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Visible Light Induced Reversible Extrusion of Nitric Oxide from a Ruthenium(II) Nitrosyl Complex: A Facile Delivery of Nitric Oxide

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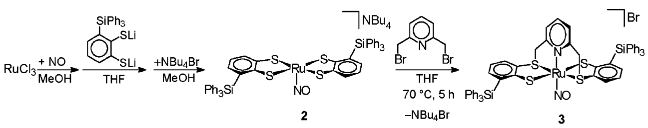
After the discovery of the role of nitric oxide (NO) in various physiological processes, such as regulation of blood pressure, neurotransmission, inhibition of tumor growth, and immune response,[1] the chemistry of metal nitrosyl complexes has become the focus of much attention.[2] The application of new NO drugs to medicine[3] has reinvigorated the NO research, particularly in developing new storage-release systems or methodologies for delivering NO to desired targets.[4] The photochemical labilization of NO from metallonitrosyls is one of the convenient methods for NO delivery.[5] In recent years, ruthenium is the metal of choice for nitrosyl complexes[6] because a number of ruthenium compounds with anticancer activity appear to penetrate tumors and are unusually effective in suppressing the immune response.[7] Moreover, the thermal stability of the Ru−NO bond enhances the probability that the complex will survive under physiological conditions.[6a,b] Even though many rutheniumnitrosyls are known to release NO upon energy-intensive UV light irradiation,[2d,6] reports on visible light NO labilization of rutheniumnitrosyls are rare.[8] In addition, the Ru^{III}−solvent complexes that result after irradiation inevitably undergo undesired side reactions in solution. One continuing challenge is, therefore, to find a Ru−NO complex that could release NO reversibly under very mild conditions without any metal-bound side reactions for biological applications.

We have reported previously that $[Ru^{II}(NO)(py^{bu}S_4)]Br$ (**1**) ($py^{bu}S_4$ = 2,6-bis(3,5-di-*tert*-butyl-2-sulfanylphenylthiomethyl)pyridine) releases NO upon exposure to UV light to form $[Ru^{III}(Br)(py^{bu}S_4)]$ (**1a**).[9] Now, we found that **1** releases NO even on irradiation with visible light (Supporting Information, Figure 1S). However, the reverse reaction was slow, and traces of other NO species were also formed (Figure 2S). Moreover, **1a** readily loses the Br^- ligand to form $[Ru^{III}(py^{bu}S_4)]_2Br_2$ (**1b**) via Ru−S(thiolate) bridges in solution (Figure 3S), which exhibits no affinity toward NO. Herein, we report a new ruthenium compound $[Ru^{II}(NO)(py^{si}S_4)]Br$ (**3**) ($py^{si}S_4$ = 2,6-bis(3-triphenylsilyl-2-sulfanylphenylthiomethyl)pyridine), containing sterically bulky $SiPh_3$ groups in *ortho* position with regard to the thiolate donors, that exhibits a remarkable reactivity of reversible NO release upon visible light irradiation.

The ligand $^{si}S_2-H_2$ (3-triphenylsilyl-1,2-benzenedithiol) was synthesized by *ortho* lithiation of benzenedithiol,[10] followed by treatment with $SiPh_3Cl$ and subsequent hydrolysis. The compound $Bu_4N[Ru^{II}(NO)(^{si}S_2)_2]$ (**2**) was prepared according to Scheme 1 in 70% yield. The structure of **2** (Figure 1a) reveals a five-coordinated Ru center with a square-pyramidal geometry. The NO group is at the apical position, and the thiolate donors are in the basal plane. The two $SiPh_3$ groups are *trans* to each other. Reaction of **2** with 2,6-bis(bromomethyl)pyridine (Scheme 1) leads to the formation of purple microcrystalline **3** in high yield. In the solid state, **3** is stable toward air and light, and well soluble in MeOH, DMF, and DMSO. The IR (KBr) spectrum of **3** displays νNO at 1858 cm^{-1} (1872 cm^{-1} in MeOH), indicative of the linearity of the Ru−N−O bond.[11] The well-resolved ^1H and ^{13}C NMR spectra of **3** indicate its ground state spin is zero and are typical for a complex having C_2 symmetry. Due to the NO group, the bridging CH_2 protons are more acidic and undergo H^+/D^+ exchange with CD_3OD. The cyclic voltammogram of **3** exhibits two quasi-reversible one-electron waves at $E_{1/2} = 0.46$ and -0.38 V in the region between 1.0 and -0.8 V (Figure 4S). The anodic and cathodic waves are assigned to the redox couples of $[\mathbf{3}]^{0/+1}$ and $[\mathbf{3}]^{0/-1}$, respectively. This is in accordance with **1**,[12] indicating that the 19 valence-electron neutral species $[Ru^{II}(NO)(py^{si}S_4)]$ exists in solution at approximately 0.0 V. **3** crystallizes in the monoclinic space group $P2_1/n$ (Figure 1b). The local geometry of the Ru^{II} site is a pseudooctahedron composed of two N and four S donors. The two thiolate and two thioether S atoms comprise in the equatorial plane in mutual *trans* position, with the pyridine and nitrosyl N atoms occupying the axial positions. The Ru−N(O) distance (1.748(4) Å) is slightly longer than that of the complex **1** (1.721(6) Å).[13] The Ru−S distances compare well with those in other thioether−thiolate complexes.[14] The Ru−N−O bond angle of 178.8(4)° suggests that the sp-hybridized N atom of the NO ligand formally coordinates as $Ru^{II}-NO^+$.[2b]

Scheme 1



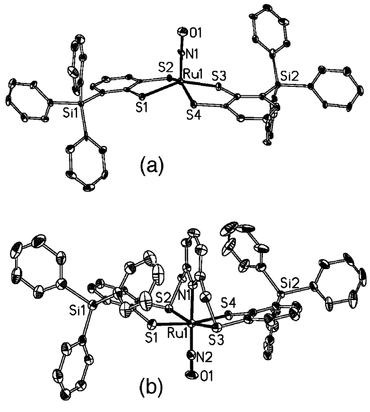


Figure 1. ORTEP diagrams of (a) the anion of **2** and (b) the cation of **3** (50% probability ellipsoids; H atoms and solvent molecules omitted). Selected distances [Å] and angles [°] for **2**: Ru1−N1 1.699(5), Ru1−S1 2.338(2), Ru1−S2 2.321(2), N1−O1 1.195(7), N1−Ru1−S1 108.2(2), N1−Ru1−S2 104.9(2), S1−Ru1−S2 85.43(6), S1−Ru1−S3 148.65(7), S2−Ru1−S4 151.78(7), Ru1−N1−O1 177.4(6). **3**: Ru1−N1 2.099(4), Ru1−N2 1.748(4), Ru1−S1 2.393(2), Ru1−S2 2.345(2), Ru1−S3 2.363(2), Ru1−S4 2.371(2), N2−O1 1.144(5), N1−Ru1−N2 178.1(2), N1−Ru1−S1 85.7(2), N2−Ru1−S1 96.2(2), S1−Ru1−S2 87.36(4), S1−Ru1−S4 170.26(5), S2−Ru1−S3 164.51(4), Ru1−N2−O1 178.8(4).

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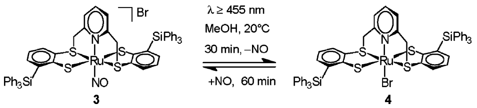
Scheme 2



When a red solution of **3** in MeOH is kept in dark, the color or IR spectrum does not change appreciably even after 10 days. However, when the solution is subjected to photolysis with visible light (Scheme 2), the color changes to green, and subsequently, green microcrystals of [Ru^{III}(Br)($py^{si}S_4$)] (**4**) precipitated from the solution. The IR spectral changes during the conversion of **3** to **4** are depicted in Figure 2. When the suspension is stirred in dark under an atmosphere of NO for about 60 min, it goes back to the red solution and the NO band of **3** reappeared, showing this reaction to be reversible. It is quite interesting that no thiolate-bridged dinuclear compound or any other side product is observed.

Complex **4** has been isolated in the solid state with very high yield (92%) and is soluble in THF, CH_2Cl_2, and acetone. It exhibits two quasi-reversible one-electron waves at $E_{1/2} = -0.58$ and 0.41 V. The cathodic and anodic waves are ascribed for the redox couples of $[\mathbf{4}]^{0/-1}$ and $[\mathbf{4}]^{0/+1}$, respectively. In a multi-sweep experiment, both the waves showed complete reversibility over several cycles confirming that **4** is stable in solution. Crystals of **4** suitable for X-ray structure analysis were obtained from a THF/DMF mixture at 20 °C. The Ru^{III} center is in pseudooctahedral geometry (Figure 3) with the Br ligand being *trans* to the pyridine N donor. **4** possesses a crystallographically imposed C_2 symmetry with the C_2 axis lying along N1−Ru1−Br1 bonds. All four Ru−S distances lie in the same range (av. 2.31 Å), which is in contrast to the Ru^{II} complexes, where the Ru−S(thiolate) distances (av. 2.38 Å) are usually longer than Ru(thioether) distances (av. 2.30 Å).[14]

When irradiation of **3** (similar to Scheme 2) was carried out with low-intensity UV light source (xenon lamp 150 W, λ ≥ 320 nm), the NO band of **3** disappeared completely in 5 min (Figure 5S), and the resulting bromo derivative **4** was isolated in the solid state as high as 86% yield.

Although the spectroscopic, electrochemical, and structural data of **3** and **1** (Table 1S) did not show any significant deviations, the NO releasing ability varies dramatically. Complex **3** releases NO much faster than **1** on visible light (λ ≥ 455 nm) irradiation. In the case of **3**, the reaction is completely reversible, without involving any metal-bound side reaction. The facile lability of the NO group of **3** can directly be related to the presence of $SiPh_3$ groups in the vicinity of the thiolate donors. Due to the steric effect of the $SiPh_3$ groups, formation of a thiolate-bridged dimer is hindered, which indirectly helps to stabilize the Ru−Br bond of **4** in solution.

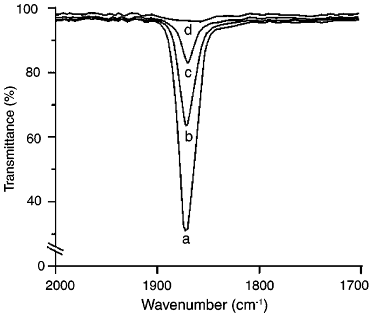


Figure 2. IR spectra of **3** in MeOH, before (a) and after 10 (b), 20 (c), and 30 min (d) of irradiation (λ ≥ 455 nm) at 20 °C.

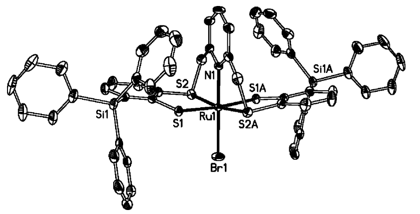


Figure 3. ORTEP diagram of **4** (50% probability ellipsoids; H atoms and solvent molecules omitted). Selected distances [Å] and angles [°]: Ru1−N1 2.055(3), Ru1−Br1 2.5239(4), Ru1−S1 2.3153(6), Ru1−S2 2.3101(6), N1−Ru1−Br1 180.000(1), N1−Ru1−S1 86.90(2), N1−Ru1−S2 84.66(2), S1−Ru1−S2 88.14(2), S1−Ru1−S1A 173.79(3), S2−Ru1−S2A 169.33(3).

In conclusion, the new rutheniumnitrosyl compound **3**, containing sterically bulky $SiPh_3$ groups *ortho* to the thiolate donors, has been synthesized. In solution, **3** releases NO on visible light (λ ≥ 455 nm) irradiation to afford the bromo compound **4**. The reverse reaction was also achieved efficiently with no metal-bound side reaction. The reaction is unique because the Br^- ion plays a dual role as counterion and nucleophile, which prevented the formation of a labile Ru^{III}−solvent complex. Thus, **3** has the potential to serve as NO deliverer to various targets. However, efforts are underway to make a water-soluble derivative of this type to use as a NO delivering agent to biological targets.

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Supporting Information Available: IR spectra (Figures S1, S2, and S5), X-ray structure (Figure S3), cyclic voltammogram (Figure S4), comparative spectroscopic and structural data (Table 1), CIF files and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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