Communication

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Phenol Reduces Nitrite to NO at Copper(II): Role of a Proton-Responsive Outer Coordination Sphere on Phenol Oxidation

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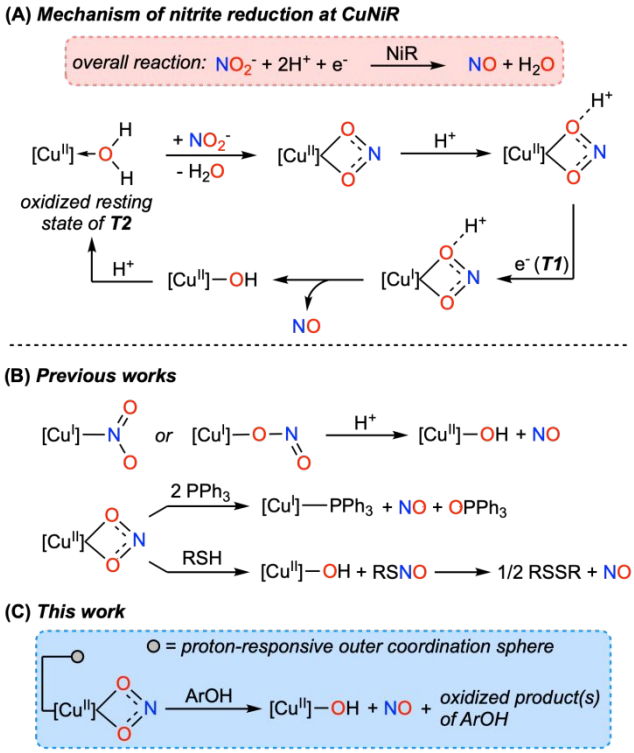
Supporting Information Placeholder

ABSTRACT: In the view of physiological significance, the transition metal-mediated routes for nitrite (NO_2^-) to nitric oxide (NO) conversion and phenol oxidation are of prime importance. Probing the reactivity of substituted phenols towards nitrito copper(II) cryptate [mC]Cu(κ^2-O_2N)(ClO_4) (**1a**), this report illustrates NO release from nitrite at copper(II) following a proton-coupled-electron-transfer (PCET) pathway. Moreover, a different protonated state of **1a** with a proton hosted at an outer coordination sphere [mCH]Cu(κ^2-O_2N)(ClO_4)$_2$ (**3**) also reacts with substituted phenols via a primary electron-transfer from the phenol. Intriguingly, the alternative mechanism operative due to the presence of a proton at the remote site in **3** facilitates an unusual anaerobic pathway for phenol nitration.

Since the recognition of nitric oxide (NO) as a signaling molecule in vasodilation and neurotransmission, the chemical routes leading to NO generation are of paramount interest.[1] NO generated from nitrite offers an O_2-independent route and aids in hypoxia rehabilitation by enhancing blood-oxygenation and -flow.[2] While heme-Fe dependent cofactors such as deoxyhemoglobin, cytochrome *c* oxidase (C*c*O) mediate the one-electron reduction of NO_2^- to NO ($NO_2^- + 2H^+ + e^- \rightarrow NO + H_2O$) in mammals,[3] prokaryotic organisms employ copper nitrite reductase (CuNiR) for reducing NO_2^- to NO as a critical step in the denitrification route of the biogeochemical nitrogen cycle.[4]

CuNiR enzyme consists two mononuclear copper sites: a type 1 (*T1*) Cu site with $(His)_2$(Met)Cu(Cys) entity for electron transfer (ET) and a type 2 (*T2*) Cu site with $(His)_3$Cu-OH_2 coordination motif for substrate binding and reduction.[5] It is noteworthy that the proton-responsive amino acid residues such as Asp98 and His255 are suitably located near the *T2* site and facilitate proton transfer (PT).[5,6] A combination of steady-state kinetics and pulse radiolysis experiments suggest that

Scheme 1

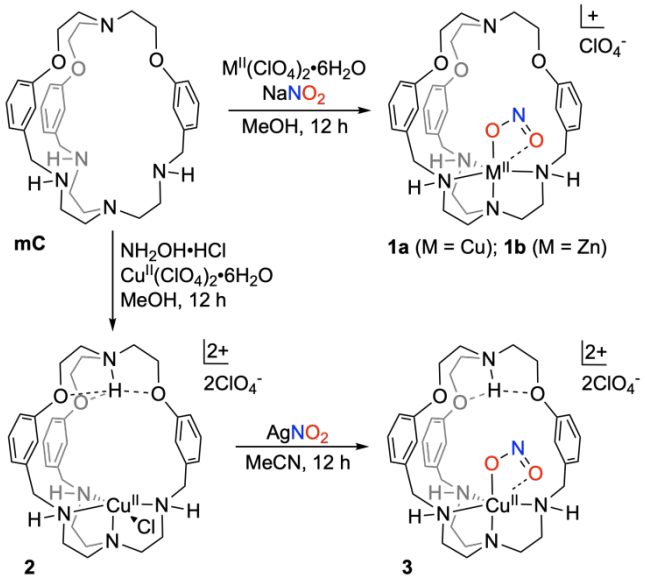


the electron transfer (ET) from *T1* to *T2* during nitrite reduction is promoted by an initial proton transfer (PT) (Scheme 1).[7,8] Furthermore, a recent study employing serial femtosecond crystallography (SFX) and synchrotron radiation crystallography (SRX) data corroborates that nitrite binding and protonation assist the electron transfer (ET) during the CuNiR activity.[9]

While both the reduced and oxidized forms of the *T2* site of CuNiR bind nitrite in κ^2-*O,O'* fashion,[5] CuNiR model complexes typically exhibit κ^1-*N* (in the reduced state) and κ^2-*O,O'* (in the oxidized state) binding modes.[4,10,11,12] Notably, most of the previous reports illustrate the release of NO from copper(I) nitrite complexes in presence of exogenous proton source such

as acetic acid.[10,12] Interestingly, a transient copper(I) κ^1-*O* nitrite adduct species supported by a proton-responsive tripodal ligand is depicted to participate in nitrite reduction through a ligand assisted proton and electron transfers.[13] Surprisingly, only a handful examples of NO release from copper(II) nitrito complexes are documented (Scheme 1).[11,14] For instance, β-diketiminato [Cu^{II}](κ^2-O_2N) complex transfers oxygen-atom to triphenyl phosphine and releases NO.[11] Another recent report illustrates that a nucleophilic attack of thiol on the nitrito moiety in an electron deficient β-diketiminato [Cu^{II}](κ^2-O_2N) complex affords *S*-nitrosothiol, which rapidly decomposes to disulphide and NO.[14] Electrocatalytic reduction of NO_2^- to NO at Cu^{II} sites has been illustrated very recently.[15] We herein disclose reduction of nitrite to NO at a mononuclear Cu^{II} cryptate featuring a remote proton-responsive functional group. Along with the illustration of phenol-mediated reduction of nitrite to NO through proton-coupled-electron-transfer (PCET) pathway, this report outlines new bio-relevant routes for O_2-independent oxidative modifications of phenol including nitration.

Scheme 2. Syntheses of 1a, 1b, 2, and 3.



Metalation of the tripodal heteroditopic cryptand (**mC**) with $Cu(ClO_4)_2$•$6H_2O$ followed by nitration with $NaNO_2$ in methanol results in an air-stable bluish-green complex [mC]Cu(κ^2-O_2N)(ClO_4) (**1a**) in 84% yield (Scheme 2). The molecular structure of **1a** obtained from single crystal X-ray diffraction depicts that the copper site (Cu1–N1 2.0302(14) Å, Cu1–N2 2.0767(15) Å, Cu1–N3 2.2358(15) Å, Cu1–N4 2.0566(15) Å, Cu1–O4 1.9570(12) Å, and Cu1···O5 2.626 Å) is best described as a distorted octahedral geometry (Figures 1A and S1) with an unsymmetrical κ^2-*O,O'* binding of nitrite anion (O4–N6 1.280(2) Å, O5–N6 1.230(2) Å, and O4–N6–O5 114.01(14)°). The UV-vis absorption spectrum of **1a** in acetonitrile exhibits a broad and low-intensity absorption centered at λ_{max}/nm (ε/$M^{-1}cm^{-1}$) = 670 (190), which presumably arises from the low energy *d-d* transitions of an S = ½ d^9 Cu^{II} centre (Figure S2). Moreover, the X-band electron paramagnetic resonance (EPR) spectrum of **1a** in acetonitrile at 77 K shows a spectral pattern typical of an S = ½ d^9 Cu^{II} centre in a distorted octahedral geometry (Figure S3).[16]

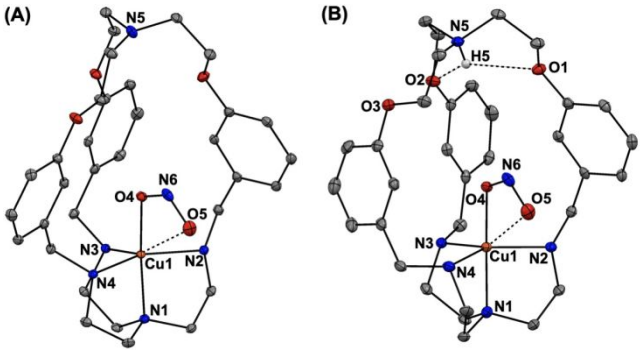


Figure 1. X-ray crystal structures of {[mC]Cu(κ^2-O_2N)}$^+$ (in **1a**) and {[mCH]Cu(κ^2-O_2N)}$^{2+}$ (in **3**) cores. H-atoms (except N5-H5 for **3**) have been omitted for clarity.

Intrigued by the availability of a well-define free cavity in **1a** consisting of an apical tertiary amine site N5 (Cu···N5 7.175 Å) with three ethereal oxygen sites as H-bond acceptors, we anticipate that the N5 site may serve as a proton-responsive moiety. Hence, we strive to isolate the protonated form of the {[mC]Cu(κ^2-O_2N)}$^+$ core. A controlled protonation of **mC** employing NH_2OH•HCl in methanol followed by metalation with $Cu(ClO_4)_2$•$6H_2O$ affords [mCH]$CuCl(ClO_4)_2$ (**2**) in 72% yield (Figures S7-S10). Subsequently, a treatment of an acetonitrile solution of **2** with an equimolar amount of $AgNO_2$ yields [mCH]Cu(κ^2-O_2N)(ClO_4)$_2$ (**3**) in 94% yield. X-ray crystallographic analysis reveals that the copper site in **3** possess a distorted octahedral geometry with an unsymmetrically bound nitrite anion in κ^2-*O,O'* fashion (Figures 1B and S11). While the Cu1–N/O4 distances and the binding mode of nitrite anion in **3** are comparable to those in **1a** (Table S1), the Cu1···O5 interatomic distance in **3** is slightly longer (Cu1···O5 2.754 Å). Interestingly, refinement of the N-H moieties in **3** obtained from the difference map renders the protonated amine N5–H5 engaged in the H–bonding interactions with two ethereal oxygen sites (O1···H5 2.277 Å and O2···H5 2.228 Å). Notably, the interatomic distance between O4···H5 (3.829 Å) is significantly longer relative to the sum of their van der Waals radii 2.72 Å, thereby indicating noninteraction between the nitrite anion and the protonated outer coordination sphere. The UV-vis spectrum of **3** in acetonitrile displays a low-intensity, broad band centered at λ_{max}/nm (ε/$M^{-1}cm^{-1}$) = 660 (180) (Figure S12). Furthermore, the oxidation state of Cu in **3** has been verified by EPR spectroscopy (Figure S13).[16]

Influenced by the previously reported NO releasing reactivity of nitrite at copper(I) upon protonation,[10,12] we envision that nitrite bound to a copper(II) site conceivably lead to the generation of NO in presence of a H-atom (H^+, e^-) source. Illustrating the reaction of nitrite at a copper(II) site with a H-atom (H^+, e^-) source, an equimolar reaction of **1a** with 2,4-di-*tert*-butylphenol (2,4-DTBP) at 65 °C under anaerobic condition leads to a color change (Figure 2). Mass spectroscopic and elemental analyses on the inorganic byproduct suggest the formation of [mC]Cu(OH)(ClO_4) (**4**) (Figures S15-S19). ^{1}H NMR and GC-MS analyses of the resultant reaction mixture indicate the formation of oxidatively coupled phenol 3,3',5,5'-tetra-*tert*-butyl-(1,1'-biphenyl)-2,2'-diol (**5**) in 43% yield with concomitant generation of NO as trapped by $(dtc)_2Fe$ (dtc = *N,N*-diethyldithio carbamate) (Figures S20-S24).[17] In presence of an excess equivalent of substituted phenol (2,4-DTBP) at 65 °C, the absorption feature of **1a** at 670 nm changes to a distinguishable lower intensity d-d band obeying first-order kinetics and the resulting pseudo-first-order rate constant (k_{obs}) is found to be proportional to the concentration of 2,4-DTBP (Figures 2B, S26, S37). Thus, the kinetic experiments illustrate that the reaction between **1a** and substituted phenol (ArOH) follows a simple bimolecular reaction with the rate law of

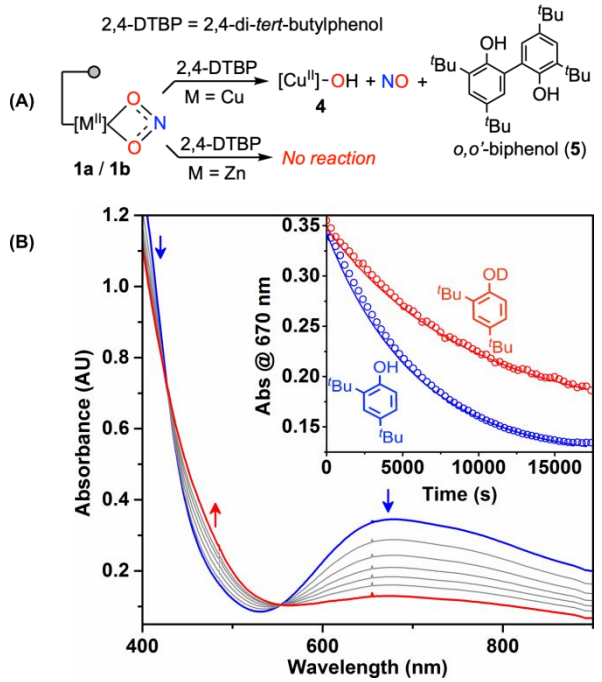
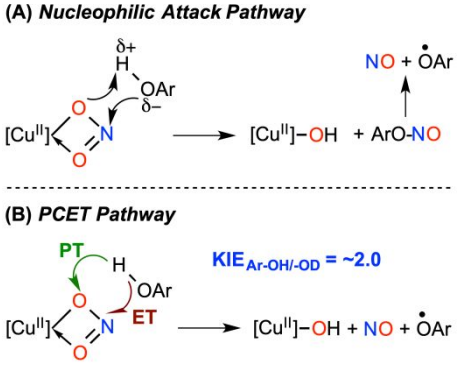


Figure 2. (A) Reactions of 2,4-di-*tert*-butylphenol (2,4-DTBP) with $\{[mC]M^{II}(\kappa^2\text{-}O_2N)\}^+$ cores in **1a** and **1b**. (B) Changes in the UV-vis absorption features of **1a** upon addition of 200 equiv 2,4-DTBP-OH at 65 °C. Inset: The time traces for the changes in 670 nm band in presence of 200 equiv of 2,4-DTBP-OH (blue trace) and 2,4-DTBP-OD (red trace) at 65 °C.

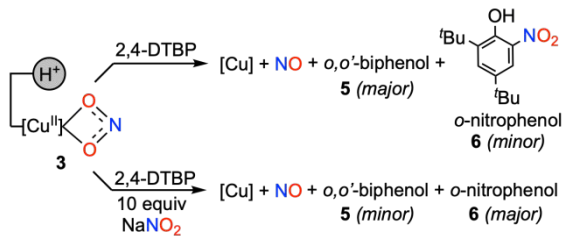
k_2[**1a**]×[ArOH].

Mechanistically, two distinct pathways may be envisaged for such a bimolecular interaction between **1a** and ArOH (Scheme 3). Prompted by the previous report on nitrite-mediated nitrosation of nucleophiles at a copper(II) site,[14] we considered a possible nucleophilic attack by ArOH on the activated nitrite anion of $\{[Cu^{II}](\kappa^2\text{-}O_2N)\}^+$ core in **1a** followed by a decomposition of the resultant *O*-nitrosated product (ArO-NO) yielding NO. To probe this hypothesis, we carried out a reaction between [mC]Zn(κ^2-O_2N)(ClO_4) (**1b**) and excess 2,4-DTBP at 65 °C for several days, but **1b** does not react with 2,4-DTBP (Figure 2A, Figures S25).[18] Thus, this observation disfavors the consideration of nucleophilic attack by phenol on the nitrite anion in a $\{[M^{II}](\kappa^2\text{-}O_2N)\}^+$ core (Scheme 3A). Alternatively, phenol may reduce nitrite to NO through a concerted or stepwise transfer(s) of H^+ and e^-. Assessing the mechanism further, a kinetic isotope effect (KIE) on the second-order rate constant k_2(OH)/k_2(OD) is found to be 2.01 and 2.06 for 2,4-DTBP-OH/OD and 4-MeO-C_6H_4-OH/OD, respectively (Figures S27, S29). The definite influence of the deuteration of the phenolic OH on k_2 clearly suggests the engagement of a proton-transfer (PT) in the rate-determining-step.[19,20] In addition, the plot of log k_2 *versus* one-electron oxidation potentials of substituted phenols (E_{ox}) exhibits a negative slope, thereby suggesting the contribution of an electron-transfer (ET) in the rate-determining-step (Figure S30). Hence, these results corroborate that the ET from phenol to **1a** is coupled with a concomitant PT, thereby suggesting the proton-coupled-electron-transfer (PCET) mechanism for phenol-mediated nitrite to NO transformation at Cu^{II} (Scheme 3B).[21] Notably, similar kinetic investigations with comparable KIE values (1.2–1.56) and log k_2 *versus* E_{ox} correlations have been demonstrated for the oxidation of substituted phenols by copper-oxygen species following PCET route.[20,21] Subsequent to the PCET from ArOH to **1a**, transient intermediates such as $\{[Cu^{I}](NO_2H)\}^+$ and $\{[Cu^{II}](OH)(NO)\}^+$ may be involved prior to NO release.[22]

Scheme 3. Mechanistic pathways considered for the reaction of phenol with $[Cu^{II}](\kappa^2\text{-}O_2N)$.



Scheme 4



Strikingly, a stoichiometric reaction between [mCH]Cu(κ^2-O_2N)(ClO_4)$_2$ (**3**) and 2,4-di-*tert*-butylphenol (2,4-DTBP) at 65 °C under anaerobic condition evolves NO and yields oxidative products of phenol consisting of **5** (31%) and 2,4-di-*tert*-butyl-6-nitrophenol (**6**) (8%) (Scheme 4, Figures S22-S24). While phenols are known to react with free NO_2,[23] phenol nitration in the biological milieu is proposed to occur via an electrophilic aromatic substitution employing NO_2^+/NO_2 electrophiles *in situ* generated from a metastable peroxynitrite intermediate.[24] Notably, the peroxynitrite species forms through an O_2-dependent pathway involving the interaction between a formal superoxide species and free NO.[25] In the present case, however, phenol nitration proceeds through an O_2-independent route. Interestingly, monitoring of the reaction of excess 2,4-DTBP with **3** in acetonitrile at 65 °C by UV-vis analysis reveals that the overall reaction is slower as compared to that with **1a** and does not follow a pseudo-first-order decay profile (Figure S31). Moreover, the employment of 2,4-DTBP-OD does not alter the time-trace of the reaction (Figure S32) significantly, thereby indicating the non-involvement of the proton-transfer (PT) in the rate-determining step. Notably, interactions of triflic acid with high-valent Mn-oxo species has been illustrated to accelerate ET rate and leads to a switchover of the H^+/e^- transfer mechanism.[26] We, therefore, postulate that the presence of a proton in the outer coordination sphere of [mCH]Cu(κ^2-O_2N)(ClO_4)$_2$ (**3**) reduces the rate of PT from the phenol. Unlike the reaction between **1a** and 2,4-DTBP proceeding with comparable rates of proton and electron transfers, the reaction of **3** presumably proceeds via a primary electron-transfer (ET) from ArOH to generate a transient $[ArOH]^{\bullet+}$ species, a portion of which reacts with NO_2^- as a nucleophile to afford the nitrated phenol.[27] To experimentally probe this hypothesis, a stoichiometric reaction between **3** and 2,4-DTBP was carried out in presence of excess free NO_2^- to intercept the *in situ* generated $[ArOH]^{\bullet+}$ species. Notably, presence of 10 equiv of $NaNO_2$ during the equimolar reaction of **3** with 2,4-DTBP indeed affords a relatively higher yield of 2,4-di-*tert*-butyl-6-nitrophenol (**6**) (20%) along with a lower yield of *o,o'*-biphenol (**5**) (18%) (Scheme 4, Figures S22-S24, Table S3).[28]

To conclude, this study illustrates phenol-mediated reduction of nitrite to NO, which is reminiscent of the increase of NO flux from the interactions of dietary polyphenols and nitrite in stomach.[29,30] The mechanistic investigations utilizing a structurally characterized nitrito copper(II)-cryptate [mC]Cu(κ^2-O_2N)(ClO_4) (**1a**) imply the involvement of proton-coupled-electron-transfer (PCET) in nitrite reduction. In addition, this report outlines that the controlled protonation of the outer coordination sphere of **1a** causes the mechanistic switchover, thereby turning on an unprecedented anaerobic pathway for the nitration of phenol, even though the proton-responsive moiety is remote from the [Cu](κ^2-O_2N) site. Hence, the current study not only reveals a new route for the reduction of nitrite to NO, but also offers a lens to view an unusual anaerobic pathway for oxidative phenol nitration. A detailed mechanism of anaerobic phenol nitration is the subject of our future study.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. UV-vis, EPR, NMR, X-ray crystallographic, and experimental details (PDF).

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Notes

The authors declare no competing financial interest.

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(17) While the released NO was trapped qualitatively, the quantitation of NO was hampered due to relatively slow reaction rate at ambient conditions.

(18) Complex **1b** is a structurally characterized nitrito Zn^{II} cryptate analogous to **1a**. See supporting information, Figure S5, Table S1 for the molecular structure of **1b**.

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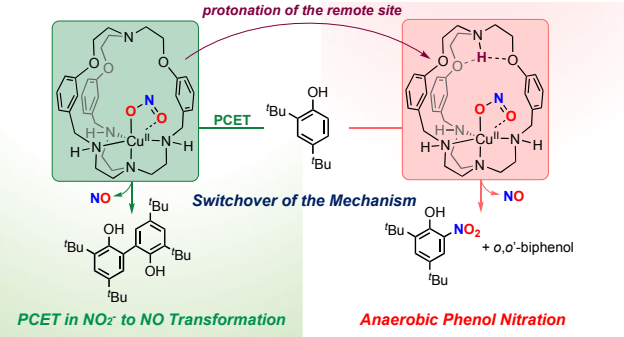
protonation of the remote site
PCET
NO
Switchover of the Mechanism
NO
NO2
+ o,o'-biphenol
PCET in NO2- to NO Transformation
Anaerobic Phenol Nitration