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$[Ru^{II}(hedta)]^-$ complexes of 2,2′-dipyridylamine (dpaH) and a bifunctional tethered analog, *N*,*N*,*N*′,*N*′-tetrakis(2-pyridyl)adipamide (tpada)

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Abstract

$[Ru^{II}(hedta)L]^-$ complexes ($hedta^{3-}$ = *N*-hydroxyethylethylenediamine-*N*,*N*,*N*′-triacetate); L = dpaH (2,2′-dipyridylamine) and tpada (*N*,*N*,*N*′,*N*′-tetrakis(2-pyridyl)adipamide)) have been studied by ^1H NMR and electrochemical methods in aqueous solution. The bidentate rings of dpaH and tpada are differentiated as shown by NMR upon coordination to Ru^{II} due to differences in the local environment. The dpa–R headgroup of each ligand binds 'in-plane' with the en backbone of $hedta^{3-}$ and with one pyridyl ring being nearer the amine of $hedta^{3-}$ having the pendant glycinato group (matching the known arrangement with bpy (2,2′-bipyridine)). $Ru^{II/III}$ $E_{1/2}$ values follow the order dpaH (0.32 V) < tpada (0.47 V) < bpy (0.54 V), showing that dpaH is a weaker π-acceptor ligand than bpy, and that the withdrawing carbonyl functionality enhances the π-acceptor capacity for the tpada ligand, approaching the stability imparted by bpy. Only the 1:1 $[Ru^{II}(hedta)(dpaH)]^-$ complex forms even in the presence of excess dpaH. $[Ru^{II}(hedta)(dpaH)]$ has a pK_a of the dipyridylamine proton of approximately 5.0 with $[Ru^{III}(hedta)(dpa^-)]$ undergoing aquation ($k_{H_2O} = 1.4 \times 10^{-2}$ s^{-1}) and OH^--assisted dissociation ($k_{OH} = 1.33 \times 10^4$ M^{-1} s^{-1}). The $\{[Ru^{II}(hedta)]_2(tpada)\}^{2-}$ complex serves as a water-soluble model as to how $\{[ML']_2(tpada)\}$ complexes might act as an extended bridge between two metal binding sites, potentially those of metallo-derivatized DNA strands, or between one DNA strand and a protein crosslink. In this model M represents an appropriate metal for DNA derivatization such as Ru^{II}, Pt^{II} or Pd^{II} and L′ represents the attachments to DNA nucleobase sites, aminocarboxylates/peptide coordination for antitumor purposes.

Keywords: Ruthenium complexes; Dipyridylamine complexes; Polydentate ligand complexes

1. Introduction

2,2′-Dipyridylamine (dpaH) is an aromatic amine in some ways similar to 2,2′-bipyridine (bpy), but the central amine unit introduces several differences: (1) dpaH coordinates with six-membered chelate rings instead of five-membered rings for bpy; (2) the coordinated pyridine rings are not necessarily forced to near coplanarity as in bpy; (3) the ligand field strength of dpaH is greater than ethylenediamine, but closer to that of a single aromatic amine, e.g. that dpaH is less of a π-acceptor ligand than bpy [1]. The two pyridine rings of dpaH are flexible in their coordination with metal centers, adopting either nearly coplanar or tilted pyridyl ring planes that vary from 2° to 42° of tilt. This can be induced either electronically or stereochemically. For example, Cu^{II} complexes span the 2–42° range based on the various other ligands; structures of $[Cu(dpaH)_2]^{2+}$, and $[Cu(dpaH)_2X]^+$ and $[Cu(dpaH)L']$ (L′ = acac, etc.) have been widely studied in this regard [2–5]. $[Ru^{II}(dpaH)_3]^{2+}$ and the series $[Ru(bpy)_{3-n}(dpaH)_n]^{2+}$ ($n = 0$–2) have been shown by ^1H and ^{13}C NMR methods to have rapidly flapping dpa pyridyl donors that undergo an inversion of the relative tilt of the two pyridyl planes of dpa. These motions average the chemical shifts of the ring H-6 and H-6′ protons of $[Ru(dpaH)_3]^{2+}$ [6a]. The dihedral angle of 35° was found for the only reported structure of a Ru^{II} complex, $[Ru(Me_2bpy)_2(dpaH)](PF_6)_2$ [6d].

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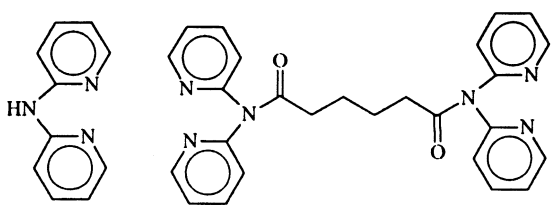
There are fewer reports of dpaH complexes of Ru(II), Pt(II) or Pd(II), metals of current biomedical interest. Pt(II) and Pd(II) complexes have been prepared having formulas of $[M^{II}(dpaH)(AA)]$ and $[M^{II}(dpaH)(pyc)]^+$ (AA = amino acid anion, pyc = pyridine-2-carboxylate; $M^{II} = Pd^{II}$, Pt^{II}). Some of these have shown antitumor activity toward P388 leukemia cells that equal or exceed the activity of cisplatin [7,8]. The binding of these Pt^{II} and Pd^{II}–dpaH complexes to calf thymus DNA is reported to be non-covalent via the minor groove [7,8].

Derivatized ligands, with an R group attached to the central amine of dpaH in place of H, have found uses as electrochemical mediators in the detection of glucose using Os(dpa–R) funtionalities as linkages to electrode surfaces [9a], and as models of hydrolytic enzymes for ATP and UTP with Cu^{II}(dpa–R) tethered to an adenosine recognition site [9b]. The concept of two dpa chelating sites linked by a suitable tether has not been exploited previously in the preparation of bimetallic complexes.

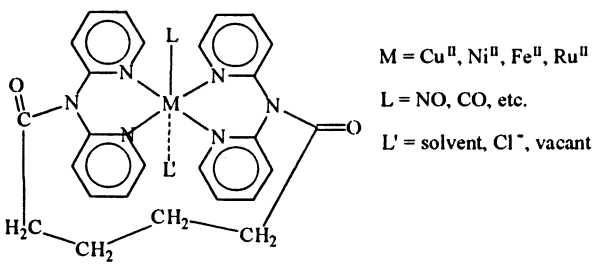
The previous reports of bpy complexes of Ru(II)-polyaminopolycarboxylates, including $[Ru(hedta)(bpy)]^-$, [10–13] serve as a useful starting point for interpreting aspects of the coordination of dpaH and dpa-like-ligands toward Ru(II) and heavier metals such as Pt(II) and Pd(II). The $Ru^{II/III}$ $E_{1/2}$ value and the ^{1}H NMR chemical shifts for ligand coordinated to $[Ru^{II}(hedta)]^-$ can be used to estimate the π-acceptor power of the ligand. We have synthesized a ligand relative of dpaH, *N*,*N*,*N*′,*N*′-tetrakis(2-pyridyl)adipamide (tpada):



dpaH tpada

The tpada ligand may be suited for the delivery of Ru(II), Pt(II) or Pd(II) metal centers as interstrand cross-linking reagents toward DNA, much in the manner reported for Farrell's polyamine groove-spanning chelates [14–18] and related binuclear Pt(II) complexes designed by Beck [19] and by Taylor [20].

In this paper we present data concerning the $[Ru^{II}(hedta)(dpaH)]^-$ and $\{[Ru(hedta)]_2(tpada)\}^{2-}$ complexes which allow the π-acceptor power of the ligands to be established as bpy > 1/2(tpada) > dpaH > dpa^-. Further studies with tpada in forming binuclear metal chelates in the extended arrangement as for $\{[Ru(hedta)]_2(tpada)\}^{2-}$, or in the multidentate arrangement toward one metal center as in species **3**, are being explored for a variety of transition metals in our laboratory. Complexes such as **3** with L = NO may have several possible medical uses in the antisepsis or antitumor arena.



(3)

2. Experimental

2.1. Material

K[Ru(hedta)Cl] was prepared as described previously [21–23]. 2,2′-Dipyridylamine was obtained from Aldrich. Ar gas was used as supplied by Valley Welding Supply. Ar was passed through Cr(II) scrubbing towers followed by a deionized water rinse tower to remove traces of O_2 from the inert gas stream and to saturate the inert gas with H_2O vapor in order to avoid dehydration of aqueous samples. When samples were prepared in D_2O for NMR studies, the tank Ar gas was used as received to avoid enrichment of the D_2O with unwanted amounts of HOD. All other reagents were reagent grade.

2.2. Sample preparation

The starting K[Ru(hedta)Cl] was weighed out together with the ligand of interest to achieve 0.80:1.00, 1:00:1:00, 1:00:2.00 or 2:00:1.00 $[Ru^{II}(hedta)]^-$: ligand stoichiometries upon reduction to Ru(II) as specified in the individual experiments. The samples were prepared in Ar-purged 10 ml glass round-bottom flasks, sealed with rubber septa. A total of 3.0–5.0 ml of D_2O together with a few small chips of Zn/Hg and a small rice-sized stirring bar were included with the [Ru(hedta)]/ligand samples. Stirring was maintained magnetically while a stream of Ar purged the 10 ml flask and an NMR tube receiver, connected in series by syringe needles and syringe tubing. For ^{1}H NMR experiments the solvent was adjusted initially with DCl solution to give pD ~3 in order to assure reduction of Ru(III) by the Zn/Hg surface. Transfer of the reduced $[Ru^{II}(hedta)L]^-$ samples was made under Ar pressure through the tubing connections. After filling an NMR tube with the desired solution via the septum top/needle assembly, the tube was removed and the septum area

was wrapped with parafilm to provide an additional barrier toward O_2.

2.3. Instrumentation

^1H and ^{13}C NMR spectra were obtained on Bruker AC300 NMR spectrometers following standard procedures reported previously [24–27]. ^1H NMR spectra obtained in D_2O were referenced against DSS (0.00 ppm). Those obtained in $CHCl_3$ for ligands were referenced against added TMS (0.00 ppm). ^{13}C NMR spectra were referenced against *p*-dioxane (69.1 ppm) or TMS (0.00 ppm).

Electrochemical studies were performed on approximately 2.61×10^{-3} M solutions in Ar or N_2-purged 0.100 M NaCl plus the desired complex at 22°C. These samples were prepared from reacting the proper mass amounts of K[Ru(hedta)Cl] and ligand dissolved in the electrolyte solvent in contact with Zn/Hg chips in a glass bubbler apparatus having septum-sealed 14/20 joints. The glass bubbler was connected to a slowly flowing Ar stream which provided the constant mixing during reaction of dpaH or tpada with $[Ru^{II}(hedta)(H_2O)]^-$. Samples were transferred by syringe techniques into an N_2-purged cell compartment of an IBM 225 electrochemical analyzer for cyclic voltammetry and differential-pulse polarography detection. The standard three-electrode arrangement was used having a glassy carbon working electrode, a platinum wire auxiliary electrode, and a saturated sodium chloride calomel electrode reference. Calibration methods have been reported previously [28,29]. A flowing stream of Ar or N_2 was maintained above the electrochemical samples to prevent air oxidation. Prior work has shown sample stability up to 24 h by these methods, although the samples in the present study were analyzed within 1 h of contact time within the sample cell. pH adjustment was made by the addition of 1 M HCl or 1 M NaOH via a syringe into the cell contents. Mixing was provided by the rice-sized stirring bar rotation and by the mixing provided by Ar or N_2 bubbling the sample via a small tube that could be raised above the sample surface or lowered to provide purging and mixing.

2.4. Ligand synthesis

2.4.1. tpada

1,2-Dimethoxyethane (J.T. Baker) was dried for 6 h with stirring over pieces of Na metal. The DME solvent was then vacuum distilled, collecting the vapors in a dry ice chilled receiver tube. A total of 200 ml of the dried solvent was placed in a three-necked 500 ml round-bottom flask with a stirring bar. A total of 9.34 g (0.0546 mol) of 2,2′-dipyridylamine recrystallized from hot ethanol/acetone and vacuum dried, was added to the solvent. Magnetic stirring was maintained as 2.13 g of K (0.0546 mol) metal in small pieces was added via one side arm, keeping exposure to the atmosphere minimal. The necks of the flask contained a center reflux condenser, an inlet valve for a flowing N_2 stream and the glass-stopper port for adding reagents. The exit tube for gas passed out through a mineral oil trap to provide pressure release. After purging for sufficient time to remove O_2 from the apparatus, the gas flow was stopped and the exit was connected to a drying tube filled with dryerite to prevent atmospheric moisture from reentry. The sample was stirred for a day to allow time for the K metal to react with the dpa to form the $K^+(dpa^-)$ salt. It was observed that the K flakes were coated with yellow $K^+(dpa^-)$ at this time. To complete the formation of $K^+(dpa)$, the solution was heated to 40°C while maintaining the stirring. This induced more rapid conversion to the $K^+(dpa)$ product as the K surface was continuously exposed to dpaH in solution. The solution appeared yellow and a small amount of solid was present. A total of 4.0 ml (0.0273 mol). Adipoyl chloride (Aldrich) was transferred to a glass Hamilton syringe inside a glove bag to prevent H_2O vapor exposure. The syringe was connected to the reaction flask via the addition portal which was sealed with a septum. With stirring, the adipoyl chloride was slowly added to the sample over a period of 2 h. The syringe was finally rinsed with a small volume of DME to assure the transfer of all of the adipoyl chloride to the reaction flask. Stirring was maintained at room temperature. A yellow–white solid appeared as the additions continued. The solids were filtered off as product although significant amount of solid appeared from the filtrate with evaporation. The solid product was washed with cold water, ethanol and ether. The product was not appreciably soluble in diethyl ether. This is a fortunate result since the unreacted dpaH is soluble in diethyl ether. Any unreacted dpaH can be conveniently removed. The product was virtually insoluble in H_2O unless treated with HCl; the product was soluble in $CHCl_3$. Small amounts of the product were dissolved in $CDCl_3$ and in D_2O/DCl in order to obtain ^1H and ^{13}C NMR data. The dried solid (tpada) was used for preparation of the $[Ru^{II}(hedta)]$-derivatized sample assuming the molecular weight of 452.53 implied by the formula. The ^1H NMR data showed that the isolated product was free of unreacted dpaH since the integration of pyridyl ring protons to aliphatic protons is correctly 2:1 (16:8). The isolated product exhibits traces of the DME solvent coprecipitated in the lattice of the solid; but DME does not interfere in the coordination of $[Ru^{II}(hedta)]^-$.

2.4.2. Computer-assisted structural analysis

Molecular mechanics energy minimization calculations were performed for $\{[Ru(hedta)]_2(tpada)\}^{2-}$ using CHEM PRO-3D software on a 7100 MacIntosh Power PC

Table 1
^{1}H NMR shifts for dpaH and tpada [a]

Ligand/solvent	H-6	H-5	H-4	H-3	$-CH_2-CH_2-$	$-CH_2-\overset{O}{\overset{\|}{C}}-$
dpaH/D_2O	8.17(d)	7.02(t)	7.76(t)	7.28(d)		
$dpaH_2^{+}$/D_2O	8.27(d)	7.23(t)	8.03(t)	7.23(d)		
$tpadaH_2^{2+}$/D_2O	8.65(d)	7.77(t)	8.32(t)	7.41(d)	1.61(s)	2.35(s)
tpada/$CDCl_3$	8.44(d)	7.18(t)	7.73(t)	7.48(d)	1.67(m)	2.27(t)

[a] $dpaH_2^{2+}$, $tpadaH_2^{2+}$, refer to the dipyridyl protonation of the neutral ligand.

computer. The software allows for print out of a spacial perspective of all atom coordinates with size of atoms as perceived from the viewer's perspective.

3. Results and discussion

3.1. Ligands

The tpada ligand was synthesized as described in Section 2. ^{1}H NMR data are given in Table 1 for these ligands and for dpa for comparison. Solubility problems for the tpada ligand required acidification with CF_3COOD to afford solubility as $tpadaH_2^{2+}$.

For this reason, data for the related $dpaH_2^{+}$ [38] have been given. Protonation of the pyridyl rings of dpaH produce downfield shifts of -0.10 ppm (H-6), -0.21 ppm (H-5) and -0.27 (H-6). Comparable effects can be assumed for $tpadaH_2^{2+}$. The shifts of the tether protons of $tpadaH_2^{2+}$ are in similar chemical environments as for the α and β methylene protons of *n*-butanoic acid. The α_{CH_2} and β_{CH_2} shifts are 2.31 and 1.68 ppm, respectively, for *n*-butanoic acid which confirms the assignments in Table 1 for $tpadaH_2^{2+}$. ^{13}C NMR data for the free tpada ligand was obtained in $CHCl_3$ referenced against *p*-dioxane. The ^{13}C shift data for tpada is given in Table 2, fully confirming the presence of all chemical functionalities of the tpada structure. The assignments of C-3 and C-5 carbons are interchangeable, being virtually identical shifts and both carbons having one proton which eliminates their resolution from a proton-coupled spectrum.

3.2. [Ru(hedta)(dpaH)]$^-$ complex

$[Ru(hedta)(H_2O)]^-$ reacts with monodentate *N*-heterocyclic bases in two sequential additions for L = pyridine, pyrimidine, pyrazine [30,31] (Eqs. (1) and (2)). There are three possible stereochemical isomers for the 1:1 complexes, $[Ru(hedta)L]^-$ that have been identified: *cis*-equatorial, *trans*-equatorial

$$[Ru(hedta)(H_2O)]^- + L \rightleftharpoons Ru(hedta)L^- + H_2O \quad (1)$$

$$[Ru(hedta)L]^- + L \rightleftharpoons [Ru(hedta)(L)_2]^- \quad (2)$$

and *cis*-polar, the main species being *cis*-equatorial [32–34]. The bis complexes have both L ligands in the equatorial plane; the same stereochemistry is adopted for bidentate (LL) donors such as bpy and *o*-phen. The $[Ru^{II}(hedta)]^-$ complexes behave identically with that of mono and bis L complexes of $[Ru(edta)]^{2-}$ [33,34]. $[Ru(hedta)(bpy)]^-$ shows no ^{1}H NMR differentiation of the H-6 and H-6′ protons [11], but $[Ru(hedta)(dpaH)]^-$ exhibits such a differentiation. However, the dpaH ligand also exhibits differentiated H-6 and H-6′ resonances in $[Ru(bpy)_2(dpaH)]^{2+}$ [6] and *trans*-$[Ru(dpaH)_2(NO)(OH)]^{2+}$ [35]. The influence is attributed to geometric differences in the former [6] and has been attributed to hindrance of the dpaH flapping motion in the latter [35].

^{1}H NMR samples of $[Ru^{II}(hedta)]^-$:dpaH were prepared at 1:1, 1:2 and 2:1 ratios with $[Ru^{II}(hedta)]^- = 2.61 \times 10^{-2}$ M. The test of the molar ratios is necessary in order to show whether two dpaH ligands can displace all three carboxylates of the original $[Ru(hedta)(H_2O)]^-$ complex, whether a bridged-binuclear species forms in which each pyridyl donor of dpaH might donate to one $[Ru(hedta)]^-$ center, or if the coordination behavior of dpaH is simply as a bidentate chelate in the manner of bpy in $[Ru(hedta)(bpy)]^-$. Substitution reactions forming bis-substituted $[Ru(hedta)L_2]^-$ complexes are complete within 1 h for L = py, pym or pz complexes. However, both steps of the reaction appear to be nearly as rapid as the initial substitution process for bpy since only the bidentate species is detectable within the time to mix a

Table 2
^{13}C NMR shifts for the tpada ligand in ppm

Ring C	C-2	C-3	C-4	C-5	C-6
	154.14	121.61	127.75	121.83	148.59
Tether C	C=O	CH_2CO	CH_2CH_2		
	172.94	35.66	24.27		

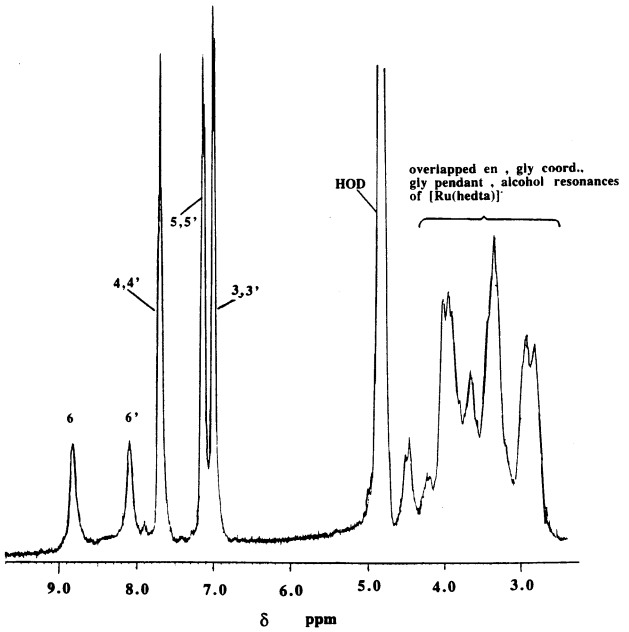


Fig. 1. 300 MHz ^{1}H NMR spectrum of $[Ru^{II}(hedta)(dpaH)]^-$ in D_2O. [complex] = 2.61×10^{-2} M, $T = 25$°C, p$D = 6.0$.

sample and to tune the NMR for recording data. That is, ring closure to form the bidentate complex with bpy is more rapid than addition of a second monodentate donor. For the $[Ru(hedta)]^-$:dpaH sample at 1:2 ratio a reaction time of 5 h, much longer than deemed necessary to reach the equilibrium state in which both dpaH ligands have added to the Ru(II) center, showed a set of resonances at exactly the same shift as the 1:1 sample after 7 h, as well as an equivalent of free ligand. Electrochemical data show there is no free $[Ru(hedta)(H_2O)]^-$ remaining after 7 h for a 1:1 ratio. In Fig. 1 of the ^{1}H NMR spectrum there are broad singlets for the 1:1 complex at 8.81 and 8.08 ppm for H-6 and H-6′ protons of a coordinated dpaH, 7.68 ppm for coordinated dpaH's H-4(t) set, 7.13 ppm for H-3(d) set and 6.98 ppm for an H-5(t) set. The H-4, H-5 and H-3 sets integrate to show that these are pairwise matching but differentiated H-4, H-4′, H-5, H-5′, and H-3, H-3′ sets of resonances. Additionally in the 1:2 sample under acidic conditions which assure solubility of dpaH, there are equal amplitude resonances to that of the coordinated dpaH for the free protonated ligand at 8.24, 7.97 and 7.19 ppm for the H-6, H-6′, H-4, H-4′, and the overlapped H-3, H-3′ and H-5, H-5′ protons, respectively. These results show that dpaH displaces two coordination sites of $[Ru(hedta)(H_2O)]^-$, but will not displace the remaining two carboxylate donors even in the presence of excess ligand.

Comparison of the $[Ru(hedta)]^-$:dpaH samples at 1:1 and 2:1 ratios showed identical coordinated dpaH spectra, allowing 8 h to achieve equilibria. Since the H-6 and H-6′ resonances remain differentiated, the dpaH ligand must be bidentate toward one Ru(II) center rather than bridging between two separate Ru(II) sites. Therefore, the nature of the $[Ru(hedta)(dpaH)]^-$ complex appears to be analogous to $[Ru(hedta)(bpy)]^-$ in adopting a bidentate coordination. This is presumably in the equatorial plane which produces *trans*-O carboxylate coordination, well-known for the $[Ru(hedta)(L)_2]^-$ series. However, the $hedta^{3-}$ chelate rings lead to differentiation and broadening of the H-6, H-6′ resonances of dpaH.

The conclusions drawn on the basis of the dpaH ^{1}H NMR splitting pattern are further supported by observations of the $Ru^{II/III}$ wave by differential-pulse polarography (DPP) on 2.61×10^{-3} M solutions. At 1:1 ratio $[Ru(hedta)(dpaH)]^-$ exhibits a single DPP wave at 0.24 V versus NHE for a neutral solution (see Fig. 2). However, if the sample is made acidic (pH ≅ 5.50) the wave shifts slightly to 0.29 V. Under basic solution conditions (pH ≅ 9.50) the wave shifts markedly to 0.07 V. When the sample is acidic, scanning beyond the original waves to positive potentials shows no evidence of ligand loss (which promotes $Ru^{III/IV}$ waves at high potentials (0.8–1.2 V)). However, the neutral sample shows a small additional wave at 0.91 V versus NHE of 12.5% amplitude of the $Ru^{II/III}$ 0.24 V wave. Under basic solution, the 0.91 V wave, indicative of a $2e^-$ oxidation is markedly enhanced, being nearly twice the amplitude of 0.07 V wave. These observations are consistent with a pH-dependent redox couple (Eq. (3)) for the wave in the 0.29–0.07 V region:

$$[Ru^{II}(hedta)(dpa)]^- + H_3O^+ + e^- \rightleftharpoons [Ru^{II}(hedta(dpaH)^- + H_2O] \quad (3)$$

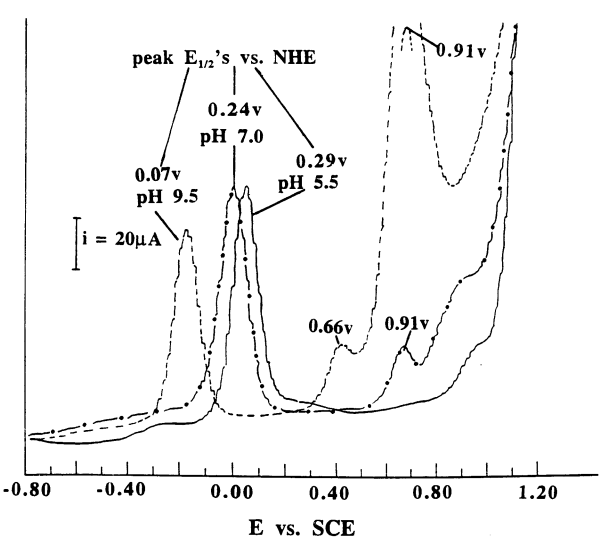


Fig. 2. Differential pulse voltammogram of $[Ru^{II}(hedta)(dpaH)]^-$. $[complex]_0 = 2.61 \times 10^{-3}$ M, $\mu = 0.10$ (NaCl), $T = 22$°C, under N_2 purge; dashed line, pH 9.50; dash-dot-dash line, pH 7.00; solid line, pH 5.50.

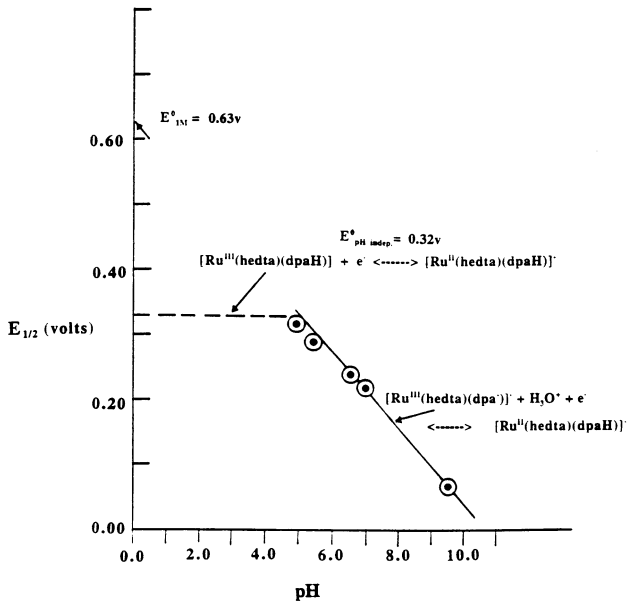


Fig. 3. pH-dependence of the $Ru^{III/II}$ reduction potentials for $[Ru^{II}(hedta)(dpaH)^-$ and $[Ru^{II}(hedta)(dpa^-)]^{2-}$ species. $[complex]_0 = 2.61 \times 10^{-3}$ M, $T = 22°C$, under an N_2 purge; $E_{1/2}$ was independent of pH below 5.0.

A plot of the measured $E_{1/2}$ versus pH is given in Fig. 3. The theoretical half-cell value under 1.00 M H_3O^+ standard state conditions would be $+0.63$ V. However, dissociation of carboxylates and/or a switch to the half-reaction involving a neutral dpaH ligand coordinated to both Ru^{III} and the Ru^{II} form preclude operation of this couple in the range of 1.00 M H_3O^+. The dependence of the $E_{1/2}$ to a 59.5 mV/pH change (Fig. 3) implies that the Ru^{III} complex is deprotonated and that the equilibrium 4 has a pK_a of approximately 5.0.

$$[Ru^{III}(hedta)(dpaH)] \rightleftharpoons [Ru^{III}(hedta(dpa)]^- + H_3O^+ \quad (4)$$

Data from the $[Ru(dpaH)_3]^{2+}$ and $[Co(dpaH)_3]^{3+}$ complexes establish pK_a values of approximately 11.0 and 5.0 for dpaH ligands coordinated to Ru(II) and Co(III), respectively [6b,c]. Since the influence of Ru(III) is usually about 1 pK_a unit more acidic than the analogous Co(III) or Rh(III) metal clusters on the pK_a of a coordinated ligand such a H_2O or imidazole when the remaining ligand are neutral amines [36], and since an $edta^{4-}$ anionic ligand environment raises the pK_a of a second ligand by about 1.5 log units [34b], one anticipates the pK_a of $[Ru^{III}(hedta)(dpaH)]$ to be approximately 5.5 in good agreement with the electrochemically-based estimate.

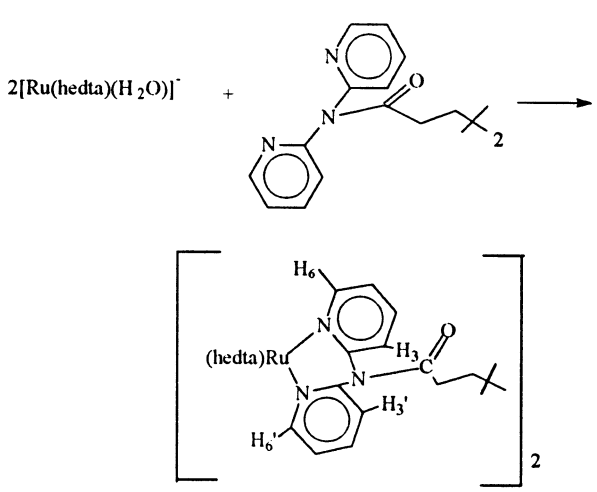
The pK_a of the Ru(III) complexes cannot be obtained directly because of the aquation of the $[Ru^{III}(hedta)(dpa)]^-$ complex in basic solution. This is observed in the DPP scans for solutions of pH 7 and above. When $[Ru^{III}(hedta)(dpa)]^-$ is present as shown by the wave near 0.07 (pH 9.5) or 0.22 V (pH 7.0), H_2O or OH^- displaces the dpa^- ligand within the scanning time from 0.07 up to 1.00 V. This produces $[Ru^{III}(hedta)(OH)_2]^{2-}$ and dpaH at the electrode surface. The $[Ru^{III}(hedta)(OH)_2]^{2-}$ undergoes further oxidation by a $2e^-$ process at 0.91 V [21,19]. The $[Ru^{V}O(hedta)]^{2-}$ species generated at the electrode surface at 0.91 V reacts with another $[Ru^{III}(hedta)(OH)_2]^{2-}$ species to form the well-known bridged Ru(IV) species [21,29]. Since the amplitude of the 0.91 V wave increases from pH $\cong$ 7 to 9.5, OH^- must be involved in the displacement of dpa^- as summarized in Scheme 1.

If we assume parallel solvent H_2O and OH^- pathways for the displacement of dpa^-, the kinetic split illustrated from Scheme 1 places limits on $k_{H_2O} \leq 0.014$ s^{-1} and $k_{OH^-} \cong 1.33 \times 10^4$ M^{-1} s^{-1}. The solvent pathway carries less than 3% of the events at pH 9.5. Under acidic conditions the H_2O-dependent pathway would survive if the dpa^- ligand remained deprotonated. However, the scans at pH $\leq$ 5.50 showed almost no wave at 0.91 V. Nor was there a large wave at approximately 1.15 V versus NHE indicative of $[Ru^{III}(hedta)(H_2O)]$ undergoing oxidation. Hence, the Ru^{III} complex is stable to aquation as the $[Ru^{III}(hedta)(dpaH)]$ complex, and it exhibits a pH-independent redox couple with $E_{1/2} \cong 0.32$ V for solutions of pH $\leq$ 4.0 (Eq. (5)):

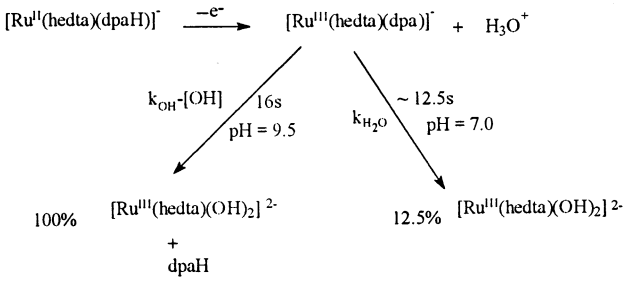
$$Ru^{III}(hedta)(dapH)] + e^- \overset{E_{1/2} \cong 0.32\ V}{\rightleftharpoons} [Ru^{II}(hedta)(dpaH)]^- \quad (5)$$

3.3. $\{[Ru(hedta)]_2(tpada)\}^{2-}$ complex

The binuclear tpada complex was prepared using a 2:1 ratio of $[Ru(hedta)(H_2O)]^-$ to the ligand tpada as in Eq. (6). The purpose of these experiments is to show that the tpada ligand can be a useful carrier of two metal sites at the termini of the central tether of tpada.



(6)



Scheme 1.

The ^{1}H NMR features of the resultant binuclear complex are shown in Fig. 4. At first there appears to be two sets of differentiated H-6 and H-6′ protons. However, the splittings would require J_{5-6} or $J_{5'-6'}$ couplings of 32 and 27 Hz, too large for normal pyridyl rings. Values nearer 5.0 Hz are observed for $[Pt^{II}(dpaH)(glycine)]^+$ or $[Pt^{II}(dpaH)(2\text{-pyridine-carboxylate}]^+$ as models of coordinated dpaH chromophores [7,8]. A structural model of the headgroups of tpada coordinated to $[Ru^{II}(hedta)]$ proved to be informative. Additional differentiated H-3 and H-3′ resonances appear at 7.84 and 7.72 ppm indicative of the fact that the amide carbonyl functional group is not rapidly rotating. This places the carbonyl in close contact with the H-3 or H-3′ protons. Planarity of the amide carbonyl functionality forces a differentiation of the H-3 and H-3′ protons in order to preserve delocalization between the dpa–R pyridyl rings. Thus, 50% of the H-3 population is near the amide carbonyl. Further away the H-6 and H-6′ protons are strongly differentiated by the placement of the dpa–R headgroup in the equatorial plane. Since 50% of each of these rings is aligned with the carbonyl, each H-6 or H-6′ set is further electronically perturbed, such that two types of H-6 and two types of H-6′ are created upon coordination. We assign the two rotamers A and B as in Table 3 for the coordinated tpada complex. The tether chain protons exhibit small downfield shifts due to inductive effects caused by metallation of the dpa–R headgroups of approximately -0.05 ppm for the central methylenes, and -0.35 ppm for the methylenes nearer the carbonyl and metal center.

The electrochemical data for $\{[Ru(hedta)]_2(tpada)\}^{2-}$ presented in Fig. 5 are consistent with aspects already discussed for the $[Ru(hedta)(dpaH)]^-$ complex. The binuclear tethered complex exhibits only one DPP wave for the $Ru^{II/III}$ couple in either acidic or neutral pH media at 0.47 V versus NHE. In basic solution (pH $\cong$ 10.0) the wave appears at 0.43 V, and again tpada dissociation from the $Ru^{III}(hedta)$ unit is observed by a new wave at 0.91 V versus NHE that is absent in neutral or acidic solution. These results are anticipated based on the outcome of the $[Ru(hedta)(dpaH)]^-$ study. There should be no influence due to a titratable N–H proton with the binuclear tpada complex. The small change to 0.43 V (basic solution) versus NHE compared to 0.47 V (neutral solution) may involve some replacement of an axial

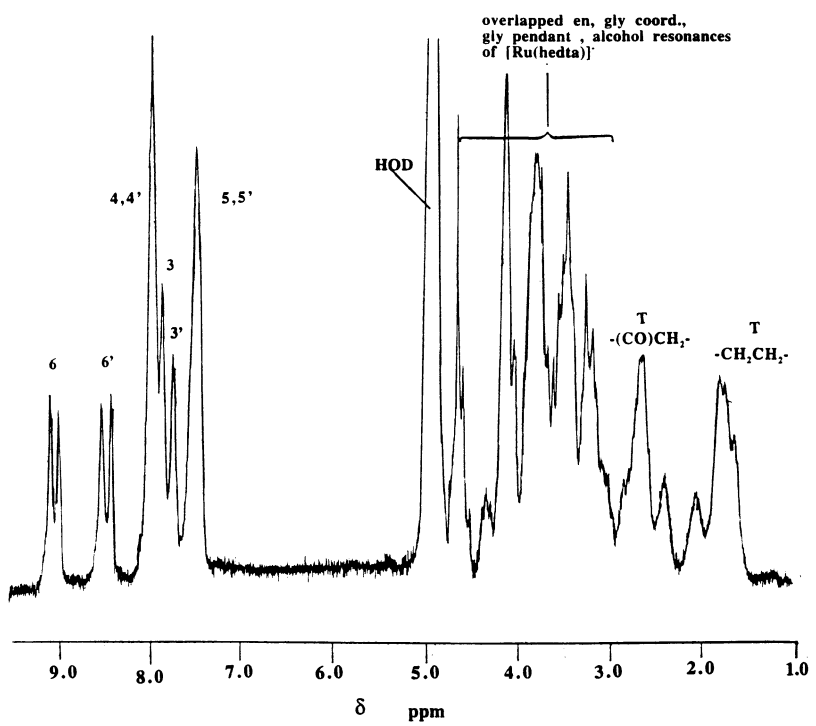


Fig. 4. 300 MHz ^{1}H NMR spectrum of $\{[Ru^{II}(hedta)]_2(tpada)]\}^{2-}$ in D_2O. $[complex]_0 = 1.31 \times 10^{-2}$ M, $T = 25$°C, p$D = 6.0$.

Table 3
^{1}H NMR shifts for {[Ru(hedta)]$_2$(tpada)} (shifts in ppm) for tether protons

	H-6	H-6′	H-5	H-4	H-3	H-3′
Rotamer A	9.08	8.51	7.44	7.94	7.84	7.71
Rotamer B	8.97	8.40	7.44	7.94	7.84	
	CH_2–C=O		CH_2CH_2			
Rotamers A, B	2.61		1.72			

carboxylate by OH^- or a medium effect. The shift relative to neutral solution (0.04 V) is much less than for the dpaH complex (0.17 V). Once oxidized to Ru^{III}, both the dpa^- ligand or the dpa–R units of tpada dissociate in basic solutions, as detected by the appearance of the $Ru^{III/IV}$ wave at 0.91 V. The product is 38.3% converted to $[Ru^{III}(hedta)(OH)_2]^{2-}$ in 7.5 s. Therefore, the loss of tpada is about six times slower than dpa^- at pH 9.5. The presence of this feature in the DPP scan for the tpada complex also rules out that the 0.91 V oxidation wave has anything to do with association of the depronated amide's lone-pair for Ru^{III} in the $[Ru^{III}(hedta)(dpa)]^-$ complex, but rather is a feature of ligand dissociation from the Ru^{III} species in each case.

It is useful to point out that the $Ru^{II/III}$ wave for $\{[Ru(hedta)]_2(tpada)\}^{2-}$ is more positive of the $[Ru(hedta)(dpaH)]^-$ complex by 0.15 V using the pH-independent couple for dpaH in the comparison. This indicates that the tpada headgroup is a better π-acceptor/poorer π-donor than dpaH alone. This is anticipated on the basis of the withdrawing effect of the carbonyl group of tpada. Since the $E_{1/2}$ value for $[Ru(hedta)(bpy)]^-$ is 0.54 V, the effect of the carbonyl is not large enough to make tpada as good of a π-acceptor as bpy, but it is still better than dpaH in its π-acceptor capacity as detected by the extent that the ligand stabilizes Ru^{II} and makes the $E_{1/2}$ value of the $Ru^{II/III}$ couple more positive:

$Ru^{II}(hedta)L$	H_2O	≪	dpaH	< tpada	< bpy
$E_{1/2}$ (V)	0.00		0.32	0.47	0.56

As anticipated for such a long insulating tether chain, there is virtually no coupling except through space between the $[Ru^{II}(hedta)]^-$ headgroups. Had there been such a coupling along the chain, there should be a splitting of the $Ru^{II/III}$ wave such that the corrected comproportionation constant may be calculated by $1/4(e^{-\Delta E/0.05916})$. No evidence for a wave separation is detected in Fig. 4, indicative of insulated metal binding sites.

4. Conclusions

2,2′-Dipyridylamine (dpaH) has been widely studied in its Cu^{II} complexes, but far less so with softer metal centers. Herein, coordination of dpaH to $[Ru^{II}(hedta)]^-$ has been utilized to establish that dpaH is much less π-accepting than bpy. DpaH stabilizes Ru^{II} versus Ru^{III} by 0.22 V less than bpy. Also, dpaH and dpa^- dissociate from $[Ru^{III}(hedta)]$, whereas bpy does not readily do so. Beginning studies of the dpaH-related ligand, tpada, in which two dpa headgroups are linked by a six-atom tether linkage are reported. The tpada ligand is shown to form binuclear metal species of the type $\{[(LM)]_2(tpada)\}$. In the present study, the $hedta^{3-}$ ligand assists the solubilization of Ru^{II} attached to tpada. The chemical and electrochemical behavior of the Ru^{II}-tpada derivatized site is similar to $[Ru^{II}(hedta)(dpaH)]^-$ with tpada acting as an even better π-acceptor ligand than dpaH, approaching the π-acceptor power of bpy. An energy-minimized computer-generated structure for $\{[Ru^{II}(hedta)]_2(tpada)\}$ is shown in Fig. 6.

The perspective of the Ru^{II} site at the left is along an axis that allows the viewing of the axial carboxylato

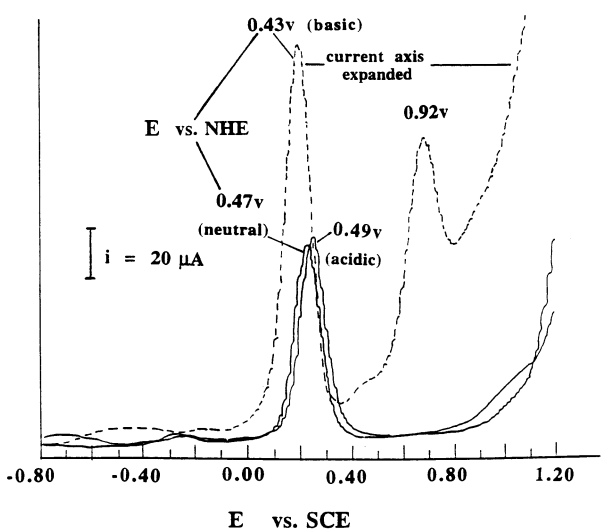


Fig. 5. Differential pulse voltammogram of the binuclear complex $\{[Ru^{II}(hedta)]_2(tpada)]^{2-}$. [complex] = 2.61×10^{-3} M, $T = 22$°C, $\mu = 0.10$ (NaCl), under N_2 purge. Dashed curve, pH 9.50; solid lines, pH 7.0 and 3.0 (virtually the same).

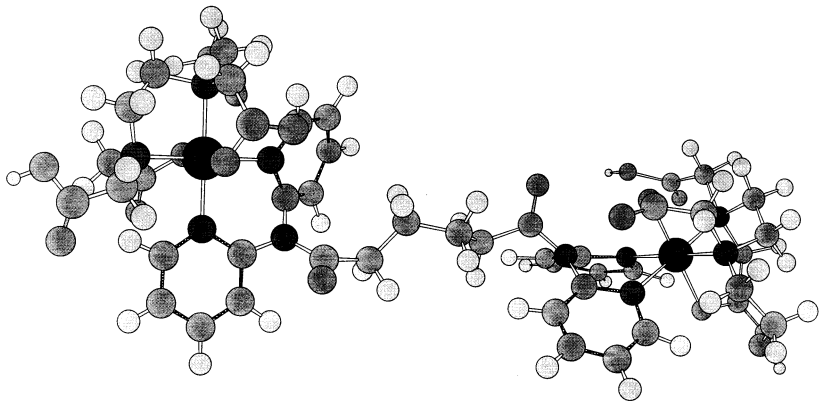


Fig. 6. Computer-generated, energy-minimized structure of $\{[Ru^{II}(hedta)]_2(tpada)\}^{2-}$ by MM2 calculation.

donors and the plane containing the 'en-backbone' donors of the $hedta^{3-}$ portion. Toward the forefront is the attachment of the 'dpa-like' headgroups of the tpada ligand which has rings that are greatly non-coplanar. At the opposite end of the tether, the second Ru^{II} center repeats the motif. But the second 'dpa-like' headgroup is rotated to minimize contacts along the tether and for long-range avoidance of the other Ru^{II} sites's 'dpa' connection. All calculated bond distances were found to be normal with Ru^{II}–N distances near 2.0–2.1 Å. The $hedta^{3-}$ portion of each metal site is relatively unhindered with respect to the 'dpa headgroup' coordination.

The tpada ligand appears to be useful in forming tethered binuclear metal centers that could be used to span the major groove of DNA. On-going studies are aimed at other $Ru^{II}L$ headgroups that have labile coordination sites for making DNA attachments, as well as tpada chelation. The present $\{[Ru(hedta)]_2(tpada)\}^{2-}$ complex illustrates how a central $Ru_2^{II}(tpada)$ core might be transported into cells by iminocarboxylate ligands or small peptides to increase the solubility. These carrier ligands would need to be replaced by purine bases of the DNA strand, or stronger donors of a protein in order for the system to make useful DNA–DNA or DNA–DNA–protein cross-links. Once the DNA–DNA or DNA–DNA–protein cross-links are formed, further repair processes in the major groove are blocked. Such linkages have shown to be cytotoxic when the trapped protein is a repair enzyme for removal of metallo-DNA-lesions [15].

Parallel studies with Pd^{II} have recently generated $\{[PdCl_2]_2(tpada)\}$ and $[Pd(tpada)Cl]^+$, 2:1 and 1:1 complexes [37]. NMR evidence has shown that the 2:1 species exists in the extended chain arrangement as for $\{[Ru^{II}(hedta)]_2(tpada)\}^{2-}$. The 1:1 complex is too strained to allow for all four pyridyl groups to be bound as in structure **3**. Rather three pyridyl donors are coordinated to Pd^{II} with one pyridyl arm remaining pendant [37]. The tpada ligand satisfies many desirable properties as a chelate for softer metal centers for use as bimetallic delivery agent. The ligand, itself, and its complexes have solubility limitations which are being addressed by adding hydroxyl attachments along the tether chain.

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