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Oxidative Cyclization of a Phenolic Schiff Base and Synthesis of a Cyclometalated Ruthenium Nitrosyl Complex: Photoinduced NO Release by Visible Light

Kaushik Ghosh,* Sushil Kumar, Rajan Kumar, Udai P. Singh, and Nidhi Goel

Department of Chemistry, Indian Institute of Technology (IIT) Roorkee, Roorkee 247667, Uttarakhand, India

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The reactivity of σ-arylruthenium cyclometallate $[Ru(L^{SB1})(PPh_3)_2Cl]$ [**1**; $L^{SB1}H_2$ = 4-methyl-2-(4-nitrobenzylideneamino)phenol] with nitric oxide (NO) gave rise to nitrosylation at the metal center, ring nitration, and oxidative cyclization, affording benzoxazole derivative formation. The molecular structure of the resultant nitrosyl complex, $[Ru(L^{PB1})(PPh_3)_2(NO)Cl](ClO_4)$ [**2**; $L^{PB1}H$ = 5-methyl-7-nitro-2-(4-nitrophenyl)benzoxazole] was determined, and a different σ-arylruthenium cyclometallate was characterized in which the benzoxazole derivative was found to be coordinated to the metal center. The crystal structure and IR and NMR spectral data confirmed the formation of a diamagnetic $\{RuNO\}^6$ species with a $S = 0$ ground state and a $\{Ru^{II}NO^{+}\}^6$ description of the $\{RuNO\}^6$ moiety. Coordinated NO in the resultant complex **2** was photolabile under visible light and was transferred to reduced myoglobin.

Nitric oxide (NO) has been found to be an important signaling molecule involved in several physiological processes namely, blood pressure regulation, immune and endocrine response, neurotransmission, cell death, etc.[1] At the cellular level, NO is produced from L-arginine catalyzed by NO synthase (NOS); however, production of NO below the physiological level initiates different diseases like cardiovascular, neurological, and pulmonary diseases, atherosclerosis, and cancer.[2] In recent years, there has been considerable interest in the studies on the interaction of metal complexes with NO[2,3] and the synthesis of metal nitrosyl complexes by which NO could be delivered to a specific target on demand. Moreover, NO interaction with metal complexes, especially ruthenium complexes, is also important for scavenging of NO.[4] Metal complexes that can deliver NO upon light irradiation are important in photodynamic therapy.[5] Rose and Mascharak recently reviewed[6] research on photolabile ruthenium nitrosyl complexes by different research groups; however, in no instance was there an example of a cyclometalated ruthenium complex. On the other hand, there has been an upsurge of interest in the studies on cyclometalated ruthenium complexes because of their interesting photochemical and photophysical properties, which demand their application in solar cell and sensor devices.[7] Recently, Pfeffer and his co-workers reviewed[8] applications of cycloruthenated complexes, but none of them were utilized for light-induced delivery of NO.

We are interested in studying the interaction of NO with different ruthenium cyclometalates and their related complexes. Our quest was to synthesize cycloruthenated nitrosyl complexes that could deliver NO upon illumination of light. Herein we communicate the results of our NO interaction studies with a particular class of organoruthenium complexes $[Ru(L^{SB1})(PPh_3)_2Cl]$ [**1**; $L^{SB1}H_2$ = 4-methyl-2-(4-nitrobenzylideneamino)phenol and H_2 = dissociable protons; shown in Scheme 1]. The reactivity of NO with **1** afforded ruthenium cyclometalate $[Ru(L^{PB1})(PPh_3)_2(NO)Cl](ClO_4)$ [**2**; $L^{PB1}H$ = 5-methyl-7-nitro-2-(4-nitrophenyl)benzoxazole and H = dissociable proton]. Ligand nitration in the ring containing a phenolato function was also observed in the resultant nitrosyl complex. It has been found out that, in the resultant nitrosyl complex, coordinated NO is photolabile under irradiation of visible light and the liberated NO has been trapped by reduced myoglobin (Mb).

The organoruthenium precursor complex was synthesized by following the reported procedure.[9] We obtained the Schiff base ligand ($L^{SB1}H_2$) by condensation of 4-nitrobenzaldehyde and 2-amino-*p*-cresol, and **1** was synthesized. One $-CH_3$ group was introduced into the ligand frame to stop the formation of a ring-nitrated side product during NO interaction.[10]

*To whom correspondence should be addressed. E-mail: ghoshfcy@iitr.ernet.in.

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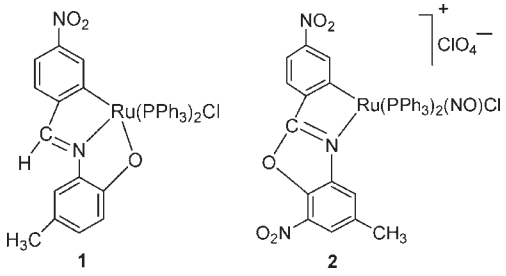
Scheme 1



The color of complex **1** was green in a dichloromethane solution. This green solution was treated with an acidified $NaNO_2$ solution with continuous stirring for 1 h. Acidified $NaNO_2$ is known to generate NO,[10] and we observed a color change from green to orange yellow. Considering substitution of Cl^- by the noninnocent ligand NO, we decided to provide ClO_4^- to the cationic ruthenium complex and isolated microcrystalline complex derived from **1** (details of the synthetic procedure are described in the Supporting Information). Recrystallized **2** gave rise to a characteristic ν_{NO} near 1830 cm^{-1} in the IR spectrum (in a KBr disk) along with peaks at 1090 and 630 cm^{-1}, which confirmed the presence of a ClO_4^- ion. Complex **2** was found to be diamagnetic and provided ^1H and ^{31}P NMR spectra (shown in the Supporting Information). The ^1H NMR spectrum clearly indicated the presence of methyl protons at ~2.5 ppm along with other protons present in the complex. The ^{31}P NMR spectrum provided a single peak at ~20 ppm, confirming the trans disposition of the PPh_3 groups.[11] All of these data supported the formation of ruthenium cyclometallate, with the most probable composition of $[Ru(L^{SB1})(PPh_3)_2(NO)](ClO_4)$ having a diamagnetic $\{Ru-NO\}^6$ moiety[12] and a $S = 0$ ground state being suggested. However, molecular structure determination revealed the formation of a different cycloruthenated complex, **2**, and the structure is shown in Figure 1.

During our studies on the reactivity of NO with other complexes of the family,[9] we observed that variation of the substituents in the ring containing the aldehyde group and the ring containing the phenolato function gave rise to a mixture of complexes and/or unstable products. We have not been successful yet in determining the molecular structures of those complexes; however, we observed during synthesis that substituent(s) in both rings exert significant effects on the stability of the resultant complexes. Complex **1** having $-NO_2$ and $-CH_3$ substituents in the ligand frame afforded **2** with good yield.

Complex **2** was found to be a ruthenium cyclometallate ligated to a substituted 2-phenylbenzoxazole derivative. The phenolato ligand got detached from the ruthenium center during NO interaction probably because of the trans effect of carbanion, and 180° rotation of the $N_{im}-C$ single bond gave rise to the proximity of the H atom of the HC=N− moiety and the phenolato function. These resulted the formation of an intramolecular C−O bond via oxidative cyclization and afforded a σ-arylorganoruthenium complex of substituted 2-phenylbenzoxazole. Ring nitration was also observed in the resultant nitrosyl complex, and nitration was found at the position ortho to the phenolato functional group. No reactivity was observed for the precursor complex with an acidified water solution without $NaNO_2$.

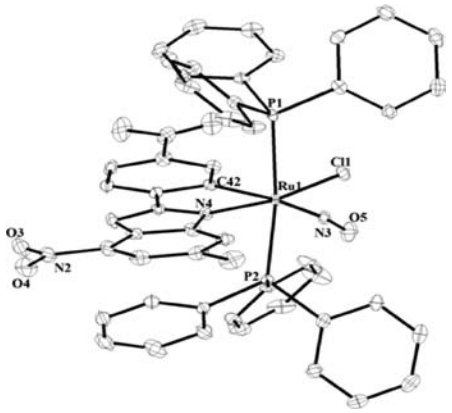


Figure 1. ORTEP diagram (50% probability level) of the cation of complex $2\cdot CH_2Cl_2$. All H atoms and solvent molecules are omitted for clarity. Selected bond distances (Å) and bond angles (deg): Ru1−Cl1 2.3616(6), Ru1−N3 1.802(2), Ru1−P1 2.4351(6), Ru1−P2 2.4742(7), Ru1−C42 2.109(2), Ru1−N4 2.099(2), N3−O5 1.134(3); Ru1−N3−O5 171.70(19), C42−Ru1−Cl1 91.80(7), C42−Ru1−N3 170.55(9), N3−Ru1−Cl1 97.35(6), N4−Ru1−Cl1 168.37(6), P1−Ru1−P2 167.73(2).

The molecular structure of the nitrosyl complex, **2**, clearly showed distorted octahedral geometry around the metal center. Carbanion and nitrogen from the substituted 2-phenylbenzoxazole moiety along with Cl^- and NO ligands constituted the equatorial plane, whereas two *trans*-PPh_3 groups acted as the axial ligands. This was consistent with our ^{31}P NMR data.[11] The $Ru-N_{NO}$ distance was found to be 1.802 Å, which is close to the value reported by Crutchley and co-workers.[7] However, it is longer than the distances reported in the literature,[13] maybe because of the trans effect of the carbanion.[14] The N−O distance in $2\cdot CH_2Cl_2$ was found to be the lowest among the values known in the literature.[13] These data and the Ru−N−O angle (171.9°) supported the $\{Ru^{II}NO^+\}^6$ description of the $\{Ru-NO\}^6$ moiety.[6] Complex **2** exhibited a quasi-reversible cyclic voltammogram (shown in Figure S8 in the Supporting Information) with an $E_{1/2}$ value of −0.246 V vs Ag/AgCl in dichloromethane. These data, along with metal−ligand distances, indicated the presence of Ru^{III} in **2**.[15]

At this stage, we are not sure whether NO or the complex itself is responsible for the unusual oxidative cyclization; however, the reaction of $L^{SB1}H_2$ with an acidified $NaNO_2$ solution was analyzed by UV−vis spectrometry[16] and gas chromatography−mass spectrometry (GC−MS; shown in the Supporting Information). These data indicated the possible role of NO in oxidative cyclization. In such types of reactions, the formation of a phenoxyl radical was predicted during cyclization and benzoxazole formation from the corresponding Schiff base.[17]

We speculate that NO probably was responsible for phenoxyl radical generation, and ultimately benzoxazole was synthesized

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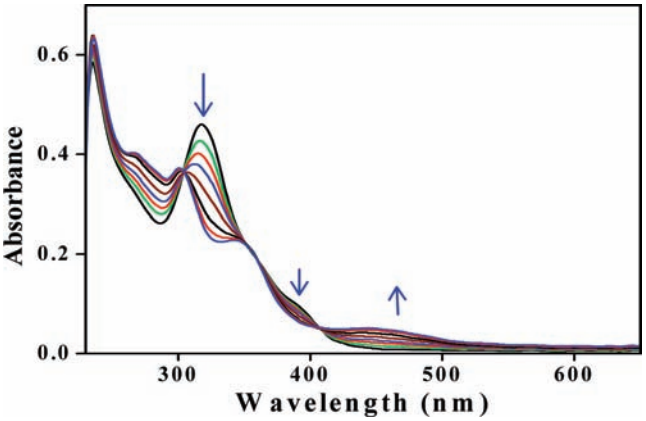

Figure 2. Photodissociation of complex **2** ($\sim 1.8 \times 10^{-5}$ M) in CH_3CN under illumination with a 60 W tungsten lamp. Repetitive scans were taken in 1 min intervals.

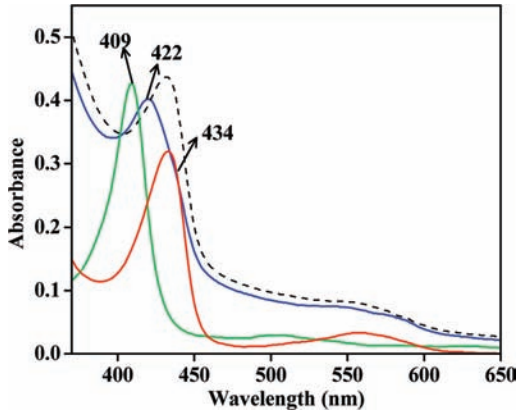

Figure 3. Electronic spectra of the conversion of reduced Mb to the Mb−NO adduct upon reaction with **2** in a buffer solution (50 mM phosphate buffer, pH 6.8) under exposure to the light of a 60 W tungsten lamp: green line, oxidized Mb (intense band at 409 nm); red line, reduced Mb (at 434 nm, with an excess of sodium dithionite); black dotted line, reduced Mb + solution of **2** in the dark for 30 min; blue line, Mb−NO adduct (at 422 nm), obtained by Mb + solution of **2** exposed to the light of a 60 W tungsten lamp for 10 min.

through C−O bond formation. The nitrosyl complex **2** is soluble in methanol, acetonitrile, dimethylformamide, acetone, dimethyl sulfoxide, and dichloromethane. In the dark, a solution containing the nitrosyl complex is stable; however, it loses NO when an acetonitrile solution of **2** is exposed to a 60 W tungsten lamp. The photolability of the coordinated NO was examined by UV−vis spectrometry with clear isosbestic points at 298 and 402 nm (Figure 2). After photocleavage of NO, the orange-yellow solution became brownish-red. Isolation and characterization of this brownish-red complex are in progress. The photolability of the coordinated nitrosyl was also confirmed by trapping liberated NO by reduced Mb. The peak at 422 nm designated the formation of Mb−NO species (shown in Figure 3).[15]

In summary, complex **2** was synthesized from **1** by acidified $NaNO_2$. We report here, to the best of our knowledge, the first example of a cyclometalated ruthenium complex that could deliver NO on demand. The role of the carboxamido N atom and the phenolato ligand was discussed[6] for the coordination and photolability of NO in ruthenium nitrosyl complexes; however, we are trying to reveal the role of the trans-directing carbanion ligand in this regard. The resultant nitrosyl complex **2** rapidly releases NO upon illumination of visible light; hence, these types of complexes could be used as potential NO donors in photodynamic therapy. To the best of our knowledge, this is the first example of an orthometalated ruthenium complex of 2-phenylbenoxazole, and these results open up avenues for the synthesis of orthometalated complexes and studies on their photophysical properties.[18] Coordination of 2-phenylbenzoxazole dye may be important in the photolability of coordinated NO.[19] Moreover, oxidative cyclization affording intramolecular C−O bond formation during NO interaction with ruthenium organometallics may provide us with the facile synthesis of biologically important[20] benzoxazole derivatives. Details of NO interaction and investigation of the mechanism along with studies on related complexes are in progress, and we are also trying to explore the photophysical and biological applications of the resultant complexes.

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Supporting Information Available: Experimental procedures and characterization by IR, ^1H and ^{31}P NMR, GC−MS, and cyclic voltammetry and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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