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Insight into the Photoinduced Ligand Exchange Reaction Pathway of *cis*-$[Rh_2(\mu\text{-}O_2CCH_3)_2(CH_3CN)_6]^{2+}$ with a DNA Model Chelate

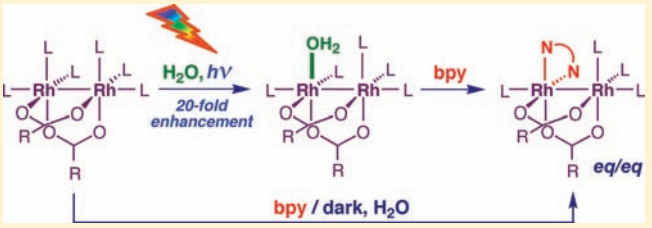
Helen T. Chifotides,[‡] Daniel A. Lutterman,[†] Kim R. Dunbar,*[,‡] and Claudia Turro*[,†]

[†]Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, United States

[‡]Department of Chemistry, Texas A&M University, College Station, Texas 77843, United States

Supporting Information

ABSTRACT: We previously showed that $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ binds to dsDNA only upon irradiation with visible light and that photolysis results in a 34-fold enhancement of its cytotoxicity toward Hs-27 human skin fibroblasts, making it potentially useful for photodynamic therapy (PDT). With the goal of gaining further insight on the photoinduced binding of DNA to the complex, we investigated by NMR spectroscopy the mechanism by which 2,2′-bipyridine (bpy), a model for biologically relevant bidentate nitrogen donor ligands, binds to $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ upon irradiation in D_2O. The photochemical results are compared to the reactivity in the dark in D_2O and CD_3CN. The photolysis of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ with equimolar bpy solutions in D_2O with visible light affords $[Rh_2(O_2CCH_3)_2(eq/eq\text{-bpy})(CH_3CN)_2(D_2O_{ax})_2]^{2+}$ (***eq/eq***) with the reaction reaching completion in ∼8 h. Only vestiges of ***eq/eq*** are observed at the same time in the dark, however, and the reaction is ∼20 times slower. Conversely, the dark reaction of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ with an equimolar amount of bpy in CD_3CN affords $[Rh_2(O_2CCH_3)_2(\eta^1\text{-bpy}_{ax})(CH_3CN)_5]^{2+}$ (***η¹-bpy$_{ax}$***), which remains present even after 5 days of reaction. The photolysis results in D_2O are consistent with the exchange of one equiv CH_3CN*eq* for solvent, and the resulting species quickly reacting with bpy to generate ***eq/eq***; the initial *eq* ligand dissociation is assisted by absorption of a photon, thus greatly enhancing the reaction rate. The photolytic reaction of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$:bpy in a 1:2 ratio in D_2O affords the ***eq/eq*** and $(eq/eq)_2$ adducts. The observed differences in the reactivity in D_2O vs CD_3CN are explained by the relative ease of substitution of *eq* D_2O vs CD_3CN by the incoming bpy molecule. These results clearly highlight the importance of dissociation of an *eq* CH_3CN molecule from the dirhodium core to attain high reactivity and underscore the importance of light for the reactivity of these compounds, which is essential for PDT agents.



INTRODUCTION

In photodynamic therapy (PDT), a nontoxic photosensitizing drug localized in tumor tissue is activated through irradiation with visible or near-IR light, thus becoming toxic.[1,2] PDT provides a means to circumvent drawbacks of conventional cancer therapies because of its low systemic toxicity, localized action to irradiated areas, and low level of invasiveness.[3] PDT is now recognized as an alternative, and, in some cases, a superior approach to conventional treatments in dermatology and for endoscopically accessible tumors, including those of the lung and bladder, and for gastrointestinal, esophageal, prostate, and gynecological lesions.[3−9] PDT emerged as a treatment for both early and late stage head and neck cancers,[3,10] and has achieved great success in inoperable early central lung cancer lesions.[11] To date, the types of compounds that have been pursued for PDT are organic molecules whose mode of action relies on the sensitization of $^1O_2$ in order to effect cell death. Significant advances in PDT require the development of drugs that function via a different mechanism,[2,12] including the exploration of new PDT agents based on transition metal complexes.[12,13]

In previous studies, we showed that excitation of $Rh_2(O_2CCH_3)_4$ with visible light, in the presence of electron acceptors, results in DNA photocleavage,[14] and direct cleavage of dsDNA was observed for dirhodium complexes with lowest-energy metal-to-ligand charge transfer (MLCT) excited states.[15] Transition metal complexes exhibit enhanced spin−orbit coupling afforded by the metal, significantly increasing the rate constant of intersystem crossing from the singlet to the triplet manifold, thus populating longer-lived triplet states in high yield.[16] For complexes possessing ligands with extended π-systems, the ligand-centered $^3\pi\pi^*$ state may lie below the corresponding ^{3}MLCT state, which results in long excited state lifetimes (20−30 μs) and nearly 100% quantum yield of $^1O_2$.[17−19] Because the ligands with extended π-systems intercalate between the DNA bases, irradiation of these complexes with visible light leads to efficient photocleavage of the duplex mediated by $^1O_2$.[17−19] In addition to systems with high production of singlet oxygen, Ru(II) complexes that are able to bind to DNA upon irradiation are promising since their action is independent of the presence of O_2 in tissue.[20]

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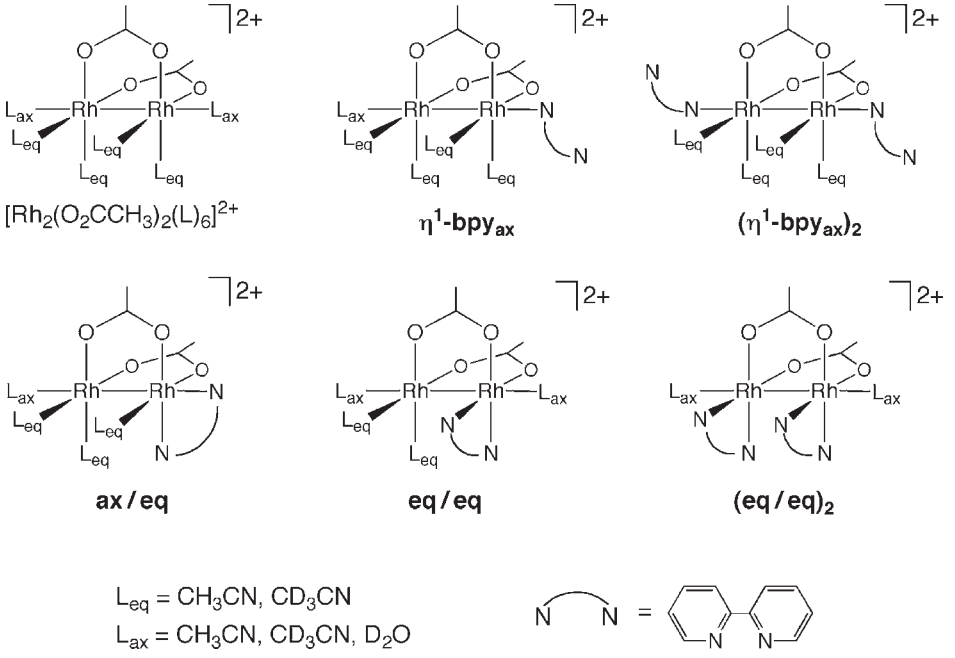
Chart 1



More recently, studies from our laboratories provide evidence that $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ (Chart 1), with four equatorial (*eq*) and two axial (*ax*) CH_3CN ligands, covalently binds to dsDNA upon photolysis and that there is a 34-fold increase in cytotoxicity when human skin fibroblast Hs-27 cells are irradiated with 400−700 nm light as compared to the dark control.[21] Such an increase in toxicity upon irradiation, as well as the fact that the photoreactivity and photoinduced DNA binding of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ are oxygen-independent, are highly desirable for the exploration of new potential PDT agents whose action differs significantly from those currently in use. Despite establishing that photoinduced ligand exchange is operative in the dsDNA binding to $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ upon absorption of a photon, the mechanism of ligand substitution has not been explored in detail. In particular, photolabile ligands in the *eq* positions that do not exchange in the dark were shown to be important for the observed increase in toxicity upon irradiation.[21] On the contrary, the presence of *eq* ligands that undergo facile ligand exchange in the dark are known to render the systems highly toxic in the absence of light,[22] and therefore not useful as potential PDT agents. The previous findings underscore the importance of the ligand lability at *eq* sites for the reactivity of dirhodium compounds *vis-à-vis* their reactions with DNA.

It is well established that purine nucleobases,[22−28] oligonucleotides,[29−37] and double-stranded DNA[38] bind to related dirhodium[39] compounds at *ax* and *eq* sites, primarily upon thermal activation.[40] Understanding the reactivity of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ with nucleic acids, which can bind to the bimetallic core in a bidentate fashion at *eq* sites,[29−33] is crucial for future PDT studies and the design of complexes with improved properties. Herein, we used bpy (2,2′-bipyridine) as a model bidentate ligand of the DNA nucleobases on the dirhodium core to elucidate the mechanism of the reaction upon photolysis. It was previously reported that the chelating ***eq*/*eq*** product (Chart 1) is formed after stirring $Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ with bpy in CH_3CN for 24 h at room temperature ($[Rh_2]$:[bpy] ratio 1:1).[41] Similar results were reported for the substitution of *eq* CH_3CN by 1,10-phenanthroline (phen) upon refluxing the complex in CD_3CN, resulting in the formation of the ***eq*/*eq*** product within 48 h through the ***ax*/*eq*** intermediate.[42] The previous study led to the conclusion that exchange of *eq* acetonitrile ligands in $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ is very difficult (slow), requiring high temperatures for ligand dissociation to take place in CD_3CN (at 100 °C, $t_{1/2}$ = 4 h for CH_3CN to CD_3CN exchange).[42] Findings from our laboratories, however, show that ambient light plays a significant role in some of the aforementioned reactions. Comparison of the products from the reaction between $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ and bpy performed in the dark (in CD_3CN and D_2O) and under irradiation (in D_2O) provides insight into the photoinduced mechanism and underscores the importance of light for the activity of these compounds as successful PDT agents.

EXPERIMENTAL SECTION

Materials. The compounds *cis*-$[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$[43] and $[Rh_2(O_2CCH_3)_2(bpy)_2(CH_3CN)_2](BF_4)_2$[44] were prepared from $Rh_2(O_2CCH_3)_4$ by published procedures and characterized by ^1H NMR spectroscopy. The reagent 2,2′-bipyridine (bpy) was purchased from Fluka. Ampules of deuterated acetonitrile (CD_3CN-d_3) and D_2O-d_2 were purchased from Cambridge Isotope Laboratories (CIL).

Instrumentation and Methods. The ^1H NMR spectra were recorded on a 500 MHz Varian Inova spectrometer with a 5-mm switchable probe head or on a Bruker NMR spectrometer (DPX-400). The 2D (two-dimensional) NMR [$^1H-^1H$] COSY (correlation spectrocopy), [$^{13}C-^1H$] HMBC (heteronuclear multiple bond coherence) and [$^{13}C-^1H$] HMQC (heteronuclear multiple quantum coherence) NMR spectra were collected on a Bruker NMR spectrometer (DPX-400). The ^1H NMR spectra in CD_3CN-d_3 were referenced to the residual proton impurity of CD_3CN-d_3, and those in D_2O-d_2 were referenced to an external reference sample of DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate).

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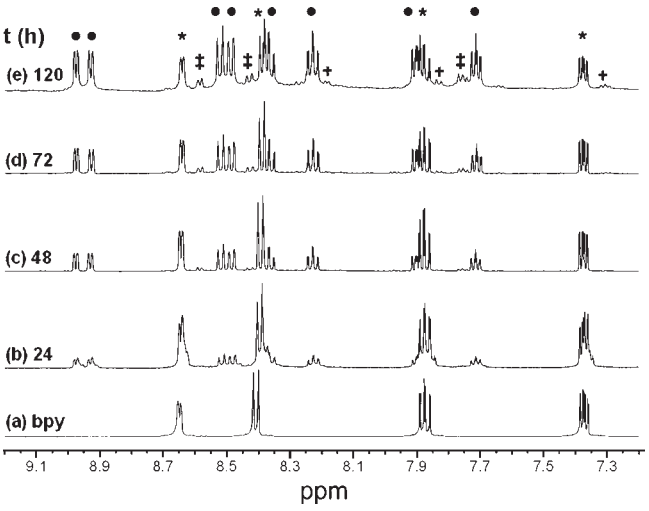

Figure 1. ^{1}H NMR spectra for the reaction of 35 mM bpy (a) with 35 mM $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ in CD_3CN in the dark after (b) 24 (c) 48 (d) 72 and (e) 120 h. The resonances marked with ∗ correspond to unreacted bpy, whereas those marked with ● or ‡ or † correspond to the $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ or ***eq/eq*** or $(\boldsymbol{eq/eq})_2$ adducts, respectively.

A 150 W Xe arc lamp in a PTI housing (Milliarc Compact Lamp Housing) powered by an LPS-220 power supply (PTI) with an LPS-221 igniter (PTI), was used in the steady-state photolysis experiments; the wavelength of the light reaching the sample was controlled with long-pass filters (CVI).[45] The power dependence experiments were carried out using neutral density filters with absorption of 0.1, 0.5, 0.6, and 1.0 throughout the visible region. Electrospray mass spectra were acquired on an MDX Sciex API Qstar Pulsar mass spectrometer (Toronto, Canada).

Reactions. *a. Dark in CD_3CN (35 mM).* A clear, colorless solution of bpy (5.4 mg, 0.034 μmol) in CD_3CN-d_3 (0.5 mL) was added to a purple solution of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ (25 mg, 0.034 μmol) in CD_3CN-d_3 (0.5 mL) and the mixture was stirred at room temperature in the dark. The reaction vial was wrapped with foil and kept in a dark room during the course of the reaction to avoid exposure to room light. The progress of the reaction was monitored for 5 days by recording ^{1}H NMR spectra at various time intervals.

b. Dark in D_2O (27 mM). Bpy (4.3 mg, 0.027 μmol) in D_2O (0.5 mL) was added to a violet solution of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ (20 mg, 0.027 μmol) in D_2O (0.5 mL) and the mixture was stirred at room temperature in the dark as described above. The reaction solution progressively changed color to an intense red with time. The progress of the reaction was monitored at various time intervals by ^{1}H NMR spectroscopy; the reaction reached completion in 2 days.

c. Dark in D_2O (7 mM). The reaction described in *b* was repeated at a lower concentration as follows: bpy (1.1 mg, 7.0 μmol) in D_2O (0.5 mL) was added to a violet solution of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ (5.2 mg, 7.0 μmol) in D_2O (0.5 mL). The mixture was stirred and kept at room temperature in the dark as described above. The progress of the reaction was monitored for several days by ^{1}H NMR spectroscopy.

Photolysis. *a. 6.7 mM.* A small amount of bpy (2.1 mg, 13.4 μmol) in D_2O (1 mL) was sonicated until completely dissolved and subsequently added to an equimolar solution of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ (10 mg, 13.4 μmol) in D_2O (1 mL). The solution was thoroughly mixed, placed in an NMR tube, and photolysis experiments were conducted; the reaction progress was monitored by changes in the ^{1}H NMR spectra as a function of irradiation time.

b. In a similar photolysis experiment, but with a $[Rh_2]$:[bpy] 1:2 stoichiometric ratio, a D_2O solution (1 mL) of bpy (6.7 mM) and $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ (3.35 mM), was photolyzed and the reaction was monitored by ^{1}H NMR spectroscopy.

RESULTS AND DISCUSSION

Reactivity in the Dark. *a. $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ and bpy (1:1 ratio) in CD_3CN.* The reaction of 35 mM $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ and an equimolar amount of bpy was followed by ^{1}H NMR in CD_3CN at 295 K keeping it protected from room light. After 24 h in the dark, the aromatic region of the ^{1}H NMR spectrum of the reaction mixture exhibits eight new resonances at 8.98, 8.93, 8.52, 8.49, 8.36, 8.23, 7.90, and 7.71 ppm, in addition to those from unreacted, free bpy at 8.65, 8.41, 7.87, and 7.37 ppm (Figure 1a). The eight resonances, which are attributed to the *ax* $[Rh_2(O_2CCH_3)_2(\eta^1\text{-bpy}_{ax})(CH_3CN)_5]^{2+}$ or $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ adduct (Chart 1), remain present at the same chemical shifts even after several days of reaction and increase in intensity relatively slowly over a period of 5 days. Figure 1 depicts a comparison of the aromatic regions between free bpy (Figure 1a) and those of the reaction solution between 24 to 120 h (Figure 1b−e). It is evident from the spectrum in Figure 1e that a significant amount of free bpy still remains after 5 days of reaction in the dark.

Accordingly, in the aliphatic region of the ^{1}H NMR spectrum, apart from the resonances of unreacted $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ observed at 2.54 (CH_3CN_{eq}), 2.04 ($CH_3CO_2^-$), and 1.95 (CH_3CN_{ax}) ppm in CD_3CN,[43] new resonances in a 1:1 ratio due to $[Rh_2(O_2CCH_3)_2(\eta^1\text{-bpy}_{ax})(CH_3CN)_5]^{2+}$, are observed at 1.70, 2.31 ($CH_3CO_2^-$) ppm, 2.17, 2.24, 2.34, 2.58 (CH_3CN_{eq}), and 1.95 ppm (CH_3CN_{free}) after 24 h. The presence of eight nonequivalent bpy protons, as well as the nonequivalent CH_3CN_{eq} protons in the aliphatic region of the ^{1}H NMR spectrum, are also consistent with the formation of the $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ adduct $[Rh_2(O_2CCH_3)_2(\eta^1\text{-bpy}_{ax})(CH_3CN)_5]^{2+}$, which is also supported by the presence of an ES-MS peak for the 24 h reaction solution at m/z = 648.9 (Figure S1) corresponding to $[Rh_2(O_2CCH_3)_2(\eta^1\text{-bpy}_{ax})(CH_3CN)_3(CD_3CN)-1]^+$ (loss of *ax* acetonitrile is easy in the MS experiment). Therefore, only this *ax* product with bpy is observed in CD_3CN at room temperature in the dark apart from minute amounts of the ***eq/eq*** species $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_4]^{2+}$ (Chart 1), which is discernible in the ^{1}H NMR spectrum after 5 days of reaction (Figure 1e; ∼ 5%), with four bpy resonances in the aromatic region at 8.59, 8.43, 8.23, 7.76 ppm and aliphatic resonances at 2.24 (CH_3CN_{eq}), 1.89 ($CH_3CO_2^-$), and 1.95 (CH_3CN_{ax}) ppm in CD_3CN.[41] At 5 days, there is no evidence of the expected ***ax/eq*** intermediate in the ^{1}H NMR spectrum of the reaction solution despite the small amount of the ***eq/eq*** product being present. After 1 month, the ^{1}H NMR spectrum of the reaction indicates complete formation of the ***eq/eq*** product in the dark with a small amount of $(\boldsymbol{eq/eq})_2$ product $[Rh_2(O_2CCH_3)_2(bpy)_2(CH_3CN)_2]^{2+}$ indicated by ^{1}H NMR aromatic resonances at 7.31, 7.74, 7.84, and 8.18 ppm (Figure S2; Chart 1).[44] The NMR data are supported by the mass spectrometry results, since the reaction solution after 1 month gives rise to an ES-MS peak at m/z = 578 corresponding to $[Rh_2(O_2CCH_3)_2(bpy_{eq/eq})(CH_3CN)_2(H_2O_{ax}) - 1]^+$ consistent with the major ***eq/eq*** product (Chart 1). It is notable that, when the above reaction (with the same reactant concentrations) is performed in a vessel open to room light, the ***eq/eq*** product $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_4]^{2+}$ is formed in 24 h as evidenced by the ^{1}H NMR

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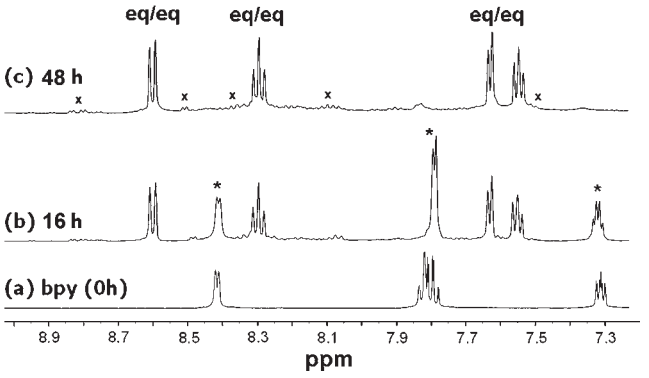

Figure 2. ^{1}H NMR spectra for the reaction of 27 mM bpy (a) with 27 mM $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ in D_2O in the dark after (b) 16 and (c) 48 h. The resonances marked with ∗ correspond to unreacted bpy, and those with **x** correspond to vestiges of ***ax/eq*** adduct.

spectrum acquired in CD_3CN (with four resonances in the aromatic region at 8.59, 8.43, 8.23, and 7.76 ppm);[41] this compound is identical to that previously reported by Christou et al., wherein protection of the reaction from room light was not mentioned.[41] It should also be noted that photolysis of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ in CD_3CN alone also results in the exchange of CH_3CN_{eq} ligands for solvent, as evidenced by the growth of the ^{1}H NMR resonance area corresponding to free CH_3CN (1.95 ppm).[21] This exchange does not occur when the solution is protected from light.

b. $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ and bpy (1:1 ratio) in D_2O. Owing to the potential use of the complexes for therapeutic applications, it is important to understand the reactivity of the system in water. It is known that the *ax* CH_3CN ligands of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ readily exchange with solvent molecules,[21] in this case D_2O, to form the solvated adduct $[Rh_2(O_2CCH_3)_2(CH_3CN)_4(D_2O_{ax})_2]^{2+}$. The reactivity of a 27 mM solution of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ mixed with an equimolar solution of bpy in D_2O at 295 K, while protected from room light, was followed by ^{1}H NMR spectroscopy. Within 16 h of reaction, the aromatic region of the ^{1}H NMR spectrum exhibits four new resonances at 8.58, 8.27, 7.61, and 7.53 ppm (Figure 2b), in addition to those of unreacted bpy at 7.29, 7.77, 7.79 (overlapping), and 8.40 ppm (Figure 2a).[46] These four new resonances are attributed to the ***eq/eq*** product $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O_{ax})_2]^{2+}$ (Chart 1), which also displays aliphatic resonances at 2.40 (CH_3CN_{eq}), 1.92 ($CH_3CO_2^-$), and 1.85 (CH_3CN_{free}) ppm. The ^{1}H NMR data indicate that the reaction to the ***eq/eq*** product is complete in 2 days (Figure 2c).

At lower reactant concentrations (7 mM), however, the reaction in D_2O is considerably slower in the dark. When the sample is protected from room light, there is no evidence of the dirhodium $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ species at 295 K but vestiges of the ***eq/eq*** product (with four new resonances at 8.58, 8.27, 7.61, 7.53 ppm) are apparent between 15 and 21 h; these new resonances slowly increase with time until the reaction is complete in 156 h (6.5 days; Figure 3). This finding is also supported by the ES-MS analysis of the reaction solution at m/z = 563.9 after 5.5 days, corresponding to $[Rh_2(O_2CCH_3)_2(eq/eq\text{-bpy})(CH_3CN)(CD_3CN)-1]^+$. It should be noted that, even after 3 days (~70 h), a significant amount of free bpy (resonances marked with * at 7.29, 7.77, 7.79, and 8.40 ppm; Figure 3) and unreacted dirhodium complex are still present in solution.

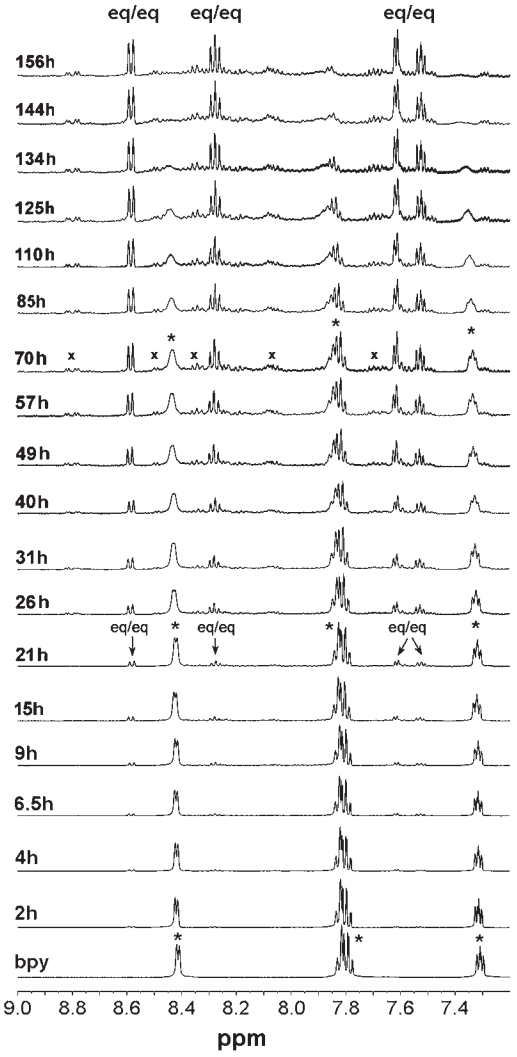

Figure 3. ^{1}H NMR spectra for the reaction between 7 mM bpy with 7 mM $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ in D_2O in the dark between 2 and 156 h. The * indicate the positions for the resonances of unreacted bpy, and those with **x** indicate vestiges of ***ax/eq*** adduct.

c. Mechanism in the Dark. It is well-known that the *ax* ligands of dirhodium compounds readily exchange with solvent molecules as a result of the strong *trans*-influence and *trans*-effect of the Rh−Rh bond,[47] and that various ligands typically enter the coordination sphere of dirhodium compounds via *ax* site ligand substitution.[39] In this context, based on the ^{1}H NMR data from the reaction of bpy with $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ in CD_3CN in the dark, the monoaxial $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ adduct is formed by substitution of the *ax* ligand CD_3CN (step A in Scheme 1). The formation of the *ax* $[Rh_2(O_2CCH_3)_2(\eta^1\text{-bpy}_{ax})(CH_3CN)_5]^{2+}$ adduct in the dark reaction in CD_3CN is supported by the presence of eight new resonances in the aromatic region which increase in intensity and remain at the same positions for many days (Figure 1). The exchange of *eq* CH_3CN ligands from the dirhodium core in $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ with the solvent (CD_3CN) is slow and consistent with a dissociative mechanism,[47] requiring 100 °C with $t_{1/2}$ = 4 h for the exchange.[42] As indicated by the ^{1}H NMR spectra reported in this study at 295 K in the presence of bpy, *eq* CH_3CN ligands are exchanged very slowly from the dirhodium core in the dark, resulting in the

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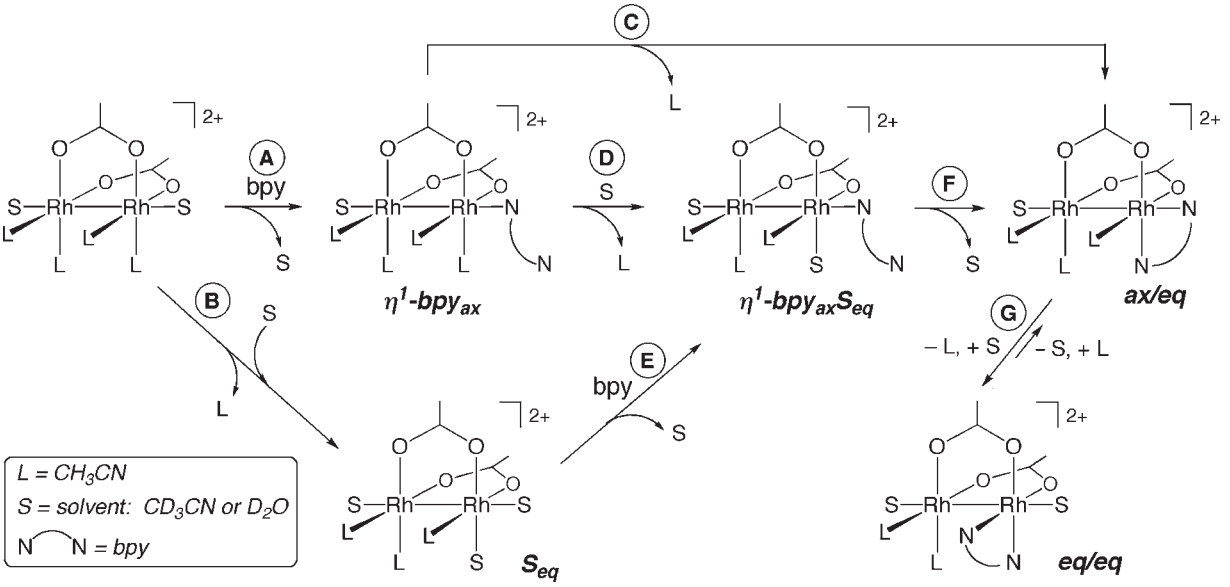
Scheme 1. Proposed Intermediates for the Ligand Exchange in the Dark to Generate the *eq/eq* Product from $[Rh_2(O_2CCH_3)_2(CH_3CN)_4 \cdot 2S]^{2+}$ (S = CD_3CN, D_2O)



presence of 1 equiv of free CH_3CN in the ^1H NMR spectrum after 24 h in CD_3CN. The formation of $\boldsymbol{\eta^1}$**-bpy**$_{ax}$**CD$_3$CN**$_{eq}$ (Scheme 1) is also supported by the ES-MS of the solution mixture collected after 24 h, with a peak at *m/z* 648.9 corresponding to $[Rh_2(O_2CCH_3)_2(\eta^1\text{-bpy}_{ax})(CH_3CN)_3(CD_3CN)-1]^+$ (Figure S1). The $\boldsymbol{\eta^1}$**-bpy**$_{ax}$**CD$_3$CN**$_{eq}$ intermediate can be formed through step D from the $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ species (Scheme 1) observed in the ^1H NMR spectrum (Figure 1). The formation of $\boldsymbol{\eta^1}$**-bpy**$_{ax}$**CD$_3$CN**$_{eq}$ from the initial *eq* exchange of CH_3CN for CD_3CN (step B in Scheme 1), followed by *ax* coordination of bpy (step E), cannot be ruled out, but it is known that the initial *ax* coordination of certain bidentate ligands (such as bpy, 1,10-phenanthroline, or certain phosphines) to $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ enhances the rate of exchange between CH_3CN_{eq} and solvent.[47] These prior findings also support the formation of the $\boldsymbol{\eta^1}$**-bpy**$_{ax}$**CD$_3$CN**$_{eq}$ intermediate through steps A and D (Scheme 1).

Although the ^1H NMR and MS data indicate the presence of the $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ and $\boldsymbol{\eta^1}$**-bpy**$_{ax}$**CD$_3$CN**$_{eq}$ species, the ***ax/eq*** adduct is not observed in the ^1H NMR spectra in CD_3CN (Figure 1), which indicates that step F in Scheme 1 is very slow in CD_3CN at 295 K. It is expected that formation of the ***eq/eq*** product, observed after 1 month of reaction, however, proceeds via the ***ax/eq*** intermediate (step G in Scheme 1). Since the ***ax/eq*** species is not observed in the ^1H NMR spectra in CD_3CN, it may be proposed that in the dark reaction in CD_3CN, the substitution of CH_3CN_{eq} or CD_3CN_{eq} for the dangling pyridine ring nitrogen atom of the axially coordinated bpy ligand required to form the ***ax/eq*** product (step F in Scheme 1), is the rate-limiting step of the reaction. Under these conditions, the formation of the ***eq/eq*** from the ***ax/eq*** species (step G) must be much faster than step F, such that the steady-state concentration of the latter is very low in CD_3CN solutions. A minute amount of the final ***eq/eq*** product appears after 2 days of reaction in CD_3CN but its concentration increases only slightly with time (Figure 1c–e). On the contrary, the reaction proceeds to the final ***eq/eq*** product in CH_3CN/CD_3CN under ambient light in 24 h, also consistent with the reports by Christou[41] and Chisholm et al.[42]

The presence of vestiges of the $(\boldsymbol{eq/eq})_2$ complex at 4 days of reaction in CD_3CN (Figure 1e), albeit in very small quantities, can be explained by a statistical distribution of η^1-ax bpy species in solution at the early stages of the reaction, together with slow reactivity from the $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ species to ***ax/eq*** (Chart 1). Because each molecule of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ has two rhodium centers to which bpy can bind axially, the initial 1:1 stoichiometry of complex:ligand in solution results in a statistical mixture of dirhodium starting material with no *ax* bpy (25%), $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ (50%) and $(\boldsymbol{\eta^1}\text{-bpy}_{ax})_2$ (25%) species (Chart 1). This scenario is evident in the aliphatic region of the ^1H NMR spectra collected between 1 day and 1 month, wherein resonances corresponding to unreacted $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$, as well as those of $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ and $(\boldsymbol{\eta^1}\text{-bpy}_{ax})_2$ are present. The $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ product eventually forms the ***eq/eq*** complex, whereas $(\boldsymbol{\eta^1}\text{-bpy}_{ax})_2$ generates $(\boldsymbol{eq/eq})_2$ (Chart 1). Accordingly, the integration areas of the $(\boldsymbol{eq/eq})_2$ resonances in the aromatic region are approximately half of the corresponding ones for the ***eq/eq*** species (Figure S2).

Due to its biological relevance, the reaction between $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ and bpy was also monitored in D_2O in the dark at two different reactant concentrations. In D_2O, at high reactant concentrations (27 mM) that are comparable to the corresponding reaction in CD_3CN described above, aromatic resonances attributed to the ***eq/eq*** product $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O)_2]^{2+}$ are observed at times when the reaction in CD_3CN exhibits only the $\boldsymbol{\eta^1}$**-bpy**$_{ax}$ adduct (Figure 2b and c). After 2 days of reaction in D_2O in the dark, the formation of the final product $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O)_2]^{2+}$ is complete with bpy binding in an *eq/eq* fashion.

Given the difference in reactivity in the two solvents (CD_3CN vs D_2O), it may be inferred that there is a difference in the rate of formation of the ***ax/eq*** intermediate, which is very slow in CD_3CN and relatively more facile in D_2O. It is evident from Scheme 1 that the formation of ***ax/eq*** is expected to be dependent on the ability of the *eq* solvent molecule in $\boldsymbol{\eta^1}$**-bpy**$_{ax}$**S**$_{eq}$ to be

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displaced by the free pyridine ring nitrogen atom of the bpy ligand. In CD_3CN, the $\boldsymbol{\eta^1}$-$\mathbf{bpy}_{ax}\mathbf{CD_3CN}_{eq}$ species begins to form after 1 day in the dark, whereas in the case of the reaction in D_2O, the *ax* bpy adduct is not observed. Therefore, the CH_3CN_{eq} ligand is exchanged for D_2O, thus generating the $\mathbf{D_2O}_{eq}$ species shown in Scheme 1 through step B. Moreover, since the $\boldsymbol{\eta^1}$-$\mathbf{bpy}_{ax}$ species is not observed in D_2O, it may be concluded that once formed, $\mathbf{D_2O}_{eq}$ proceeds quickly to the ***ax/eq*** species (steps E and F), and the final ***eq/eq*** product (step G). In the $\mathbf{D_2O}_{eq}$ intermediate, the *eq* D_2O ligand is less basic than CD_3CN_{eq}, and thus more labile, allowing for easier displacement by the incoming bpy ligand and facilitating the formation of the *ax/eq* adduct $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_3(D_2O)]^{2+}$ in this solvent. In contrast, in the dark reaction in CD_3CN, exchange of CH_3CN_{eq} for a solvent molecule does not result in the presence of a more labile ligand in the *eq* position (since the incoming *eq* ligand is CD_3CN). In support of this contention is the report that the exchange rate of H_2O_{ax} in $[Rh_2(eq\text{-}H_2O)_8(ax\text{-}H_2O)_2]^{4+}$ is 10^6 times faster than the CH_3CN_{eq} exchange in $[Rh_2(eq\text{-}CH_3CN)_8(ax\text{-}CH_3CN)_2]^{4+}$.[48] In light of the lower lability of the CH_3CN_{eq} as compared to the D_2O_{eq} ligand on the dirhodium core, it is significantly more difficult for the dangling pyridine ring of the bpy ligand to chelate in CD_3CN and thus the adducts remain $\boldsymbol{\eta^1}$-$\mathbf{bpy}_{ax}$ or $\boldsymbol{\eta^1}$-$\mathbf{bpy}_{ax}\mathbf{CD_3CN}_{eq}$ proceeding very slowly to the ***ax/eq*** species. The vestiges of ***ax/eq*** intermediate in the reactions in D_2O in the dark (indicated by **x** marks in Figures 2 and 3) indicate that there is an equilibrium between the ***ax/eq*** and ***eq/eq*** adducts (step G), which greatly favors the ***eq/eq*** and that as soon as the ***ax/eq*** species is formed, it quickly proceeds to the final ***eq/eq*** product $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O)_2]^{2+}$. It is evident from the data presented herein that at high concentration (27 mM), the reaction in D_2O proceeds to the ***eq/eq*** product more efficiently as compared to that in CD_3CN at a similar concentration (34 mM).

At lower reactant concentrations (7 mM) in D_2O in the dark, however, only vestiges of the ***eq/eq*** product are apparent between 15 and 21 h. The reaction is complete in 156 h (6.5 days) but even after 3 days, a considerable amount of unreacted bpy is still present (7.29, 7.77, 7.79, and 8.40 ppm; Figure 3). In contrast to the slow and limited reactivity observed in the dark at these reactant concentrations in D_2O, photolysis of the solution greatly enhances the *eq* ligand exchange within the 8 h reaction time, as detailed in a later section.

Photoreactivity. *a. $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ with bpy (1:1 ratio) in D_2O.* The progress of the reaction involving the coordination of bpy (6.7 mM) to $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ (6.7 mM) in D_2O as a function of irradiation time was monitored by ^{1}H NMR spectroscopy over a period of 8 h ($\lambda_{irr} \geq 455$ nm). As expected, the exchange of the two *ax* CH_3CN ligands for D_2O solvent molecules is observed prior to the photolysis of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ in D_2O.[21] In the aromatic region, the resonances of unreacted free bpy at 8.40, 7.79, 7.77, and 7.23 ppm are initially present (Figure 4; top spectrum). Between 2 and 4 h of irradiation, however, 4 triplets and 4 doublets appear in the ^{1}H NMR spectrum, attributable to an intermediate with 8 nonequivalent aromatic protons. Such spectral features are indicative of an intermediate with low symmetry, which is assigned to the *ax/eq* $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_3(D_2O)]^{2+}$ (Chart 1), also possessing one *ax* D_2O solvent molecule. A related adduct, namely $Rh_2(O_2CCH_3)_4(bpy)$ with an *ax/eq* bpy ligand and one chelating acetate group, exhibits 8 nonequivalent ^{1}H NMR bpy resonances and has been reported to form under different

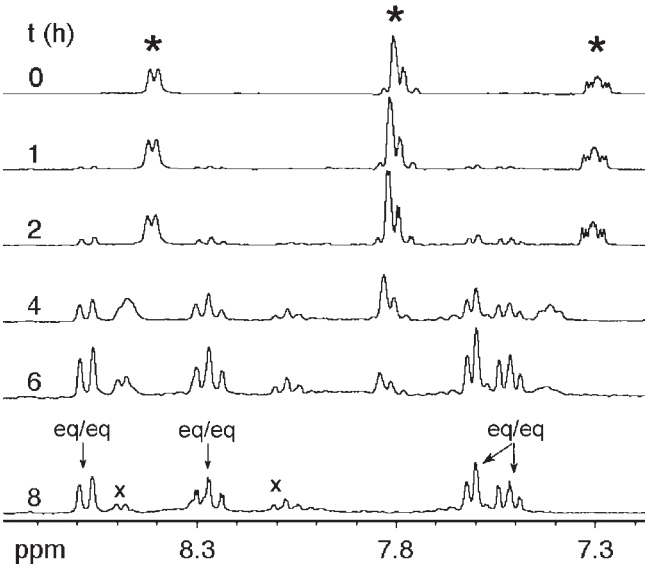

Figure 4. Changes in the aromatic region of the ^{1}H NMR spectrum for the photolysis ($\lambda_{irr} > 455$ nm) of 6.7 mM $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ and 6.7 mM bpy in D_2O from 0 to 8 h. The * indicate the positions for the resonances of unreacted bpy, and the **x** indicate vestiges of ***ax/eq*** adduct.

experimental conditions.[41,49] By analogy to the corresponding reaction in the dark, photolysis results in the formation of small amounts of the ***ax/eq*** adduct following the photodissociation of one *eq* CH_3CN. The absorption of a photon by $[Rh_2(O_2CCH_3)_2(CH_3CN)_4(D_2O)_2]^{2+}$ likely results in the initial formation of the solvated complex $[Rh_2(O_2CCH_3)_2(CH_3CN)_3(D_2O)_3]^{2+}$, with one *eq* and two *ax* D_2O molecules. Although this intermediate is not observed in the presence of bpy in solution, photolysis of $[Rh_2(O_2CCH_3)_2(CH_3CN)_4(D_2O)_2]^{2+}$ in D_2O in the absence of bpy was previously shown to result in the increase of the ^{1}H NMR resonance area corresponding to free CH_3CN as a function of irradiation time, indicative of the exchange of *eq* CH_3CN ligands with the solvent.[21] These results in the absence of bpy indicate that photons accelerate step B in Scheme 1.

In this study, in the presence of bpy, the initial production of the $\mathbf{D_2O}_{eq}$ adduct by photolysis (step B in Scheme 1) results in the formation of the ***ax/eq*** intermediate (through steps E and F, Scheme 1), which is in equilibrium with the ***eq/eq*** adduct $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O)_2]^{2+}$ and greatly favors the latter (step G, Scheme 1). After 8 h of photolysis, a small amount of the ***ax/eq*** intermediate is still present (indicated by **x** in Figure 4), but at later times only 4 resonances (2 doublets and 2 triplets) are observable at 8.58, 8.27, 7.61, and 7.53 ppm, corresponding to the ***eq/eq*** product. In the aliphatic region, there is a concomitant growth of the resonance area corresponding to free CH_3CN, whereas the single CH_3CN_{eq} resonance integration area of the starting material $[Rh_2(O_2CCH_3)_2(CH_3CN)_4(D_2O)_2]^{2+}$ decreases. It is notable that the power dependence of the photolysis of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ ($\lambda_{irr} \geq 455$ nm, 1 h) is consistent with the formation of the ***eq/eq*** adduct $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O)_2]^{2+}$ via a one-photon process, because plots of log (I) vs. log (rate) have a slope of ~1 (I = light intensity). This result indicates that only the first ligand dissociation step (B, Scheme 1) requires the absorption of a photon, and the remaining steps that ultimately result in the formation of the ***eq/eq*** product do not require light.

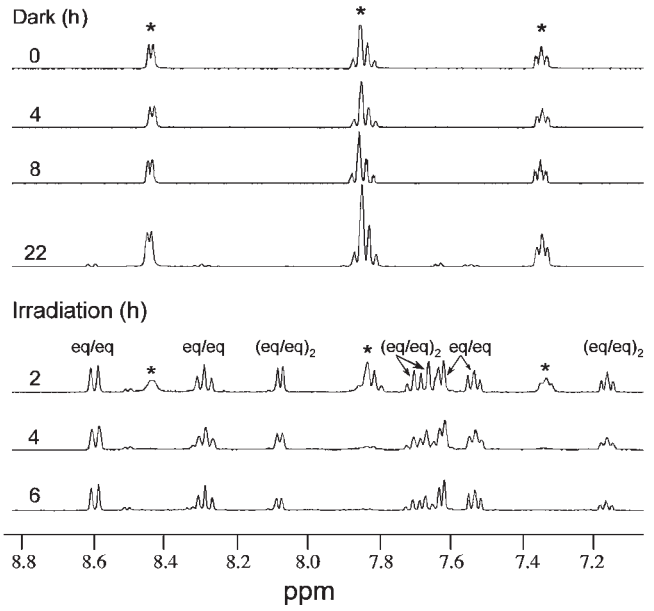

Figure 5. ^{1}H NMR spectra of the 1:2 reaction between $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ (3.35 mM) and bpy (6.7 mM) in D_2O in the dark (upper) and photolyzed (λ_{irr} > 455 nm) at various irradiation times (lower). The * indicate the positions for the resonances of unreacted bpy.

b. $[Rh_2(O_2CCH_3)_2(CH_3CN)_6](BF_4)_2$ and bpy (1:2 ratio) in D_2O. Irradiation of a solution with 2 equiv of bpy (6.7 mM) in the presence of 3.35 mM $[Rh_2(O_2CCH_3)_2(CH_3CN)_4(D_2O)_2]^{2+}$ results in spectral changes similar to those described above for the 1:1 photolysis (λ_{irr} > 455 nm). Coordination of bpy to the dirhodium complex is evident from the appearance of several new resonances in the aromatic region of the ^{1}H NMR spectrum of the reaction (Figure 5). In general, two bpy ligands are available to bind to the dirhodium core, and at the end of the photolysis, resonances corresponding to free bpy ligand (at 7.29, 7.77, 7.79, and 8.40 ppm) are not observed. For comparison sake, it is evident in the upper panel of Figure 5 that no spectral changes are observed in the dark during the same period of time under similar experimental conditions and reactant concentrations.

As evidenced from the 1:1 $[Rh_2]$:[bpy] reaction, absorption of a photon by $[Rh_2(O_2CCH_3)_2(CH_3CN)_4(D_2O)_2]^{2+}$ ($\lambda_{irr} \geq$ 455 nm, 1 h) in D_2O results in the formation of the ***eq/eq*** adduct $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O)_2]^{2+}$ with 4 resonances (2 doublets and 2 triplets) at 8.58, 8.27, 7.61, and 7.53 ppm (Figure 4). Likewise, in the 1:2 $[Rh_2]$:[bpy] reaction at 2 h of irradiation in D_2O, formation of the same ***eq/eq*** adduct is evidenced by the set of four resonances at the same chemical shifts (lower panel of Figure 5, marked ***eq/eq***). In the ^{1}H NMR spectrum of the 1:2 photolysis reaction in D_2O, however, four additional new resonances are observed at 8.10, 7.72, 7.68, and 7.18 ppm (lower panel of Figure 5, marked $(eq/eq)_2$) at 2 h of irradiation. These resonances are attributed to the bis-bpy adduct $(eq/eq)_2$ (Chart 1), which was unequivocally identified by preparing $[Rh_2(O_2CCH_3)_2(bpy)_2(CH_3CN)_2](BF_4)_2$ by a published procedure[44] and acquiring the ES-MS (m/z = 318 for $[Rh_2(O_2CCH_3)_2(bpy)_2]^{2+}$) and ^{1}H NMR spectra in D_2O (Figure 6). Vestiges of the $(eq/eq)_2$ adduct were also produced in the photolyzed 1:1 $[Rh_2]$:[bpy] reaction (Figure S3).

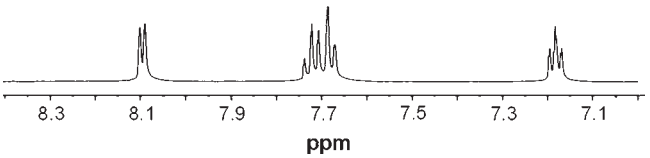

Figure 6. ^{1}H NMR of $[Rh_2(O_2CCH_3)_2(bpy)_2(CH_3CN)_2](BF_4)_2$ $(eq/eq)_2$ in D_2O.

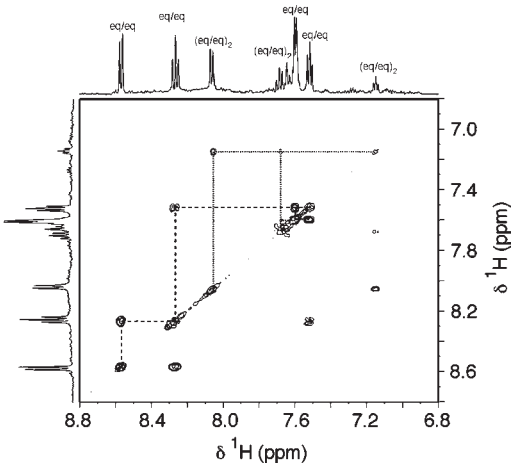

Figure 7. [^{1}H−^{1}H] COSY NMR spectrum collected for the 1:2 $[Rh_2]$:[bpy] reaction solution in D_2O after 6 h of irradiation. Cross-peaks marked with dashed or dotted lines and the corresponding resonances are assigned to the ***eq/eq*** and $(eq/eq)_2$ adducts, respectively.

The 2D [^{1}H−^{1}H] COSY spectrum for the 1:2 $[Rh_2]$:[bpy] reaction solution after 6 h of irradiation in D_2O (Figure 7) was used to confirm, via scalar couplings, the sets of resonances that were previously associated with the ***eq/eq*** and $(eq/eq)_2$ products. In Figure 7, the doublet at 8.58 ppm exhibits cross-peaks with the triplet at 8.28 ppm, which also gives cross-peaks with the resonance at 7.53 ppm and the latter with the doublet at 7.61 ppm. From these data, the resonances at 8.58, 8.27, 7.61, and 7.53 ppm (their cross-peaks are marked with dashed lines in Figure 7) are assigned to the ***eq/eq*** product, whereas the resonances labeled with dotted lines are attributed to the $(eq/eq)_2$ adduct.

The 2D [^{13}C−^{1}H] HMQC and HMBC correlation spectra were collected on the photolyzed 1:2 $[Rh_2]$:[bpy] reaction solution in D_2O after 6 h of irradiation (Figure S4). The single- and two- to three- bond couplings, as well as the proton and carbon connectivities for the ***eq/eq*** adduct were determined; the cross-peaks of the $(eq/eq)_2$ adduct are much weaker. For the ***eq/eq*** adduct, there are four strongly coupled ^{13}C−^{1}H single-bond resonances in the HMQC spectrum displayed in Figure S4 (green cross-peaks); the two triplets at 7.52 and 8.28 ppm are coupled to the carbon atoms with ^{13}C NMR resonances at 130 and 143 ppm, respectively, whereas the two doublets at 7.61 and 8.58 ppm are coupled to the carbon atoms with ^{13}C resonances at 151 and 128 ppm, respectively. The ^{13}C NMR resonance that appears at 155 ppm in the HMBC spectrum (Figure S4; red cross-peaks) is assigned to C2/C2′ because there is no single-bond coupling between it and a proton. The only ^{1}H NMR resonance not coupled to the ^{13}C NMR resonance at 155 ppm - (C2/C2′) is the triplet at 7.52 ppm, which is attributed to

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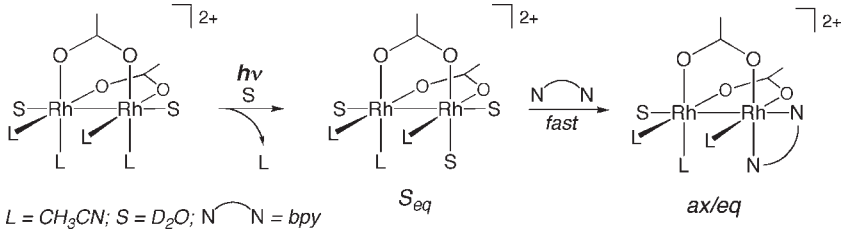
Scheme 2. Proposed Mechanism for the Photochemical Formation of the *ax/eq* Species



H5/H5′, because there are four bonds between it and C2/C2′. Table S1 has the complete assignments for the bpy proton and carbon atoms of the ***eq/eq*** adduct.

c. Photolysis Mechanism. The importance of photoactivation for the progress of the reaction is clearly indicated by comparison of the ^{1}H NMR data of the lower concentration 1:1 reactions (7 mM) in D_2O in the presence and absence of photolysis (λ_{irr} > 455 nm). In the dark, at 9 h of reaction, only minute amounts of the ***eq/eq*** product $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O)_2]^{2+}$ are observed, whereas under photolysis, the formation of the ***eq/eq*** product is complete in the same time period (Figures 3 and 4). Additionally, in the dark, even after 3 days (~70 h), the ^{1}H NMR spectrum of the 1:1 reaction solution is still dominated by a significant amount of free bpy and unreacted dirhodium complex (Figure 3) and vestiges corresponding to the ***ax/eq*** adduct are apparent. This difference may be explained by the dissociation of the first *eq* CH_3CN accelerated by the absorption of a photon, thus generating a significant amount of $\boldsymbol{D_2O_{eq}}$ (step B in Scheme 1 and initial step in Scheme 2), which quickly proceeds to the ***ax/eq*** intermediate in the presence of bpy (Scheme 2). The initial *eq* CH_3CN ligand exchange with D_2O is the rate-limiting step in the dark reaction, but the photodissociation of the CH_3CN_{eq} ligand permits the accumulation of the ***ax/eq*** intermediate under steady-state photolysis conditions such that it can be observed in the ^{1}H NMR spectra (Scheme 2, Figure 4) as compared to the smaller amounts of ***ax/eq*** adduct formed in the corresponding reaction in the dark.

The ***ax/eq*** species rearranges nearly completely to the corresponding ***eq/eq*** adduct $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O)_2]^{2+}$ after 8 h without the requirement of irradiation, as evidenced by the overall one-photon power dependence of the ***eq/eq*** product formation. The thermal nature of the ***ax/eq*** → ***eq/eq*** rearrangement (step G in Scheme 1) is also supported by the observation of the ***eq/eq*** product in the ^{1}H NMR spectra of the dark reaction in D_2O (Figures 2b,c and Figure 3—after 21 h) as well as by the reported interconversion data for amp (2-aminomethylpyridine) in $[Rh_2(O_2CCH_3)_2(O_2CCH_3)(amp)_2][ClO_4]$.[50] In summary, the results point to initial photoaquation of one *eq* CH_3CN ligand of $[Rh_2(O_2CCH_3)_2(CH_3CN)_4(D_2O_{ax})_2]^{2+}$ in D_2O, which is the rate-determining step in the dark, followed by the generation of the ***ax/eq*** intermediate (Scheme 2). Thermal displacement of a second *eq* CH_3CN ligand in the ***ax/eq*** species generates the ***eq/eq*** complex, which is greatly favored (step G in Scheme 1).

In the 1:2 $[Rh_2]$:[bpy] reaction in D_2O under irradiation ($\lambda_{irr} \geq 455$ nm), both the bis-bpy $[Rh_2(O_2CCH_3)_2(bpy)_2(CH_3CN)_2]^{2+}$, $(\boldsymbol{eq/eq})_2$,[44] and the mono-bpy ***eq/eq*** adducts are formed. The presence of both the ***eq/eq*** and $(\boldsymbol{eq/eq})_2$ adducts was confirmed by acquiring the ^{1}H NMR spectra of the reaction at several time intervals (Figure 5) as well as by collecting the $[^1H-^1H]$ COSY NMR spectrum after 6 h of irradiation (Figure 7). The compound $[Rh_2(O_2CCH_3)_2(bpy)_2(CH_3CN)_2](BF_4)_2$ has been previously prepared from $Rh_2(O_2CCH_3)_4$ and bpy (ratio 1:2) by refluxing in CH_3CN for 24 h.[44] Presently, the same compound $(\boldsymbol{eq/eq})_2$ (Figure 6) was formed in 2 h from $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ and bpy (ratio 1:2) by irradiation in D_2O. This further confirms the necessity of photolysis for the reactions between $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ and bpy to proceed efficiently to the final ***eq/eq*** and $(\boldsymbol{eq/eq})_2$ products in H_2O at low concentrations.

■ CONCLUSIONS

The importance of the availability of the *eq* sites on the dirhodium core is well-documented from the reactions of these complexes with nucleobases and oligonucleotides, as well as single- and double-stranded DNA, which result in the formation of biologically relevant bidentate adducts at *eq* sites.[30−40] In light of our previous study which showed that $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ binds to dsDNA and that photolysis results in a 34-fold enhancement of its cytotoxicity toward Hs-27 human skin fibroblasts,[21] we investigated, by NMR spectroscopy, the mechanism by which a model for biologically relevant bidentate nitrogen donor ligands, i.e., bpy, binds to $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$. The results reported herein clearly highlight the importance of light activation for the enhancement of the initial *eq* ligand exchange, which requires the dissociation of an *eq* molecule of CH_3CN from the dirhodium core to form the ***ax/eq*** product. The combination of data for the reaction in the dark and upon irradiation lead to the conclusion that *eq* CH_3CN dissociation is the rate-limiting step of the reaction in the dark. Photoaquation of the first *eq* CH_3CN ligand of $[Rh_2(O_2CCH_3)_2(CH_3CN)_6]^{2+}$ is essential for the progress of the dirhodium reactions with ligands of biological relevance, modeled using bpy in the present work.

In the absence of photoactivation in D_2O at low reactant concentrations, the reaction is approximately 20 times slower in reaching completion. In the dark, at 9 h of reaction, only vestiges of the *eq/eq* $[Rh_2(O_2CCH_3)_2(bpy)(CH_3CN)_2(D_2O)_2]^{2+}$ product are observed, whereas the formation of the ***eq/eq*** product is complete in the same time period under photolysis, thus supporting the great enhancement of the reaction rate under irradiation. Because PDT requires reactivity at low concentrations with light activation, these results emphasize the requirement of photon absorption for ligand exchange at the first *eq* site to take place at the dirhodium core and thus render these compounds potentially effective PDT agents. The information garnered in regards to the mechanism of photolysis from such studies may be incorporated in designing new successful PDT agents.

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■ ASSOCIATED CONTENT

Supporting Information. Mass spectrometry data, additional NMR spectra, and resonance assignments. These materials are available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors
*E-mail: dunbar@mail.chem.tamu.edu; turro@chemistry.ohio-state.edu.

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