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COMMUNICATIONS

Published on Web 04/04/2007

Photosensitization via Dye Coordination: A New Strategy to Synthesize Metal Nitrosyls That Release NO under Visible Light

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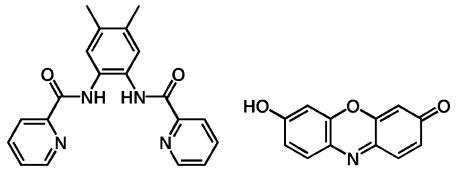
The recent discovery of the roles of nitric oxide (NO) in various biological processes such as blood pressure control, neurotransmission, immune response, and cell apoptosis[1,2] has raised interest in exogenous NO donors that can deliver NO to specific targets under controlled conditions.[3] NO donors that provide NO upon exposure to light have drawn special attention because of their utility in photodynamic therapy (PDT) for selected types of cancer.[4] To date, a number of iron, manganese, and ruthenium complexes of NO (metal nitrosyls) have been identified that release NO upon illumination.[5−8] The photosensitivity of these nitrosyls is largely governed by the location of the $d_\pi(M) \rightarrow \pi^*(NO)$ transition in their electronic absorption spectra. For example, Ru−NO complexes such as $[Ru(PaPy_3)(NO)](BF_4)_2$ and [Ru(salen)(NO)(Cl)] exhibit metal-to-ligand charge transfer (MLCT) bands only in the UV region (λ_{max} = 300−450 nm), and hence their photosensitivity is limited to UV light.[5c,6b] Nitrosyls such as [(Me$_2$bpb)Ru(NO)(Cl)] or [(Me$_2$bpb)-Ru(NO)(py)]$^+$ (where H_2Me_2bpb = 1,2-bis(pyridine-2-carboxamido)-4,5-dimethyl benzene; H = dissociable protons), reported by us recently, also release NO when exposed to UV light.[8] Since one major requirement of a potential NO donor for PDT is sensitivity toward visible light, further modification(s) of these nitrosyls is necessary to impart significant absorption in the visible (≥450 nm) region.

To increase the photosensitivity of such ruthenium nitrosyls to visible light, we decided to utilize strongly colored dye molecules as ligands to sensitize the metal center. Our intention was to enhance the photolability of the Ru−NO moiety in the visible range by energy transfer from a light-absorbing pendant chromophore to the Ru−NO unit. In this work, we have employed the tricyclic dye resorufin (Resf) that displays intense absorption ($\epsilon \approx 105\,000\ M^{-1}\ cm^{-1}$) in the visible range ($\lambda_{max}$ = 600 nm). This dye also contains a phenolato-O donor that facilitates direct ligation of this sensitizer to a metal center. We now report that the coordination of Resf to the Ru center of [(Me$_2$bpb)Ru(NO)(Cl)] indeed photosensitizes the Ru−NO moiety toward visible light.



H_2Me_2bpb Resorufin

The dye-tethered nitrosyl [(Me$_2$bpb)Ru(NO)(Resf)] (**1**) was synthesized via replacement of the chloride ligand of [(Me$_2$bpb)-Ru(NO)(Cl)] with Resf. A slurry of [(Me$_2$bpb)Ru(NO)(Cl)] was first treated with 1 equiv of $AgBF_4$ in hot MeCN to obtain the solvato species [(Me$_2$bpb)Ru(NO)(MeCN)]. Following removal of AgCl, the brown-green filtrate was mixed with 1 equiv of the purple sodium salt of Resf and the mixture was heated to reflux for 12 h. The resulting bright red solution was then concentrated and stored at −20 °C. Bright red crystals of **1** were isolated after 24 h (yield: 65%). Vapor diffusion of pentane into a $CHCl_3$ solution of **1** at 35 °C afforded dark-red crystals suitable for diffraction study. The structure of **1** (Figure 1) reveals that Resf is coordinated to the Ru center through the phenolato-*O* donor center, trans to the NO moiety. The planar, tricyclic dye is bent away from the equatorial plane (Ru−O4−C23 bond angle = 128.46(11)°). As expected, the Ru−N bond distances associated with the Me_2bpb^{2-} ligand are similar to those noted for [(Me$_2$bpb)Ru(NO)(Cl)]. The nearly linear Ru−N−O bond angle of 178.13(15)°, short N−O bond (1.1259-(2) Å), ν_{NO} value of 1843 cm^{-1} (KBr disk), and clean diamagnetic ^{1}H NMR spectrum (see Supporting Information) of **1** are all typical of {RuNO}^{6} nitrosyls.[5−8] Unlike many other {RuNO}^{6} complexes, **1** is highly stable in aqueous solutions (pH 7) and hence suitable for potential biological use.

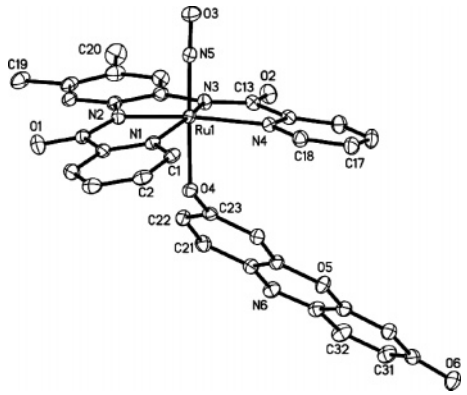


Figure 1. ORTEP diagram (50% probability level) of [(Me$_2$bpb)Ru(NO)-(Resf)] (**1**). Selected bond distances (Å) and angles (deg): Ru−N5 = 1.7347(16), N5−O3 = 1.159(2), Ru−N1 = 2.1250(15), Ru−N2 = 1.9862-(15), Ru−N3 = 1.9803(15), Ru−N4 = 2.1384(15), Ru−O4 = 2.0110(13), Ru−N5−O3 = 178.13(15), Ru−O4−C23 = 128.46(11).

Complex **1** exhibits an intense absorption band at 500 nm ($\epsilon \approx$ 12 000 $M^{-1}\ cm^{-1}$, Figure 3) and unlike [(Me$_2$bpb)Ru(NO)(Cl)], rapidly releases NO (detected by NO electrode, Figure 3 inset) when exposed to visible light (≥455 nm). The loss of NO generates new peaks at 360 and 750 nm, with clean isosbestic points at 420 and 515 nm (Supporting Information, Figure S1). The paramagnetic Ru(III) photoproduct (solvato species) exhibits strong EPR signal with g = 2.26, 2.22, and 2.04 (Supporting Information, Figure S2). To unequivocally demonstrate the photosensitizing effect of dye coordination in **1**, we have also synthesized [(Me$_2$bpb)Ru(NO)-(OH)] (**2**) by heating [(Me$_2$bpb)Ru(NO)(MeCN)] in moist MeCN containing a few drops of aniline (as a base).

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10.1021/ja070247x CCC: $37.00

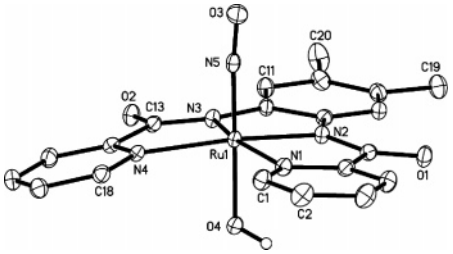

Figure 2. ORTEP diagram (50% probability level) of [(Me_2bpb)Ru(NO)(OH)] (**2**). Selected bond distances (Å) and angles (deg): Ru−N5 = 1.7538(13), N5−O3 = 1.1648(18), Ru−N1 = 2.1408(13), Ru−N2 = 1.9950(13), Ru−N3 = 1.9900(13), Ru−N4 = 2.1235(13), Ru−O4 = 1.9457(11), Ru−N5−O3 = 172.67(12), Ru−O4−H4a = 111.2(16).

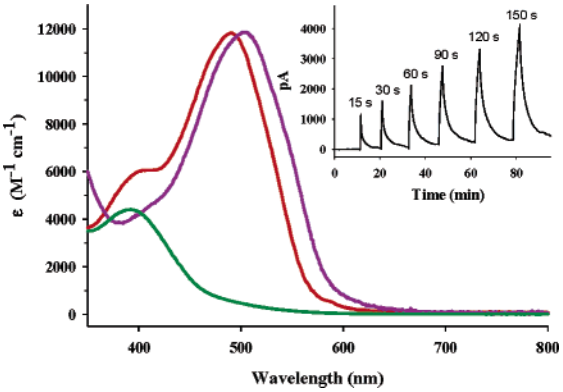

Figure 3. Electronic absorption spectra in DMF of the dye-bound complex [(Me_2bpb)Ru(NO)(Resf)] (**1**) (red line, λ_{max} = 500 nm), [(Me_2bpb)Ru(NO)(OH)] (**2**) (green line, λ_{max} = 395 nm) and [(Me_2bQb)Ru(NO)(Resf)] (**3**) (violet line, λ_{max} = 510 nm). The inset shows the NO amperogram indicating photorelease of NO from **1** in aqueous solution (pH 7) with short pulses of visible light (≥455 nm) for the indicated time periods.

The structure of **2** (Figure 2) is nearly identical to that of **1** (including the N_5O donor set) except for the dye ligand. As a consequence, the pale orange solution of **2** exhibits negligible absorbance near 500 nm (Figure 3); the only band observed is near ∼400 nm, corresponding to the d_π(Ru) → π^*(NO) transition commonly observed with {RuNO}[6] nitrosyls. *No photorelease of NO* is observed with **2** under illumination with the same visible light.

The efficiency of NO release by **1** has been determined in solvents such as DMF and water. Exposure of a solution of **1** in DMF to visible light (≥455 nm, 300 mW) causes rapid release of NO ($t_{1/2} \approx 6$ min). In water, the $t_{1/2}$ value is 5 min under the same light. The energy transfer from the chromophore to Ru−NO unit is also apparent in the fluorescence properties. While unbound resorufin in solution is highly fluorescent, **1** exhibits a strongly quenched fluorescence (∼90% quenched, λ(ex) = 500 nm) compared to the unbound dye. This indicates efficient energy transfer between the coordinated dye and the Ru−NO unit.[9,10] The quantum yield (ϕ) of NO photorelease from **1** at 500 nm (0.052 ± 0.008) also confirms that **1** is an efficient NO donor.

Finally, to bring the λ_{max} of the Ru−NO band (the d_π(Ru) → π^*(NO) transition) closer to the absorption band of the Resf (Figure 3) and improve the extent of energy transfer, we have utilized a more conjugated ligand Me_2bQb^{2-} (H_2Me_2bQb = 1,2-bis(quinaldine-2-carboxamido)-4,5-dimethyl benzene; H = dissociable protons), in which extended quinoline units replace pyridines in the ligand frame.[8] Previously, we reported a ∼50 nm shift in the λ_{max} in going from [(Me_2bpb)Ru(NO)(Cl)] to [(Me_2bQb)Ru(NO)(Cl)]. In the present work, we have isolated the dye-bound nitrosyl [(Me_2bQb)Ru(NO)(Resf)] (**3**) from [(Me_2bQb)Ru(NO)(Cl)] by following a synthetic protocol similar to **1** (^{1}H NMR spectrum shown in Figure S3, Supporting Information). Much to our expectation, **3** exhibits convergence of the λ_{max} of the nitrosyl moiety with that of the coordinated dye resulting in a single band near 510 nm (Figure 3) and releases NO more efficiently ($\phi_{500} = 0.102 \pm 0.009$). The dye-sensitized nitrosyls **1** and **3** are significantly more efficient than other Ru−NO complexes studied in the visible region, such as [Ru(NH$_3$)$_5$(pz)Ru(bpy)$_2$(NO)](PF$_6$)$_5$ ($\phi_{532} = 0.025$).[11] *Direct coordination* of the dye to the metal center appears to be crucial, as other NO donors with peripheral chromophores (not bonded to the metal center) such as fluorescein-derivatized Roussin's salts exhibit much smaller ϕ values ($\phi_{436} = 0.0036 \pm 0.0005$).[9] This is further corroborated by negligible photoactivity of the hydroxide-bound complex **2** ($\phi_{500} < 0.001$) under visible light.

In summary, we have shown that ruthenium nitrosyls with photoactive bands in the UV region can be photosensitized to visible light by coordination of a strongly absorbing dye molecule. Using the red dye resorufin, we have substantially increased the photoactivity of two ruthenium NO donors in the visible region. Aqueous solutions of these complexes generate rapid bursts of NO upon exposure to light pulses (Figure 3 inset). This property could have potential use in biological systems.

Acknowledgment. This research was supported by a grant from the National Science Foundation (Grant CHE-0553405). Experimental assistance from Christine Beavers is gratefully acknowledged.

Supporting Information Available: Changes in electronic absorption spectrum observed upon photolysis of **1** (Figure S1), EPR spectrum of the photoproduct of **1** (Figure S2), ^{1}H NMR spectra of **1**−**3** (Figure S3), and X-ray crystallographic data in CIF format for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA070247X