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Nitric oxide monooxygenation (NOM) reaction of cobalt-nitrosyl {Co(NO)}^{8} to Co^{II}-nitrito {Co^{II}(NO$_2^-$)}: base induced hydrogen gas (H$_2$) evolution†

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Here, we report the nitric oxide monooxygenation (NOM) reactions of a Co^{III}-nitrosyl complex (1, {Co-NO}^{8}) in the presence of mono-oxygen reactive species, *i.e.*, a base (OH$^-$, tetrabutylammonium hydroxide (TBAOH) or NaOH/15-crown-5), an oxide (O^{2-} or Na$_2$O/15-crown-5) and water (H$_2$O). The reaction of 1 with OH$^-$ produces a Co^{II}-nitrito complex {3, (Co^{II}-NO$_2^-$)} and hydrogen gas (H$_2$), *via* the formation of a putative N-bound Co-nitrous acid intermediate (2, {Co-NOOH}$^+$). The homolytic cleavage of the O–H bond of proposed [Co-NOOH]$^+$ releases H$_2$ *via* a presumed Co^{III}-H intermediate. In another reaction, 1 generates Co^{II}-NO$_2^-$ when reacted with O^{2-} *via* an expected Co^I-nitro (4) intermediate. However, complex 1 is found to be unreactive towards H$_2$O. Mechanistic investigations using ^{15}N-labeled-^{15}NO and ^{2}H-labeled-NaO^{2}H (NaOD) evidently revealed that the N-atom in Co^{II}-NO$_2^-$ and the H-atom in H$_2$ gas are derived from the nitrosyl ligand and OH$^-$ moiety, respectively.
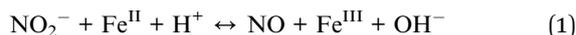
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As a radical species, nitric oxide (NO) has attracted great interest from the scientific community due to its major role in various physiological processes such as neurotransmission, vascular regulation, platelet disaggregation and immune responses to multiple infections.[1] Nitric oxide synthase (NOS),[2] and nitrite reductase (NiR)[3] enzymes are involved in the biosynthesis of NO. NOSs produce NO by the oxidation of the guanidine nitrogen in L-arginine.[4] However, in mammals and bacteria, NO$_2^-$ is reduced to NO by NiRs in the presence of protons, *i.e.*, NO$_2^-$ + e$^-$ + 2H$^+$ → NO + H$_2$O.[5] Biological dysfunctions may cause overproduction of NO, and being radical it leads to the generation of reactive nitrogen species (RNS), *i.e.*, peroxynitrite (PN, OONO$^-$)[6] and nitrogen dioxide ($^\bullet$NO$_2$),[7] upon reaction with reactive oxygen species (ROS) such as superoxide (O$_2^{\bullet-}$),[8] peroxide (H$_2$O$_2$),[9] and dioxygen (O$_2$).[10] Hence, it is essential to maintain an optimal level of NO. In this regard, nitric oxide dioxygenases (NODs)[11] are available in bio-systems to convert excess NO to biologically benign nitrate (NO$_3^-$).[12]

$$NO_2^- + Fe^{II} + H^+ \leftrightarrow NO + Fe^{III} + OH^- \quad (1)$$

$$[M–NO]^n + 2OH^- \rightarrow [M–NO_2]^{(n-2)} + H_2O \quad (2)$$

NOD enzymes generate NO$_3^-$ from NO;[11b,12–13] however, the formation of NO$_2^-$ from NO is still under investigation. Clarkson and Bosolo reported NO$_2^-$ formation in the reaction of Co^{III}-NO and O$_2$.[14] Nam and co-workers showed the generation of Co^{II}-NO$_2^-$ from Co^{III}-NO upon reaction with O$_2^{\bullet-}$.[15] Recently, Mondal and co-workers reported NO$_2^-$ formation in the reaction of Co^{II}-NO with O$_2$.[16] Apart from cobalt, the formation of Cu^{II}-NO$_2^-$ was also observed in the reaction of Cu^I-NO and O$_2$.[17] For metal-dioxygen adducts, *i.e.*, Cr^{III}-O$_2^{\bullet-}$ and Mn^{IV}-O$_2^{2-}$, NOD reactions led to the generation of Cr^{III}-NO$_2^-$ (ref. 18) and Mn^V=O + NO$_2^-$,[19] respectively. However, the NOD reaction of Fe^{III}-O$_2^{\bullet-}$ and Fe^{III}-O$_2^{2-}$ with NO and NO$^+$, respectively, generated Fe^{III}-NO$_3^-$ *via* Fe^{IV}=O and $^\bullet$NO$_2$.[20] Ford suggested that the reaction of ferric-heme nitrosyl with hydroxide leads to the formation of NO$_2^-$ and H$^+$.[12] Lehnert and co-workers reported heme-based Fe-nitrosyl complexes[21] showing different chemistries due to the Fe^{II}-NO$^+$ type electronic structures. On the other hand, Bryan proposed that the one-electron reduction of NO$_2^-$ to NO in ferrous heme protein is reversible (eqn (1)).[22] Also, it is proposed that excess NO in biological systems is converted to NO$_2^-$ and produces one equivalent of H$^+$ upon reaction with $^\bullet$OH.[23] Previously reported reactivity of M–NOs of Fe[24] with OH$^-$ suggested the formation of NO$_2^-$ and one equivalent of H$^+$, where H$^+$ further reacts with one equivalent of OH$^-$ and produces H$_2$O (eqn (2)).[25]

Here in this report, we explore the mechanistic aspects of nitric oxide monooxygenation (NOM) reactions of the Co^{III}-nitrosyl complex, [(12TMC)Co^{III}(NO$^-$)]$^{2+}$/{Co(NO)}^{8} (1),[15,26]
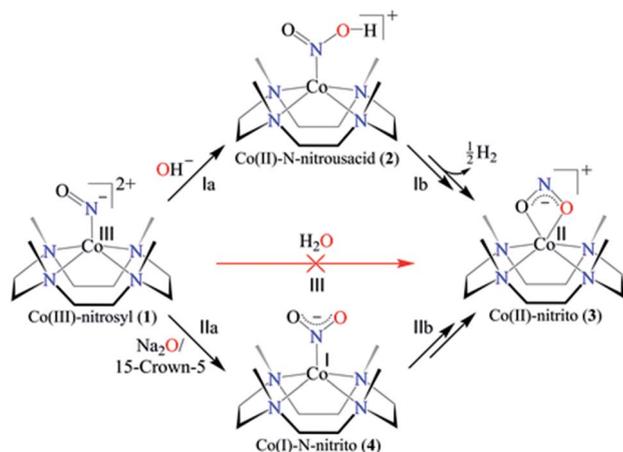
Scheme 1 Nitric oxide monooxygenation (NOM) reactions of cobalt-nitrosyl complex (**1**) in the presence of a base (OH⁻), sodium oxide (Na₂O) and water (H₂O).
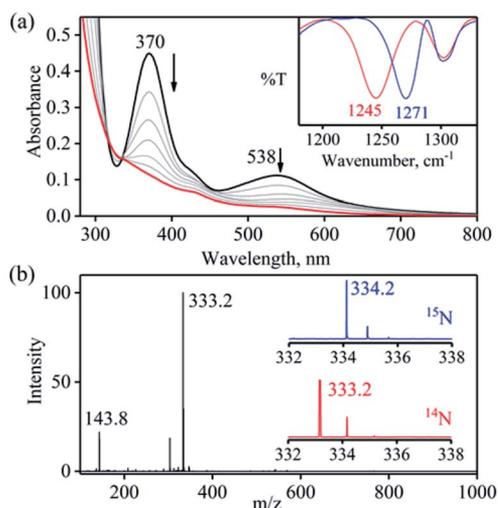

Fig. 1 (a) UV-vis spectral changes of **1** (0.50 mM, black line) upon addition of OH⁻ (1 equiv.) in CH₃CN under Ar at 273 K. Black line (**1**) changed to red line (**3**) upon addition of OH⁻. Inset: IR spectra of **3**-^{14}NO₂⁻ (blue line) and **3**-^{15}NO₂⁻ (red line) in KBr. (b) ESI-MS spectra of **3**. The peak at 333.2 is assigned to [(12TMC)Co^{II}(NO₂)]⁺ (calcd m/z 333.1). Inset: isotopic distribution pattern for **3**-^{14}NO₂⁻ (red line) and **3**-^{15}NO₂⁻ (blue line).

bearing the 12TMC ligand (12TMC = 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclododecane) with mono-oxygen reactive species (O^{2-}, OH⁻ and H₂O) (Scheme 1). Complex **1** reacts with the base (OH⁻, tetrabutylammonium hydroxide (TBAOH)/or NaOH in the presence of 15-crown-5 as the OH⁻ source) and generates the corresponding Co^{II}-nitrito complex, [(12TMC)Co^{II}(NO₂⁻)]⁺ (**3**), with the evolution of hydrogen gas (H₂) *via* the formation of a plausible N-bound Co-nitrous acid intermediate ([Co-NOOH]⁺, **2**) in CH₃CN at 273 K (Scheme 1, reaction (I)). Also, when **1** reacts with the oxide (O^{2-} or Na₂O in the presence of 15-crown-5), it generates the Co^{II}-nitrito complex (**3**) *via* a probable Co^{I}-nitro, [(12TMC)Co^{I}(NO₂⁻)] (**4**), intermediate (Scheme 1, reaction (II)); however, **1** does not react with water (Scheme 1, reaction (III)). Mechanistic investigations using ^{15}N-labeled-^{15}NO, D-labeled-NaOD and ^{18}O-labelled-^{18}OH⁻ demonstrated, unambiguously, that the N and O-atoms in the NO₂⁻ ligand of **3** resulted from NO and OH⁻ moieties; however, the H-atoms of H₂ are derived from OH⁻. To the extent of our knowledge, the present work reports the very first systematic study of Co^{III}-nitrosyl complex reactions with H₂O, OH⁻ and O^{2-}. This new finding presents an alternative route for NO₂⁻ generation in biosystems, and also illustrates a new pathway of H₂ evolution, in addition to the reported literature.[12,27]

To further explore the chemistry of [(12TMC)Co^{III}(NO⁻)]$^{2+}$ (**1**),[15,26] and the mechanistic insights of NOM reactions, we have reacted it with a base (OH⁻), an oxide (O^{2-}), and water (H₂O). When complex **1** was reacted with TBAOH in CH₃CN, the color of complex **1** changed to light pink from dark pink. In this reaction, the characteristic absorption band of **1** (370 nm) disappears within 2 minutes (Fig. 1a; ESI, Experimental section (ES) and Fig. S1a†), producing a Co^{II}-nitrito complex, [(12TMC)Co^{II}(NO₂⁻)]⁺ (**3**), with H₂ (Scheme 1, reaction (Ib)), in contrast to the previous reports on base induced NOM reactions (eqn (2)).[12,25,28] The spectral titration data confirmed that the ratio-metric equivalent of OH⁻ to **1** was 1 : 1 (ESI, Fig. S1b†). **3** was determined to be [(12TMC)Co^{II}(NO₂⁻)](BF₄) based on various spectroscopic and structural characterization experiments (*vide infra*).[15,26b]

The FT-IR spectrum of **3** showed a characteristic peak for nitrite stretching at 1271 cm⁻¹ (Co^{II}-^{14}NO₂⁻) and shifted to 1245 cm⁻¹ (Co^{II}-^{15}NO₂⁻) when **3** was prepared by reacting ^{15}N-labeled NO (Co^{III}-^{15}NO) with OH⁻ (Inset, Fig. 1a and Fig. S2†). The shifting of NO₂⁻ stretching ($\Delta = 30$ cm⁻¹) indicates that the N-atom in the NO₂⁻ ligand is derived from Co^{III}-^{15}NO. The ESI-MS spectrum of **3** showed a prominent peak at m/z 333.2, [(12TMC)Co^{II}(^{14}NO₂⁻)]⁺ (calcd m/z 333.2), which shifted to 334.2, [(12TMC)Co^{II}(^{15}NO₂⁻)]⁺ (calcd m/z 334.2), when the reaction was performed with Co^{III}-^{15}NO (Inset, Fig. 1b; ESI, Fig. S3a†); indicating clearly that NO₂⁻ in **3** was derived from the NO moiety of **1**. In addition, we have reacted **1** with Na^{18}OH (ES and ESI†), in order to follow the source of the second O-atom in **3**-NO₂⁻. The ESI-MS spectrum of the reaction mixture, obtained by reacting **1** with Na^{18}OH, showed a prominent peak at m/z 335.2, [(12TMC)Co^{II}(^{18}ONO⁻)]⁺ (calcd m/z 335.2), (SI, Fig. S3b†) indicating clearly that NO₂⁻ in **3** was derived from ^{18}OH⁻. The ^{1}H NMR spectrum of **3** did not show any signal for aliphatic protons of the 12TMC ligand, suggesting a bivalent cobalt center (Fig. S4†).[26b] Furthermore, we have determined the magnetic moment of **3**, using Evans' method, and it was found to be 4.62 BM, suggesting a high spin Co(ɪɪ) metal center with three unpaired electrons (ESI† and ES).[29] The exact conformation of **3** was provided by single-crystal X-ray crystallographic analysis (Fig. 2b, ESI, ES, Fig. S5, and Tables T1 and T2†) and similar to that of previously reported Co^{II}-NO₂⁻/M^{II}-NO₂⁻.[15,26b] Also, we have quantified the amount of nitrite (90 ± 5%), formed in the above reaction, using the Griess reagent (ESI, ES, and Fig. S6†).

As is known from the literature, a metal-nitrous acid intermediate may form either by the reaction of a metal-nitrosyl with a base[27] or by the metal-nitrite reaction with an acid (nitrite reduction chemistry);[26b] however, the products of both the
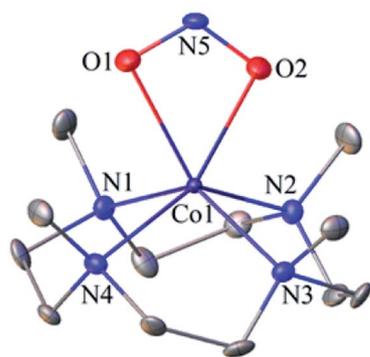
Fig. 2   Displacement ellipsoid plot (20% probability) of **3** at 100 K. Disordered C-atoms of the TMC ring, anion and H-atoms have been removed for clarity.

reactions are different. Here, for the first time, we have explored the reaction of Co^{III}-nitrosyl (**1**) with a base. In this reaction, it is clear that the formation of Co^{II}-nitrito would be accomplished by the release of H$_2$ gas *via* the generation of a transient N-bound [Co-(NOOH)]$^+$ intermediate (Scheme 2, reaction (II)). The formation of Co^{II}-NO$_2^-$ (**3**) from the [Co-(NOOH)]$^+$ intermediate is likely to proceed by either (i) homolytic cleavage of the O–H bond and release of H$_2$ *via* the proposed Co^{III}-H transient species (Co^{III}-H = Co^{II} + 1/2H$_2$)[30] (Scheme 2, reaction (III)), as reported in previous literature where the reduced cobalt, in a number of different ligand environments, is a good H$^+$ reduction catalyst and generates H$_2$ gas *via* a Co^{III}-H intermediate[31] or (ii) heterolytic cleavage of the O–H bond and the formation of Co^I-NO$_2^-$ + H$^+$.[27] In the present study, we observed the formation of **3** and H$_2$ *via* the plausible homolytic cleavage of the NOO–H moiety of **2** as shown in Scheme 2, in contrast to the previous reports on base-induced reactions on metal-

nitrosyls (eqn (3)).[27] Taking together both possibilities, (i) is the most reasonable pathway for the NOM reaction of complex **1** in the presence of a base (as shown in Scheme 2, reaction (III)). And the reaction is believed to go through a Co^{III}-H intermediate as reported previously in Co^I-induced H$^+$ reduction in different ligand frameworks and based on literature precedence, we believe that complex **1** acts in a similar manner.[31]

In contrast to an O-bound Co^{II}-ONOH intermediate, where N–O bond homolysis of the ON-OH moiety generates H$_2$O$_2$ (Scheme 2, reaction (IV)),[26b] the N-bound [Co-(NOOH)]$^+$ intermediate decomposes to form NO$_2^-$ and a Co(III)-H transient species, arising from β-hydrogen transfer from the NOO–H moiety to the cobalt-center (Scheme 2, reaction (II)).[30a,c,32] The Co(III)-hydrido species may generate H$_2$ gas either (a) by its transformation to the Co(II)-nitrito complex (**2**) and H$_2$ gas as observed in the case of Co^{III}-H intermediate chemistry[30a,c,e–g] as proposed in the chemistry of the Co^I complex with H$^+$ reduction[31] and other metal-hydrido intermediates[32] and also explained in O$_2$ formation in PN chemistry[17,33] or (b) by the reacting with another [Co-(NOOH)]$^+$ intermediate (Scheme 2, reaction (III)).

Furthermore, we have confirmed the H$_2$ formation in the NOM reaction of **1** with OH$^-$ by headspace gas mass spectrometry (Fig. 3a). Also, carrying out the reaction of **1** with NaOD leads to the formation of the [Co-(NOOD)]$^+$ intermediate, which then transforms to a Co^{III}-D transient species. Further, as described above, the Co^{III}-D species releases D$_2$ gas, detected by headspace gas mass spectrometry (Fig. 3b), which evidently established that H$_2$ gas formed in the reaction of **1** with OH$^-$. In this regard, we have proposed that in the first step of this reaction, the nucleophilic addition of OH$^-$ to {Co-NO}^{8} generates a transient N-bound [Co-(NOOH)]$^+$ intermediate that is generated by an internal electron transfer to Co^{III} (Scheme 2, reaction (I)). By following the mechanism proposed in the case
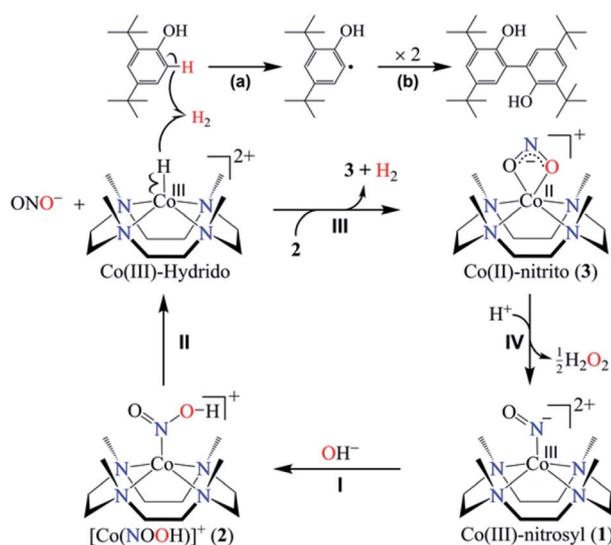
Scheme 2   NOM reaction of complex **1** in the presence of OH$^-$, showing the generation of Co^{II}-nitrito (**3**) and H$_2$ *via* a Co(III)-hydrido intermediate.
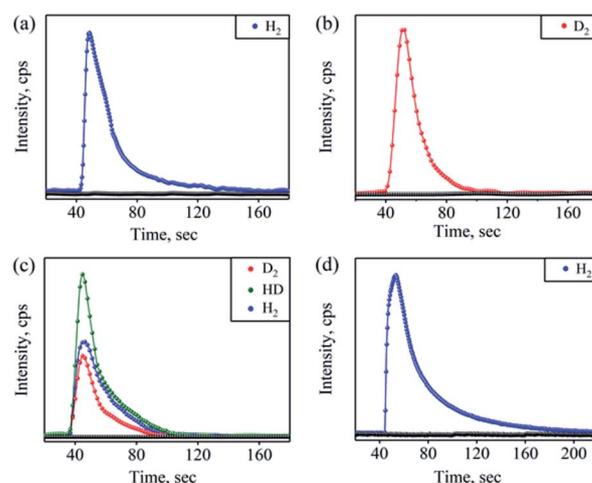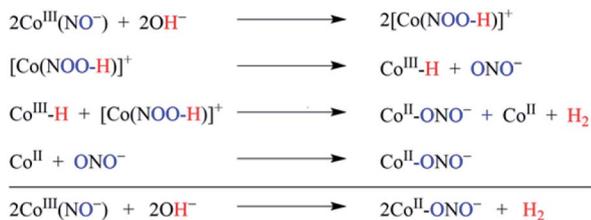

Fig. 3   Mass spectra of formation of (a) H$_2$ in the reaction of **1** (5.0 mM) with NaOH (5.0 mM), (b) D$_2$ in the reaction of **1** (5.0 mM) with NaOD (5.0 mM), (c) D$_2$, HD, and H$_2$ in the reaction of **1** (5.0 mM) with NaOD/NaOH (1 : 1), and (d) H$_2$ in the reaction of **1** (5.0 mM) with NaOH in the presence of 2,4 DTBP (50 mM).

$$2Co^{III}(NO^-) + 2OH^- \longrightarrow 2[Co(NOO\text{-}H)]^+$$

$$[Co(NOO\text{-}H)]^+ \longrightarrow Co^{III}\text{-}H + ONO^-$$

$$Co^{III}\text{-}H + [Co(NOO\text{-}H)]^+ \longrightarrow Co^{II}\text{-}ONO^- + Co^{II} + H_2$$

$$Co^{II} + ONO^- \longrightarrow Co^{II}\text{-}ONO^-$$

$$2Co^{III}(NO^-) + 2OH^- \longrightarrow 2Co^{II}\text{-}ONO^- + H_2$$

Scheme 3 NOM reaction of complex **1** in the presence of OH⁻, showing the different steps of the reaction.

of Co^{III}-H,[30a–c] O$_2$,[15] and H$_2$O$_2$ (ref. 26b) formation, we have proposed the sequences of the NOM reaction of **1**, which leads to the generation of Co^{II}-nitrito and H$_2$ (Scheme 2, reaction (I)–(III) and Scheme 3). In the second step, O–H bond homolytic cleavage generates a Co^{III}-H transient species + NO$_2^-$ via a β-hydrogen elimination reaction of the [Co-(NOOH)]$^+$ intermediate.[32] The Co^{III}-H intermediate may undergo the following reactions to generate H$_2$ gas and Co^{II}-nitrito either (a) by the natural decomposition of the Co^{III}-H transient species to generate H$_2$,[30a,c,e–g] or (b) by the H-atom abstraction from another [Co-(NOOH)]$^+$ intermediate (Scheme 3). Also, to validate our assumption that the reaction goes through a plausible N-bound [Co-(NOOH)]$^+$ intermediate followed by its transformation to the Co^{III}-H species (vide supra), we have performed the reaction of **1** with NaOH/NaOD (in 1 : 1 ratio). In this reaction, we have observed the formation of a mixture of H$_2$, D$_2$, and HD gases, which indicates clearly that the reaction goes through the formation of Co^{III}-H and Co^{III}-D transient species via the aforementioned mechanism (Fig. 3c). This is the only example where tracking of the H atoms has confirmed the H$_2$ generation from an N-bound NOO–H moiety as proposed for H$_2$ formation from Co^{III}-H.[30]

While, we do not have direct spectral evidence to support the formation of the transient N-bound [Co-(NOOH)]$^+$ intermediate and its decomposition to the Co^{III}-H transient species via β-hydrogen transfer from the NOOH moiety to the cobalt center, support for its formation comes from our finding that the reactive hydrogen species can be trapped by using 2,4-di-tert-butyl-phenol (2,4-DTBP).[34] In this reaction, we observed the formation of 2,4-DTBP-dimer (2,4-DTBP-D, ~67%) as a single product (ESI, ES, and Fig. S7†). This result can readily be explained by the H-atom abstraction reaction of 2,4-DTBP either by [Co-(NOOH)]$^+$ or Co^{III}-H, hence generating a phenoxyl-radical and **3** with H$_2$ (Fig. 3d and Scheme 2, reaction (a)). Also, we have detected H$_2$ gas formation in this reaction (ESI,† ES, and Fig. 3d). In the next step, two phenoxyl radicals dimerized to give 2,4-DTBP-dimer (Scheme 2c, reaction (II)). Thus, the observation of 2,4-DTBP-dimer in good yield supports the proposed reaction mechanism (Scheme 2, reaction (a) and (b)). Further, the formation of 2,4 DTBP as a single product also rules out the formation of the hydroxyl radical as observed in the case of an O-bound nitrous acid intermediate.[26b]

Furthermore, we have explored the NOM reactivity of **1** with Na$_2$O/15-crown-5 (as the O^{2-} source) and observed the formation of the Co^{II}-nitrito complex (**3**) via a plausible Co^I-nitro (**4**)

intermediate (Scheme 1, reaction (IIa); also see the ESI† and ES); however, **1** was found to be inert towards H$_2$O (Scheme 1, reaction (III); also see the ESI, ES and Fig. S8†). The product obtained in the reaction of **1** with O^{2-} was characterized by various spectroscopic measurements.[15,26b] The UV-vis absorption band of **1** ($\lambda_{max} = 370$ nm) disappears upon the addition of 1 equiv. of Na$_2$O and a new band ($\lambda_{max} = 535$ nm) forms, which corresponds to **3** (ESI, Fig. S9†). The FT-IR spectrum of the isolated product of the above reaction shows a characteristic peak for Co^{II}-bound nitrite at 1271 cm^{-1}, which shifts to 1245 cm^{-1} when exchanged with ^{15}N-labeled-NO (^{15}N^{16}O) (ESI, ES, and Fig. S10†), clearly indicating the generation of nitrite from the NO ligand of complex **1**.[26b] The ESI-MS spectrum recorded for the isolated product (vide supra) shows a prominent ion peak at m/z 333.1, and its mass and isotope distribution pattern matches with [(12-TMC)Co^{II}(NO$_2$)]$^+$ (calc. m/z 333.1) (ESI, Fig. S11†). Also, we quantified the amount of **3** (85 ± 5%) by quantifying the amount of nitrite (85 ± 5%) using the Griess reagent test (ESI, ES, and Fig. S6†).

In summary, we have demonstrated the reaction of Co^{III}-nitrosyl, [(12-TMC)Co^{III}(NO$^-$)]$^{2+}$/{CoNO}^{8} (**1**), with mono-oxygen reactive species (O^{2-}, OH$^-$ and H$_2$O) (Scheme 1). For the first time, we have established the clear formation of a Co^{II}-nitrito complex, [(12TMC)Co^{II}(NO$_2^-$)]$^+$ (**3**), and H$_2$ in the reaction of **1** with one equivalent of OH$^-$ via a transient N-bound [Co-(NOOH)]$^+$ (**2**) intermediate. This [Co-(NOOH)]$^+$ intermediate undergoes the O–H bond homolytic cleavage and generates a Co^{III}-H transient species with NO$_2^-$, via a β-hydrogen elimination reaction of the [Co-(NOOH)]$^+$ intermediate, which upon decomposition produces H$_2$ gas. This is in contrast to our previous report, where acid-induced nitrite reduction of **3** generated **1** and H$_2$O$_2$ via an O-bound Co^{II}-ONOH intermediate.[26b] Complex **1** was found to be inert towards H$_2$O; however, we have observed the formation of **3** when reacted with O^{2-}. It is important to note that H$_2$ formation involves a distinctive pathway of O–H bond homolytic cleavage in the [Co-(NOOH)]$^+$ intermediate, followed by the generation of the proposed Co^{III}-H transient species (Co^{II} + 1/2H$_2$)[30] prior to H$_2$ evolution as described in Co^I chemistry with H$^+$ in many different ligand frameworks.[31] The present study is the first-ever report where the base induced NOM reaction of Co^{III}-nitrosyl (**1**) leads to Co^{II}-nitrito (**3**) with H$_2$ evolution via an N-bound [Co-(NOOH)]$^+$ intermediate, in contrast to the chemistry of O-bound Co^{II}-ONOH[26b], hence adding an entirely new mechanistic insight of base induced H$_2$ gas evolution and an additional pathway for NOM reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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