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Finding a new pathway for acid-induced nitrite reduction reaction: formation of nitric oxide with hydrogen peroxide

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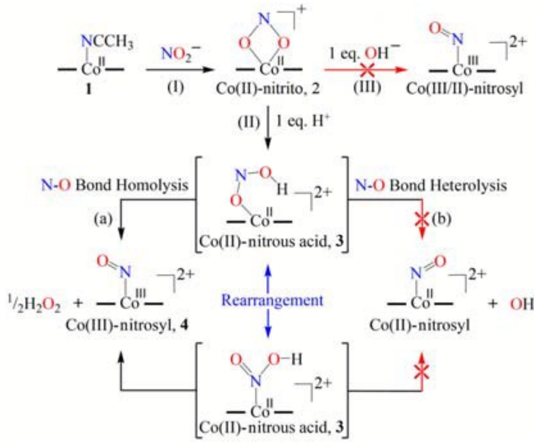
Here, we report a new pathway for nitrite reduction chemistry, formation of Cobalt-Nitrosyl ($\{Co^{II}\text{-}NO\}^8$) with H_2O_2 in the reaction of Co^{II}-nitrito complex with one fold acid (H^+) via the formation of Co^{II}-nitrous acid intermediate ($\{Co^{II}\text{-}ONOH\}$). Mechanistic investigations using ^{15}N-labeled-$^{15}NO_2^-$ revealed that the N-atom in the $\{Co^{II}\text{-}NO\}^8$ complex is derived from nitrito ligand, and H_2O_2 came from the homolysis of ON-OH moiety. Spectral evidences supporting the formation of Co^{II}-ONOH intermediate and the generation of H_2O_2 are also presented.

Nitric oxide (NO), a significantly important biological molecule, has attracted enormous interest from chemists as well as biochemists for its major role in various physiological processes such as neurotransmission, vascular regulation, platelet disaggregation and immune response to multiple infections.[1-5] Furthermore, NO inadequacy may worsen the pathogenic effects like atherosclerosis, diabetic hypertension, etc.[6] The NO immune response towards harmful pathogens is related to its oxidized species, peroxynitrite ($ONOO^-$)[7-9] or/ nitrogen dioxide ($\bullet NO_2$)[10, 11], however, these species may also lead to various toxicological behavior[8, 12-14]. Therefore, it is essential to maintain an optimal concentration of NO for various physiological processes (homeostasis). In this regards, nitrite reductase (NiR)[15-17] and endothelial nitric oxide synthase (eNOS)[17-19] enzymes are available for NO biosynthesis. For NOS system, the key substrate for the generation of NO is L-arginine, which changes to citrulline with the simultaneous release of NO through the catalytic activity.[18, 19] However, in mammals, bacteria, and fungi, the NiR enzymes are either Cu or heme Fe proteins, which reduces NO_2^- to NO. NiR enzymes catalyze the conversion of NO_2^- to NO in the presence of 2 equiv. of protons (H^+), i.e., $NO_2^- + e^- + 2H^+ \rightarrow NO + H_2O$ (eq. **1**).[15-17] In mammalian systems, Brooks *et al.* proposed the NiR activity of deoxygenated ferriheme protein Hb, which upon reaction with NO_2^- formed metHb and NO, i.e., $Hb + NO_2^- + 2H^+ \rightarrow metHb + NO + H_2O$ (eq. **2**).[20] Sometimes, biological dysfunction may result in the overproduction of NO by NiR or NOS, in such cases, nitric oxide dioxygenase (NOD) enzymes are available in vivo to convert the overproduced NO into biologically benign nitrate (NO_3^-).[21, 22] The NiR and NOS reactions have not been explored extensively, and therefore, the exact mechanism of these reactions is yet to be discovered. In this regards, various in vitro models have been investigated i.e. (i) oxygen atom transfer (OAT) triggered by thioether (R_2S, eq. **3**)[23] or/ thiol (RSH, eq. **4**)[24, 25]/triphenylphosphine (PPh_3, eq. **5**)[26, 27] and (ii) photo-induced reactions (eq. **6**)[28] of metal-bound nitrite. Furthermore, there are recent chemistries on biomimetic synthetic modeling of M-NOs/active sites associated to NiR and/or NOS.[29] Recently, Lehnert *et al.* have developed the synthetic approach for Fe-NOs,[30, 31], and Hayton structurally characterized the first Cu^{II}-NO[32]. Nam and coworkers probed the generation of Fe-NOs in photo-induced NiR reactivity and stabilized the Co-NOs.[28, 33, 34] Ford and coworkers reported NiR chemistries with iron heme systems and characterized the Fe-NOs formation.[35, 36]

$M\text{-}NO_2 + R_2S \rightarrow M\text{-}NO + R_2SO$ (eq. **3**)
$M\text{-}NO_2 + RSH \rightarrow M\text{-}NO + R(O)SH$ (eq. **4**)
$M\text{-}NO_2 + PPh_3 \rightarrow M\text{-}NO + OPPh_3$ (eq. **5**)
$M\text{-}NO_2 + Sub + h\nu \rightarrow M\text{-}NO + (O)Prod$ (eq. **6**)

Here in this report, we are exploring new mechanistic aspects of acid-induced nitrite reduction chemistry of cobalt-bound nitrite. In



Scheme 1. Co(II)-nitrito complex (**2**), obtained from the reaction of nitrite and complex **1**, generates Co^{III}-nitrosyl complex (**4**) and ½ H_2O_2 in presence of one fold H^+ via a Co^{II}-nitrous acid intermediate (**3**). However, substituting the H^+ by OH^- does not give the same product (Reaction III).

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this investigation, we intend to stabilize the intermediate and characterize the reaction products so that we can predict the most suitable mechanism of NiR reaction.

At the outset, we report the nitrite reduction chemistry of Co^{II}-nitrito complex bearing the 12-TMC ligand, $[(12\text{-TMC})Co^{II}(NO_2)]^+$ (**2**), 12-TMC = 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclododecane) (Scheme 1, reaction II). Complex **2** reacts with one fold perchloric acid ($HClO_4$, H^+ source) to form complex **4** formulated as a Co^{III}-nitrosyl complex, $[(12\text{-TMC})Co^{III}(NO^-)]^{2+}$ and H_2O_2 via the formation of a presumed Co^{II}-nitrous acid intermediate (Co^{II}-ONOH, **3**) in CH_3CN at 298 K (Scheme 1, reaction IIa). However, complex **2** does not form **4** upon its reaction with base (OH^-) (Scheme 1, reaction III). Mechanistic investigations using ^{15}N-labeled-$^{15}NO_2^-$ demonstrated explicitly that the N-atom in the Co^{III}-nitrosyl complex ($\{CoNO\}^8$) is derived from NO_2^- anion and H_2O_2 comes from the protonated oxygen atom of ON-OH moiety. To the extent of our knowledge, the present work reports the very first mechanistic study for the reaction of Co^{II}-NO_2^- complex with H^+ to form H_2O_2 by homolysis of ON-OH moiety, illustrating a new mechanistic approach for nitrite reduction in contrast to NiR enzyme activity. This new finding, where nitrite reduces to metal-nitrosyl and produces H_2O_2, proposes an alternative route for H_2O_2 generation in biosystems, in addition to other reported literature.[37]

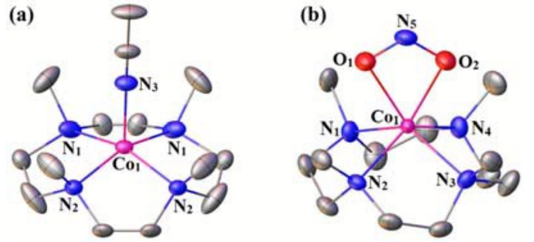

Fig. 1 Displacement ellipsoid plots (30 % probability) of (a) $[(12\text{-TMC})Co^{II}(CH_3CN)]^{2+}$ (**1**) and (b) $[(12\text{-TMC})Co^{II}(NO_2)]^+$ (**2**) at 100 K. Disorder C-atoms in the TMC ring, anions and the H atoms have been removed for clarity.

$[(12\text{-TMC})Co^{II}(NO_2)]^+$ (**2**) was prepared by the addition of 1 equiv. of $NaNO_2$ to Co^{II}-complex, $[(12\text{-TMC})Co^{II}(NCCH_3)]^{2+}$. (**1**), in CH_3CN at 298 K (Scheme 1, reaction I; also see Supporting and Experimental Section (ES)). **1** was characterized with various spectroscopic measurements including single crystal X-ray structure determination (Fig. 1a; Fig. S1).[33, 34] UV-vis absorption band of **1** (λ_{max} = 485 nm) changed to a new band (λ_{max} = 535 nm, ε = 24 M^{-1} cm^{-1}) upon addition of 1 equiv. $NaNO_2$, corresponds to **2** (Fig. S2a). FT-IR spectrum of **2** shows a characteristic peak for Co^{II}-bound nitrite at 1271 cm^{-1} which shifted to 1245 cm^{-1} when exchanged with ^{15}N-labeled-nitrite ($^{15}N^{16}O_2^-$) (Fig. S2b).[38] Electrospray ionization mass spectra (ESI-MS) recorded for **2** shows a prominent ion peaks at *m/z* 333.1, which shifted to *m/z* 334.1 when prepared with ^{15}N-labeled $Na^{15}N^{16}O_2$, their mass and isotope distribution pattern corresponds to $[(12\text{-TMC})Co(NO_2)]^+$ (calc. *m/z* 333.1) and $[(12\text{-TMC})Co(^{15}NO_2)]^+$ (calc. *m/z* 334.1), respectively (Fig. S3). Also, **2** was structurally characterized via single crystal X-ray crystallography. The complex **2** has six-coordinate distorted octahedral geometry around the Co^{II}-center possessing O, O/-chelated bi-dentate NO_2^- anion (Fig. 1b; Supplementary ES and Tables T1, and T2).

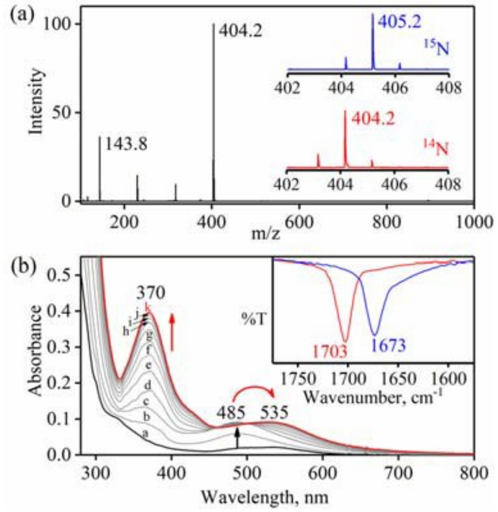

Fig. 2 (a) UV-vis spectral changes of **2** (0.50 mM, black line) upon addition of 1 equiv. of H^+ in CH_3CN under Ar at RT (recoded at every 6 min. interval). Black line (**2**) start forming a peak at 485 nm (**3**) upon addition of H^+, followed by its conversion to red line (**4**). Inset: IR spectra **4**-$^{14}NO^-$ (red line) and **4**-$^{15}NO^-$ (blue line) in KBr. (b) ESI-MS spectra of the **4**. The peak at 404.2 is assigned to $[(12\text{-TMC})Co^{III}(NO)(BF_4)]^+$ (calcd *m/z* 404.2). The peak at *m/z* 416.1 marked with asterisks is assigned to $[(12\text{-TMC})Co^{III}(NO)(ClO_4)]^+$ (calcd *m/z* 416.2). Inset: isotopic distribution pattern for **4**-$^{14}NO^-$ (red line) and **4**-$^{15}NO^-$ (blue line).

To further investigate the chemistry of Co^{II}-nitrito complex (**2**), we explored its reaction with acid (H^+) and /or base (OH^-). Complex **2** reacts with one fold of H^+ to produce $\{CoNO\}^8$ (**4**) and H_2O_2 (Scheme 1, reaction IIa) in CH_3CN under Ar at 298 K, in contrast to previous reports on NiR enzymatic reactions.[15-17] On the contrary, the reaction of **2** with OH^- does not produce **4** under the same reaction conditions (Scheme 1, reaction III). Complex **2** color changed from light pink to dark pink upon reaction with H^+ and the characteristic absorption band of **4** (370 nm) formed within 1 hour (Fig. 2a; Supplementary ES and Fig. S4). Spectral titration data confirmed that the ratio-metric equiv. of H^+ with **2** was 1:1 (Fig. S5). The compound **4** obtained in the reaction of **2** with H^+ was determined to be $\{CoNO\}^8$ on the basis of various spectroscopic and structural characterization (*vide infra*).[33, 34] Also, we quantified the amount of **4** (95 ± 2%), formed in the above reaction, by comparing its epsilon (ε) value with the reference **5**, $[(12\text{-TMC})Co^{III}(NO)](BF_4)_2$, obtained from the reaction between complex **1** and $NO_{(g)}$ (Supplementary ES and Fig. S6).[33, 34]

The FT-IR spectrum of **4** showed a characteristic peak for nitrosyl stretching at 1703 cm^{-1} $\{Co^{14}NO\}^8$ and shifted to 1673 cm^{-1} $\{Co^{15}NO\}^8$ when **4** was prepared by reacting ^{15}N-labeled-nitrite (Co^{II}-$^{15}NO_2^-$) with H^+(Inset, Fig. 2a; Fig. S7). The shifting of NO stretching (Δ = 30 cm^{-1}) indicates that N-atom in nitrosyl ligand is derived from Co^{II}-$^{15}NO_2^-$. The ESI-MS spectrum of **4** showed a prominent peak at *m/z* 404.2, $[(12\text{-TMC})Co^{III}(^{14}NO)(BF_4)]^+$ (calcd *m/z* 404.2), and shifted to 405.2, $[(12\text{-TMC})Co^{III}(^{15}NO)(BF_4)]^+$ (calcd *m/z* 405.2), when the reaction was performed with Co^{II}-$^{15}NO_2^-$ (Fig. 2b; Fig. S8a); indicates clearly that NO in **4** is derived form NO_2^- moiety. The EPR spectrum of complex **4** was silent, suggesting the trivalency of the cobalt center (Fig. S8b), additionally supported by ^1H NMR spectrum confirming the low spin diamagnetic Co^{III} center coordinated to NO^- or Co^{II}-NO• i.e., diamagnetic $\{Co(NO)\}^8$ species (Fig. S9).[33, 34] The exact conformation of **4** was provided by its single crystal X-ray crystallographic analysis which is similar to **5** (Fig. 3; Supplementary ES, and Tables T1 and T2) and also with previously reported Co^{III}-NO^- / M-NO^- having sp^2 hybridized N atom.[33, 34, 39, 40] The presence of lone pair on N-atom is responsible for the substantial bending of the Co-bound NO moiety, with Co(1)-N(5)-O(1) bond angles of 128.52(18)°

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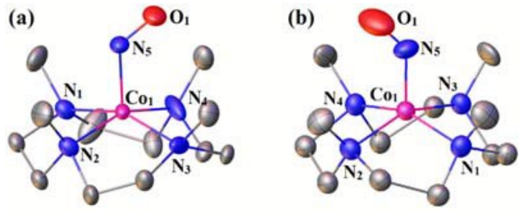


Fig. 3 Displacement ellipsoid plots (30 % probability) of (a) $[(12\text{-TMC})Co^{III}(NO)]^{2+}$ (**4**) and (b) $[(12\text{-TMC})Co^{III}(NO)]^{2+}$ (**5**) at 100 K and 298 K, respectively. Disorder C-atoms in the TMC ring, anions and the H atoms have been removed for clarity.

for **4** and therefore further consistent with the assignment of **4** as $\{CoNO\}^8$ species.

Further, we endeavored to characterize the proposed Co^{II}-ONOH intermediate (**3**) and explicate the given mechanism of its conversion to the complex **4** (Scheme 1, reaction IIa). First, UV-vis spectrum of **2** (black line) changed to a grey line upon addition of one fold H^+, which represents the proposed intermediate **3** (λ_{max} = 485 nm), with simultaneous formation of **4** (red line) over a time period of 1 hour (Fig. 2a; Fig. S4). We also found by solution IR spectroscopy that the NO_2^- peak at 1300 cm^{-1} (Fig. S10) first shifted to 1284 cm^{-1} (**3**, blue line) upon reaction with H^+, followed by its conversion to a new peak at 1710 cm^{-1} (**4**, red line; Inset, Fig. 4).[33, 34] The negative shift in the IR frequency (Δ = 16 cm^{-1}) suggests the formation of Co^{II}-ONOH by protonation of NO_2^-. In addition, the EPR spectral measurements also revealed that the intermediate (**3**) displayed a signal assignable to a d^7 Co^{II}-ion (S = 1/2) at 100 K (blue line, Fig. 4), however **4** (red line, Fig. 4) is EPR silent while **2** has a characteristic EPR signal assignable to a d^7 Co^{II}-ion (S = 3/2).[33] Additionally, time-dependent EPR measurement of the freezing solution of **2** and H^+ reaction mixtures, recorded in CH_3CN at 100 K as a function of time (0 to 60 minutes), also supports the formation of **3** and its signal intensity decreased with time and changed to an EPR inactive species **4** (Fig. 4).[33, 34, 41]

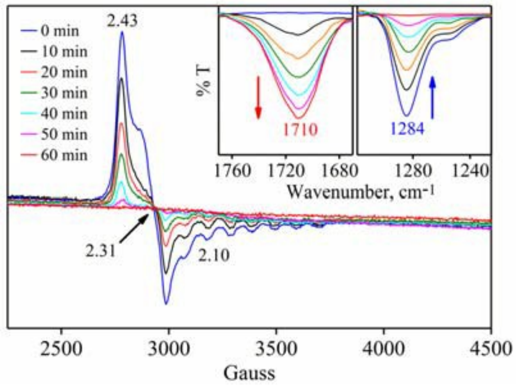
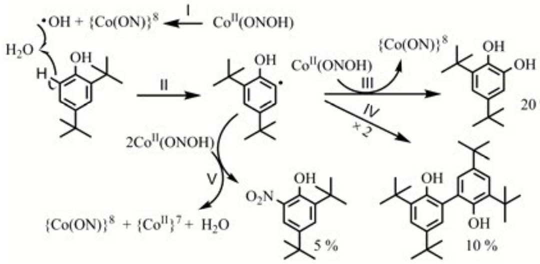


Fig. 4 Time-dependent EPR spectra of $Co^{II}(ONOH)$ intermediate (**3**; blue line) in CH_3CN at 100 K. Complex **2** and H^+ were mixed in CH_3CN at RT under Ar, and the EPR spectra were recorded for the frozen solutions as a function of time (0, 1, 10, 20, 30, 40, 50, and 60 min). Inset: Solution IR spectral changes showing the conversion of **3** (5 mM; blue line) to **4** (red line) under Ar in CH_3CN at RT in 1.0 h.

Also, we have characterized the H_2O_2 formation in the above reaction by ^1H-NMR spectroscopic measurement.[42] The ^1H-NMR spectrum of complex **2** with one fold H^+ in CD_3CN showed a characteristic signal for H_2O_2 (8.66 ppm, Fig. S11a). This spectrum was compared with the authentic samples (i) H_2O_2 plus **5** (8.66 ppm; Fig. S11b) and (ii) H_2O_2 only (8.66 ppm; Fig. S12) which confirmed the formation of H_2O_2 and hence validated our hypothesis of H_2O_2 formation in the nitrite reduction chemistry. ^1H-NMR spectral quantification of H_2O_2 using benzene as an internal standard suggested that more than 50 % H_2O_2 was formed in the reaction (Supplementary ES and Fig. S11). In addition to ^1H-NMR, we have also quantified the H_2O_2 formation by iodometric titration in one and four equiv. acid and found to be ~ 65 % and 55 %, respectively (SI, ES, and Figure S13a and S13b, respectively). Also, cyclic voltamogram of **4** was recorded which is similar to that of **4** + 0.5 equiv. H_2O_2, suggesting the coexistence of **4** in presence of H_2O_2 (SI, Figure S14). We sought more support for our mechanistic proposal, including N–O bond homolysis and •OH radical formation. To confirm the N–O bond homolysis and the formation of free •OH radical, we have performed the trapping experiment using 2,4-di-*tert*-butyl phenol (2,4-DTBP).[43, 44] We have observed the formation of 3,5-Di-*tert*-butylcatechol (3,5-DTBC, ~ 20 %) with small amount of 2,4-DTBP-dimer (2,4-DTBP-D, ~ 10 %) and nitro-2,4-DTBP (NO_2-2,4-DTBP, ~ 5 %) (SI, ES and Figure S15). This reaction suggests that the N–O bond homolysis forms •OH free radical which generate different products (Scheme 2), and hence indirectly proving the Co^{II}-nitrous acid intermediate (**3**) in the nitrite reduction reaction. The control reaction of 2,4-DTBP with equiv. amount of H_2O_2 does not form the product mixture (3,5-DTBC, 2,4-DTBP-D, & NO_2-2,4-DTBP). However, we observed the formation of 3,5-DTBC and 2,4-DTBP-D upon UV light exposure for the same reaction, suggesting UV light induced •OH radical formation[45] and their trapping by 2,4-DTBP (SI, ES). The amount of H_2O_2, remaining after the spin trap experiment, was determined Iodometrically and found to be negligible (SI, Figure 13c).



Scheme 2 Trapping of •OH radical using 2,4DTBP.

This result can readily be explained as follows: First, H-atom abstraction reaction of DTBP by Co^{II}-nitrous acid intermediate **3** gives a phenoxyl-radical and a $\{Co(NO)\}^8$ complex (Scheme 2, reaction I & II). The phenoxyl radical again reacts with one more molecule of **3** to generate 3,5-DTBC with a molecule of $\{Co(NO)\}^8$ (Scheme 2, reaction III) or can also dimerize to give 2,4-DTBP-D (Scheme 2, reaction IV). Also, it can form the NO_2-DTBP by reacting with two molecules of **3** (Scheme 2, reaction V). Thus, the trapping of •OH radical in good yield strongly supports the proposed reaction mechanism, which involves the formation of a Co^{III}-nitrosyl complex ($\{CoNO\}^8$) and H_2O_2 via homolytic N−O bond cleavage of a Co^{II}-nitrous acid intermediate.

$$
\begin{array}{lcl}
2Co^{II}(ONO^-) + 2H^+ & \longrightarrow & 2Co^{II}(ON\text{-}OH) \\
Co^{II}(ON\text{-}OH) & \longrightarrow & Co^{III}\text{-}NO^- + \dot{O}H \\
Co^{II}(ON\text{-}OH) + \dot{O}H & \longrightarrow & Co^{III}\text{-}NO^- + H_2O_2 \\
\hline
2Co^{II}(ONO^-) + 2H^+ & \longrightarrow & 2Co^{III}\text{-}NO^- + H_2O_2
\end{array}
$$

Scheme 3. Putative formation of Co^{II}-nitrous acid intermediate followed by its conversion to Co^{III}-nitrosyl complex and hydrogen peroxide.

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The idea of M^{III}-nitrosyl formation from a M^{II}-ONOH intermediate would be feasible by either (i) the release of H_2O_2 (Scheme 1, reaction IIa) or (ii) the examples where M^{II}-ONOH transformed to a M-NO + H_2O.[46] The mechanistic steps for the reaction of $Co^{II}(NO_2^-)$ with H^+ are given in Scheme 3. As known for NiR enzyme activity,[46] electrophilic addition of H^+ to **2** will produce Co^{II}-ONOH (**3**) (Scheme 1, reaction II). In contrast to the reported NiR enzyme activity where NO formed by the heterolytic cleavage of ON-OH_2 bond with the removal of H_2O,[47] for the first time, the formation of nitrosyl complex (**4**) and H_2O_2 was observed by the homolytic cleavage of ON-OH moiety with simultaneous electron transfer from Co^{II} to NO (Scheme 1, reaction IIa).

In summary, we have demonstrated the reaction of $[(12\text{-TMC})Co^{II}(NO_2)]^+$ (**2**) with acid (H^+) and/or base (OH^-) (Scheme 1). For the first time, we have demonstrated the clear formation of Co^{III}-nitrosyl complex ($\{CoNO\}^8$), $[(12\text{-TMC})Co^{III}(NO^-)]^{2+}$ (**4**), and H_2O_2 in the reaction of **2** with one fold H^+ via a Co^{II}-ONOH (**3**) intermediate. Similar results, the formation of metal nitrosyl and hydrogen peroxide, were also observed in the aqueous system. However, NiR heme protiens[20] and Co substituted Mb[48] generates NO and water from nitrite. In contrast to the nitrite reduction reaction by H^+, the reaction of **2** with OH^- do not form nitrosyl complex (**4**). It is important to note that H_2O_2 formation involves a distinctive pathway of ON-OH homolytic cleavage. The present study is the first ever report where a Co^{II}-ONOH intermediate generates $\{CoNO\}^8$ + H_2O_2 products, adding an entirely new mechanistic insight, and propose the additional pathway for nitrite reduction reactions and the generation of hydrogen peroxide in bio-systems.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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