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Proton-Induced Reactivity of NO^- from a $\{CoNO\}^8$ Complex

Melody A. Rhine,[†] Andria V. Rodrigues,[‡] Ramona J. Bieber Urbauer,[†] Jeffrey L. Urbauer,[†] Timothy L. Stemmler,[‡] and Todd C. Harrop*,[†]

[†]Department of Chemistry and Center for Metalloenzyme Studies, The University of Georgia, Athens, Georgia 30602, United States
[‡]Departments of Pharmaceutical Sciences, Biochemistry, and Molecular Biology, Wayne State University, Detroit, Michigan 48201, United States

Supporting Information

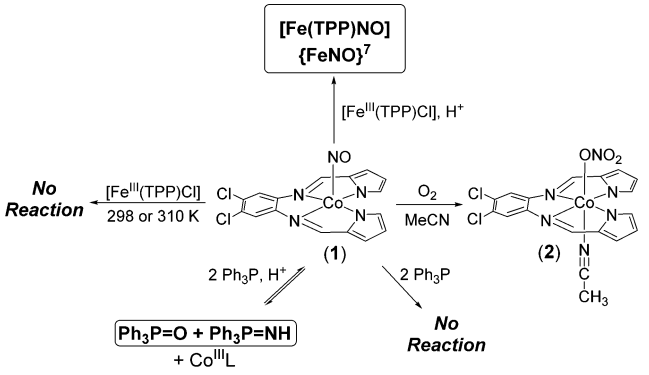
ABSTRACT: Research on the one-electron reduced analogue of NO, namely nitroxyl (HNO/NO^-), has revealed distinguishing properties regarding its utility as a therapeutic. However, the fleeting nature of HNO requires the design of donor molecules. Metal nitrosyl (MNO) complexes could serve as potential HNO donors. The synthesis, spectroscopic/structural characterization, and HNO donor properties of a $\{CoNO\}^8$ complex in a pyrrole/imine ligand frame are reported. The $\{CoNO\}^8$ complex $[Co(LN_4^{PhCl})(NO)]$ (**1**) does not react with established HNO targets such as Fe^{III} hemes or Ph_3P. However, in the presence of stoichiometric H^+ **1** behaves as an HNO donor. Complex **1** readily reacts with [Fe(TPP)Cl] or Ph_3P to afford the $\{FeNO\}^7$ porphyrin or $Ph_3P{=}O/Ph_3P{=}NH$, respectively. In the absence of an HNO target, the $\{Co(NO)_2\}^{10}$ dinitrosyl (**3**) is the end product. Complex **1** also reacts with O_2 to yield the corresponding Co^{III}-η^1-ONO_2 (**2**) nitrato analogue. This report is the first to suggest an HNO donor role for $\{CoNO\}^8$ with biotargets such as Fe^{III}-porphyrins.

Among the many biochemical and physiological roles of $NO^{\bullet}$,[1] its redox chemistry to reduced analogues such as nitroxyl (HNO/NO^-, pK_a = 11.6)[2] has not been extensively studied. This is primarily due to the rapid dimerization and dehydration of HNO to N_2O and H_2O ($k = 10^6\ M^{-1}\ s^{-1}$)[3] that makes this particular nitrogen oxide difficult to study. Despite its analogous structure, nitroxyl has demonstrated pharmacological and therapeutic advantages distinct from $NO^{\bullet}$.[4] Such properties include specific targeting of biological thiols and Fe^{III} heme proteins, increasing the plasma concentration of calcitonin gene-related peptide (CGRP, a small neuropeptide involved in vasodilation), and its positive cardiac inotrope effect (heart muscle contraction). These properties have driven the field to better understand the chemical biology of HNO through the design and synthesis of controllable donor molecules.[5] The most common donors include diazeniumdiolates such as $Na_2N_2O_3$ (Angeli's salt)[6] and *N*-hydroxysulfonamide derivatives ($R\text{-}SO_2\text{-}NH\text{-}OH$) such as Piloty's acid.[5b,7] While reliable as HNO donors, these compounds are limited as they release other potentially reactive species or function at pH > 9.[5] Clearly, the development of better HNO donors is needed.

Metal nitrosyls (MNO) could serve as an alternative platform for HNO/NO^- delivery. Indeed, the heme enzyme responsible for NO synthesis (NO synthase) has been shown to release HNO via an Fe-bound *N*-hydroxy-L-arginine intermediate in the absence of its biopterin cofactor.[8] Due to the variable redox states of NO when coordinated to metals (i.e., NO^+, $NO^{\bullet}$, NO^-), descriptions of bonding typically resort to the Enemark–Feltham (EF) notation as a result of extensive electron delocalization within the MNO moiety.[9] We reported the synthesis and properties of nonheme $\{FeNO\}^8$ complexes (a rare EF notation),[10] one which demonstrates nitroxyl-like reactivity with equine skeletal metmyoglobin under pseudo-physiological conditions.[10a] Due to the inherent reactivity of the $\{FeNO\}^8$ systems, we have now synthesized isoelectronic $\{CoNO\}^8$ complexes with more electron-deficient supporting ligands as the next logical step in our goal of customizing an HNO/NO^- delivery vehicle with more controllable properties. Herein we describe the synthesis and properties of a non-porphyrin-based $\{CoNO\}^8$ complex, the H^+-induced formation of the fleeting HNO donor intermediate, and its nitroxyl-like reaction with an Fe^{III}-heme model complex and Ph_3P.

The $\{CoNO\}^8$ complex $[Co(LN_4^{PhCl})(NO)]$ (**1**) (Scheme 1) was synthesized by purging NO(g) into an MeCN solution of in situ prepared $(Et_4N)_2[Co(LN_4^{PhCl})Cl_2]$ at 60 °C. The resulting dark-brown microcrystalline product precipitated from the reaction mixture and was isolated as analytically pure material in 72% yield. Complex **1** is stable to air, moisture, and vacuum in the solid-state. Solution samples (THF, MeCN) of **1** also

Scheme 1. Reactivity of 1[a]



[a]HNO-derived products highlighted.

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demonstrate similar stability; however, slow air exposure (1 week) to an MeCN/THF solution of **1** afforded the corresponding nitrato complex [Co(LN_4^{PhCl})(MeCN)(η^1-ONO_2)] (**2**) as single crystals (Scheme 1). This result parallels what is seen with other {CoNO}^{8}/O_2 reactions[11] and highlights the nucleophilic nature of the NO ligand in **1** which is suggestive of its NO^- character.

Recrystallization of the {CoNO}^{8} complex from 2-MeTHF/Et_2O afforded X-ray quality crystals of **1**, which revealed a square pyramidal Co center originating from the diimine-dipyrrolide N_4 ligand (basal plane) with NO in the apical position (Figure 1).

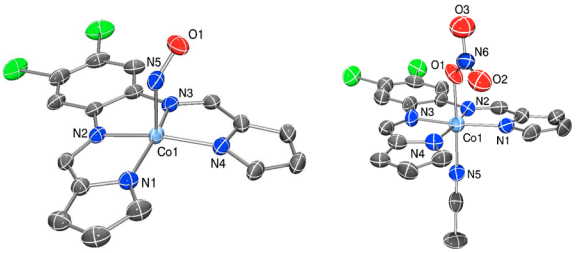

Figure 1. X-ray structures of [Co(LN_4^{PhCl})(NO)] (**1**) (left) and [Co(LN_4^{PhCl})(MeCN)(η^1-ONO_2)] (**2**) (right) (50% probability level). H atoms and distorted THF solvent of crystallization for **1** have been omitted for clarity.

Relevant X-ray data and metric parameters are provided in Tables S1 and S2. The near-perfect square pyramidal geometry in **1** is indicated by its low trigonal distortion parameter ($\tau = 0.08$)[12] and is due to the extreme planarity of the N_4 ligand with Co displaced by 0.264 Å out of the N_4 plane and toward NO. The Co−N_{imine} (avg: 1.895 Å) and Co−$N_{pyrrole}$ (avg: 1.919 Å) distances are comparable to Co−N bonds in other non-porphyrin {CoNO}^{8} complexes[13] and also in Co^{III} complexes without NO ligands such as complex **2** (avg Co−N_{imine}: 1.893 Å; avg Co−$N_{pyrrole}$: 1.926 Å; SI, Figure 1). This comparison suggests a Co^{III} oxidation state for **1**, which was further verified by X-ray absorption spectroscopic (XAS) measurements (vide infra). The Co−N(O) (1.798(3) Å) and bent Co−N−O angle (124.4(3)°) are also representative metrics of five-coordinate {CoNO}^{8} complexes.[13d] The bent nature of the Co−N−O unit in solution is further supported by the large downfield shift of the NO nitrogen in the ^{15}N NMR spectrum (δ: 688 ppm vs CH_3NO_2 in THF-d_8, Figure S2).[14] Additionally, the N−O bond distance (1.172(4) Å) is in between that reported for ^{1}HNO (1.21 Å)[15] and NO (1.15 Å), but more like the latter.[13d] Consistent with this observation is the solid-state FTIR spectrum of **1**, which exhibits ν_{NO} at 1667 cm^{-1} that shifts to 1638 cm^{-1} ($\Delta\nu_{NO}$: 29 cm^{-1}) after isolating [Co(LN_4^{PhCl})(^{15}NO)] (**1-^{15}NO**) using ^{15}NO(g) in the synthesis (Figure S3). The ν_{NO} and diamagnetic ground state (see ^{1}H NMR, Figure S1) is typical for this class of Co nitrosyls.[13d,16]

XAS measurements support the crystallographic results obtained for **1**. The X-ray absorption near edge spectrum (XANES) shows a large pre-edge feature centered at 7710.6 eV, characteristic of Co^{III} 1s → 3d electronic transitions; the measured peak area (0.387 eV) confirms the metal is coordinated in a non-centrosymmetric ligand environment (Figure 2). The first inflection energy in the XANES spectrum occurs at 7721.3 eV, as in other XAS-characterized Co^{III} compounds.[17] Simulations of the extended X-ray absorption fine structure spectral region are consistent with Co^{III} in a five-coordinate

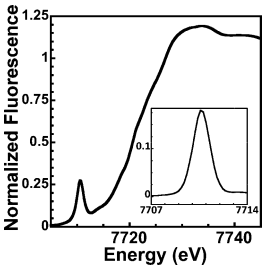

Figure 2. XANES spectrum for {CoNO}^{8} **1**. Inset: The baseline subtracted pre-edge features for **1**.

ligand environment constructed of five O/N ligands at an average distance of 1.88 Å (Figure S4). These results compare favorably to distances obtained from X-ray diffraction (avg: 1.89 Å). Taken together, these results suggest the MNO unit in **1** is best described as low-spin Co^{III} ($S = 0$) bound to singlet nitroxyl anion ($^1NO^-$; $S = 0$).

Despite the formal assignment of the NO ligand as $^1NO^-$ in other {CoNO}^{8} systems,[18] we were surprised that their chemical reactivity had not been explored in detail given their potential as HNO donors. Indeed, complexes with the {CoNO}^{8} notation are generally designated as low-spin Co^{III} coordinated to $^1NO^-$ to yield $S_{tot} = 0$.[18] Perhaps this paucity is due to the well-known kinetic inertness of low-spin d^6 metals such as Co^{III}.[19] One common and sensitive test for an HNO donor involves its reaction with Fe^{III}-porphyrins[20] or Fe^{III}-heme proteins[21] to afford the corresponding {FeNO}^{7} derivatives. Thus, the capability of **1** to reductively nitrosylate the Fe^{III}-heme model [Fe(TPP)Cl] (TPP = dianion of tetraphenylporphyrin) was performed. When a stoichiometric amount of **1** was added to the Fe^{III} heme in THF at 298 K, no reaction was observed even after 24 h (Scheme 1). Similarly, increasing the temperature to 310 K and monitoring over the same 24 h time period resulted in no reaction. However, when the reaction was repeated in the presence of 1 mol·equiv of an organic-soluble H^+ donor (HBF_4·Et_2O), an entirely different reaction resulted (Scheme 1). In this case, [Fe(TPP)Cl] was almost immediately consumed within 4 min of H^+ addition (monitored by UV−vis, FTIR) to afford the corresponding {FeNO}^{7} heme analogue [Fe(TPP)NO] (ν_{NO}: 1698 cm^{-1} in KBr). Bulk reaction studies further confirmed the near stoichiometric NO transfer between **1** and [Fe(TPP)Cl] (88% yield; Figure S7 for FTIR/EPR of the [Fe(TPP)NO] product). Using isotopically labeled **1-^{15}NO** resulted in the corresponding shift of ν_{NO} in the IR spectrum of the [Fe(TPP)^{15}NO] product (ν_{NO}: 1667 cm^{-1} in KBr, $\Delta\nu_{NO}$: 31 cm^{-1}) as well as the expected triplet-to-doublet hyperfine structural change in its X-band EPR spectrum (Figure S7).

Further insight regarding the mechanism of the reductive nitrosylation of [Fe(TPP)Cl] with **1** and HBF_4·Et_2O come from electrochemical measurements. In THF, **1** displays a quasi-reversible {CoNO}^{9}/{CoNO}^{8} wave at $E_{1/2} = -1.46$ V vs Fc^+/Fc in THF (Figure S5). One possible route to [Fe(TPP)NO] is via reduction of [Fe(TPP)Cl] from **1** to yield a {CoNO}^{7} complex that would release NO$^\bullet$ to the Fe^{II}-heme model. An irreversible E_{ox} peak at 0.75 V is observed suggesting the {CoNO}^{7} complex is unstable and likely results in loss of NO$^\bullet$. Since the $Fe^{III/II}$ couple of [Fe(TPP)Cl] is −0.90 V in THF (vs Fc^+/Fc),[22] it is doubtful that **1** can reduce Fe^{III} to Fe^{II} in this reaction. It is possible that HNO transfer is taking place upon H^+ addition to **1**. Support for this hypothesis comes from reactions performed with DNICs (mononuclear tetrahedral dinitrosyl iron com-

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plexes) and Fe^{III}-porphyrins by Darensbourg and co-workers.[23] In these studies, addition of H^+ greatly enhances the rate of HNO transfer to form the corresponding {FeNO}^{7} analogues (72 h without H^+; 9 h with 0.25 equiv of H^+). This rate enhancement of HNO transfer/release from the DNICs has been attributed to the "carrier effect" of H^+ for NO^- as the neutral HNO should be more mobile in nonpolar aprotic solvents such as CH_2Cl_2 or THF.

Additional proof that **1** behaves as an HNO donor in the presence of stoichiometric H^+ stem from its reaction with Ph_3P (Scheme 1). King established that triarylphosphines (R_3P) react selectively with HNO donors to yield the corresponding phosphine oxide ($R_3P{=}O$) and aza-ylide ($R_3P{=}NH$): HNO + $2R_3P \rightarrow R_3P{=}O + R_3P{=}NH$.[24] These molecules represent unique and quantifiable products as markers of HNO, which is measured by the amount of $R_3P{=}O$ formed ($R_3P{=}NH$ is reactive and hydrolyzes to $R_3P{=}O$). Accordingly, addition of H^+ (1.3 equiv) to the red-brown **1**/Ph_3P (1/2) mixture resulted in a lightening of this solution to a yellow-tinted transparent brown after 24 h. ^{31}P NMR analysis of this mixture clearly indicated the presence of $Ph_3P{=}O$ (δ: 26.3 ppm), $Ph_3P{=}NH$ (δ: 20.6 ppm), and unreacted Ph_3P (−6.0 ppm) (Figure S16). Additional support for $Ph_3P{=}NH$ derives from using **1**-^{15}**NO**, which afforded identical ^{31}P NMR features except for the doublet splitting of the 20.6 ppm peak arising from the ^{15}N nucleus ($^1J_{P-N}$: 135 Hz). This result is definitive proof that **1** in the presence of H^+ is an HNO donor. Control experiments with Ph_3P and **1** indicated no reaction. To evaluate the extent to which **1**/H^+ donates HNO, the amount of Ph_3P was quantified by HPLC (SI), which was determined to be 33% (2 equiv Ph_3P) after 24 h. Utilizing excess (10 equiv) Ph_3P improved the yield to 37% (Figure S19). Other peaks in the chromatogram were identified as **1** and free ligand (SI), which may account for the ∼40% yield of $Ph_3P{=}O$. R_3P-based reactions with established HNO donors have also been less than stoichiometric.[24b] Collectively, these results offer strong support that **1** and H^+ generate a compound that is capable of releasing HNO.

In an effort to verify the actual species responsible for the HNO donor property, we attempted in situ characterization of intermediates utilizing high-resolution MS. For example, the MS of the **1** and HBF_4 (1/1.3; 30 min) mixture generate a major peak at m/z: 418.974(1) that is assigned to a reduced and doubly protonated cation of general formula $[Co(LN_4^{PhCl}H_2)(NO)]^+$ (Figure 3).[25] This peak remains even after 24 h mixing.

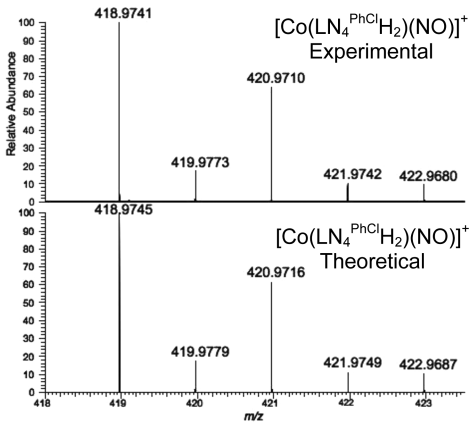
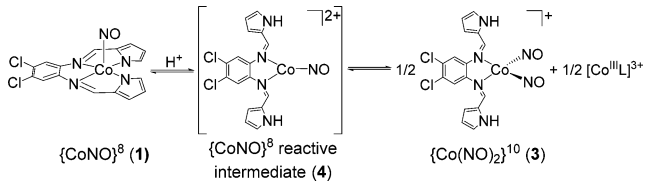


Figure 3. Top: High-resolution ESI-MS (positive mode) of the reaction of **1** + $HBF_4{\cdot}Et_2O$. Bottom: Theoretical isotopic distribution.

Fragmenting this peak afforded one signal at m/z: 388.976(1) corresponding to loss of NO (30 amu) and formation of $[Co(LN_4^{PhCl}H_2)]^+$. Experiments with **1**-^{15}**NO** provided analogous results with loss of 31 amu (^{15}NO) (Figure S14). In contrast, **1** reveals no significant peaks in the MS, consistent with its neutral charge. FTIR and ^1H NMR measurements reveal additional benchmarks that may be assigned to this intermediate (isotope-sensitive ν_{NO}: 1544 cm^{-1}; δ_{NH}: 11.5 ppm, Figures S8–S13). A $\{[Co(LN_4^{PhCl})(HNO)] + H\}^+$ {CoHNO}^{9} formulation is consistent with the MS; however, the absence of ^{15}N coupling (I = 1/2) to the 11.5 ppm peak in the NMR (using **1**-^{15}**NO**) suggest this signal to arise from protonated ligand. Overall, these observations implicate a three-coordinate, protonated pyrrole-NH and imine-N bound {CoNO}^{8} (**4**) as the first intermediate formed in the **1**/H^+ reaction (Scheme 2). After 24 h mixing, a

Scheme 2. Reactivity of 1 with H^+



new species corresponding to $[Co(LN_4^{PhCl}H_2)(NO)_2]BF_4$ (**3**) is observed. Spectroscopic analysis of the reaction mixture confirms this assignment with ^{15}N-sensitive ν_{NO} (1869, 1793 cm^{-1}) and m/z: 448.972 (Figures S9, S15). These parameters are consistent with independently synthesized and characterized **3** and other neutral N-bound {Co(NO)$_2$}^{10} complexes (Figures S20–S23).[26] A significant portion of **1** and **4** also remain and implicate the equilibrium depicted in Scheme 2.[27]

The results obtained provide insight into the potential paths traversed with **1**/H^+. In the absence of HNO targets, **4** appears as the first CoNO intermediate after H^+ addition, providing strong support that this species is likely responsible for the observed reaction chemistry based on IR, MS, and NMR. While this proposal does not completely eliminate a transient Co-HNO, none of the current evidence supports its formation. Indeed, the lack of definitive proof for Co-HNO is not too surprising as the isolation and characterization of first-row M-HNO adducts have met with limited success due to the reactive nature of the nitroxyl ligand.[28] Attempts to isolate **4** either from the reaction mixture or directly have not been successful.[29,30] One hypothesis for the reductive nitrosylation of [Fe(TPP)Cl] is the generation of a bridging {Co(μ-NO)(μ-Cl)Fe} intermediate where trans-nitroxylation occurs to yield the {FeNO}^{7} heme, a route suggested for the isoelectronic {FeNO}^{8} complex.[10b] H^+ addition simply enhances the rate of nitroxyl transfer as suggested for DNICs.[23] Such bridging intermediates have also been proposed in the dismutation of {CoNO}^{8} species to {Co(NO)$_2$}^{10} and Co^{III} indicative of formal NO^- transfer.[31] This result is analogous to the fate of **1** to give **3** in the absence of HNO-reactive molecules (Scheme 2). The reaction with Ph_3P may take place from **4** (via tautomerization) or a transient Co-HNO intermediate structurally similar to **1**. Both free and coordinated Ph_3P represent viable possibilities as well. More detailed studies were precluded by the complexity of the process and the difficulty in isolating and detecting every reaction product. Regardless, the observed results are consistent with an HNO donor property for **1**/H^+.

In conclusion, we report the synthesis of {CoNO}^{8} **1** and its reaction with H^+ to afford an HNO donating intermediate. In the

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absence of an HNO target, reaction of **1** and H^+ ultimately leads to the Co-dinitrosyl complex **3** (via intermediate **4**). To our knowledge the reaction of **1** and H^+ is the first example of a $\{CoNO\}^8$ complex that specifically behaves as an HNO donor to known HNO targets (Fe^{III}-heme and Ph_3P). Proton-induced formation of other signaling molecules such as H_2S has been observed with synthetic 2Fe-2S clusters and excess NO.[32] In contrast, **1** alone does not exhibit any reactivity from temperatures ranging 298−310 K, emphasizing the importance of HNO versus NO^- and the underexplored potential of metal nitrosyls as HNO donors. Furthermore, these results confirm that $\{CoNO\}^8$ complexes are not inert and function as sources of HNO under specific pH conditions, thereby opening up a new frontier in HNO donor research.

■ ASSOCIATED CONTENT

Supporting Information

Details of the syntheses, reactivity, spectroscopic, and crystallographic (CIF) results. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

tharrop@uga.edu

Notes

The authors declare no competing financial interest.

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