

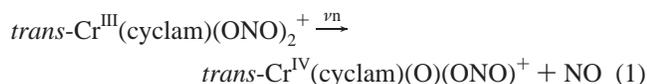
## Reversible Photolabilization of NO from Chromium(III)-Coordinated Nitrite. A New Strategy for Nitric Oxide Delivery

Malcolm De Leo and Peter C. Ford\*

Department of Chemistry, University of California  
Santa Barbara, California 93106

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Biological roles of nitric oxide have attracted considerable scrutiny over the past decade<sup>1</sup> and drawn renewed attention to the chemistry of NO.<sup>2</sup> Potential medical applications have stimulated interest in designing methodologies for NO delivery to biological targets.<sup>3</sup> Among possible methods, photochemical labilization of NO from an otherwise unreactive compound is attractive, given the opportunity to target specific tissues within an organism.<sup>4–6</sup> In this context, we have studied the photoreaction properties of several metal nitrosyl complexes including nitrosyl–iron sulfur clusters and metalloporphyrins.<sup>5,6</sup> A problem with certain systems is their thermal instability in the aerobic aqueous environments encountered under biological conditions. Accordingly, we are exploring other strategies and describe here NO generation from an air-stable, water-soluble complex via the photolytic cleavage of coordinated nitrite



Aqueous solutions of nitrite salts are known to undergo photodecomposition to give NO plus hydroxyl radicals when irradiated with UV light.<sup>7</sup> Extrusion of NO from coordinated nitrite was first suggested by Suslick et al.<sup>8</sup> as a photoreaction of Mn<sup>III</sup>(TPP)(ONO) in benzene (TPP = tetraphenylporphyrin). Later

matrix photochemistry<sup>9</sup> and laser flash photolysis studies<sup>10</sup> demonstrated this to be a minor pathway, the principal photoreaction for Mn<sup>III</sup>(TPP)(ONO) being reversible Mn–O cleavage to give Mn<sup>II</sup>(TPP) and NO<sub>2</sub>. Subsequently, Hoshino<sup>11</sup> demonstrated irreversible formation of Cr<sup>IV</sup>(TPP)(O) plus NO when Cr<sup>III</sup>(TPP)(ONO) is irradiated in benzene, the greater efficiency of N–O cleavage in this case likely due to the more oxophilic character of Cr(III). In this context, we have turned attention to the Cr(III) complex *trans*-Cr(cyclam)(ONO)<sub>2</sub><sup>+</sup> (**I**) (cyclam = 1,4,8,11 tetraazacyclotetradecane), which is indeed thermally stable in aerated aqueous solution. We report here that **I** undergoes a high quantum yield photoreaction that leads to NO formation (eq 1). Furthermore, *unlike* the precedents cited, this reaction is rapidly reversible in anaerobic media.

*trans*-[Cr(cyclam)(ONO)<sub>2</sub>](BF<sub>4</sub>) was prepared by the stoichiometric reaction of *trans*-[Cr(cyclam)Cl<sub>2</sub>]Cl with AgONO, recrystallized, and characterized by high-resolution FAB mass spectrometry and X-ray crystallography.<sup>12</sup> Its optical spectrum displays bands at λ<sub>max</sub> 336 nm (ε = 267 M<sup>-1</sup> cm<sup>-1</sup>) and 476 nm (40 M<sup>-1</sup> cm<sup>-1</sup>), and these can be assigned as an n–π\* intraligand band of coordinated nitrite (336 nm) and a Cr(III)-centered ligand field band in analogy to earlier assignments made by Harrowfield and Fee<sup>13</sup> for *trans*-[Cr(en)<sub>2</sub>(ONO)<sub>2</sub>]<sup>+</sup> (en = ethylenediamine).

When **I** was subjected to continuous photolysis (λ<sub>irr</sub> = 436 nm) in deaerated pH 7 aqueous solution (or under an Ar or NO atmosphere), a gradual shift of the absorption spectrum to that of the *trans*-Cr<sup>III</sup>(cyclam)(H<sub>2</sub>O)(ONO)<sup>+</sup> cation (**II**)<sup>14</sup> was observed. The quantum yield for this (seemingly) simple photoaquation is small (Φ<sub>aq</sub> = 0.0092 ± 0.0008), as has been noted for other *trans*-Cr(cyclam)X<sub>2</sub><sup>+</sup> cations (e.g., X = Cl) when subjected to ligand field excitation.<sup>15</sup> Aqueous solutions of **I** at pH 7 did not undergo measurable thermal reactions.

The spectral changes were entirely different when **I** was photolyzed in aerated aqueous solutions at different λ<sub>irr</sub> ranging from 365 to 546 nm (Figure 1). A new species **III** was observed, and extended photolysis gave a nearly limiting spectrum with a λ<sub>max</sub> = 364 nm and ε<sub>max</sub> ~2600 M<sup>-1</sup> cm<sup>-1</sup>.<sup>16</sup> On the basis of the spectral changes, the quantum yield for the transformation of **I** to **III** (Φ<sub>III</sub>) was determined to be 0.27 ± 0.03 at 436 nm, 30-fold larger than that for the photoaquation seen in deaerated solutions. The identity of **III** has not been firmly established. However, when **III** was isolated as a solid BPh<sub>4</sub><sup>-</sup> salt, the 298 K EPR spectrum proved to be that expected for a Cr(V) complex.<sup>17</sup> Furthermore, electrospray injection mass spectra of evolving photolysis solutions indicated the presence of a species consistent with the formulation [Cr<sup>V</sup>(cyclam)(O)(ONO)<sub>2</sub><sup>+</sup> (–H<sup>+</sup>)] (m/z =

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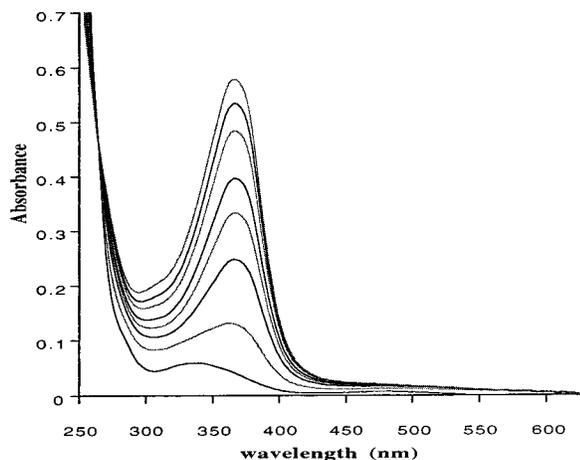
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(14) The spectral changes closely match those seen in the acid hydrolysis of **I** at pH 2 and are analogous to those reported for the acid hydrolysis of *trans*-[Cr(en)<sub>2</sub>(ONO)<sub>2</sub>]<sup>+</sup>.<sup>12</sup>

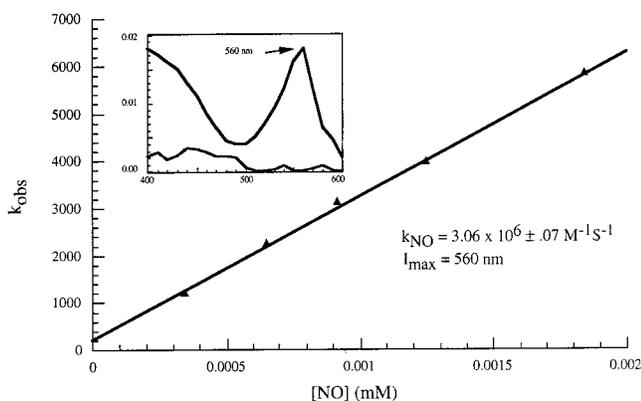
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(16) Solutions of **III** are not photoinert but evolve slowly under continued photolysis to a new species with a λ<sub>max</sub> at ~354 nm (perhaps the result of further nitrite photoaquation).

(17) (a) Lay, P. A.; Farrell, R. P. *Comments Inorg. Chem.* **1992**, *3*, 134–175. (b) The EPR spectrum of the solid isolated after long-term photolysis suggests a mixture of two Cr(V) species, one *trans*-Cr(cyclam)(O)(ONO)<sub>2</sub><sup>+</sup>, the other perhaps *trans*-Cr(cyclam)(O)<sub>2</sub><sup>+</sup>.



**Figure 1.** Continuous photolysis ( $\lambda_{\text{irr}} = 436 \text{ nm}$ ) of  $\text{trans-Cr}(\text{cyclam})\text{-(ONO)}_2^+$  in pH 7, aerated aqueous solution over 140 min.



**Figure 2.** Plot of  $k_{\text{obs}}$  vs  $[\text{NO}]$  for transient decay of **IV** in 296 K aqueous solutions. ( $\lambda_{\text{mon}} = 560$ ,  $\lambda_{\text{irr}} = 355 \text{ nm}$ ). Inset shows point by point spectrum of **IV**.

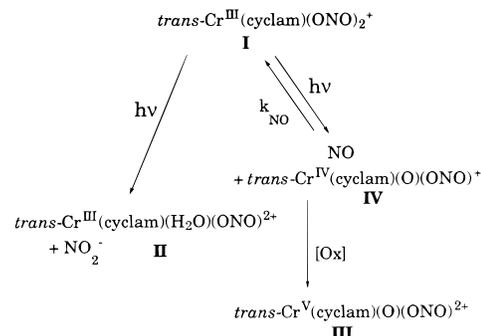
313).<sup>18</sup> Nitric oxide formation was confirmed by carrying out similar photolyses of **I** in aerated solutions in the presence of a NO-specific electrode sensor.<sup>19</sup>

The continuous photolysis experiments suggested the possibility that NO is liberated from **I**, but the back reaction is efficient unless  $\text{O}_2$  is present to trap some key intermediate. To test this model, flash photolysis experiments ( $\lambda_{\text{irr}} = 355 \text{ nm}$ ) were carried out on aqueous solutions of **I** (1 mM) using time-resolved optical (TRO) techniques with variable, single wavelength (PMT) or multiple wavelength (CCD) detection.<sup>6c</sup> In deaerated solution, a transient (**IV**) was observed with difference spectrum maxima at 400 and 560 nm (Figure 2). This decayed back to the spectrum of **I** via temporal absorbance changes which could be fit, roughly, to a second-order rate law. The kinetics behavior was more firmly established by carrying out TRO experiments with varying  $[\text{NO}]$ , under which conditions exponential decay of the 560 nm absorbance was seen. A plot of the resulting  $k_{\text{obs}}$  values vs  $[\text{NO}]$  was linear with an intercept near the origin (Figure 2); thus,  $k_{\text{obs}} = k_{\text{NO}}[\text{NO}]$  with  $k_{\text{NO}} = (3.06 \pm 0.07) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ . A similar

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### Scheme 1



flash experiment in aerated aqueous solution showed some decay back to the starting complex but gave residual absorbances consistent with some permanent photoproduct.

We interpret these observations in terms of two competing primary photoreactions of  $\text{trans-Cr}(\text{cyclam})(\text{ONO})_2^+$ , homolytic dissociation of NO from a coordinated nitrite to form the Cr(IV) intermediate **IV**<sup>20</sup> and Cr–ONO photoaquation to **II** (Scheme 1). The latter reaction is irreversible, but **IV** can either back react with NO to regenerate **I** or be trapped by oxygen to give a more stable Cr(V) complex, i.e., **III**. The latter leads to net release of NO detectable by the electrochemical experiment. In the absence of such trapping the only net photoreaction seen is the low quantum yield formation of **II**.

In summary, we have demonstrated that photolysis of  $\text{trans-Cr}(\text{cyclam})(\text{ONO})_2^+$  in aqueous solution leads to the formation of an intermediate complex believed to be  $\text{trans-Cr}^{\text{IV}}(\text{cyclam})(\text{O})(\text{ONO})^+$  with concurrent production of NO. In the presence of  $\text{O}_2$ , the putative Cr(IV) species is trapped to give a more stable Cr(V) complex. However, in the absence of such oxidative quenching, the unprecedented back reaction of **IV** with NO occurs with the second-order rate constant  $k_{\text{NO}} = 3.06 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ . Under such conditions, the only net reaction is the competing low yield photoaquation of  $\text{NO}_2^-$ . These results clearly demonstrate the viability of NO-delivery schemes based upon the photochemical decomposition of coordinated nitrite.

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(20) (a) Assigning **IV** as the Cr(IV) oxo complex  $\text{trans-Cr}(\text{cyclam})(\text{O})(\text{ONO})$  draws support from spectral comparison with the isoelectronic Mn(V) nitrido complexes  $\text{trans-Mn}^{\text{V}}(\text{cyclam})(\text{N})(\text{X})$  which display overlapping spin allowed d–d bands with  $\lambda_{\text{max}}$  at  $\sim 580$  and  $495 \text{ nm}$ .<sup>20b</sup> Also, Bakac has demonstrated that Tl(III) oxidation of  $\text{trans-Cr}^{\text{II}}(\text{cyclam})(\text{H}_2\text{O})_2^{2+}$  generates a spectrum with features analogous to **IV** and proposed this short-lived species to be  $\text{trans-[Cr}^{\text{IV}}(\text{cyclam})(\text{O})(\text{H}_2\text{O})]^{2+}$ .<sup>20c</sup> (b) Meyer, K.; Bendix, J.; Metzner-Nolte, N.; Wehermuller, T.; Wieghardt, K. *J. Am. Chem. Soc.* **1998**, *120*, 7260–7270. (c) Bakac, A., personal communication.

(21) (a) A reviewer suggested that **I** should be viewed as a precursor for photochemical generation of peroxyxynitrite ion (rather than of NO). The reasoning was that **IV** is trapped by  $\text{O}_2$ , and a likely product of that reaction is superoxide ion which is known to react very rapidly with NO to give  $\text{OONO}^-$ .<sup>21b</sup> This point indeed was probed using negative ion electrospray mass spectroscopic analysis<sup>18</sup> of photolysis products of **I** in aerated aqueous solutions. Peaks for nitrate ion (the expected product of peroxyxynitrite rearrangement) were comparable in intensity to those for nitrite (the product of NO autoxidation),<sup>21c</sup> suggesting that some NO was indeed trapped by superoxide. However, it should be emphasized that the major primary photoreaction is the high quantum yield transformation of **I** to **IV**, and flash and continuous photolysis evidence point convincingly to NO as the other primary photoproduct. (b) Blough, N. V.; Zaffiriou, O. C. *Inorg. Chem.* **1985**, *24*, 3502–3504. (c) Wink, D. A.; Darbyshire, J. F.; Nims, R. W.; Saavedra, J. E.; Ford, P. C. *Chem. Res. Toxicol.* **1993**, *6*, 23–27.