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Photoreactions of coordinated nitrite ion. Reversible nitric oxide labilization from the chromium(III) complex [*trans*-Cr(cyclam)(ONO)$_2$]$^+$

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Contents

Abstract

An overview of the observed and likely photochemistry of transition metal nitrito compounds is presented with particular attention to the potential of using such nitrite ion complexes as the photochemical source for nitric oxide delivery to biological targets. In this context, recent studies at Santa Barbara regarding the photoreactions of the chromium(III) complex *trans*-Cr(cyclam)(ONO)$_2^+$ (cyclam = 1,4,8,11 tetraazacyclo-tetradecane) to give NO plus Cr(IV) (and subsequently Cr(V) complexes in the presence of dioxygen) are described.

Keywords: Photochemistry; Metal nitrito compounds; Dioxygen; Nitric oxide

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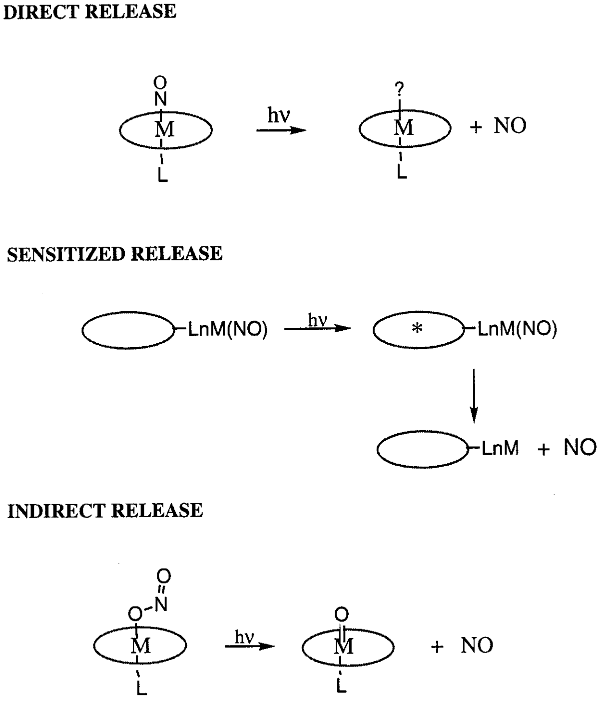
1. Introduction

The discoveries a decade ago that nitric oxide plays major roles as a bioregulator in the cardiovascular system and as an important component of immune response to pathogen invasion [1–4] have stimulated considerable recent interest in the chemistry and mammalian biology of NO [5–7]. Aspects that have drawn attention and that of others are the potential biomedical applications derived from designing new compounds and methodologies for NO delivery upon demand to specific biological targets. Besides likely cardiovascular applications, NO may find possible use as a sensitizer in the radiation therapy of solid tumors [8,9] and has been the origin of speculation regarding other cancer chemotherapeutics [10].

With this motivation, we were drawn to the idea of using photochemistry to provide the signal for labilization of NO from an otherwise unreactive compound, since this technique would allow targeting specific tissues within an organism. Consequently, studies at UC Santa Barbara have probed the quantitative photoreactivity of various metal nitrosyl complexes including heme nitrosyls [11], ruthenium porphyrin nitrosyls [12], nitroprusside [13] and the Roussin's black and red salts [14]. Each of these demonstrate the 'direct release' of NO from a metal nitrosyl chromophore (Scheme 1), and the Roussin's red salt was successfully used to generate NO upon photochemical demand in V79 Chinese hamster lung cell cultures and to demonstrate NO sensitization of radiation induced cell death [14].



Scheme 1. Strategies for photochemical NO release.

An apparent requirement of photochemical delivery is the necessity to prepare compounds which have strong absorption cross sections and are photolabile at (long) irradiation wavelengths (λ_{irr}) where tissue penetration is maximized. The Roussin's red salt is indeed photolabile toward NO release at longer λ_{irr}, however, the absorptivities are relatively low [14]. For this reason we have also turned to the preparation of related compounds which carry an additional substituent, such as a dye molecule, to serve as an internal sensitizer (Scheme 1) [15]. In such a complex, red light absorption by the antenna is followed by energy (or electron) transfer to the metal nitrosyl chromophore leading to eventual 'sensitized release' of NO.

The third approach, which is referred to as 'indirect NO release' is the subject of the present article. In this case, the source of the nitric oxide is not a metal nitrosyl but instead is another ligand such as nitrite ion which may undergo decomposition to form NO (Scheme 1).

2. Photoreactions of metal nitrito complexes

Although the photochemistry of nitrito complexes is relatively undeveloped, one might anticipate various photoaquation, photoisomerization, photoreduction and photodecomposition pathways as shown in Scheme 2.

The oxygen coordinated nitrito (as opposed to the nitrogen bound nitro) ligand is a relatively weak field ligand. Thus, one might expect it to be relatively labile toward photoaquation from metal complexes which have lowest energy ligand field excited states defined by the weaker field ligands. This would certainly be the expectation for hexacoordinate complexes of metal centers with the d^6 electronic

1. Photoaquation

$$L_xM(ONO)^{n+} + H_2O \xrightarrow{h\nu} L_xM(H_2O)^{(n+1)+} + NO_2^-$$

2. Photoisomerization

$$L_xM(ONO)^{n+} \xrightarrow{h\nu} L_xM(NO_2)^{n+}$$

3. Photoreduction

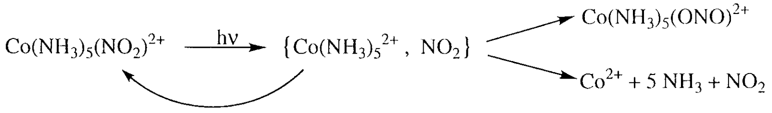
$$L_xM(ONO)^{n+} \xrightarrow{h\nu} L_xM^{n+} + NO_2$$

4. Photodecomposition

$$L_xM(ONO)^{n+} \xrightarrow{h\nu} L_xM(O)^{n+} + NO$$

Scheme 2.

configuration, although there appear to be few examples in the literature where ONO-photolabilization has been considered [16]. Photoisomerization of a nitrito complex to its nitro isomer would be the microscopic reverse of the nitro-to-nitrito linkage isomerization reported for the photolysis of cobalt(III) amine complex ions such as $Co(NH_3)_5(NO_2)^{2+}$ [17,18]. For this complex nitro-to-nitrito photoisomerization is generally attributed to competitive reactions of a radical pair $\{Co(NH_3)_5^{2+}, NO_2\}$ generated by ligand to metal charge transfer (LMCT) excitation (Eq. (1)). Geminate recombination of the $Co(NH_3)_5^{2+}$ fragment with NO_2 at the oxygen would give the nitrito isomer while reaction at the nitrogen regenerates the nitro species. The competing diffusion of the radicals out of the cage leads to net photoreduction to Co(II) [18]. Similar linkage photoisomerization has been reported for Rh(III), Ir(III) and Pt(IV) analogs [17,19]. The same type of radical pair might easily be generated from photolysis of the nitrito isomer, and, as seen below, homolytic cleavage of the metal oxygen bond to give the reduced metal center plus NO_2 is a common photoreaction pathway of the nitrito complexes. However, while there is evidence for formation of a nitro isomer in the bimolecular trapping of NO_2 with metal radicals generated by flash photolysis of a nitrito complex (see below), we are unaware of a system demonstrated to follow an ‘intramolecular’ nitrito-to-nitro mechanism via the radical pair intermediate. The common observation is net photoreduction of the metal center by homolytic α-cleavage of the M–ONO bond.



(1)

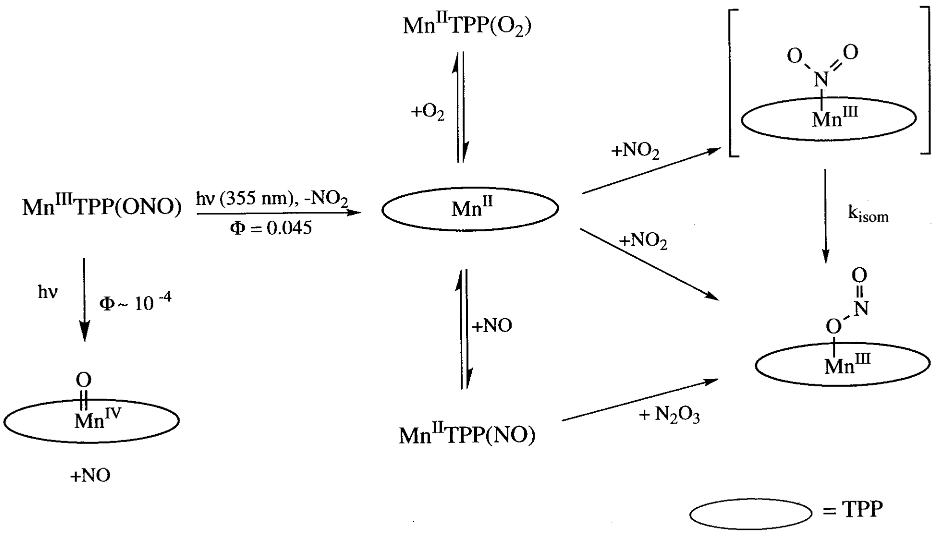
The fourth pathway illustrated in Scheme 2 is photodecomposition to NO plus an oxo-metal species via β-cleavage of an oxygen nitrogen bond, and this reaction is the focus of the research described in the present article. It is especially notable that ultraviolet irradiation of aqueous solutions of free nitrite ion leads to the generation of NO plus intermediates argued to be the hydroxyl radical (Eq. (2)) [20,21]. Analogous decomposition of nitrite bound to a redox active metal center would give the photochemistry suggested in Scheme 1 for the indirect production of NO and in Scheme 2 for the photodecomposition pathway. As will be noted below, there are several precedents for this pathway involving nitrito complexes of metal porphyrins.

$$NO^-_{2aq} \xrightarrow{hv} NO + OH^- + OH^\bullet \qquad (2)$$

The stimulus for the early investigations of the photodecomposition pathway for coordinated nitrito ligands found its origin in the report by Suslick et al. [22] which suggested that photolysis of the manganese(III) nitrito complex $Mn^{III}(TPP)(ONO)$ in benzene (TPP = tetraphenylporphyrin) led to extrusion of NO to give the oxo complex $Mn^{IV}(TPP)(O)$. The Mn^{IV} product was identified from its electronic spectrum and from its trapping by PPh_3 to give $OPPh_3$. Later low temperature matrix studies by the same laboratory concluded that the primary photoreaction was not the β-cleavage of the O–NO bond but was instead homolytic α-cleavage of the Mn–ONO bond to give Mn^{II}(TPPP) (identified spectroscopically). It was further concluded that formation of Mn^{IV} oxo complexes was the result of secondary thermal reactions [23]. Flash photolysis studies by Hoshino et al. [24] confirmed that the principal photolysis products from Mn(TPP)(ONO) were Mn^{II}(TPP) plus NO_2. However, in that same article, these authors did indeed demonstrate the β-cleavage pathway by observing the irreversible formation of Cr^{IV}(TPP)(O) plus NO when Cr^{III}(TPP)(ONO) was irradiated in benzene ($\phi = 0.1$ for $\lambda_{irr} = 355$ nm). The Cr^{IV} product was identified spectroscopically while the NO formation was demonstrated by trapping studies with Co^{II}(TPP). The greater efficiency of O–N β-cleavage in this case can be attributed to the more oxophilic character of the chromium which strengthens the Cr–O bond and weakens the O–N bond as demonstrated by the thermal decomposition of Cr^{III}(TPP)(ONO) also proceeding via the β-cleavage process (Eq. (3)).

$$Cr^{III}(TPP)(ONO) \xrightarrow{h\nu} CR^{IV}(TPP)(O) + NO \tag{3}$$

A more thorough flash photolysis investigation of Mn^{III}(TPP)(ONO) in toluene by Hoshino, Ford et al. [25] demonstrated that photoreduction to give Mn^{II}(TPP) plus NO_2 in a reversible reaction ($\phi = 0.045$ at 355 nm) is the dominant primary pathway but a minor permanent photoreaction could be attributed to net formation of Mn^{IV}(TPPP)(O) ($\phi \sim 10^{-4}$). However, the mechanism by which this minor product was formed was not explored in depth. On the other hand, the flash photolysis technique did prove to be an effective way to investigate the rapid trapping of the reactive complex Mn^{II}(TPP) by NO_2, NO and O_2 (Scheme 3). The second order rate constants at 298 K followed the order NO_2 (2.2×10^9 M^{-1}



Scheme 3. Photoreactions of Mn^{III}(TPP)(ONO).

$s^{-1}) > NO$ (5.3×10^8 M^{-1} s^{-1}) $> O_2$ (1.9×10^7 M^{-1} s^{-1}). Under the reaction conditions, the products of the latter two processes were less stable than the starting material and eventually reacted to reform $Mn^{III}(TPP)(ONO)$. Another interesting feature of Scheme 3 is that there appeared to be two products of the reaction of NO_2 with $Mn^{II}(TPP)$, the major product being the starting complex, the minor one appearing to be an isomer which subsequently undergoes unimolecular relaxation ($k_{isom} = 14$ s^{-1}) to reform $Mn^{III}(TPP)(ONO)$. It was proposed that this isomer is the nitro complex $Mn^{III}(TPP)(NO_2)$ formed by competitive trapping at the nitrogen and represents photoinduced nitrito-to-nitro linkage isomerization. However, the only evidence supporting this contention is the kinetic behavior of the various species.

Another nitrito complex that has been subjected to quantitative photochemical investigation is the molybdenum(V) species $Mo^V(TPP)(O)(ONO)$ in benzene [26]. Again the photochemistry of this species is dominated by metal center photoreduction via homolytic α-cleavage of the Mo–ONO bond ($\phi = 0.3$ at ambient temperature at both 355 and 532 nm) as might be expected for a high valent metal center. Similarly, the platinum(IV) complex fac-$PtCl_3(NO_2)_3^{2-}$ loses NO_2 upon photolysis to give a trivalent platinum complex $PtCl_3(NO_2)_2^{2-}$. This decays spontaneously with loss of a second NO_2 to platinum(II) products [27].

3. Studies of chromium(III) nitrito complexes

Hoshino's results with the Cr(TPPP)(ONO) photochemistry clearly suggested that with a sufficiently oxophilic metal, coordinated nitrite can serve as a NO precursor. In this context, we turned to the amine complexes of Cr(III) to see if this photochemical behavior had generality beyond the metalloporphyrins. Another attractive property of these amine complexes is their solubility in water, a feature likely to be desirable in biomedical applications. In addition, the spectra of the saturated amine complexes are considerably less complex than the metalloporphyrins which are dominated spectrally by the π–π* transitions of the ligands. However, the obvious disadvantage of such compounds is the absence of a strong chromophore to provide the necessary absorption cross section for practical biomedical applications as a photochemical delivery agent.

The first of such species examined was the simplest, the pentaamminechromium(III) complex $Cr(NH_3)_5(ONO)^{2+}$ (**I**). The optical absorption spectrum of **I** is defined by the Laporte forbidden ligand field (d–d) transitions, the lowest energy quartet absorption lying at 482 nm ($\varepsilon = 43$ M^{-1} cm^{-1}). A second band lies at 356 nm with an intensity (37 M^{-1} cm^{-1}) consistent with the next higher energy quartet band but also in the region where the internal ligand n–π* band of the nitrito functionality is expected [28]. Notably, the spin and Laporte forbidden transition to the lowest energy doublet state, which is probably the lowest energy state, was not discernible in the aqueous solution absorption spectrum. When freshly prepared solutions of **I** (1 mM, pH 7) were irradiated with the broad band white light from a 75 W high pressure xenon arc lamp and the formation of NO was monitored electrochemically [13], it was clear that NO was being formed in the reaction solution. The NO signal generated from **I** was compared against a standard solution of NO added as a bolus and the electrochemical behaviors of the two solutions were comparable. Control photolysis experiments with solutions of ammonia (0.2 M), sodium nitrite (0.2 M) and NO_2 (saturated solution) in the presence and absence of light were performed to rule out false positive signals. So it is clear that photolysis of **I** generates NO, although the quantum yields were not evaluated owing to the instability of this species to thermal reactions under the photolysis conditions. Furthermore, it was apparent that the $Cr(NH_3)_5(ONO)^{2+}$ ion was undergoing other photochemistry as would be predicted by Adamson's rules for Cr(III) photochemistry which propose the labilization of the stronger field ligand on the weak field axis, i.e. the ammine *trans* to the nitrito ligand [29].

With these properties in mind, we then sampled the photoreactivity of the chelating amine complex [*cis*-$Cr(cyclam)(ONO)_2^+$ (**II**) (cyclam = 1,4,8,11-tetraazacyclotetradecane), the synthesis of which had been reported by Tobe and Ferguson [30]. Again the longer wavelength absorption band of this species in aqueous solution (λ_{max} 481 nm, ε 134 M^{-1} cm^{-1}) can be assigned to excitation into the lowest energy quartet state and a more intense band at 355 nm (211 M^{-1} cm^{-1}) can be assigned as having ligand n–π* character [31]. When freshly prepared solutions of the nitrite salt of this ion (0.5 mM, pH 7) were photolyzed by output of the 75 W xenon lamp passed through different band pass filters (325–375, 380–480 and 470–560 nm), NO generation was detected in each case using the NO specific electrode. However, again owing to the relative instability of these complexes to thermal processes under the experimental conditions, quantum yields were not determined. Nonetheless these experiments clearly indicated that NO generation is a photochemical property of Cr(III) nitrito complexes even under relatively long wavelength excitation.

In this context, we turned attention to the preparation [32] and photochemical properties [33,34] of the new species *trans*-$Cr(cyclam)(ONO)_2^+$ (**III**), which is indeed thermally stable in aerated aqueous solution. This was prepared as the BF_4^- salt by the stoichiometric reaction of *trans*-$[Cr(cyclam)Cl_2]Cl$ with AgONO, precipitation by addition of excess NaBF4, recrystallized and characterized by high resolution FAB mass spectrometry and X-ray crystallography. Its optical spectrum displays bands at λ_{max} 336 nm ($\varepsilon = 267$ M^{-1} cm^{-1}) and 476 nm (40 $M^{-1}cm^{-1}$), and these can be assigned as a n–π* intraligand band of coordinated nitrite (336 nm) and a Cr(III) centered ligand field (quartet) band in analogy to earlier assignments made by Harowfield and Fee [31] for *trans*-$[Cr(en)_2(ONO)_2]^+$ (en = ethylenediamine).

When **III** was subjected to continuous photolysis ($\lambda_{irr} = 436$ 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*-$Cr^{III}(cyclam)(H_2O)(ONO)^+$ cation (**IV**) was observed. The spectral changes closely match those seen in the acid hydrolysis of **III** at pH 2, and are analogous to those reported for the acid hydrolysis of *trans*-$[Cr(en)_2(ONO)_2]^+$. Thus, we conclude that the net photoreaction under these conditions is simple photoaquation (Eq. (4)). The quantum yield for this (seemingly) simple photoaquation is small ($\Phi_{aq} = 0.0092 \pm 0.0008$), consistent with the

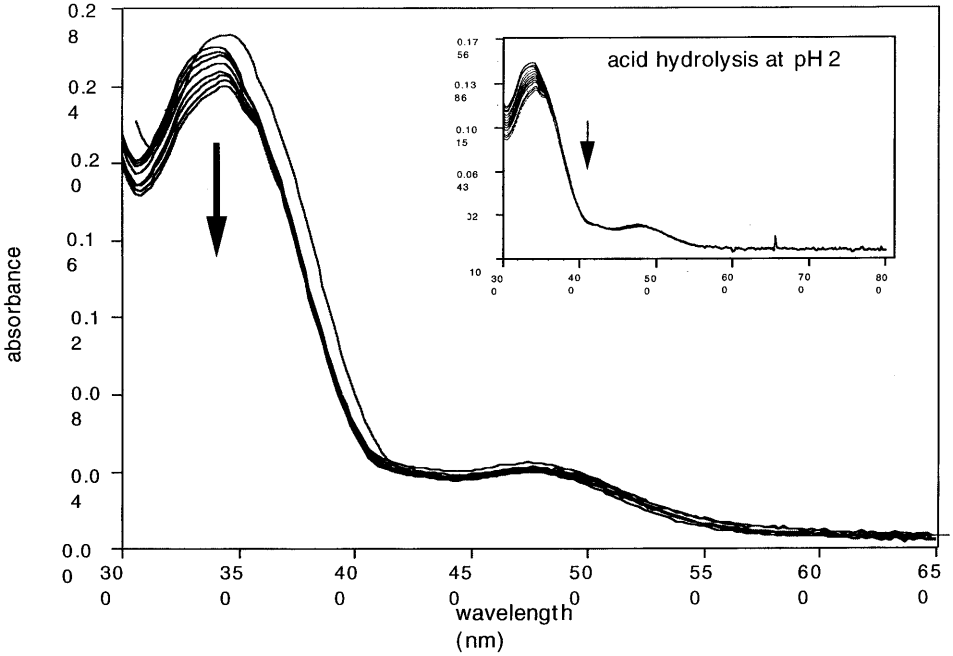


Fig. 1. Photolysis of *trans*-Cr(cyclam)(ONO)$_2^+$ in deaerated aqueous solution. Inset shows the spectral changes resulting from the slow hydrolysis at pH 2.

very low photoreactivity that has been noted for other *trans*-Cr(cyclam)X$_2^+$ cations (e.g. X = Cl) when subjected to ligand field excitation [35]. Aqueous solutions of **III** at pH 7 did not undergo measurable thermal reactions.

$$trans\text{-Cr(cyclam)(ONO)}_2^+ + H_2O \xrightarrow{h\nu} trans\text{-[Cr(cyclam)(ONO)(H}_2\text{O)}^{2+}] + \text{ONO}^- \quad (4)$$

The spectral changes were entirely different when **III** was photolyzed in aerated aqueous solutions at different λ_{irr} ranging from 365 to 546 nm (Fig. 1). A new species **V** was observed, and extended photolysis gave a nearly limiting spectrum with a $\lambda_{max} = 364$ nm and $\varepsilon_{max} \sim 2600$ M^{-1} cm^{-1}. However, solutions of **V** were not photoinert but evolved slowly under continued photolysis via a low quantum yield process to a new species with a λ_{max} at ~ 354 nm, (perhaps the result of further nitrite photoaquation.)

The spectrum of **V** was estimated by following the changes in a photolysis solution of **III** using both optical absorption spectroscopy and the electrospray injection mass spectrometry. At the point when the mass spectrum indicated complete consumption of **III**, the absorption spectrum was considered to be that of **V**. Based on this spectrum for the product, the quantum yield for the transformation of **III** to **V** (ϕ_V) was determined to be 0.27 ± 0.03 at 436 nm, 30-fold larger than that for the photoaquation seen in deaerated solutions under analogous conditions including the intensity of the light absorbed by the solution (I_a), (1.0×10^{16} quanta l^{-1} s^{-1}). It is notable, however, that this quantum yield is dependent on I_a and that ϕ_V varied from 0.14 at the relatively high I_a value of 1×10^{19} quanta l^{-1} s^{-1} to 0.50 at 4×10^{17} quanta l^{-1} s^{-1}. This type of intensity dependence is indicative of a bimolecular back reaction of reactive intermediates in competition with unimolecular processes leading to the observed products [36].

The identity of **V** has not been firmly established. When $NaBPh_4$ was added a solution deemed to have been photolyzed to near completion, **V** was isolated as a solid BPh_4^- salt. The 298 K EPR spectrum of this material proved to be that expected for a Cr(V) complex [37], although that of the solid isolated after long term photolysis suggests a mixture of two Cr(V) species, one with a nitrogen in the axial position, perhaps *trans*-Cr(cyclam)(O)(ONO)$^{2+}$, the other being the dioxo-species *trans*-Cr(cyclam)(O)$_2^+$. Furthermore, electrospray injection mass spectra of evolving photolysis solutions indicated the presence of a species consistent with the formulation [Cr^V(cyclam)(O)(ONO)$^{2+}$ $(-H^+)$] ($M/Z = 313$).

Nitric oxide formation was confirmed by carrying out similar photolysis of **III** in aerated solutions in the presence of a NO specific electrode sensor [13]. Qualitatively, these signals indicated that the efficiency of NO labilization from **III** was of the order of magnitude seen in photolyses of the Roussin's red salt anion and esters ($\Phi_{NO} \sim 0.1$) under analogous conditions [14]. The signals from **I**, however, decayed at rates faster than those generated by adding standard NO solutions, suggesting that decay processes other than autoxidation or diffusion from the solution may be playing a role.

These continuous photolysis experiments suggested that NO is liberated from **III**, but the back reaction is efficient unless O_2 is present to trap some key intermediate. To test this model, flash photolysis experiments ($\lambda_{irr} = 355$ nm) were carried out on aqueous solutions of **III** (1 mM) using time resolved optical spectral techniques with variable, single wavelength (PMT) or multiple wavelength (CCD) detection. In deaerated solution, a transient (**VI**) was observed with difference spectrum maxima at 400 and 560 nm (Fig. 2). This decayed back to the spectrum of **III** via temporal absorbance changes which could be fit, roughly, to a second order rate law. A similar flash experiment in aerated aqueous solution showed some decay back to the starting complex, but gave residual absorbances consistent with some permanent photoproduct. The kinetic behavior was firmly established by carrying out time resolved optical (TRO) experiments with excess NO at varied concentrations, under which conditions exponential decay of the 560 nm absorbance was seen. A plot of the resulting k_{obs} values versus [NO] was linear with an intercept near the origin (Fig. 2). Therefore, $k_{obs} = k_{NO}[NO]$ and $k_{NO} = (3.06 \pm 0.07) \times 10^6$ M^{-1} s^{-1}.

We interpret these observations in terms of two competing primary photoreactions of *trans*-Cr(cyclam)(ONO)$_2^+$. The major pathway is reversible homolytic dissociation of NO from a coordinated nitrite to form the Cr(IV) intermediate **VI** [20] (Eq. (5)), while a minor pathway is Cr-ONO photoaquation to **IV** (Eq. (4)). We conclude that **VI** is *trans*-Cr(cyclam)(O)(ONO)$^+$ (or the nitro isomer) and this assignment draws support from spectral comparison with the isoelectronic Mn(V) nitrido complexes *trans*-Mn^V(cyclam)(N)(X) which display overlapping spin al-

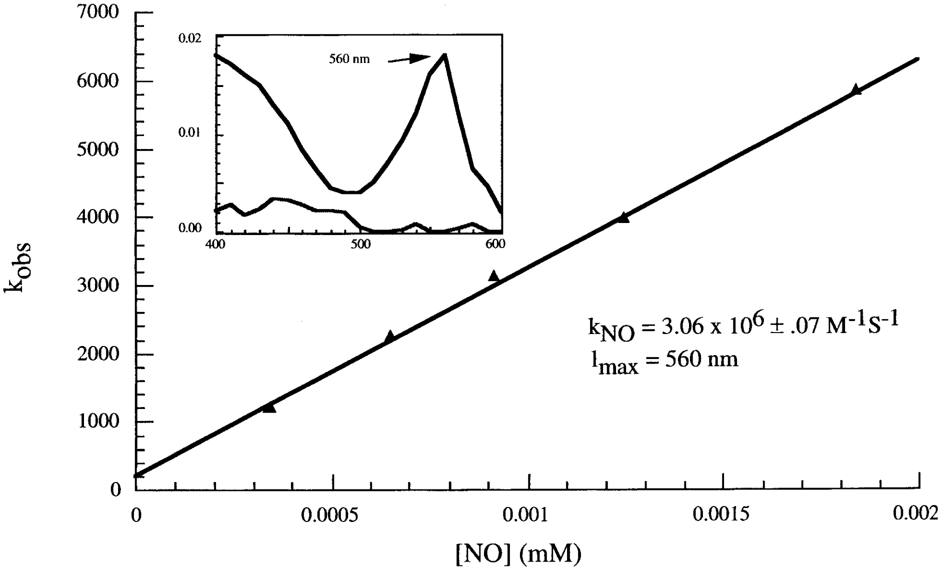


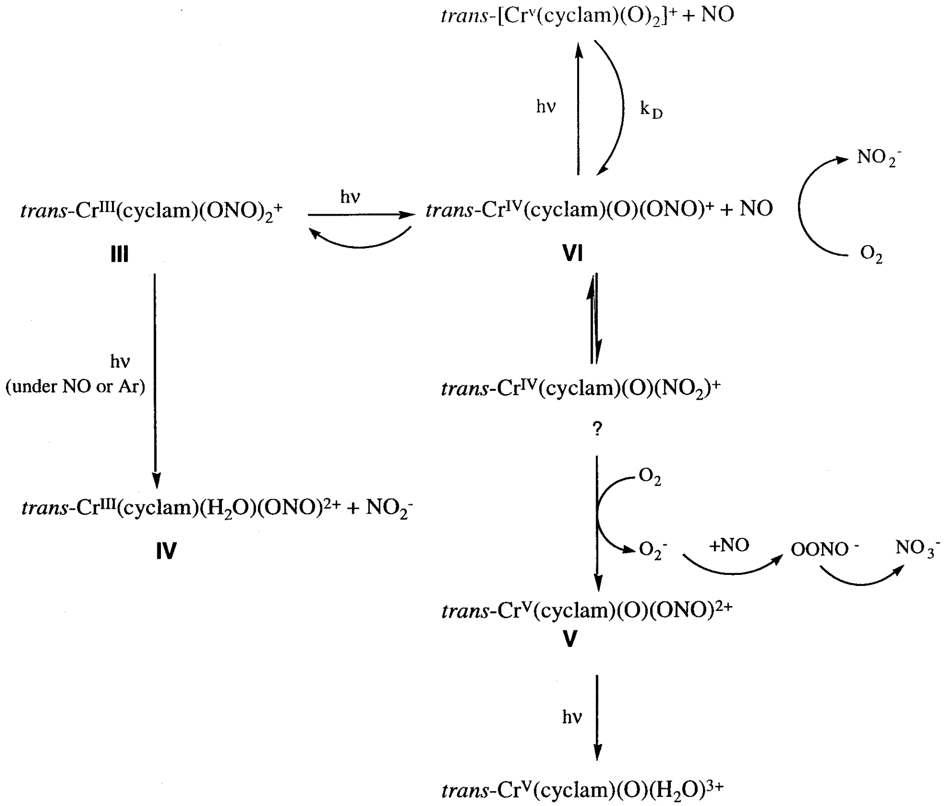
Fig. 2. Plot of k_{obs} vs. [NO] for transient decay of **VI** in 296 K aqueous solutions ($\lambda_{mon} = 560$, $\lambda_{irr} = 355$ nm). Inset shows point-by-point spectrum of **VI**.

lowed d–d bands with λ_{max} at ca. 580 and 495 nm [38]. The photoaquation appears irreversible, but **VI** can either back react with NO to regenerate **III** or be trapped by oxygen to give a more stable Cr(V) complex, i.e. **V**. 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 **IV**.

$$trans\text{-Cr(cyclam)(ONO)}_2^+ \xrightarrow{hv} trans\text{-Cr(cyclam)(ONO)(O)}^+ + \text{NO} \tag{5}$$

Scheme 4 illustrates the fundamental details outlined above but ignores some fine points in the detailed investigation reported elsewhere [34]. An example of the latter is when the photolyses were carried out under relatively low [O_2]. The mixture of the Cr(V) products changed from mostly **V** to one in which *trans*-Cr(cyclam)(O)_2^+ is apparently present in much higher proportion. This was concluded to be the result of secondary photolyses of reactive intermediates, perhaps **VI**. However, in aerated solution, the pathways outlined in this scheme are adequate to explain the product distributions.

One consequence of this mechanism is that, if **VI** is trapped by O_2, a likely product of that reaction is superoxide ion which reacts very rapidly with NO to give OONO^- [39]. This point indeed was probed using negative ion electrospray mass spectroscopic analysis of photolysis products of **I** in aerated aqueous solutions. Peaks for nitrate ion (the product of peroxynitrite rearrangement) were comparable in intensity to those for nitrite (the product of NO autoxidation) [40], suggesting that some NO was indeed trapped by superoxide.



Scheme 4.

It is also notable that the photodecomposition of the Cr(III) coordinated nitrito ligand occurs at visible range wavelengths where the only absorptions are those which can be assigned to the ligand field transitions. The weak spin allowed, but Laporte forbidden, quartet to quartet absorptions dominate the visible spectrum, although for these hexacoordinate Cr(III) complexes, it is likely that the lowest energy excited state is a ligand field doublet state. Thus, it would be interesting to explore the significance of a correlation between the ligand field doublet state and the doublet spin state of the products consisting of NO (with one unpaired electron) and **VI**, which is likely to be diamagnetic in analogy to other d^2 complexes with strong π-donor ligands. This issue will be explored further.

In summary, the photolysis of *trans*-Cr(cyclam)(ONO)$_2^+$ in aqueous solution has been demonstrated to lead to the formation of an intermediate complex believed to be *trans*-Cr^{IV}(cyclam)(O)(ONO)$^+$ with concurrent production of NO. In the presence of O_2, the putative Cr(IV) species is trapped to give a more stable Cr(V) complex. In the absence of such oxidative quenching, the unprecedented back reaction of **VI** with NO occurs with the second order rate constant $k_{NO} = 3.1 \times 10^6$ M^{-1} s^{-1}. Under such conditions, the only net reaction is the competing low yield photoaquation of NO_2^-. These results clearly demonstrate the viability of NO delivery schemes based upon the photochemical decomposition of coordinated nitrite.

Acknowledgements

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