Published in final edited form as:

J Am Chem Soc. 2013 October 9; 135(40): . doi:10.1021/ja405891n.

Reactions of a Chromium(III)-Superoxo Complex and Nitric Oxide That Lead to the Formation of Chromium(IV)-Oxo and Chromium(III)-Nitrito Complexes

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Abstract

The reaction of an end-on Cr(III)-superoxo complex bearing a 14-membered tetraazamacrocyclic TMC ligand, $[\text{Cr}^{\text{III}}(14\text{-TMC})(\text{O}_2)(\text{Cl})]^+$, with nitric oxide (NO) resulted in the generation of a stable Cr(IV)-oxo species, $[\text{Cr}^{\text{IV}}(14\text{-TMC})(\text{O})(\text{Cl})]^+$, *via* the formation of a Cr(III)-peroxynitrite intermediate and homolytic O-O bond cleavage of the peroxynitrite ligand. Evidence for the latter comes from EPR spectroscopy, computational chemistry, and the observation of phenol nitration chemistry. The Cr(IV)-oxo complex does not react with nitrogen dioxide (NO_2), but reacts with NO to afford a Cr(III)-nitrito complex, $[\text{Cr}^{\text{III}}(14\text{-TMC})(\text{NO}_2)(\text{Cl})]^+$. The Cr(IV)-oxo and Cr(III)-nitrito complexes were also characterized spectroscopically and/or structurally.

Nitric oxide (NO) is an ubiquitous signal transduction molecule which is found in a wide variety of physiological processes such as a cellular signaling leading to smooth muscle vasodilation, platelet disaggregation, and neurotransmission and in the immune response to bacterial infection.¹ However, NO itself is a toxin because of the reactivity derived from its radical character and ability to form more reactive and deleterious oxidation products, such as NO_2 and peroxynitrite (PN, oxoperoxonitrate (1^-), $^-\text{OON}=\text{O}$), in the presence of transition metals.² In this context, various life forms have constructed detoxification systems; widely occurring nitric oxide dioxygenases (NODs) are enzymes which catalyze the conversion of toxic NO to biologically atoxic nitrate (NO_3^-) with NAD(P)H (i.e., $2\text{NO} + 2\text{O}_2 + \text{NAD(P)H} \rightarrow 2\text{NO}_3^- + \text{NAD(P)}^+ + \text{H}^+$).³ In NOD reactions, including those observed with hemoglobins (Hbs) and myoglobins (Mbs), an Fe(III)-superoxo species ($\text{Fe}(\text{III})(\text{O}_2^{\bullet-})$), which is generated in the reaction of $\text{Fe}(\text{II}) + \text{O}_2$, reacts with NO to yield nitrate *via* formation of an Fe(III)-peroxynitrite intermediate.^{4,5} Here, a ferryl species ($\text{Fe}(\text{IV})(\text{O})$) is proposed to be formed *via* homolytic O-O bond cleavage of the Fe(III)-peroxynitrite species; Groves and co-workers only very recently provided time-resolved spectrophotometric evidence for the formation of such a ferryl species in the reaction of Mb with PN.⁶ However, a heme-PN moiety has not been detected due to its expected short lifetime and rapid recombination with NO_2 in a $[\text{Fe}^{\text{IV}}=\text{O} \bullet \text{NO}_2]$ cage to give a nitrate product. Thus, the study of metal-superoxo intermediates with NO is of great interest with respect to the investigation of reaction pathways or undetected intermediate reactivity, such as in the possible escape of a bound PN or NO_2 molecule.⁷

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Supporting Information. Experimental section, purification of NO, trapping experiments, spectroscopic and kinetic data, DFT calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Recently, TMC (*N*-tetramethylated cyclam)⁸ chelated redoxactive first row transition metal complexes and their peroxo (O_2^{2-}) and superoxo ($\text{O}_2^{\bullet-}$) derivatives have been systematically synthesized and investigated in various oxidation reactions.⁹⁻¹² Especially, in the case of Ni and Cr complexes with the 14-TMC¹³ and 12-TMC¹³ ligands, the TMC ring size was found to alter the structure of the resulting $[\text{M}(n\text{-TMC})(\text{O}_2)]^{n+}$ complexes; the larger ring size ligand (e.g., 14-TMC) forms metal-superoxo complexes (e.g., Ni(II)-superoxo^{10b} and Cr(III)-superoxo¹¹), whereas the smaller ring size 12-TMC chelate forms metal-peroxo complexes (e.g., Ni(III)-peroxo^{10b} and Cr(IV)-peroxo¹²). In addition, we recently reported the NOD reactivity of the Cr(IV)-peroxo complex; this species reacted with NO to give a Cr(III)-nitrate product, $[\text{Cr}^{\text{III}}(12\text{-TMC})(\text{NO}_3)(\text{Cl})]^+$, however, without detection of any intermediates such as Cr-PN or Cr-oxo species.¹²

We herein report the reactions of the end-on Cr(III)-superoxo complex bearing the 14-TMC ligand, $[\text{Cr}^{\text{III}}(14\text{-TMC})(\text{O}_2)(\text{Cl})]^+$ (**1**), with NO. Complex **1** with one equiv. of NO generates a stable Cr(IV)-oxo species, $[\text{Cr}^{\text{IV}}(14\text{-TMC})(\text{O})(\text{Cl})]^+$ (**3**), *via* the formation of a presumed Cr(III)-peroxynitrite intermediate, $[\text{Cr}^{\text{III}}(14\text{-TMC})(\text{OON}=\text{O})(\text{Cl})]^+$ (**2**) (Scheme 1, reactions a and b), unlike the NO reaction of a Cr(IV)-peroxo complex bearing the 12-TMC.¹² To the best of our knowledge, this study presents the first strong evidence for the formation of a high-valent metal-oxo complex in the reaction of a metal-superoxo species and NO. Further, **3** does not lead to a nitrate containing product with NO_2 addition, but it does react with NO to give a Cr(III)-nitrito complex, $[\text{Cr}^{\text{III}}(14\text{-TMC})(\text{NO}_2)(\text{Cl})]^+$ (**4**) (Scheme 1, reaction c). Thus, we were able to follow all the reaction pathways of metal-oxygen intermediates with NO, employing isolated or spectroscopically well-characterized Cr complexes.

The starting chromium complex, $[\text{Cr}^{\text{II}}(14\text{-TMC})(\text{Cl})]\text{Cl}$, was synthesized according to literature methods, and the Cr(III)-superoxo complex (**1**) (2 mM) was prepared by bubbling O_2 for 30 s in an CH_3CN solution containing the starting complex at -40°C , giving a dark red color.¹¹ After purging the reaction solution with Ar for 30 min at -40°C , one equiv. of NO^{14} was added and stirred for 20 min (see Supporting Information (SI), Figure S1 for a schematic diagram showing the NO purification setup), whereupon the color of the solution changed from red to yellowish green (see Figure 1 for the UV-vis spectral changes). In this experiment, the spectrum of **1** changed from blue solid line to the black dashed line immediately upon addition of NO, followed by the conversion of this intermediate (**2**) to the Cr(IV)-oxo species (**3**, red line) with λ_{max} at 603 nm ($80\text{ M}^{-1}\text{ cm}^{-1}$) over 15 min (Figure 1). This final absorption spectrum is consistent with our previous report on the Cr(IV)-oxo complex with this 14-TMC ligand,¹¹ and the conversion of **1** to **3** turned out to be quantitative. A resonance Raman (rRaman) spectrum of **3** was collected using 407-nm excitation in CH_3CN at -20°C (SI, Figure S2). The peak observed at 874 cm^{-1} is comparable to the Cr–O frequency (873 cm^{-1}) of the previously reported $[\text{Cr}^{\text{IV}}(14\text{-TMC})(\text{O})(\text{Cl})]^+$ complex.¹¹ The electrospray ionization mass spectrum (ESI-MS) of **3** also supports the generation of Cr(IV)-oxo species; the observed peak cluster centered at m/z 359.3 can be assigned to a Cr(IV)-oxo complex formulated as $[\text{Cr}^{\text{IV}}(14\text{-TMC})(\text{O})(\text{Cl})]^+$ (calcd. m/z of 359.2) (SI, Figure S3). An electron paramagnetic resonance (EPR) spectrum obtained for **3** (1 mM) in CH_3CN at 5 K was silent, consistent with the expected oxidation state of Cr^{IV} in **3**. Based on the spectroscopic characterization of **3**, we were able to conclude unambiguously that a highvalent Cr(IV)-oxo species was formed in the reaction of this Cr(III)-superoxo complex and nitric oxide.

A proposed mechanism for the generation of Cr(IV)-oxo species (**3**) in the reaction of Cr(III)-superoxo (**1**) and NO is then depicted in Scheme 1. According to widely accepted discussions on the reaction mechanism of Fe(III)-superoxo species with NO,²⁻⁶ the first step of the reaction must be a radical coupling reaction between **1** and NO to generate a Cr(III)-peroxynitrite intermediate (**2**, $\text{Cr}^{\text{III}}\text{-PN}$), $[\text{Cr}^{\text{III}}(14\text{-TMC})(\text{OON}=\text{O})(\text{Cl})]^+$ (Scheme 1,

reaction a). This species gives rise to **3** and NO₂ via O-O bond homolysis of the PN ligand (Scheme 1, reaction b). The Cr(IV)-oxo species generated does not further react with the NO₂ produced simultaneously, unlike that which occurs for NOD reactions,³⁻⁶ and it maintains its metal-oxo structure under the reaction conditions.

We then attempted to characterize the presumed Cr(III)-peroxynitrite intermediate (**2**, Cr^{III}-PN) and elucidate the mechanism of the conversion of **2** to the Cr(IV)-oxo species (**3**) (Scheme 1, reaction b). First, the UV-vis spectrum of the black dashed line in Figure 1 likely represents that of **2**. Notably, the dashed line spectrum and the following changes shown in Figure 1 were not observed when the reaction was carried out at a higher temperature (e.g., 0 °C). For this latter experiment, the spectrum changed instantly from the blue solid line (**1**) to the red line (**3**) without showing any intermediate spectra, implying that the stability of **2** depends on the reaction temperature and **2** is detectable only at a low temperature. We also found *via* EPR measurements that the intermediate species (i.e., the black dashed line in Figure 1) exhibited a signal assignable to a d³ Cr(III) ion ($S = 3/2$) at 5 K (SI, Figure S4a),¹⁵ while complexes **1** and **3** were EPR silent. Moreover, time-dependent EPR measurements reveal the clear conversion of **2** to **3**; EPR spectra in CH₃CN at 5 K obtained by freezing solutions of the **1** + NO reaction mixture as a function of time (0 to 300 sec) indicated that the signal intensity decreased as time passed, leading from EPR active **2** to EPR silent **3** (Figure 1, inset). Thus, the Cr(III) EPR signal detected for **2** supports the generation of the Cr(III)-PN species, which decomposes to the EPR silent species **3**.¹⁶ As reported previously, the lifetimes of metal-peroxynitrite species are very short for near RT generated species.¹⁷ A striking recent success is a Co(III)-peroxynitrite porphyrinate complex, yet still generated under cryogenic conditions, but thoroughly characterized by using IR-spectroscopy and isotope labeling experiments along with DFT calculations.¹⁸

Density functional theory (DFT) calculations were also performed in order to seek further support for our suppositions concerning the intermediacy of Cr(III)-PN complex **2**. Complex **1** is an $S = 1$ state species,^{9a,11b} but by adding the NO spin (up or down), the whole system can reside in two energetically degenerate states, $S = 1/2$ or $S = 3/2$. The calculations reveal that the $S = 1/2$ state features a concerted high-energy barrier for the current reaction (Figure 2) and is therefore not discussed further.¹⁹ The $S = 3/2$ state reaction pathway is shown to be able to proceed in two low-energy steps. The first step of the reaction occurs over a low barrier of 1.7 kcal/mol, such that a very fast reaction of **1** with NO would occur, and alternative reactions are unlikely. Moreover, the product is a stable O-bound peroxynitrite species **2** at -10.8 kcal/mol (SI, Figure S5). The next step of the reaction occurs over a barrier of 20.1 kcal/mol to form the Cr(IV)-oxo complex **3**. This barrier is somewhat high, but is likely a well overestimated value.²⁰ All in all, the interpretation of the calculations strongly support that the formation of the $S = 3/2$ species **2** is likely, and its transformation to **3** is quite possible.

We sought more support for our mechanistic proposal, including the formation of **3** from **2** with the liberation of NO₂. In this regard, we carried out trapping experiments using 2,4-di-*tert*-butylphenol (DTBP) to obtain evidence that NO₂ is produced concomitantly with the Cr(IV)-oxo formation (Scheme 1, reaction b).²² After the generation of **3** as discussed above, 1 equiv. of DTBP was added to the resulting solution and stirred for 20 min under Ar, while also monitoring the reaction's UV-vis spectral changes (see SI, Figure S6). ESI-MS analysis of the resulting solution revealed the presence of a Cr(III)-hydroxo species at m/z 360.2 ([Cr^{III}(14-TMC)(OH)(Cl)]⁺, calcd. m/z of 360.3) (SI, Figure S6). Further, product analysis was performed using GC and ¹H NMR spectroscopic measurements; nitrated DTBP (2,4-di-*t*-butyl-6-nitrophenol, nitro-DTBP) and oxidatively dimerized DTBP (2,2'-dihydroxy-3,3',5,5'-tetra-*t*-butylbiphenol, DTBP-dimer) products were found in 46% and 12% yields, respectively (see SI, Experimental Section). The results can be readily explained

as follows: First, H-atom abstraction reaction of DTBP by **3** gives a phenoxyl radical and a Cr(III)-hydroxo complex (Scheme 2, reaction I). The phenoxyl radical traps gaseous NO₂ to give nitro-DTBP (Scheme 2, reaction II) or dimerizes to give DTBP-dimer (Scheme 2, reaction III). Thus, the results that we successfully trapped and recovered the NO₂ in good yield also strongly support the proposed reaction mechanism involving the formation of a Cr(IV)-oxo complex and NO₂ via the homolytic O-O bond cleavage of a Cr^{III}-PN intermediate (Scheme 1, reaction b).

In heme and nonheme systems, the reaction of a ferryl species and NO has been of great interest in terms, for example, in the inhibition of cytochrome *bd* oxidase reactivity;²³ here, a ferryl heme species reacts with NO to generate a ferric species and nitrite (Fe(III) + NO₂⁻),^{23,24} while a ferryl nonheme complex ([Fe^{IV}(14-TMC)(O)(OAc)]⁺) with added NO produces a ferrous species and nitrite (Fe(II) + NO₂⁻).²⁵ The reactions of other metal-oxo complexes and NO have also been discussed.²⁶ Since we did not observe nitrate (NO₃⁻) formation via a coupling between the Cr(IV)-oxo complex (**3**) and NO₂ (*vide supra*) and the formation of a Cr(III)-nitrito complex, [Cr^{III}(14-TMC)(NO₂)(Cl)]⁺ (**4**), was observed when an excess amount of NO was used in the reaction of a Cr(III)-superoxo complex (**1**), we decided to check if the Cr(IV)-oxo complex **3** could react with NO, not with NO₂, to form **4** (Scheme 1, reaction c). Indeed, this is the case. After generating **3** as described above, the solution was degassed by Ar-bubbling to remove NO₂ (*vide supra*), and then excess NO was added over the top of the solution at -40 °C. The UV-vis spectral changes for **3** upon addition of NO and the ESI-MS of the resulting solution are depicted in Figure 3; the characteristic absorption band of **3** at 603 nm disappeared gradually over 5 min, and a molecular ion peak corresponding to **4** appeared at *m/z* 388.9. When **1** was prepared with isotopically labeled ¹⁸O₂ and used in the subsequent reaction with NO, a peak corresponding to [Cr^{III}(14-TMC)(N¹⁸O¹⁶O)(Cl)]⁺ (calcd. *m/z* of 391.2) was found at *m/z* 390.9 (Figure 3, inset). The two mass unit shift observed upon substitution of ¹⁶O with ¹⁸O indicates that **3** has one ¹⁸O oxygen (out of two) in it and its origin is the Cr(III)-superoxo complex (**1**) via Cr(IV)=O species (**3**) (Scheme 1, reaction c). Additionally, an EPR spectrum of **4** in CH₃CN at 5 K showed a signal assigned to a d³ Cr(III) ion (*S* = 3/2)¹⁵ (SI, Figure S3b). Based on the results presented above, we conclude that one electron reduction in Cr occurs through the reaction between **3** and NO, resulting in the formation of [Cr^{III}(14-TMC)(NO₂)(Cl)]⁺ (**4**; SI, Figure S6).

In summary, we have demonstrated the generation of a stable Cr(IV)-oxo species (**3**) in the reaction of a Cr(III)-superoxo complex (**1**) and nitric oxide. This is the first clear observation of metaloxo species generation in the reaction of a metal-superoxo complex and NO via metal-peroxynitrite formation and its subsequent homolytic O-O bond cleavage. This opens the way to utilize such an approach to generate biochemical or synthetic higher-valent metaloxo species. Interestingly, the Cr(IV)-oxo species didn't show any reactivity toward NO₂, unlike NOD reactions, but it readily reacted with NO to form a Cr(III)-nitrito complex (**4**). In addition, we have shown that the ring size of the TMC ligand has a significant effect not only on the determination of metal-O₂ structures but also on the reactivity of the resulting metal-oxo complexes (e.g., Cr(IV)-oxo species) towards NO and NO₂.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge research support of this work by the NRF of Korea through CRI (2-2012-1794-001-1 to W.N.) and GRL (2010-00353 to W.N.) and the U.S. National Institutes of Health (K.D.K.).

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13. Abbreviations used: 12-TMC, 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclododecane; 14-TMC, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane.
14. A NO-saturated solution was prepared under 1 atm at 298 K; the concentration of the NO in CH₃CN at 293 K was approximated to be 14 mM. For the published values for NO solubilities in organic solvents, see: Young, C. L. (1981) Solubility Data Series Vol. 8 Oxides of Nitrogen, International Union of Pure and Applied Chemistry The purification of NO is described in Supporting Information (experimental section and Figure S1).

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16. The characterization of the Cr(III)-PN (**2**) species with ESI-MS was in this case unsuccessful due to its thermal instability. We note that there is no example of rRaman spectroscopic characterization of a metalperoxynitrite complex, probably, due to photodecay of the intermediate during measurements, see: Tran NG, Kalyvas H, Skodje KM, Hayashi T, Moënne-Loccoz P, Callan PE, Shearer J, Kirschenbaum LJ, Kim E. *J Am Chem Soc.* 2011; 133:1184–1187. [PubMed: 21244001] .
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19. This would correspond to a reaction where the added NO abstracts an O-atom from the superoxo complex to directly produce NO₂.
20. Inclusion of entropy and other correction factors, even though this process includes a formal error (see SI, DFT methods)²¹ gives an estimated barrier of 16.7 kcal/mol (see SI, Table S1). In addition, dissociation entropy of NO₂ is expected to stabilize the products even more than what is calculated, thereby indirectly further lowering the transition state.
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Figure 1.

UV-vis spectral changes of **1** (2 mM) upon addition of 1 equiv. NO in CH₃CN at -40 °C under Ar. The initial blue solid line spectrum (**1**) changed immediately to the black dashed line spectrum (**2**) upon addition of NO, followed by the conversion to the red solid line spectrum (**3**) over 15 min. Inset; time-dependent EPR spectra of Cr(III)-PN (**2**) in CH₃CN at 5 K; **1** and NO are mixed in CH₃CN at -40 °C under Ar and EPR spectra were obtained by freezing such solutions as a function of time (0, 30, 60, 100, 150, and 300 sec).

Figure 2. DFT-calculated pathways for the reaction of $[\text{Cr}^{\text{III}}(14\text{-TMC})(\text{O}_2)(\text{Cl})]^+$ (1) with NO. The low-energy two-step pathway giving PN complex 2 and then $\text{Cr}^{\text{IV}}\text{=O}$ species 3 occurs on the $S = 3/2$ surface (red, ■), while the $S = 1/2$ surface (green, ●) exhibits a concerted pathway that does not feature a (stable) peroxyxynitrite intermediate (2).

Figure 3.

UV-vis spectral changes of **3** (black line) upon addition of NO (10 cm³) into the headspace above a solution of **3** in CH₃CN at -40 °C under Ar. Inset; ESI-MS spectrum of [Cr^{III}(14-TMC)(NO₂)(Cl)]⁺ (**4**) (calcd. *m/z* of 389.1) and isotope distribution patterns for **4**-¹⁶O (red) and **4**-¹⁸O (blue). The peaks at 359.1 and 378.1 with asterisk are assigned to [Cr^{IV}(14-TMC)(O)(Cl)]⁺ (calcd. *m/z* of 359.2) and [Cr^{III}(14-TMC)(Cl₂)]⁺ (calcd. *m/z* of 378.1), respectively.

Scheme 1.

Scheme 2.