Tables III and IV) is 20–50% of that observed previously with $M(NH_3)_5^{2+}$ (M^{II} = Ru^{II}, Os^{II}) complexes of styrene and 1,3-butadiene, where 1.7–2.3 ppm upfield shifts are seen for Ru^{II} and 1.7–2.6 ppm upfield shifts are observed for

Table III. ^{1}H NMR Data for Ru^{II}(hedta)$^-$ Complexes[a] of Ligands Related to Uridine

ligand	coord posn of Ru^{II} complex	$E_{1/2}$, V	δ(6-H) (Δδ)	δ(5-H) (Δδ)	δ(1-CH_3) (Δδ)	δ(3-CH_3) (Δδ)	δ(5-CH_3) (Δδ)
uracil			7.42	5.69			
	C-5–C-6	0.62	7.65 (−0.23)	4.89 (0.80)			
	N-1		7.52 (−0.10)	5.89 (−0.11)			
	N-3	−0.06; 1.00[b]	7.05 (0.37)	4.35 (1.34)			
1-methyluracil			7.65	5.84	3.40		
	C-5–C-6	0.62	7.78 (−0.13)	4.93 (0.91)	3.43 (−0.03)		
	N-3	−0.11	7.07 (0.58)	4.48 (1.36)	3.40 (0.0)		
1,3-dimethyluracil			7.60	5.87	3.41	3.29	
	C-5–C-6	0.63	7.80 (−0.21)	5.02 (0.85)	3.46 (−0.05)		
uridine			7.85	5.89			
	C-5–C-6	0.61	7.44 (0.31)	4.61 (1.28)			
	N-3	0.08; 0.98[b]	7.80 (0.05)	6.13 (−0.24)			
3-methyluridine			7.86	5.94		3.28	
	C-5–C-6	0.62 (1)[c]	7.83 (0.03)	4.89 (1.05)		2.99 (0.29)	
		0.62 (2)[c]	7.58 (0.28)	4.74 (1.19)		2.98 (0.30)	
thymidine			7.67				1.91
			7.63 (0.04)				1.87 (0.04)

[a] δ values in ppm. Δδ values in parentheses: a negative Δδ is a downfield shift; a positive Δδ is an upfield shift. [b] High-pH chelated form. [c] Stereochemical isomers 1 and 2.

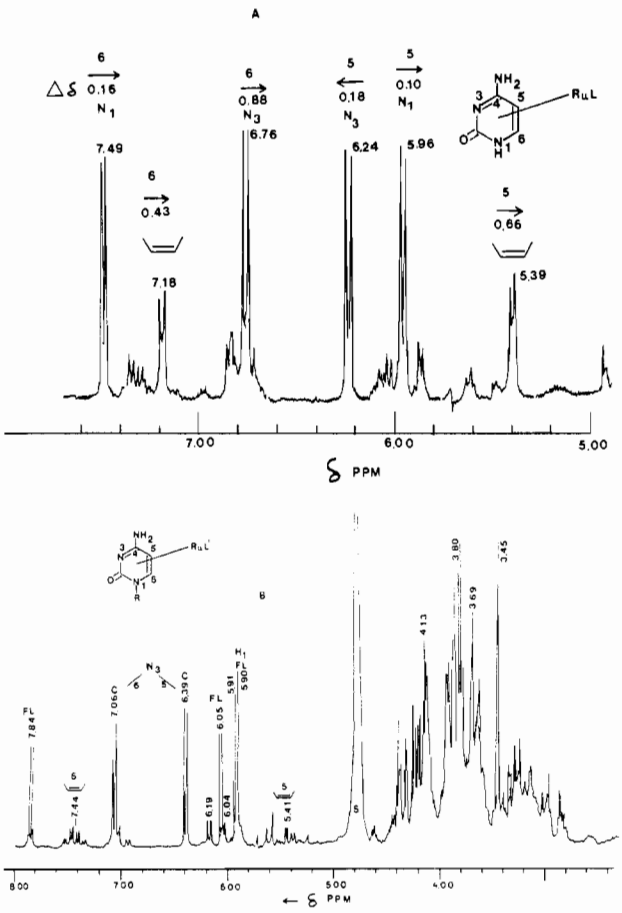


Figure 6. ^{1}H NMR spectrum of the Ru(hedta)$^-$–cytosine and Ru(hedta)$^-$–cytidine systems: (A) cytosine complexes (L′ = $hedta^{3-}$ resonances omitted); (B) cytidine complexes (FL = free ligand cytidine; S = HOD solvent resonance).

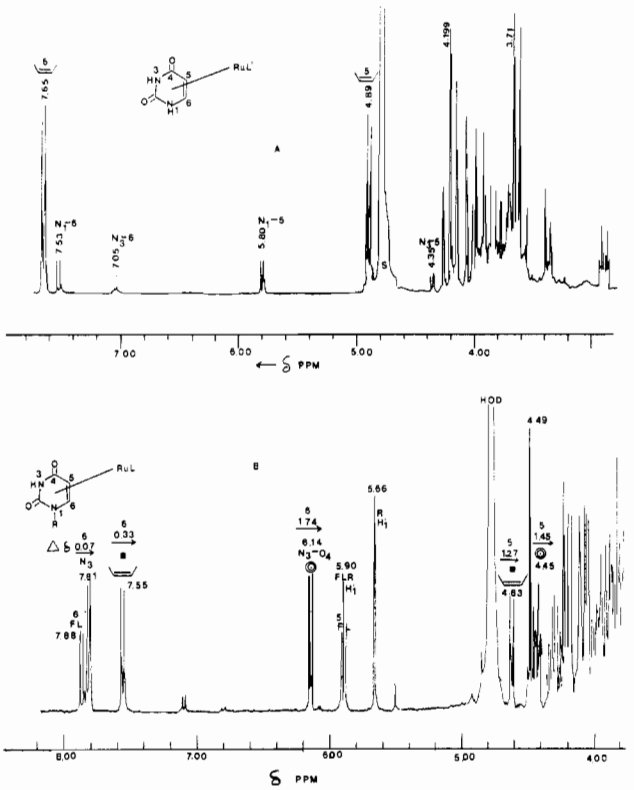


Figure 7. ^{1}H NMR spectrum of the Ru(hedta)$^-$–uracil and Ru(hedta)$^-$–uridine systems: (A) uracil complexes (N_3-6 and N_3-5 positions indicate N-3–4-O chelated form (see text); L′ = $hedta^{3-}$; S = HOD); (B) uridine complexes (FL = free ligand pyrimidine resonance; FLR = free ligand ribose resonance).

Os^{II}.[29,30] The shift assignments and coordination position assignments have been made on the basis of decoupling procedures and the known shift behavior of ortho, meta, and para hydrogens on simple pyrimidines and pyridines where only ring N-binding is observed. The shifts of the 1,3-DMU complexes are also diagnostic,[19] as well as the evidence supplied by using CH_3 or ribose blocking groups at N-1 and N-3 (described in a later section). The three isomer species that are identifiable by ^{1}H decoupling in the ^{1}H NMR spectra of the complexes of Ru^{II}(hedta)U and Ru^{II}(hedta)C occur in the proper integrated amounts to coincide with the areas of the DPP curves of the solution at the same pH.

The species other than the ones associated with the 0.64-V wave exhibit a different shift behavior of the C-5 and C-6 protons, responding to the σ withdrawal and downfield shift for the C-5 (meta) and C-6 (ortho) positions with Ru^{II}(hedta)$^-$ at N-1. Protons for N-3 coordination shift upfield for both C-5 and C-6 protons due to back-donation of Ru^{II} into the pyrimidine ring. Thus, the species coordinated at N-3 of uridine ($E_{1/2} \sim -0.078$ V) or cytidine ($E_{1/2} = +0.07$ V) accounts for the wave at lowest potential. These are assigned in Table III.

1-Methyluracil and 3-Methyluridine Complexes. The complexes formed with 1-methyluracil and 3-methyluridine are complementary to the data sets obtained with uracil and uridine (Table III). The $E_{1/2}$ values found in CV and DPP studies of 1-methyluracil were 0.62 V (olefinic coordination mode) and −0.11 V (coordination via N-3). No N-1-coordinated isomer is observed

Table IV. ^1H NMR Data for $Ru^{II}(hedta)^-$ Complexes[a] of Ligands Related to Cytidine

ligand	coord posn of Ru^{II} complex	$E_{1/2}$, V	δ(6-H) (Δδ)	δ(5-H) (Δδ)	δ(1-CH_3) (Δδ)	δ(3-CH_3) (Δδ)
cytosine			7.65	6.06		
	C-5–C-6	0.62	7.19 (0.46)	5.40 (0.66)		
	N-1		7.49 (0.16)	5.96 (0.10)		
	N-3	−0.05; 1.02[c]	6.77 (0.88)	6.25 (−0.19)		
1-methylcytosine			7.56	5.96	3.36	
	C-5–C-6	0.62	7.32 (0.24)	5.44 (0.52)	3.26 (0.10)	
	N-3	(0.07; 1.00)[b]	6.79 (0.77)	6.25 (−0.29)	3.20 (0.16)	
cytidine			7.84	6.06		
	C-5–C-6[b]	0.64	7.44 (0.40)[b]	5.41 (0.65)[b]		
	N-3	0.07; 1.03[c]	7.06 (0.78)	6.39 (−0.33)		
3-methylcytidine			8.13	6.30		3.50
	C-5–C-6 (1)[d]	0.64	7.99 (0.14)	4.98 (1.32)		3.21 (0.29)
	C-5–C-6 (2)		7.85 (0.28)	4.92 (1.38)		3.20 (0.30)

[a] δ values in ppm. Δδ values in parentheses: a negative Δδ is a downfield shift; a positive Δδ is an upfield shift. [b] Tentative assignment of a low intensity isomer of the more dominant N-3 form. [c] High-pH chelated form. [d] Isomers 1 and 2.

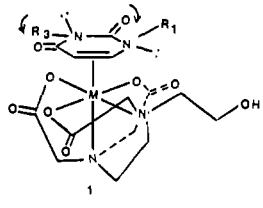
by ^1H NMR spectroscopy, as anticipated by blocking the N-1 position with CH_3.

Comparable Δδ values are observed for H-6, H-5, and N-1 CH_3 in olefin-bound forms for the 1-methyluracil complex and the uracil or 1,3-dimethyluracil cases. For example, the H-6 Δδ values are −0.23, −0.13, and −0.21 ppm for uracil, 1-methyluracil, and 1,3-DMU, respectively. H-5 values for Δδ are nearly the same for these ligands: 0.80, 0.91, and 0.85 ppm. The shift of N-1 CH_3 is −0.03 ppm for 1-methyluracil and −0.05 ppm for 1,3-DMU. The olefin-bound uridine complex obeys the same upfield shift pattern for H-5 and H-6, but the magnitude is about 0.4 ppm greater than that for the derivatives containing substituents less bulky than a ribose unit at N-1. The larger positive Δδ values of the H-5 and H-6 protons are also observed for the 3-methyluridine system (Table III).

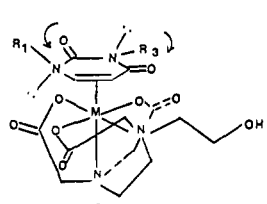
The N-3-coordinated form of 1-methyluracil exhibits the same electrochemical behavior of the N-3-bound form of uracil and thymidine, with respective $E_{1/2}$ values of −0.11, −0.06, and −0.09 V for the $Ru^{III/II}$ wave. The H-6 positions experience −0.23 and −0.13 ppm shifts for uracil and 1-methyluracil complexes, while their H-5 protons show nearly identical Δδ values of 1.34 and 1.36 ppm.

The 3-methyluridine olefinically bound complex shows evidence of two stereochemical isomers in the ratio of 3:2. This most probably reflects the relative positions taken by the $Ru^{II}(hedta)$ moiety at the C-5–C-6 bond, the N-3–methyl unit, and the ribose sugar at N-1. No evidence of stereochemical isomers is found with other uridine-related ligands for even the doubly substituted 1,3-DMU complex.

Models show that the pyrimidine rings, having different substituents at N-1 and N-3, possess two differing spatial attachments to $Ru(hedta)^-$. These two isomers place the bulky ribose of 3-methyluridine or 3-methylcytidine either near the *N*-hydroxyethyl moiety of $Ru(hedta)^-$ or away from it. This is shown in for the 3-methyluridine case as follows:



1



2

Due to the loss of planarity of the pyrimidine ring with localization of the C-5–C-6 bond, the CH_3 moiety of N-3 and the keto functionality at C-2 are turned out of plane in order to place the bulky ribose unit in a position of least strain. If the methyl group at N-3 is removed (e.g. the uridine ligand), two orientations are still possible, but the one having the ribose away from the *N*-hydroxyethyl moiety of $Ru(hedta)^-$ appears to be favored by many fewer repulsions. The isomer at 40% abundance for the 3-methyluridine complex (assigned number 2 in Table III) exhibits ^1H NMR shifts of H-5 and H-6 protons very close to those of the uridine complex. The other 60% abundant isomer (1) has smaller upfield shifts for the H-5 and H-6 positions by ca. 0.2 ppm. Since this isomer is more abundant, it is logical that there is less steric repulsion between the $Ru^{II}(hedta)^-$ moiety and the CH_3 group in this isomer; e.g. the CH_3 group points more away from the $Ru^{II}(hedta)^-$ unit attached to the C-5–C-6 bond in isomer 1 than 2.

1-Methylcytosine and 3-Methylcytidine Complexes. The 1-methylcytosine complex is most closely related to the cytidine (C) complex. This is clearly reflected in the $E_{1/2}$ and ^1H NMR data (Table IV). For N-3 coordination, identical $E_{1/2}$ values of 0.07 V for the $Ru^{III/II}$ waves are observed with cytidine and 1-methylcytosine. The high-pH, chelated forms show $E_{1/2}$ values of the $Ru^{IV/III}$ wave at 1.00 and 1.03 V.

The influences of N-3 coordination on the Δδ values for 1-methylcytosine, cytosine, and cytidine are very similar, as shown by the respective order of upfield shifts of 0.77, 0.88, and 0.78 ppm for H-6; H-5 of these three complexes experiences a downfield shift of −0.29, −0.19, and −0.33 ppm, respectively.

The C-5–C-6 bound forms of 1-methylcytosine, cytosine, and cytidine also exhibit very similar Δδ shifts at H-6 (0.24, 0.46, 0.40 ppm) and at H-5 (0.52, 0.66, 0.65 ppm).

The case of 3-methylcytidine as a ligand for $Ru^{II}(hedta)^-$ is comparable to the 1,3-DMU and 3-methyluridine complexes in that coordination at N-1 and N-3 is blocked by substitution. Like the 1,3-DMU and 3-methyluridine systems, only coordination at the olefinic C-5–C-6 bond is observed ($E_{1/2}$ = 0.64 V). Also, like the 3-methyluridine system described above, there are two stereochemical isomers observed for the coordination of 3-methylcytidine at C-5–C-6. The isomers appear in the ratio close to 1:1 (0.46:0.54) for isomers 1 and 2 in Table IV. Again, the less abundant isomer exhibits the smaller Δδ values about 0.1 ppm less than the slightly more abundant isomer (2).

^{13}C NMR Studies. Confirmatory evidence for the presence of only one C-5–C-6 coordination isomer in the cases of 1-methyluracil and 1,3-DMU and the presence of two stereochemical isomers for the 3-methyluridine complex was obtained from the ^{13}C NMR spectra of these complexes. The chemical shift positions of the pyrimidine base ^{13}C NMR resonances are given in Table V. The C-5 and C-6 carbons are readily distinguished from the C-2 and C-4 carbonyl carbons on the basis of intensity, as the C-5 and C-6 carbons have the proton substituents, which enhance their signals. The methyl carbons are assigned on the basis of the ^{13}C spectra for the ligand rings that bear only one CH_3 group each. From Table V it is observed that the C-4 carbons experience a downfield shift of ca. 10–12 ppm, C-5 carbons experience upfield shifts of ca. 47–50 ppm and C-6 carbons are shifted upfield 38–43 ppm. The two stereochemical isomers of 3-methyluridine are also distinguished by ^{13}C NMR spectroscopy. These show the strongest differences in the C-2 carbonyl and N-3 CH_3 carbons. However, the trends in the ^{13}C shifts of the C-2 and N-3 CH_3 positions are not sufficiently established by these data to justify additional stereochemical inferences. When $(NH_3)_5Ru^{2+}$ is coordinated to

Table V. ^{13}C NMR Data for Olefinically Coordinated Ligands with $Ru^{II}(hedta)^-$ [a]

	δ (Δδ) values					
	C-2	C-4	C-5	C-6	1-CH_3	3-CH_3
	Ligand = 1-Methyluracil					
ligand	155.31	169.71	103.58	150.81	38.54	
complex	155.51 (−0.20)	181.13 (−11.42)	55.58 (48.00)	107.74 (43.07)	38.58 (−0.04)	
	Ligand = 1,3-Dimethyluracil					
ligand	155.58	168.64	102.81	148.33	39.63	30.29
complex	155.83 (−0.25)	180.32 (−11.68)	55.80 (47.01)	106.63 (41.70)	39.97 (−0.34)	30.28 (−0.01)
	Ligand = 3-Methyluridine					
ligand	154.59	168.02	104.02	142.12		30.24
complex (1)[b]	153.94 (0.65)	180.26 (−12.24)	54.07 (49.95)	102.71 (39.40)		29.95 (0.29)
complex (2)[b]	155.68 (−1.09)	178.58 (−10.56)	54.01 (50.01)	104.27 (37.85)		30.33 (−0.09)

[a] δ values in ppm. Δδ relative to the free ligand: a positive Δδ is an upfield shift, a negative Δδ is a downfield shift. [b] Isomer number.

an olefin bond such as with 1,3-butadiene or styrene, the coordinated olefin carbons experience 54–86 ppm upfield shifts.[29,30] The influence of the $Ru^{II}(hedta)^-$ moiety on the rings derived from uracil appears to be about 90% of the effect of the simple olefin complexes at C-5 and 70% as great at C-6.

Absence of the Thymidine Olefin Complex. Although propylene coordinates to $Ru(NH_3)_5^{2+}$ and $Ru^{II}(hedta)^-$, no hindered olefin with three substituents has been observed to coordinate.[29] In the case of the pyrimidine rings, two of the "substituents" of the olefin-bondable region are components of the pyrimidine ring itself. The situation of thymidine, with a methyl group at C-5, is similar to the case of three substituents at the olefinic bond. When $Ru^{II}(hedta)(H_2O)^-$ (3.0×10^{-3} M) was combined with 20% excess thymidine (T), and CV/DPP analysis (Figure 8) showed the absence of any wave near 0.64 V vs NHE. However, both the low-potential ($E_{1/2} \cong -0.09$ V) and high-potential waves ($E_{1/2} \cong 1.00$ V) were observed for complexation by T. The former indicates coordination at N-3 of T as the 4-hydroxyl tautomer, as shown above for U. The high-potential $Ru^{IV/III}$ wave increased substantially at pH 9.57 compared to pH 6.78 (see Figure 8). This provides additional evidence that the waves observed for U and C near 0.64 V are due to the olefin-bound forms of the Ru^{II}-(hedta)L complexes (L = U and C). At high pH the N-3–O-4 or N-3–O-2 chelated binding mode becomes important for T as for U and C. In concert with the observations for thymidine, the thymine complex exhibited only a wave near 0.00 V for N-1 or N-3 coordination and a high-pH form with $E_{1/2}$ at 1.02 V. The ^1H NMR data for the N-3-bound form of the thymidine complex are given in Table III.

Ru^{II}(hedta)(2-pyridone)$^-$ Complex. The increase in Ru(hedta)U, Ru(hedta)C, and Ru(hedta)T species at highest potential suggests chelation between N-3 and exocyclic donor in the 4-position (O for U and T, $-NH_2$ for C or possibly O-2 with C).[50] This conclusion was confirmed by examination of the behavior of the α-pyridone complex, Ru(hedta)(α-pyridone)$^-$. $Ru^{II}(hedta)^-$ (3.0×10^{-3} M) was combined under Ar in an electrochemical cell with 3.6×10^{-3} M α-pyridone. The electrochemical behavior (CV and DPP) between −0.6 and +1.2 V vs NHE was examined as a function of pH after 2 h to allow for complexation in the N-bound $Ru^{II}(hedta)$(α-pyridone)$^-$ complex at pH 6.81. The α-pyridone complex is more yellow than $Ru(hedta)(H_2O)^-$ alone due to an MLCT band. The complex shows only one wave at pH 4.48 ($E_{1/2}$ = 0.01 V) and two species at pH 6.86 ($E_{1/2}$ = 0.01 and 1.012 V) (Figure 9). The amount of the species with the wave at 1.012 V grows by 600% at pH 10.75. Analysis of the areas of the DPP curves at pH 9.32, 10.15, and 10.75 gave an estimated pK_a of 10.48 ± 0.02 for the $Ru^{II}(hedta)$(α-pyridone)$^-$ complex. Reacidification rapidly eliminates the high-pH form, yielding a wave at 0.09 V for the $Ru^{III/II}$ couple, but the original

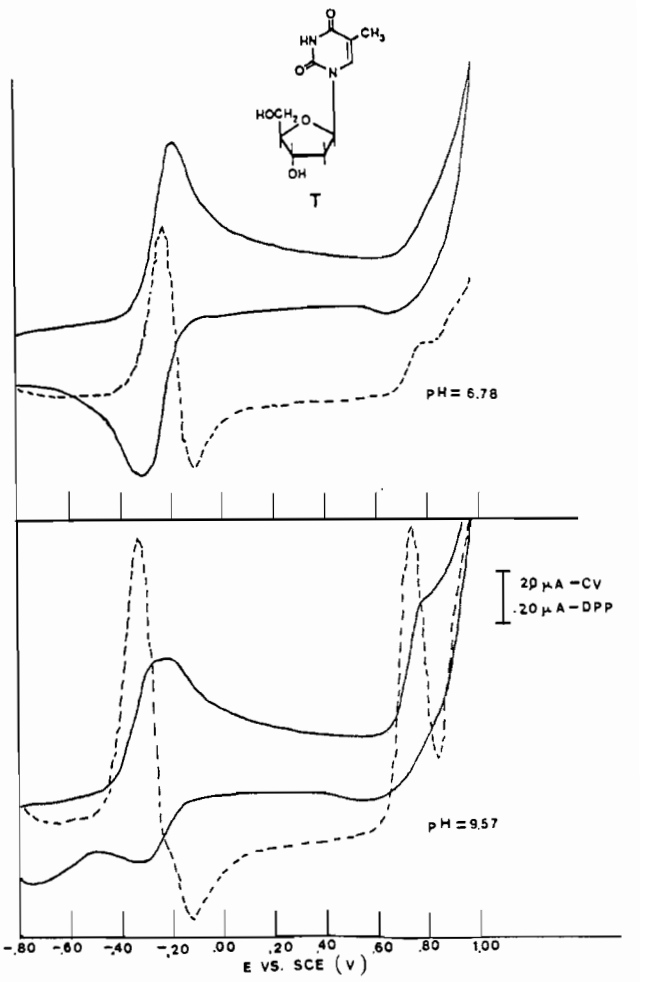


Figure 8. Cyclic voltammetry and differential-pulse polarography data for the $Ru(hedta)^-$–thymidine system at 15 h: (A) pH 6.78; (B) pH 9.57; other conditions as in Figures 2 and 3.

pH ~4.15 wave at 0.01 V for the $Ru^{III/II}$ wave returns more slowly with a rate of 1.2×10^{-2} s^{-1}, suggesting re-formation of a Ru^{II}–carboxylate chelate that was displaced by α-pyridone anion chelation at high pH (Scheme I). A chelate of 2,2′-bipyridine also forms by displacement of one glycinate ring of $Ru(hedta)^-$, as shown by ^1H NMR spectroscopy.[49]

Ru^{II}(hedta)(py)$^-$ Complex. The implications of the chelation mode proposed for U, C, T, and α-pyridone at high pH was further tested with the Ru(hedta)(py)$^-$ complex. For pyridine, there is no possibility of chelation due to the absence of the 2-hydroxyl substituent. However, the pH dependence of the pyridine complex was deemed an important test to rule out the coordination of an external hydroxy group from the solvent as responsible for the electrochemical wave near 1.0 V as seen for C, U, T, and α-pyridone. The complexation reaction at a ligand:Ru^{II} ratio of 4.0, pH 5.31, is shown in Figure 10 at 30 min (A), 60 min (B), and 135 min (C). The differential-pulse waves are most diagnostic in revealing the formation of Ru(hedta)(py)$^-$. The final curve (C) determines an $E_{1/2}$ value for the $Ru^{III/II}$ couple of the pyridine complex of 0.13 V vs NHE. The uncoordinated complex is also detectable at $E_{1/2}$ of 0.00 V vs NHE. Evidence for a bis complex with its wave at ca. 0.39 V also is present. When pyridine is in large excess (pH 7.46), the additional wave increases at 0.39 V (Curve B in Figure 11). The requirement for higher concentration of pyridine and an $E_{1/2}$ value similar to the 0.48-V $E_{1/2}$ value determined for the 1:1 2,2′-bipyridine complex,[49] suggest that the species is the bis complex, $Ru(hedta)(py)_2^-$. The effect of raising the pH for the Ru(hedta)(py)$^-$ complex is shown for curves A, C, and D in Figure 11 at pH values of 5.31, 9.94, and 10.52. A curve at pH 10.75 identical with curve D is not shown. No new wave at ca. 1.0 V vs NHE appears in the CV or DPP curves of the Ru(hedta)(py)$^-$ complex indicated by the arrows at Z on

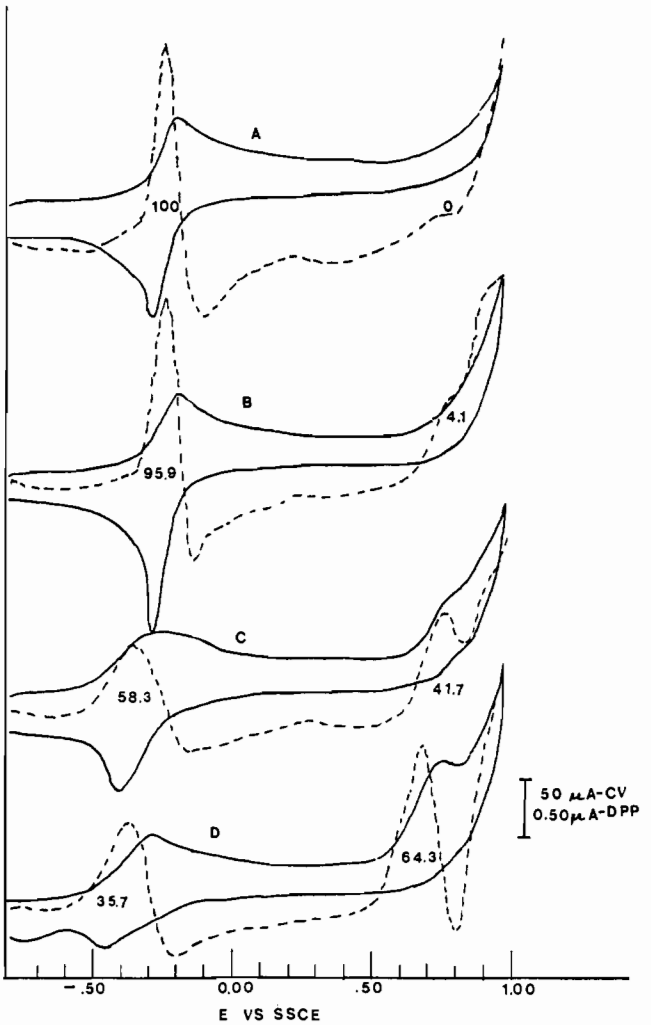


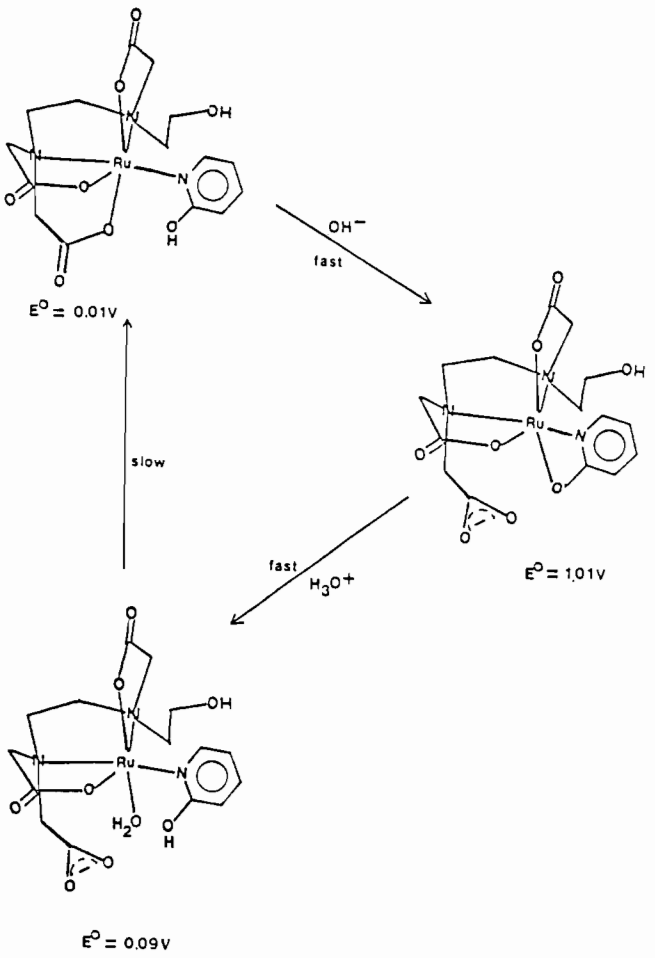
Figure 9. Cyclic voltammetry and differential-pulse polarography data for the Ru(hedta)(2-pyridone)$^-$ Complex: (A) pH 2.55; (B) pH 6.86; (C) pH 9.32; (D) pH 10.75. Conditions: $[Ru^{II}\ complex]_{tot} = 2.87 \times 10^{-3}$ M; [2-pyridone] = 3.53×10^{-3} M; $\mu = 0.10$ (NaCl); $T = 22$ °C; numbers on the DPP curves denote percentage of the total species of complex.

Figure 11. A wave at 1.13 V, which remains constant at all pH values in Figures 10 and 11, is due to the presence of a known $Ru^{III/IV}$ wave of an oxo-bridged dimer of $Ru^{III}(hedta)$.[39] At the higher pH values of 9.94 and 10.52 the free pyridine:$[Ru^{II}]_{int}$ ratio is 4.0; at pH 5.31 this ratio is 2.0. The greater free py promotes formation of some of the bis complex, $Ru(hedta)(py)_2^-$, indicated by X on DPP curves C and D of Figure 11. The main influence at higher pH in the pyridine system is formation of the new species Y with its $Ru^{III/II}$ $E_{1/2}$ value of −0.53 V vs NHE. This change presumably represents replacement of a carboxylate functionality by hydroxide, stabilizing Ru^{III}. The absence of any new wave near 1.0 V further supports the requirement of a chelating moiety for this wave as is available in the $Ru(hedta)L^-$ complexes of C, U, T and α-pyridone. For those complexes containing an α-hydroxyl, which can deprotonate and chelate, the $Ru^{IV/III}$ wave is then shifted to more negative potentials from the 1.13 V for the aqua complex to ca. 1.0 V in the pyrimidine-chelated complexes.

Discussion

The high-pH α-pyridone chelate, $E_{1/2} \sim 1.012$ V, properly models the electrochemical behavior of the +1.03- and +1.01-V waves for the chelated forms of $Ru^{II}(hedta)(U^-)$, $Ru^{II}(hedta)(T^-)$, and $Ru^{II}(hedta)(C^-)$.[40,41] Thus, we have demonstrated attachment of $Ru^{II}(hedta)^-$ in the positions shown in Chart I (percentages are amounts at pH ~7), as determined by ^1H NMR integrations and the areas under the DPP waves for U and C. The nature of the chelated form at high pH for C cannot be unambiguously assigned as the N-3, 4-NH^- chelate; the coordination as N-3, O-2 chelate remains a possibility.[50] The former choice is favored

Scheme I



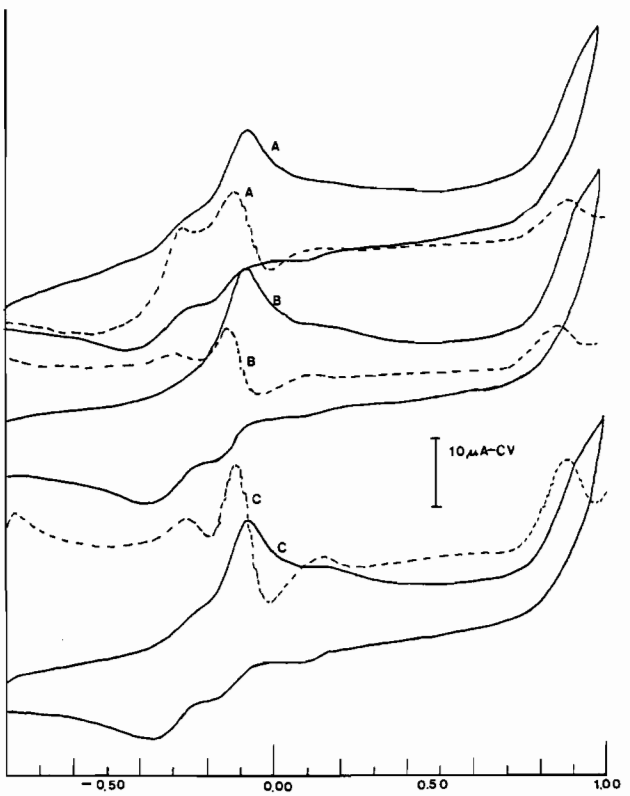


Figure 10. Time dependence of the cyclic voltammetry and differential-pulse data for the Ru(hedta)$^-$–pyridine system. Conditions: $[Ru^{II}]_{tot} = 2.90 \times 10^{-3}$ M; $[py]_{tot} = 1.16 \times 10^{-2}$ M; pH 5.31; $\mu = 0.10$ (NaCl); $T = 22$ °C; CV at 5μA/cm, DPP at 2.5μA/cm. Reaction times: (A) 30 min; (B) 60 min; (C) 135 min.

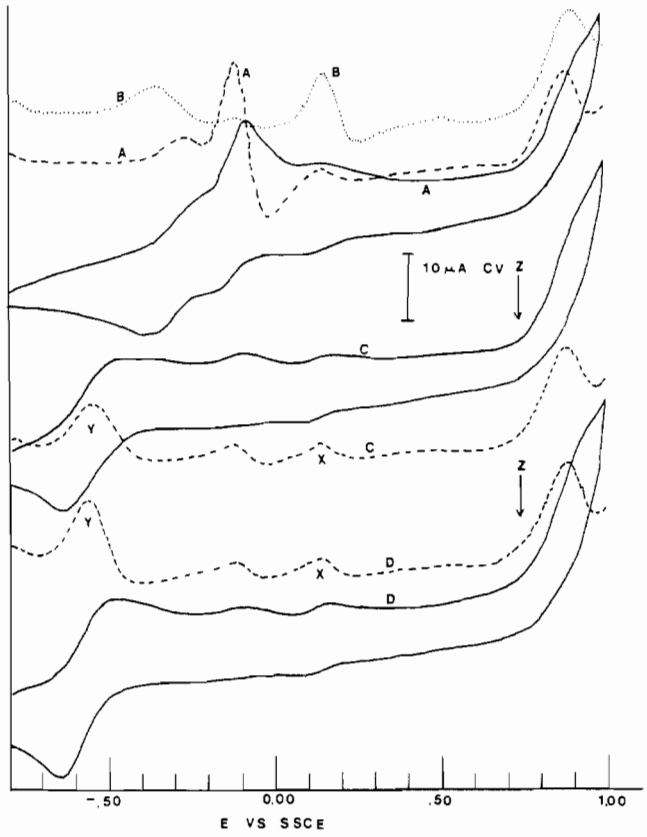


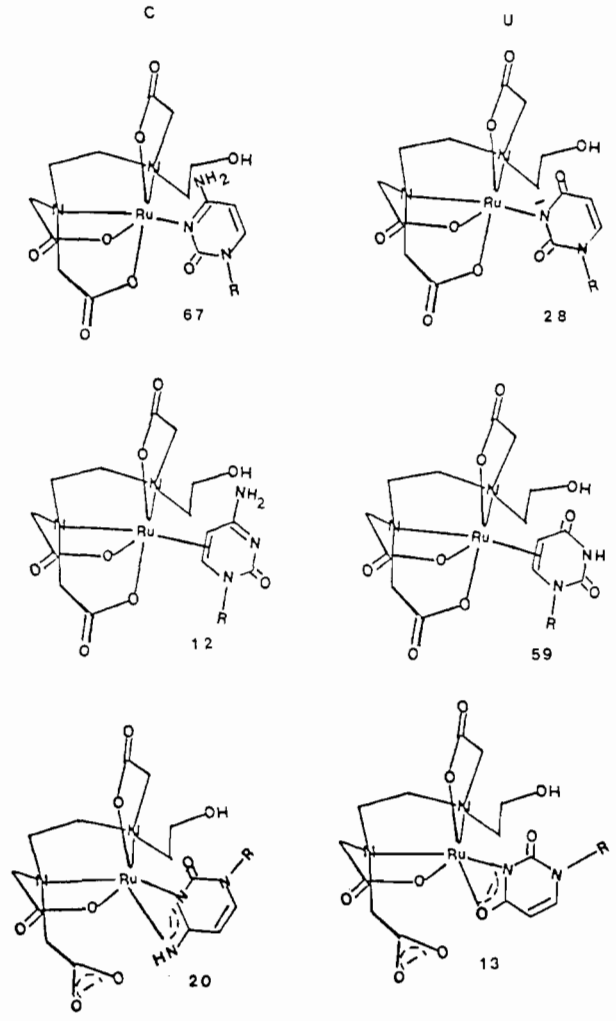
Figure 11. pH dependence of the cyclic voltammetry and differential-pulse data for the Ru(hedta)$^-$–pyridine system. Conditions: $[py]_{tot}$: $[Ru^{II}]_{tot}$ = 4.00; pH (A) 5.31, (B) 7.46, (C) 9.94, (D) 10.52. Note that a large excess of free pyridine was added to the cell to record DPP curve B after curves A, C, and D. All settings are the same as those in Figure 10.

somewhat on steric grounds and chelation to Pt(IV) between N-3 and 4-NH$^-$ is known.[8] The absence of olefin binding to T indicates that only the C base is a potential candidate for olefinic coordination with a DNA polymer. Since RNA's also have U as component in their structures, the olefinic coordination mode is a viable possibility for the RNA's.

Binding to C has been observed at N-3 ($E_{1/2}$ = 0.07 V), 4-NH$^-$ ($E_{1/2}$ = −0.078 V), olefinic C-5–C-6 ($E_{1/2}$ = 0.64 V), and the exo-chelated forms ($E_{1/2}$ = 1.01 V). Binding to U occurs at N-3 ($E_{1/2}$ = −0.078 V), olefinic C-5–C-6 ($E_{1/2}$ = 0.62 V), and exo-chelated ($E_{1/2}$ = 0.94 V) positions. Binding to T occurs only at N-3 ($E_{1/2}$ = −0.09 V) and in the chelated form ($E_{1/2}$ = 1.00 V). The ^{1}H NMR shifts of the C-5–C-6-coordinated forms of the Ru(hedta)L$^-$ complexes (L = 1,3-DMU, U) show large upfield shifts for the C-5 H protons in about 50% of the shifts observed for simple Ru^{II}–olefin chromophores. Smaller shifts or downfield shifts are produced with coordination at N-1 of ligands related to U or C. The large upfield shifts for the C-5 H and the C-5 position argue for the total disruption of any ring aromaticity for U and C upon coordination at the C-5–C-6 olefinic bond.

Confirming evidence for C-5–C-6 metalation has been obtained with the M(NH$_3$)$_5$(1,3-DMU)$^{2+}$ (M^{II} = Ru^{II}, Os^{II}) and the Os(NH$_3$)$_5$(3-methyluridine)$^{3+}$ complexes[19,49] and in the present study with Ru^{II}(hedta)$^-$ and its 1,3-DMU, 3-methyluridine, and 3-methylcytidine complexes. In these cases coordination at N-1 or N-3 is sterically blocked; *only* the olefinic coordination mode is observed together with rehybridization of the ring.[19,49] A similar disruption of the aromaticity of benzene and related aromatic rings has been noted by Harman and Taube upon binding of Os(NH$_3$)$_5^{2+}$ in the η^2 fashion with "aromatic" rings.[32-35] The disruption of the aromatic character in the benzene case is sufficient to permit normal olefin-like reactivity, such as low-pressure reduction by H_2 in the remainder of the C_6H_6 ring.[35] The finding of a localization of olefin-bond character in the C-5–C-6 region

Chart I



of C and U upon coordination by Ru^{II}(hedta)$^-$ suggests that the ability of these units to match with G and A during replication would be highly altered, and most probably mutagenic, if C or U were metalated at the olefin site. Further studies into the potential of the C-5–C-6 olefinic coordination as a possible metal ion probe of DNA structure or as an additional site to promote antitumor action are being currently pursued.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (Grant CHE-8417751) for support of this work.

Registry No. **1**, 3438-46-8; **2**, 298-95-2; **3**, 5413-85-4; **4**, 109-08-0; **5**, 290-37-9; **6**, 125108-67-0; **7**, 98-97-5; **8**, 66-22-8; **9**, 71-30-7; **10**, 874-14-6; 1-MeU, 615-77-0; U, 58-96-8; T, 50-89-5; C, 65-46-3; Ru^{II}(hedta)(η^2-C^5,C^6-uracil)$^-$, 125137-61-3; Ru^{II}(hedta)(N^1-uracil)$^-$, 125137-78-2; Ru^{II}(hedta)(N^3-uracil)$^-$, 125137-79-3; Ru^{II}(hedta)(η^2-C^5,C^6-1-MeU)$^-$, 125108-68-1; Ru^{II}(hedta)(N^3-1-MeU)$^-$, 125137-80-6; Ru^{II}(hedta)(η^2-C^5,C^6-1,3-DMU)$^-$, 125137-62-4; Ru^{II}(hedta)(η^2-C^5,C^6-U)$^-$, 125137-63-5; Ru^{II}(hedta)(N^3-U)$^-$, 125137-81-7; Ru^{II}(hedta)(η^2-C^5,C^6-3-methyluridine)$^-$, 125137-64-6; Ru^{II}(hedta)(N^3-T)$^-$, 125137-65-7; Ru^{II}(hedta)(η^2-C^5,C^6-cytosine)$^-$, 125137-66-8; Ru^{II}(hedta)(N^1-cytosine)$^-$, 125137-82-8; Ru^{II}(hedta)(N^3-cytosine)$^-$, 125137-83-9; Ru^{II}(hedta)(η^2-C^5,C^6-1-methylcytosine)$^-$, 125137-67-9; Ru^{II}(hedta)(N^3-1-methylcytosine)$^-$, 125137-84-0; Ru^{II}(hedta)(η^2-C^5,C^6-C)$^-$, 125137-68-0; Ru^{II}(hedta)(N^3-C)$^-$, 125137-85-1; Ru^{II}(hedta)(η^2-C^5,C^6-3-methylcytidine), 125137-69-1; Na[Ru^{II}(hedta)H$_2$O], 118170-03-9; Na[Ru^{II}(hedta)(4-CH$_3$pym)], 125137-70-4; Na[Ru^{II}(hedta)(pym)], 125137-71-5; Na[Ru^{II}(hedta)(ADCpym)], 125137-72-6; Na[Ru^{II}(hedta)(2-CH$_3$pz)], 125137-73-7; Na[Ru^{II}(hedta)(pz)], 125137-74-8; Ru^{II}(hedta)(2-CH$_3$pzH$^+$), 125137-75-9; Na[Ru^{II}(hedta)(2-pzCOOH)], 125137-76-0; Ru^{II}(hedta)(*N*-CH$_3$pz$^+$), 125137-77-1; (NH$_3$)$_5$Ru(1,3-DMU)$^{2+}$, 125108-69-2; 3-methyluridine, 2140-69-4; 1-methylcytosine, 1122-47-0; 3-methylcytidine, 2140-64-9.