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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**, $\{Co\text{-}NO\}^8$) 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_2O/15-crown-5) and water (H_2O). The reaction of **1** with OH^- produces a Co^{II}-nitrito complex {**3**, ($Co^{II}\text{-}NO_2^-$)} and hydrogen gas (H_2), *via* the formation of a putative N-bound Co-nitrous acid intermediate (**2**, $\{Co\text{-}NOOH\}^+$). The homolytic cleavage of the O–H bond of proposed $[Co\text{-}NOOH]^+$ releases H_2 *via* a presumed Co^{III}-H intermediate. In another reaction, **1** generates $Co^{II}\text{-}NO_2^-$ when reacted with O^{2-} *via* an expected Co^{I}-nitro (**4**) intermediate. However, complex **1** is found to be unreactive towards H_2O. Mechanistic investigations using ^{15}N-labeled-^{15}NO and ^2H-labeled-NaO^2H (NaOD) evidently revealed that the N-atom in $Co^{II}\text{-}NO_2^-$ and the H-atom in H_2 gas are derived from the nitrosyl ligand and OH^- moiety, respectively.

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.*, $NO_2^- + e^- + 2H^+ \rightarrow NO + H_2O$.[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_2O_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]

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

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

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 $Co^{II}\text{-}NO_2^-$ 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 $Cu^{II}\text{-}NO_2^-$ was also observed in the reaction of Cu^{I}-NO and O_2.[17] For metal-dioxygen adducts, *i.e.*, $Cr^{III}\text{-}O_2^{\bullet-}$ and $Mn^{IV}\text{-}O_2^{2-}$, NOD reactions led to the generation of $Cr^{III}\text{-}NO_2^-$ (ref. 18) and $Mn^{V}{=}O + NO_2^-$,[19] respectively. However, the NOD reaction of $Fe^{III}\text{-}O_2^{\bullet-}$ and $Fe^{III}\text{-}O_2^{2-}$ with NO and NO^+, respectively, generated $Fe^{III}\text{-}NO_3^-$ *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 $Fe^{II}\text{-}NO^+$ 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_2O (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]

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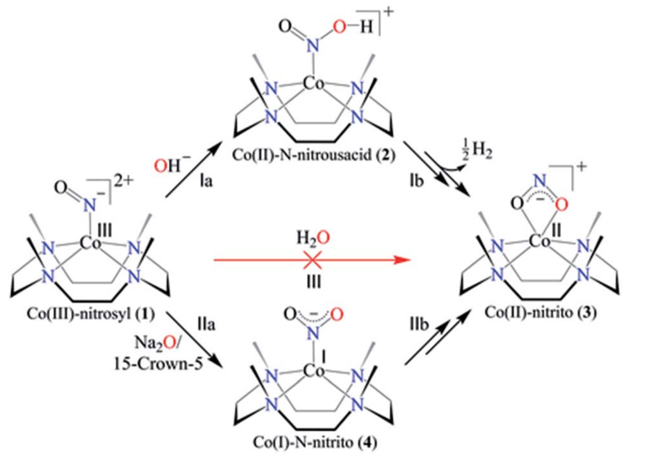


Scheme 1 Nitric oxide monooxygenation (NOM) reactions of cobalt-nitrosyl complex (1) in the presence of a base (OH^-), sodium oxide (Na_2O) and water (H_2O).

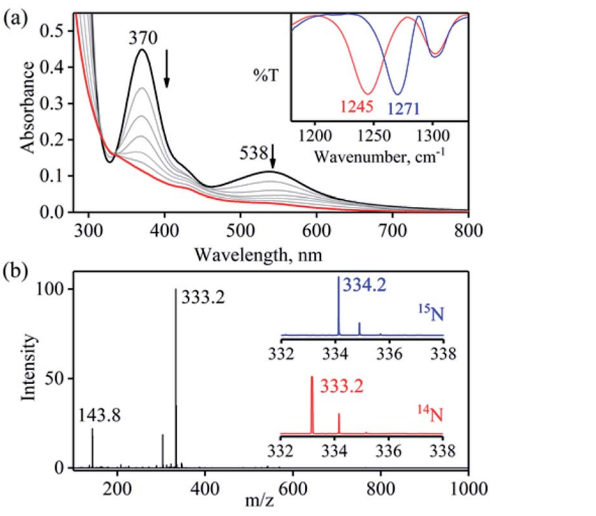


Fig. 1 (a) UV-vis spectral changes of 1 (0.50 mM, black line) upon addition of OH^- (1 equiv.) in CH_3CN under Ar at 273 K. Black line (1) changed to red line (3) upon addition of OH^-. Inset: IR spectra of 3-$^{14}NO_2^-$ (blue line) and 3-$^{15}NO_2^-$ (red line) in KBr. (b) ESI-MS spectra of 3. The peak at 333.2 is assigned to $[(12TMC)Co^{II}(NO_2)]^+$ (calcd *m/z* 333.1). Inset: isotopic distribution pattern for 3-$^{14}NO_2^-$ (red line) and 3-$^{15}NO_2^-$ (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 H_2O) (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, $[(12TMC)Co^{II}(NO_2^-)]^+$ (3), with the evolution of hydrogen gas (H_2) *via* the formation of a plausible N-bound Co-nitrous acid intermediate ($[Co\text{-}NOOH]^+$, 2) in CH_3CN at 273 K (Scheme 1, reaction (I)). Also, when 1 reacts with the oxide (O^{2-} or Na_2O in the presence of 15-crown-5), it generates the Co^{II}-nitrito complex (3) *via* a probable Co^I-nitro, $[(12TMC)Co^I(NO_2^-)]$ (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 NO_2^- ligand of 3 resulted from NO and OH^- moieties; however, the H-atoms of H_2 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 H_2O, OH^- and O^{2-}. This new finding presents an alternative route for NO_2^- generation in biosystems, and also illustrates a new pathway of H_2 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 (H_2O). When complex 1 was reacted with TBAOH in CH_3CN, 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, $[(12TMC)Co^{II}(NO_2^-)]^+$ (3), with H_2 (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 $[(12TMC)Co^{II}(NO_2^-)](BF_4)$ 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}-$^{14}NO_2^-$) and shifted to 1245 cm^{-1} (Co^{II}-$^{15}NO_2^-$) 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 NO_2^- stretching ($\Delta = 30\ cm^{-1}$) indicates that the N-atom in the NO_2^- ligand is derived from Co^{III}-^{15}NO. The ESI-MS spectrum of 3 showed a prominent peak at *m/z* 333.2, $[(12TMC)Co^{II}(^{14}NO_2^-)]^+$ (calcd *m/z* 333.2), which shifted to 334.2, $[(12TMC)Co^{II}(^{15}NO_2^-)]^+$ (calcd *m/z* 334.2), when the reaction was performed with Co^{III}-^{15}NO (Inset, Fig. 1b; ESI, Fig. S3a†); indicating clearly that NO_2^- 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-NO_2^-. 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 NO_2^- in 3 was derived from $^{18}OH^-$. The ^1H 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(II) 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}-NO_2^-/M^{II}-NO_2^-.[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

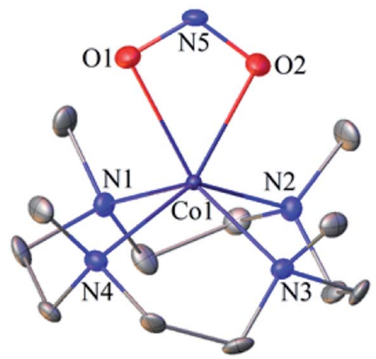
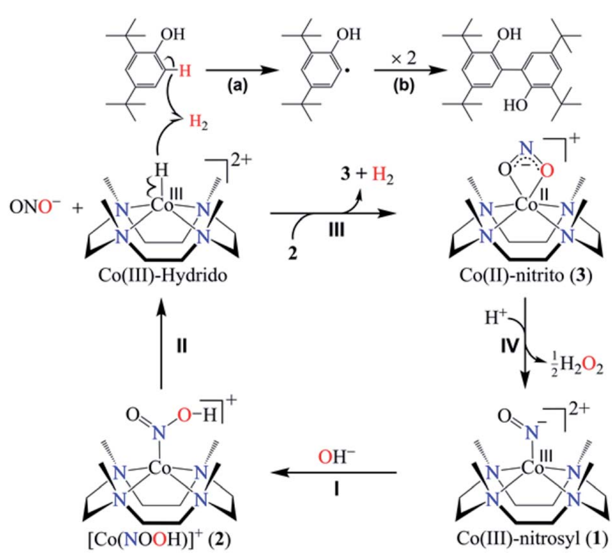


Fig. 2 Displacement ellipsoid plot (20% probability) of **3** at 100 K. Disordered C-atoms of the TMC ring, anion and H-atoms have been removed for clarity.

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 $[Co\text{-}(NOOH)]^+$ intermediate (Scheme 2, reaction (II)). The formation of $Co^{II}\text{-}NO_2^-$ (**3**) from the $[Co\text{-}(NOOH)]^+$ 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 ($Co^{III}\text{-H} = Co^{II} + 1/2H_2$)[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 $Co^{I}\text{-}NO_2^- + H^+$.[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_2O_2 (Scheme 2, reaction (IV)),[26b] the N-bound $[Co\text{-}(NOOH)]^+$ 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 $[Co\text{-}(NOOH)]^+$ 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 $[Co\text{-}(NOOD)]^+$ 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 $\{Co\text{-}NO\}^8$ generates a transient N-bound $[Co\text{-}(NOOH)]^+$ 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.

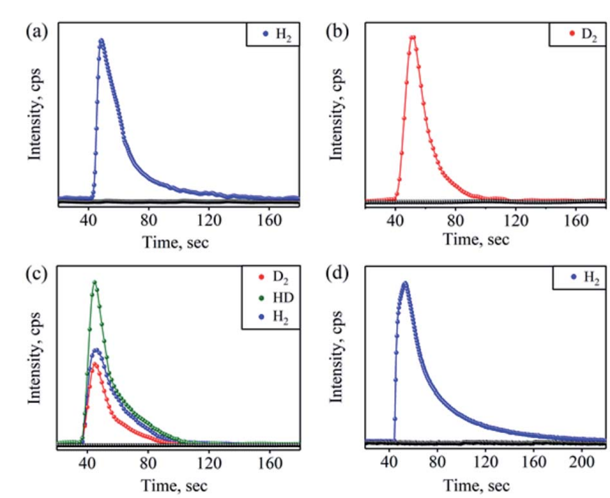
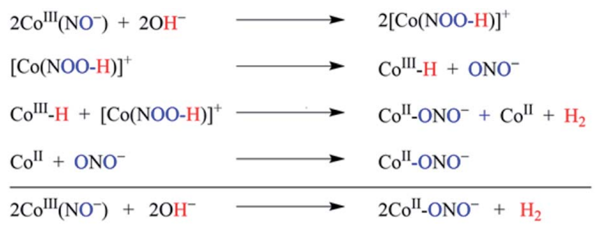


Fig. 3 Mass spectra of formation of (a) H_2 in the reaction of **1** (5.0 mM) with NaOH (5.0 mM), (b) D_2 in the reaction of **1** (5.0 mM) with NaOD (5.0 mM), (c) D_2, HD, and H_2 in the reaction of **1** (5.0 mM) with NaOD/NaOH (1 : 1), and (d) H_2 in the reaction of **1** (5.0 mM) with NaOH in the presence of 2,4 DTBP (50 mM).



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_2O_2 (ref. 26*b*) 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 $[Co\text{-}(NOOH)]^+$ 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 $[Co\text{-}(NOOH)]^+$ intermediate (Scheme 3). Also, to validate our assumption that the reaction goes through a plausible N-bound $[Co\text{-}(NOOH)]^+$ 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 $[Co\text{-}(NOOH)]^+$ 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 $[Co\text{-}(NOOH)]^+$ 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_2O/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_2O (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_2O 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 $[(12\text{-TMC})Co^{II}(NO_2)]^+$ (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, $[(12\text{-TMC})Co^{III}(NO^-)]^{2+}/\{CoNO\}^8$ (**1**), with mono-oxygen reactive species (O^{2-}, OH^- and H_2O) (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 $[Co\text{-}(NOOH)]^+$ (**2**) intermediate. This $[Co\text{-}(NOOH)]^+$ 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 $[Co\text{-}(NOOH)]^+$ 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_2O_2 *via* an O-bound Co^{II}-ONOH intermediate.[26b] Complex **1** was found to be inert towards H_2O; 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 $[Co\text{-}(NOOH)]^+$ 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 $[Co\text{-}(NOOH)]^+$ 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.

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