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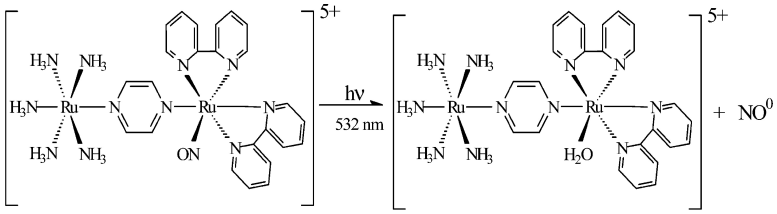

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Photoinduced NO Release by Visible Light Irradiation from Pyrazine-Bridged Nitrosyl Ruthenium Complexes

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In recent years, there has been a considerable upsurge of interest in the development of nitrosyl complexes due to the possibility of using those compounds as nitric oxide (NO) delivery agents.[1,2] Nitric oxide is a gaseous free radical that is an important modulator of immune and endocrine response. It also serves in mammalian bioregulation including cardiovascular control and neuronal signaling,[3−5] and it plays an important role in the induction of apoptosis.[6] The radical nature of free NO leads to this molecule being used in the photodynamic therapy (PDT) of cancer, which is a very promising technique.

Among the nitrosyl complexes, the polypyridyl ruthenium species have been long investigated by Meyer and co-workers due to their very interesting spectroscopic and electrochemical properties.[7−9] Those nitrosyl derivatives of ruthenium are thermally stable but labile to near-UV irradiation concerning the NO release. An example could be observed for *cis*-$[Ru(bpy)_2L(NO)]^{3+}$ (L = 4-picoline, pyridine, and 4-acetylpyridine) which releases NO when an aqueous solution of the complex was irradiated at 355 nm,[10] but no photochemical reaction was observed when the solution was irradiated in the visible region. As one of the interests of our research group involved the synthesis and photochemical study of ruthenium nitrosyl complexes,[10,11] we decided to focus our study on the photochemistry of a nitrosyl binuclear complex, which absorbs in the visible region. Our aim in this work is to exploit the opportunities of combining a fragment, which absorbs in the visible region, and a moiety that contains the nitrosyl ligand into the same molecule. The possibility of having nitric oxide released based on the photoinduced electron-transfer reaction by irradiation with visible light can also be a fundamental component in the design of a molecular device applied to drug development. Here, we describe the synthesis, spectroscopic data, and photochemical behavior of the $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)]^{5+}$ complex in an aqueous solution.

The $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)](PF_6)_5$ complex was synthesized from *cis*-$[Ru(NO_2)(bpy)_2(NO)](PF_6)_2$ and $[Ru(NH_3)_5(pz)](PF_6)_2$. These mononuclear complexes were prepared according to reported methods.[7,12] To 0.150 g (1.92×10^{-4} mol) of *cis*-$[Ru(NO_2)(bpy)_2(NO)](PF_6)_2$ dissolved in acetone (15 cm^3) was added dropwise 1.92×10^{-4} mol of NaN_3 dissolved in methanol (5 cm^3). The mixture was kept under stirring, and after 10 min a solution of 0.107 g of $[Ru(NH_3)_5(pz)](PF_6)_3$ (1.92×10^{-4} mol) in acetone (10 cm^3) was added and the reaction was allowed to proceed for 22 h. After hexafluorophosphoric acid (65%, 1 cm^3) and ethanol (200 cm^3) were added to the ruthenium solution, a dark red precipitate was formed and collected by filtration. The binuclear complex salt was then dissolved in acetone and reprecipitated by addition of ethanol. The purity of the complex was tested by HPLC. Yield 47.9%. Anal. Calcd for $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)](PF_6)_5$: C, 20.08; N, 11.72; H, 2.44. Found: C, 19.98; N, 11.56; H, 2.50.

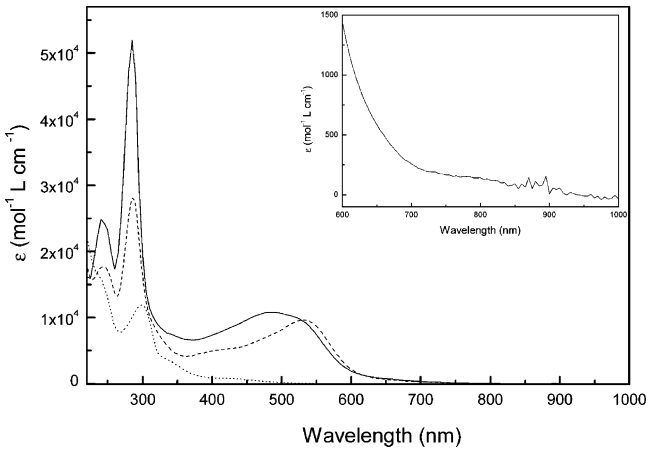

Figure 1. UV−vis spectra in acetate buffer solution of species *cis*-$[Ru(bpy)_2(pz)(NO)]^{3+}$ (dot), $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)]^{5+}$ (dash), and $[Ru^{III}(NH_3)_5(pz)Ru^{II}(bpy)_2(H_2O)]^{5+}$ (solid line).

The $[Ru^{III}(NH_3)_5(pz)Ru^{II}(bpy)_2(H_2O)]^{5+}$ complex was synthesized in situ using $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)](PF_6)_5$ as the precursor. To 0.011 g (7.6×10^{-6} mol) of the nitrosyl binuclear complex dissolved in acetone (5 cm^3) was added dropwise 7.6×10^{-6} mol of NaN_3 dissolved in methanol (3 cm^3). The mixture was kept under stirring, and after 10 min the solvent was evaporated under vacuum. A volume of 10 cm^3 of distillated water was added, and this solution was electrolyzed at 0.60 V versus Ag/AgCl to oxidize the $[Ru^{II}(NH_3)_5(pz)Ru^{II}(bpy)_2(H_2O)]^{4+}$ complex.

The spectroscopic behavior of ruthenium(II) complexes containing pyrazine as a ligand is usually discussed in various spectroscopic transitions including ligand-centered and metal−ligand charge transfer. The UV−vis spectra in acetate buffer solution at pH 4.5 of $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)]^{5+}$ and $[Ru^{III}(NH_3)_5(pz)Ru^{II}(bpy)_2(H_2O)]^{5+}$ complexes present bands in the UV−vis−near-IR region (Figure 1). The bands in the UV region were attributed to the intraligand (IL) transition mainly centered in *N*-heterocyclic ligands. The IL bands are sufficiently intense to mask a MLCT band involving $d_\pi Ru(II)-\pi^*(NO)$ which is observed in the 340 nm region as assigned in a UV−vis spectrum of *cis*-$[Ru(bpy)_2(pz)NO]^{3+}$ (Figure 1). The band in the visible region in the electronic spectrum of $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)]^{5+}$ in aqueous solution was attributed to the metal ligand charge-transfer $d_\pi Ru(II)-\pi^*(pz)$ type. The band in the near-infrared region of the $[Ru^{III}(NH_3)_5(pz)Ru^{II}(bpy)_2(H_2O)]^{5+}$ complex was attributed to the intervalence band.

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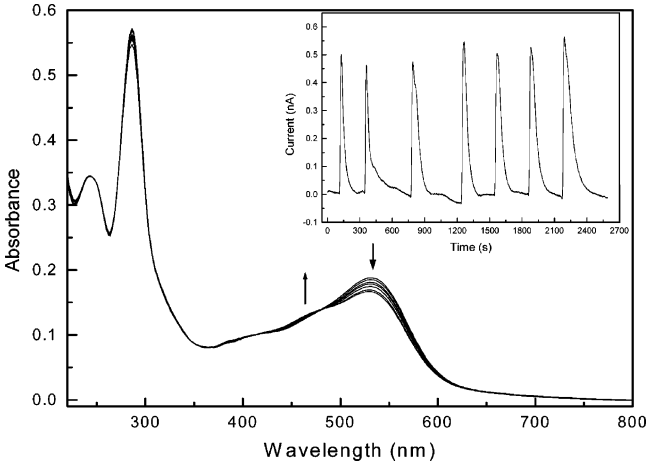


Figure 2. (a) Temporal spectral change, and (b) chronoamperogram of NO released by flash photolysis of 1.95×10^{-5} mol L^{-1} $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)]^{5+}$ in pH 4.5 acetate buffer solution during flash photolysis with 532 nm light irradiation.

The FTIR spectrum of $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)](PF_6)_5$ shows a NO stretching at 1942 cm^{-1} in KBr pellet, indicating that the complex is of the $\{Ru^{II}\text{-}NO^+\}$ type.[7−11,13]

The photolysis of the binuclear complex in an acetate buffer solution at pH 4.5 and ionic strength of 0.1 mol L^{-1} adjusted with $NaBF_4$ was performed using a laser flash-photolysis apparatus consisting of a continuum Q-switched Nd:YAG laser (Continuum, Santa Clara, CA) with excitation provided by a second harmonic at $\lambda = 532$ nm. The pulse length was 8 ns, the beam diameter incident on the sample was 6 mm, and the repetition rate was 10 Hz. The pulse energy was typically 10 mJ $pulse^{-1}$ measured with a Field Master power-meter with an L-30 V head. NO releasing was detected and measured with an ISO-NOP NO meter from World Precision Instruments that directly detects NO concentration by an amperometric technique.

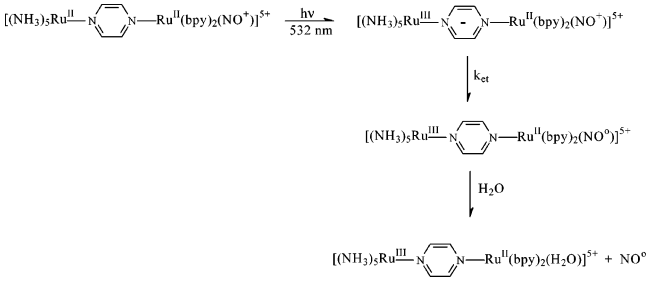
The NO calibration curve was constructed as previously described.[10] Light intensity was determined by actinometry using Reinecke's salt solution before each photolysis experiment. The NO quantum yield production (0.025 ± 0.004 mol $einsten^{-1}$ at 532 nm) was calculated on the basis of NO concentrations obtained by NO meter measurement.

The change in the UV−vis spectrum during flash photolysis is shown in Figure 2a. The band at 530 nm diminishes slightly and a shoulder in the 470 nm region appears, which is consistent with the UV−vis spectrum of the $[Ru^{III}(NH_3)_5(pz)Ru^{II}(bpy)_2(H_2O)]^{5+}$ complex in aqueous solution (Figure 1). The photoreactivity of the nitrosyl complex was accompanied by in situ NO detection, which is an indubitable way to prove the photochemical pathway. The signal recorded by the NO sensor rose quickly when photolysis was initiated, and then decreased when the light was turned off because of NO consumption via various pathways, principally autooxidation[3,4] (Figure 2b).

A similar experiment was run with the *cis*-$[Ru(bpy)_2(pz)NO]^{3+}$ complex in aqueous solution, but no NO signal was observed when the solution was irradiated at 532 nm.

Considering that the primary product for the photolysis of $d_\pi Ru^{II}-\pi^*(L)$ in $[Ru(NH_3)_5L]^{2+}$ and $d_\pi Ru^{II}-\pi^*(NO)$ for the *cis*-$[Ru(bpy)_2L(NO)]^{3+}$ complex, where L is a pyridine-type ligand, is $[Ru(NH_3)_5L]^{3+}$ and *cis*-$[Ru(bpy)_2L(H_2O)]^{3+}$, respectively,[10,14] and based on the NO measurement for the photolysis of $[Ru(NH_3)_5(pz)Ru(bpy)_2(NO)]^{5+}$, we can infer the photochemical pathway for the binuclear complex as described in Scheme 1.

Scheme 1



The simultaneous coordination of pz^-, obtained upon external stimulation, and NO^+ in the binuclear complex gives rise to a very interesting donor−acceptor complex. The high affinity of NO^+ for the photosensitizer should result in an intramolecular electron transfer (ET). This explanation is confirmed by following the NO release using a NO sensor at substantially shorter time scales. This mechanism is also supported by the UV−vis spectrum once a new band appears in the 470 nm region after photolysis.

Many different approaches are being followed with metalo nitrosyl complexes, but the overall goal involves the establishment of the design features that permit NO generation upon external stimulation mainly for the use of NO in photodynamic therapy.[15,16] In this context, the complex studied here constitutes an interesting class of compounds that can deliver NO upon irradiation in a visible region. A complete study involving the synthesis and photochemical studies of $[Ru(NH_3)_4L(pz)Ru(bpy)_2(NO)]^{5+}$, where L is a *N*-heterocyclic ligand, is in progress and will be submitted later for publication.

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