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Bio-inspired Cobalt Complexes for Homogeneous Nitrite Reduction: A Mini Review

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Abstract

Ammonia (NH_3) is one of the most indispensable feedstocks for many fertilizers/chemicals and pharmaceutical products and Haber-Bosch process is the process which makes synthetic ammonia available on an industrial scale, with most of this ammonia used for fertilizers. Despite decades of research, no milder alternative has replaced the Haber–Bosch process. Electrocatalytic reduction of nitrate and nitrite to produce ammonia offers an effective approach for fixing the artificial nitrogen cycle and replacing energy demanding Haber-Bosch process. Nitrite reduction can also help to alleviate global nitrite accumulation problems in wastewater due to anthropogenic activities, which have caused severe nitrogen unbalance and pose a threat to human health. Moreover, Nitrite reduction catalysts can function as models of nitrite reduction enzymes such as cytochrome c nitrite reductases and the siroheme-containing nitrite reductase. However, nitrite reduction is complicated by a variety of factors. Nitrite has complex aqueous phase chemistry with the formations several species like NO_2^-, HNO_2, and NO^+ depending on the acidity of the solution. Additionally, multiple thermodynamically favoured nitrite reduction products exist, many of which have similar reduction potentials, presenting a concern on selectivity of the products. Hence the mechanism of converting nitrite into ammonia warrants careful investigation. Molecular cobalt catalysts are regarded as promising systems for nitrite reduction reactions (NO_2^-RR). However, designing and controlling the coordination environment of molecular catalysts is crucial for studying the mechanism of NO_2^-RR and catalyst design. In the review, we tried to focus on cobalt based molecular electrocatalysts reported so far for homogeneous reduction of nitrite.

Keywords: Electrocatalytic nitrite reduction, cobalt catalysts, ammonia synthesis, ligand design

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Introduction

The nitrogen cycle is a critical natural process that maintains the balance of nitrogen in the atmosphere, soil, and living organisms even though human activities have created a significant disturbance to this cycle largely through the massive application of ammonia-based fertilizers. The inorganic nitrogen cycle is composed of a diverse range of redox reactions mediated by some metalloenzymes (for example, nitrogenase).These reactions involve the reduction of dinitrogen (N_2), nitrate (NO_3^-), nitrite (NO_2^-), nitric oxide (NO), and nitrous oxide (N_2O) and the oxidation of ammonium (NH_4^+) and hydroxylamine (NH_2OH). These interesting systems as ideal models motivate many researchers to investigate their redox chemistry [1-4)]. Nitrite (NO_2^-) is a key player in the nitrogen cycle, which interconverts inert dinitrogen (N_2) with bio-available nitrogen species including ammonium (NH_4^+) and nitrate (NO_3^-). Given the importance of nitrite in the nitrogen cycle as well as its impacts on human health, there is considerable interest in understanding and mimicking nature's transformations of nitrite. A two-step production of NH_3 which consists of the oxidation of N_2 to give nitrite (NO_2^-) and (NO_3^-), followed by its reduction to NH_4^+ in aqueous solution seems to be an alternative and energy efficient method. This strategy recently triggered the interest of chemists to design efficient systems for the electrocatalytic reduction of NO_2^- to NH_3, since NO_2^- is much more easily reduced than N_2 both thermodynamically and kinetically [5].

Discovering a homogenous molecular catalyst for nitrite reduction presents a number of challenges for catalyst design. First, nitrite has a complex aqueous phase chemistry and can access a number of different electroactive forms, with NO_2^-being dominant in alkaline and neutral solutions, HNO_2 in moderately acidic solutions, and NO^+ in highly acidic solutions. Nitrous acid also disproportionate to provide free NO and nitric acid in mildly acidic solutions. Second, there are multiple possible reduction products that are thermodynamically favourable, some of which have

undesirable properties, such as N_2O, a potent greenhouse gas. Finally, intermediate species formed from partial reduction may react with nitrite to provide undesired products, particularly in acidic media, e.g., with NH_3OH^+ to give N_2O.

Focusing on structurally related complexes, particularly those that feature the same metal centre, is expected to provide insight into the design features required for the electrocatalytic reduction of aqueous NO_2^-. Thus, in this report we are freezing on cobalt complexes to get a better understanding on the key factors required to achieve an efficient catalyst for homogeneous nitrite reduction. Although cobalt is not implicated in Nature's transformations of NO_2^-, a number of cobalt complexes featuring a CoN_4center are particularly active and well-studied catalysts for NO_2^- reduction. In this context, we provide comprehensive discussions on cobalt-based nitrite reduction catalyst reported so far.

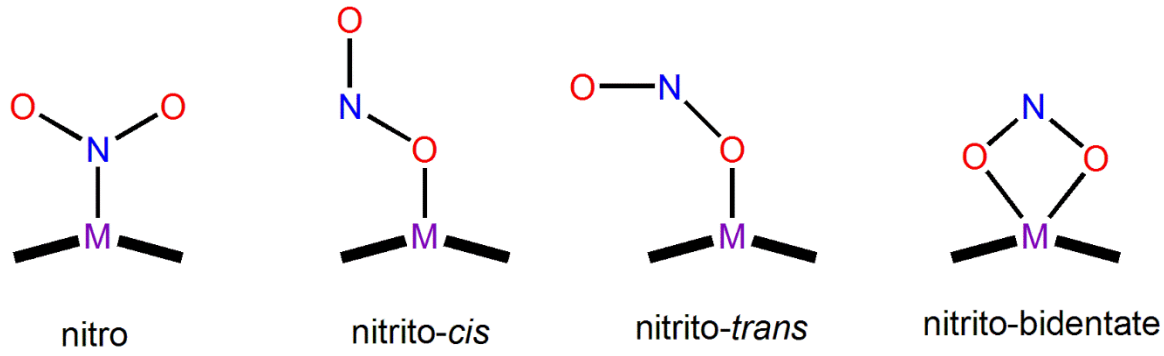
Biological reductases for Nitrite Reduction

In nature, reduction of nitrite is catalysed by two types of nitrite reductases: (1) the one-electron reduction of nitrite to nitric oxide (NO; eq 1) is catalysed by copper nitrite reductases or cytochrome cd1 nitrite reductase, (2) the complete six electron reduction to ammonium (eq 2) is catalysed by cytochrome c nitrite reductase (CcNiR; dissimilatory pathway) or the siroheme-containing nitrite reductase (SCNiR; assimilatory pathway):

$$NO_2 + e + 2H^+ \rightarrow NO + H_2O \quad (1)$$

$$NO_2 + 6e + 8H^+ \rightarrow NH_4^+ + 2H_2O \quad (2)$$

Nitrite binding to metal is obvious for all these processes to happen and mode of nitrite binding is very important for understanding the mechanism. All possible binding modes of nitrite to the metal (M) is shown below (**Scheme 1**). In the nitro mode, nitrite binds the metal via nitrogen atom. The nitrito mode of binding can be three types. Nitrite can bind to the metal through one of the oxygen atoms in cis or trans conformation. A bidentate nitrito mode is also possible where nitrite binds the metal through both the oxygen atoms.



Scheme 1 Nitrite binding modes to the metal atom

Nitrite reduction to Nitric Oxide

By copper-containing nitrite reductases (CuNIR)

Various bacteria remove nitrogen from their systems using the process of denitrification. This involves reduction of nitrite ions to NO and nitrous oxide (N_2O) followed by a further, final reduction to dinitrogen gas. The first step in this denitrification pathway is the reduction of nitrite to NO. The reaction catalysed by copper-containing nitrite reductases (CuNIR). CuNIR contains two copper centres: the type-1 Cu centre is surrounded by two histidine (imidazole-type) ligands, a cysteine ligand and a methionine ligand, whilst the distorted tetrahedral type-2 Cu centre is coordinated by 3 histidine ligands and a single water molecule [6]. Nitrite is thought to be reduced on thetype-2 Cu centre using electrons donated by the type-1 centre to the type-2 centre. Numerous studies have contributed to the current level of understanding with respect to the mechanism of action of the type-2 centre in CuNIR[6-15], which is presented in **Figure 1**. In this proposed mechanism, nitrite displaces water and binds to the Cu^{II}centre of CuNIR through its two oxygen atoms, producing a distorted square-based pyramidal geometry at the copper. Reduction of the Cu^{II}centre then occurs because of electron transfer from a type-1 centre, and this electron transfer is probably triggered by protonation of a nearby conserved aspartate residue [14, 16-23]. The bound nitrite is then protonated at the oxygen that is to be abstracted (with this proton coming from the conserved aspartic acid previously mentioned), after which N–OH bond lysis occurs.

This bond scission is facilitated by back-bonding from the copper $dx^2–y^2$ orbital into the N–OH s* orbital. This interaction between the Cu and the oxygen atoms of the nitrite arises because of the bidentate binding mode of the NO_2^-(Scheme 1). After the N–OH is broken, protonation of the {Cu–OH} species thus formed leads to NO liberation and the generation of a Cu^{II}-aqua complex. This aqua complex can then re-enter the catalytic cycle by binding to nitrite followed by reduction (or vice-versa). It is important to note that the bidentate nitrito binding modes of the nitrite enables an effective back-bonding interaction which lowers the activation barrier for the N–OH bond cleavage and also stabilizes the Cu-OH complex to be formed [14]. The presence of the protonated aspartate is also essential for stabilization the Cu-OH complex. It should be noted that without the proton donor, the N–O cleavage would result a unstable $Cu^{II}–O^-$ complex [14].

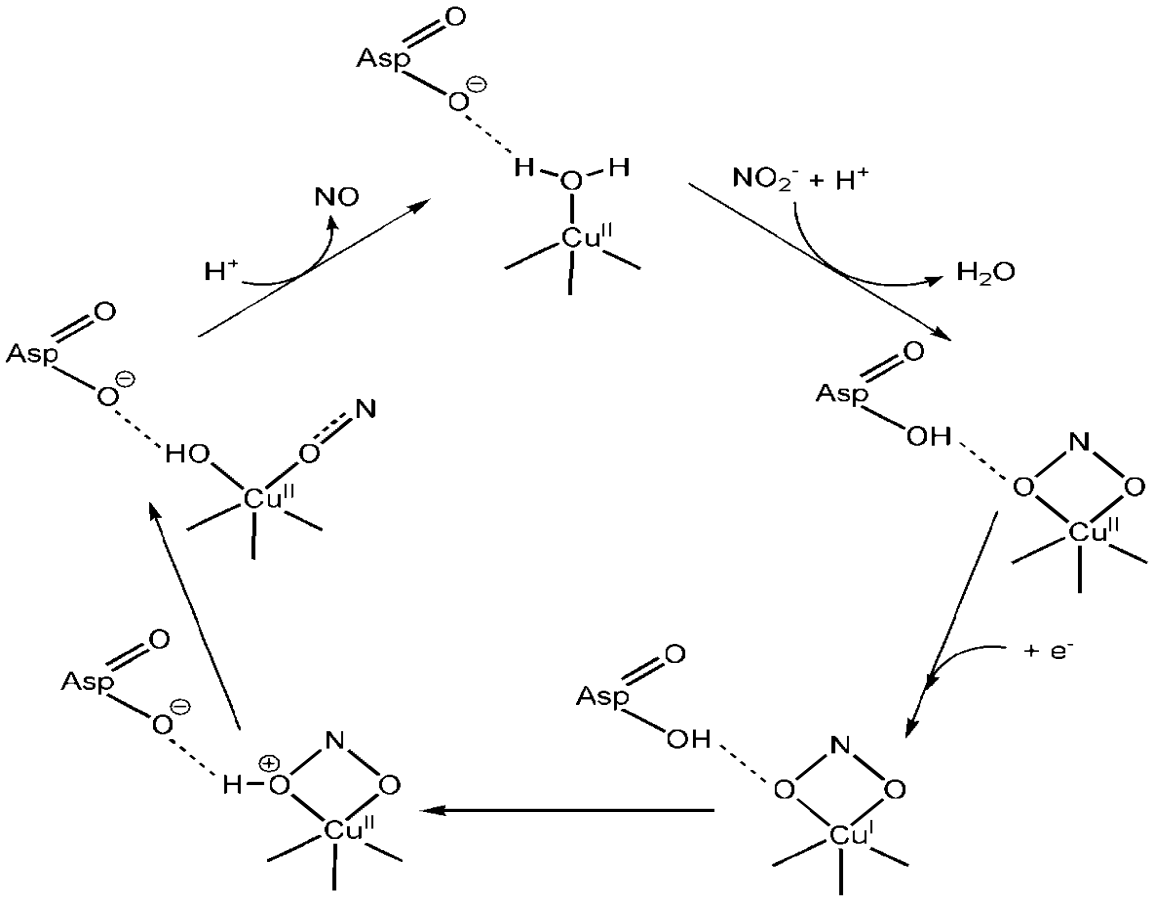


Figure 1 Simplified mechanism of nitrite reduction to NO in CuNIR [24, 25]

By c and d_1-containing nitrite reductases (Cd_1NiR)

The iron dependent nitrite reduction to NO is achieved with the d1 haem of the c and d1 haems-containing nitrite reductase (Cd_1NiR) enzymes [26, 27]. The catalytic cycle may be illustrated starting from the fully reduced enzyme ($c^{II}d_1^{II}$) that binds with nitrite in the 'nitro' mode (Scheme 1) where the nitrite oxygen atoms form hydrogen bonds with the two conserved histidine residues (**Figure 2**) [28-34]. The reaction then proceeds with the abstraction of oxygen atom, through the heterolytic cleavage of the N–O bond. To facilitate this process the oxygen has to be converted to a good leaving group, which is achieved with the addition of two protons. The two conserved histidine residue act as proton donors here. All this leads to the formation of the NO bound $\{Fe\text{-}NO\}^6$ complex, which then reduces by one electron to form $\{Fe\text{-}NO\}^7$ complex. The $\{Fe\text{-}NO\}^7$complex undergoes rapid NO-release and binds to another $NO_2^-$to complete the catalytic cycle. The dynamic hydrogen bonding network and the conformational changes act synergistically in this efficient synthesis and release of NO [34].

By Xanthine Oxidase (XO)

The mammalian signaling molybdenum-dependent nitrite reduction to NO can be achieved with the molybdenum centre of the xanthine oxidase (XO) enzyme [35, 36].

To catalyze the nitrite reduction to NO, XO enzyme, like Cd_1NiR and CuNiR, has to bind nitrite, transfer one electron, cleave one of the nitrite N−O bond, and release the NO thus formed. An outline of the mechanism can easily be drawn (**Figure 3**) taking into account the following points. Before binding to the nitrite the molybdenum(VI) centre is first reduced by xanthine and the molybdenum centre(IV) then binds to nitrite through one of its oxygen atoms (a 'nitrito' binding mode, Scheme 1) [37, 38].

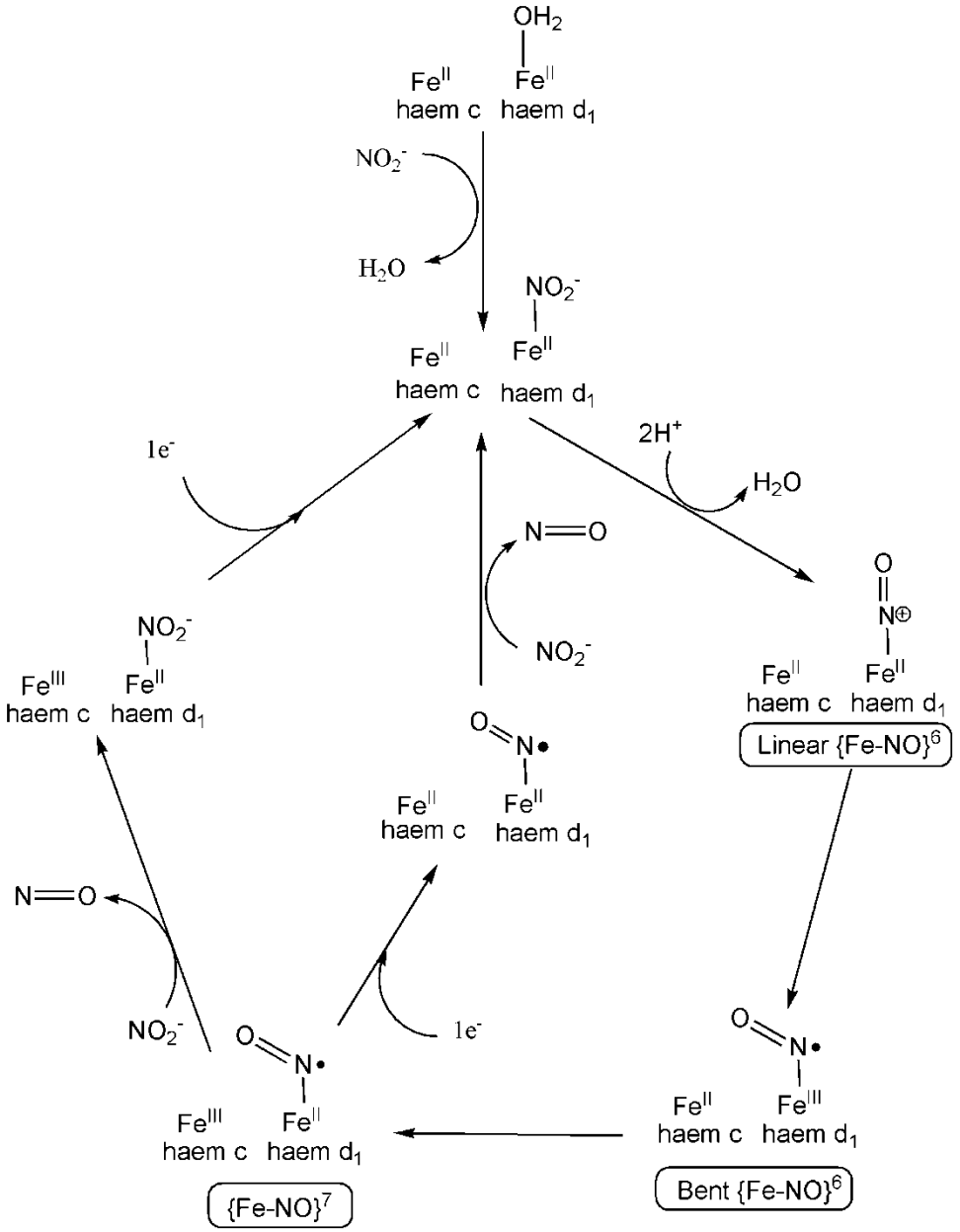


Figure 2 Mechanism of nitrite reduction to NO catalysed by cytochrome d_1-containg nitrite reductases (Cd_1NiR)

Subsequently, the reduced molybdenum transfers one electron to nitrite which results the formation of NO and oxidation of Mo^{IV} to Mo^{V}. This step is thought to be triggered by a pronation event. It is suggested that the reaction proceeds with the protonation of the nitrite oxygen atom bound to the molybdenum at the expense of a nearby protonated glutamate residue. The catalytic cycle is then suggested to proceed with the binding of a second nitrite molecule. The consumption of one proton is proposed which assist the formation of coordinated water molecule (Mo^{V}-OH_2), a good leaving group. Subsequently, the incoming nitrite displaces the water molecule and reduction of nitrite takes place to release another NO molecule. The molybdenum is now oxidised to +6 state during this process and available to start another catalytic cycle.

Nitrite reduction to Ammonia

By Cytochrome c nitrite reductases (CcNiR)

The nitrite reduction to ammonia is achieved by Cytochrome c nitrite reductases. This enzyme is able to mediate 6 elcetrons and 8 protons reduction of nitrite without releasing any potential intermediates such as NO. Neese and co-workers have proposed a mechanism of action for cytochrome c nitrite reductase based on the crystal structures of reaction intermediates and Density Functional Theory (DFT) calculations[33, 39-43], and this putative catalytic cycle is summarised in **Figure 4**. Upon binding of nitrite to the Fe^{II} centre of the haem, N–O bond heterolysis occurs to generate a haem-nitrosyl ({Fe–NO}) complex. This is facilitated by a high degree of back-bonding from the filled dxz orbital of the Fe^{II}(HOMO) to an empty orbital with p* character on the bound nitrite (LUMO) [39-42]. This back-bonding serves to both strengthen the Fe–N bonding interaction and weaken the N–O bonds, promoting heterolysis. N–O bond heterolysis is also promoted by the formation of hydrogen bonds between protein residues (especially protonated histidine and arginine residues) and the nitrite oxygens. Indeed, the unique environment provided by the protein matrix may give a local pH below 3, aiding protonation of the oxygens bound to nitrite. Successive electron and proton transfers then result in the formation of the {Fe–NH(O)} adduct, where the nitrogen coordinated to iron is protonated in preference to the remaining oxygen [44]. Further proton-coupled-electron transfers then lead to the formation of a putative iron–hydroxylamine complex ({Fe–NH_2OH}), which is then self-protonated and reduced to break the final N–OH bond, liberating water and giving the {Fe–NH_3} intermediate. Further protonation then causes release of ammonium, allowing a second molecule of nitrite to bind and permitting the enzyme to enter the next catalytic cycle.

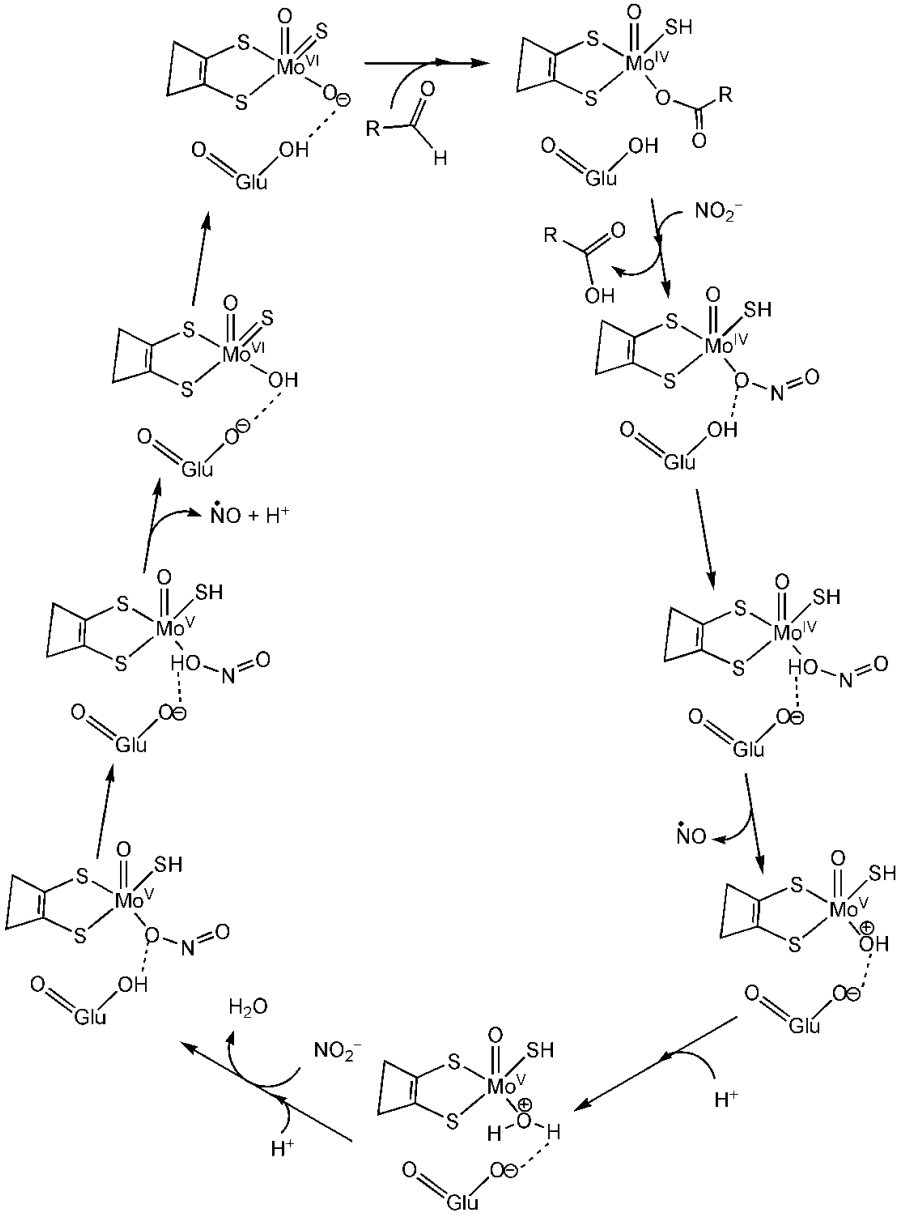


Figure 3 Proposed mechanism for Xanthine Oxidase (XO) catalysed reduction of nitrite to NO

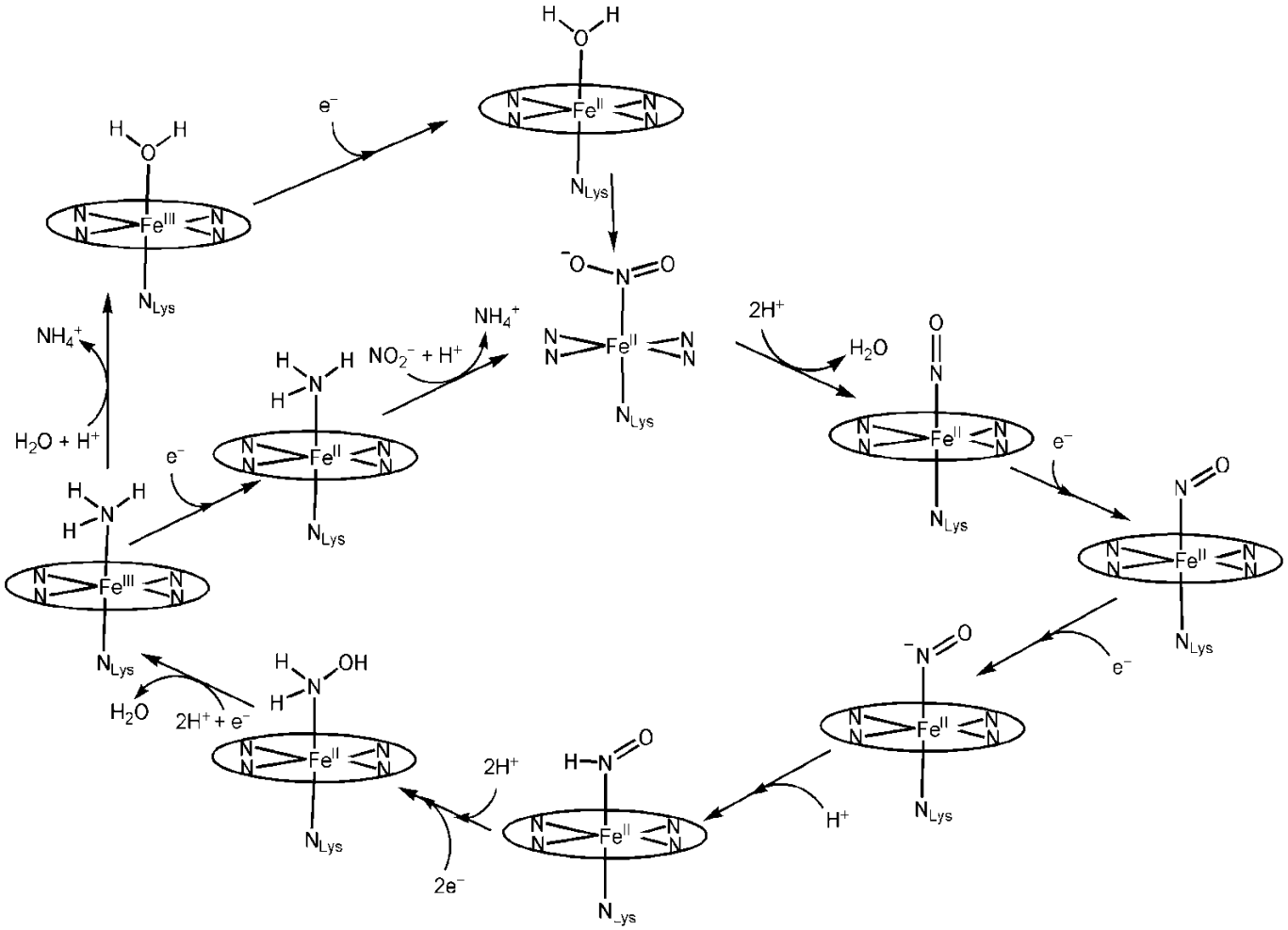


Figure 4 Mechanism of nitrite reduction catalysed by CcNiR

By Sirhaem-containing nitrite Reducuase (CSNiR)

Sirohaem-containing nitrite reductase (CSNiR) also reduces nitrite to ammonia without the release of detectable intermediates. Several biochemical, spectroscopic, and crystallographic studies support that the reaction mechanism is similar to the CcNiR one. Here the reaction is believed to start from a low spin (sirohaem)Fe^{II}–nitrite complex [45-53] which bounds through the "nitro" mode (Scheme 1), [46, 52, 53] stabilized through hydrogen bonds with positively charged Lys244, Arg179, and Arg109 residues [54, 55].The oxygen closest to Lys224 was then abstracted first, where Lys224 and Arg179 are the probable proton donors to form the first water molecule and the Fe^{II}–NO intermediate. The Fe^{II}–NH(H)OH intermediate was proposed to be formed with the protons derived from "recharged" Arg179 and Arg109 residues and from a water molecule hydrogen-bonded to the "recharged" Lys224[55].

As mentioned earlier that the mechanism of nitrite reduction by these two enzymes (CcNiR and CsNiR) are quite similar but there are some remarkable differences between them. The first obvious difference is the coordination environment around the Fe^{II}centre. One haem is c type whereas the other is siroharem type. Second one is the axial coordination i.e. a nitrogen atom from a lysine versus a sulphur atom from the cysteine-coupled Fe/S centre. Another distinctive feature is the CSNiR ability to "store" electrons. Unlike CcNiR, with its four c haems, CSNiR has only one Fe/S to hold one electron. It has also only a single ferredoxin binding site [56, 57] to receive one electron at a time, from the ferredoxin [2Fe−2S] center (i.e., the physiological partner is a one-electron donor). Those facts mean that the CSNiR must receive the necessary six electrons in one-electron steps and make the elucidation of the electron transfer particularly challenging.

By other enzymes

Tetrathionatereductase (TTR) and hydroxylamine oxidoreductase (HAOR) are two multi-haemic enzymes that were also shown to also catalyze the reduction of nitrite to ammonium [58-61]. TTR catalyzes the reduction of tetrathionate ($S_4O_6^{2-}$) to thiosulfate ($S_2O_3^{2-}$) while HAOR catalyzes the oxidation of hydroxylamine to nitrite. The structures of these two enzymes and of CcNiR show significant similarities at the haem site. Both TTR and HAOR are able to

catalyze the reduction of nitrite and hydroxylamine to ammonium as CcNiR does. The TTR catalytic specificities toward nitrite and hydroxylamine suggest that this enzyme may have a role in the biochemical cycle of nitrogen. On the other hand, HAOR can tune its activity from oxidation to reduction reactions under variety of environmental conditions. However, the HAOR specificity constants toward nitrite and hydroxylamine reduction are 2 orders of magnitude lower than the CcNiR ones.

Artificial Cobalt catalysts for Nitrite reduction

To fine-tune already existing nitrite reduction catalysts and to design more robust catalysts, it is vital to understand the actual process under the laboratory condition. In this current account, we tried to cover the overall efforts done so far in designing Co-based systems for nitrite reduction. Several cobalt (III)/(II) complexes have been reported till date and mostly they are electro-catalyst.

In 1987, Taniguchi and co-workers explored the ability of Co^{III}cyclams (cyclam =1,4,8,11 tetraazacyclo tetradecane), to electrocatalyze nitrate and nitrite reduction on a mercury electrode, giving hydroxylamine as the sole product [62]. They also speculated that the effective catalyst was probably an adsorbed Co^{I}cyclam species. Later on these metal cyclams were also found to be active at basic medium (3M NaOH) yielding exclusively hydroxylamine at significant cathodic potentials (-1.5 V vs. SCE) using Hg electrodes [63].A water soluble cobalt porphyrin, Co(2-TMPyP), cobalt tetrakis(N-methyl-2-pyridyl)porphyrin was utilised to reduce nitrite to a mixture of hydroxyiamine and ammonia under acidic condition (pH=5) [64].Uyeda and Peters demonstrated selective conversion of NO_2^- to N_2O using an unusual bimetallic diimine-dioxime cobalt complex with an outer-sphere coordinated Mg^{II}[65]. On the basis of cyclic voltammetry and electrolysis experiments they proposed a plausible electrocatalytic cycle for the reduction of nitrite as shown in **Figure 5**.

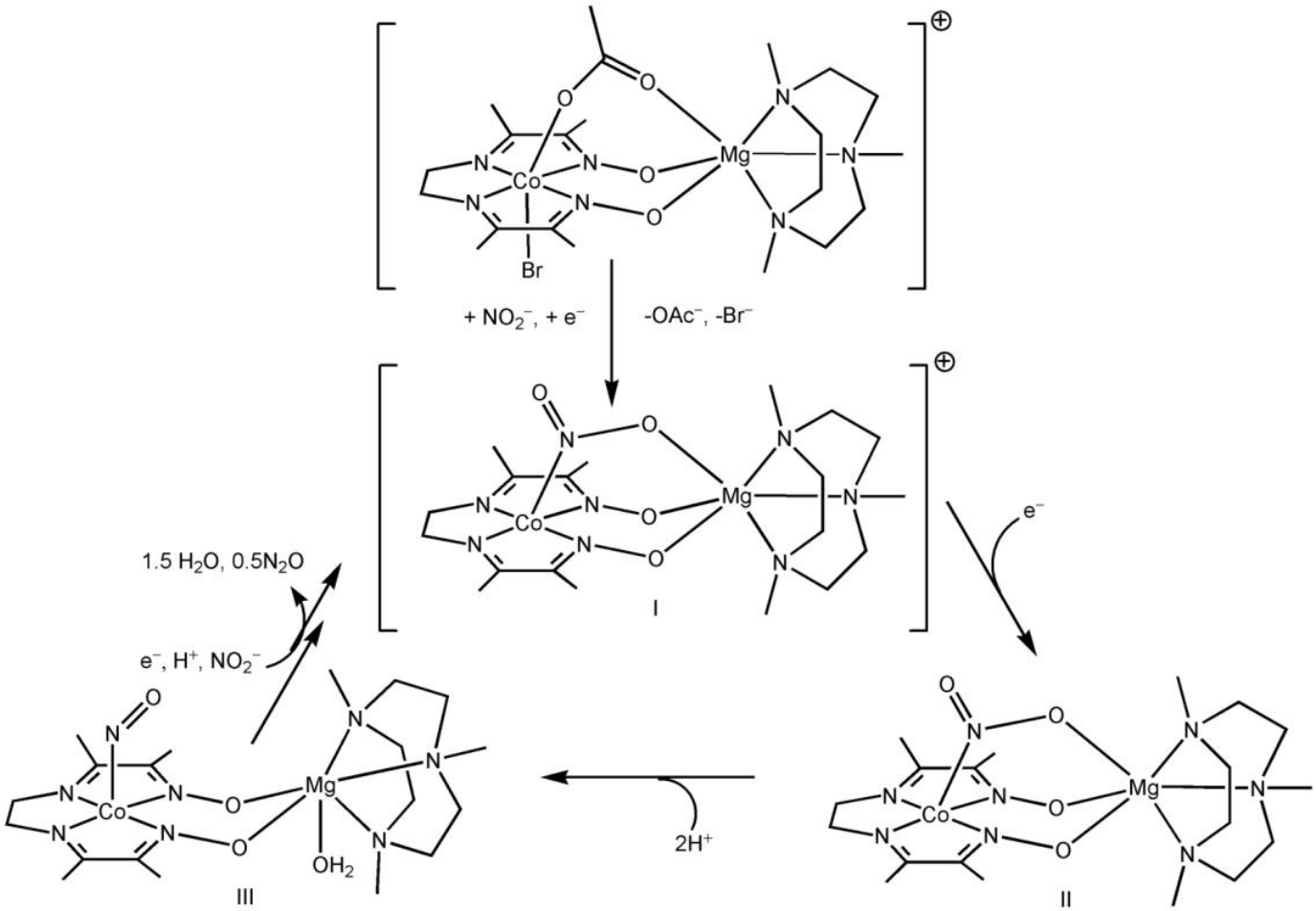


Figure 5 The mechanism of reduction of nitrite to N_2O with Uyeda and Peters' hetero-bimetallic Co-Mg catalyst (catalyst **3**, Table 1) [65]

The proposed cycle begins with reduction of the pre-catalyst by one electron, which is followed by the loss of bromide and displacement of the OAc^- ligand by nitrite to give the cationic complex I. Single electron reduction of complex I gives complex II, then subsequent protonation with two equivalents of acid yields nitrosyl complex III which, after further reduction and protonation steps, eliminates nitrous oxide and leaves a vacant site on the bimetallic catalyst to which NO_2^- can bind, regenerating complex I.

Table 1 Homogeneous cobalt catalyst for nitrite reduction

Catalyst	Condition	Applied potential (V) (Reference)	Conformed product(s)	Ref
1	3M NaOH	-1.5 (SCE)	NH_2OH	[63]
2[a]	In water, 31.3 μM catalyst, 2.0 mM $NaNO_2$, 0.3 M of pH 4.0 buffer solution. Vitreous carbon cathode	-0.7(Ag/AgCl)	NH_3OH^+, NH_4^+	[64]
3	In MeCN, 20 mM [n-Bu_4N][NO_2], 20 mM Et_3NHCl, 100 mM [$^nBu_4N$][ClO_4], 0.5 mM catalyst. Glassy carbon plate cathode	-0.96 (SHE)	N_2O	[65]
4	In CH_3CN, 1-2 equivalent of $HClO_4$		NO	[66]
5	In water, 25 μM catalyst, 0.1 M $NaNO_2$ in 1.0 M MOPS buffer, pH=7.2. hanging mercury drop electrode (HMDE) as working electrode and a Pt counter electrode	-0.9 (Ag/AgCl)	NH_3	[67]
6[b]	In water, 1 mM catalyst, 100 M $NaNO_2$, 0.1 MNa_2SO_4, neutral pH. Glassy carbon working cathode.	-0.9 (SCE)	NH_3	[68, 69]
7, 8a-g, 9, 10	In water, 1.0 mM catalyst, 50 M $NaNO_2$ in 0.25 M PH=6.7 phosphate buffer. Glassy carbon working cathode.	-0.34 (RHE)	NH_4^+	[70]
11	In water, 0.5 mM catalyst, 20 M $NaNO_2$, 0.1 MNa_2SO_4, 0.1 M Pi, neutral pH. Glassy carbon working cathode.	-0.9 (SCE)	NH_3	[71]
12	In water, 1 mM catalyst, 100 mM $NaNO_2$ in 0.1 M KCl, neutral pH. Glassy carbon rod working cathode.	-1.36 (SCE)	NH_3	[72]
12	In water, 1 mM catalyst, 100 mM $NaNO_2$ in 0.1 M Na_2SO_4 and 0.1 M PH=7 MOPS. Glassy carbon working electrode and Pt wire counter electrode	-1.16 (SCE)	NH_3	[73]

a:Mixture of NH_2OH (yield 33%) and NH_4^+ (yield 60%); b:Mixture of NH_2OH (85% faradic efficiency) and NH_4^+ (17% faradic efficiency)

Incorporation of the redox-innocent, Lewis-acidic Mg^{II}centre into the framework was found to increase the stability of the Co–NO_2^- adduct sufficiently under acidic conditions that addition of the acid [Et_3NH][BPh_4] to complex II, did not produce hydrogen (as normally observed with such Co complexes in the absence of Mg), but instead led to N_2O production via complex III. The impressive selectivity for production of N_2O over H_2, NH_2OH or NH_3 made this system unique and inspiring for further research. Another Bimetallic system was reported recently, $[(LN_8H)Cu^{II}–NO_2^––Co^{II}]^{3+}$(Catalyst **4**, **Figure 6**, **Table 1**) bearing an octadentate N8-cryptand ligand (LN_8H) where acid induced reduction of nitrite to NO and H_2O took place [66].

An engrossing Co^{III}metallotripeptide complex, Co-GGH (Catalyst **5**, Figure6, Table 1) (GGH = Gly-Gly-His model tripeptide), was reported by Guo and co-authors which rapidly reduced nitrite to ammonia with high faradaic efficiency (~90%). This complex displayed electrocatalytic reduction of nitrite at -0.90 V vs. SCE with a Hg electrode in a buffered aqueous solution at pH=7.2 with a turnover number greater than 3500 after 5.5 hours [67].

As proposed by the authors, Co^{II}-NO_2 is the active form of the catalyst which upon one electron reduction produces Co^{I}-NO_2 species (**Figure 7**). Addition of two proton additions to the resulting Co^{I}-NO_2 species then facilitate N-O bond cleavage with release of H_2O and formation of reactive Co^{II}-NO complex. One electron reduction followed by protonation of Co^{II}-NO complex produces nitroxyl species Co^{II}-HNO. Two step two electron two proton reduction of the nitroxyl intermediate generates a Co^{II}-NH_3 complex, which then reproduces the active Co^{II}-NO_2complex on protonation releasing NH_4^+ and completing the catalytic cycle. The N-terminal amine plays a vital role in this proton coupled electron transfer processes by forming hydrogen bonds with those intermediate species.

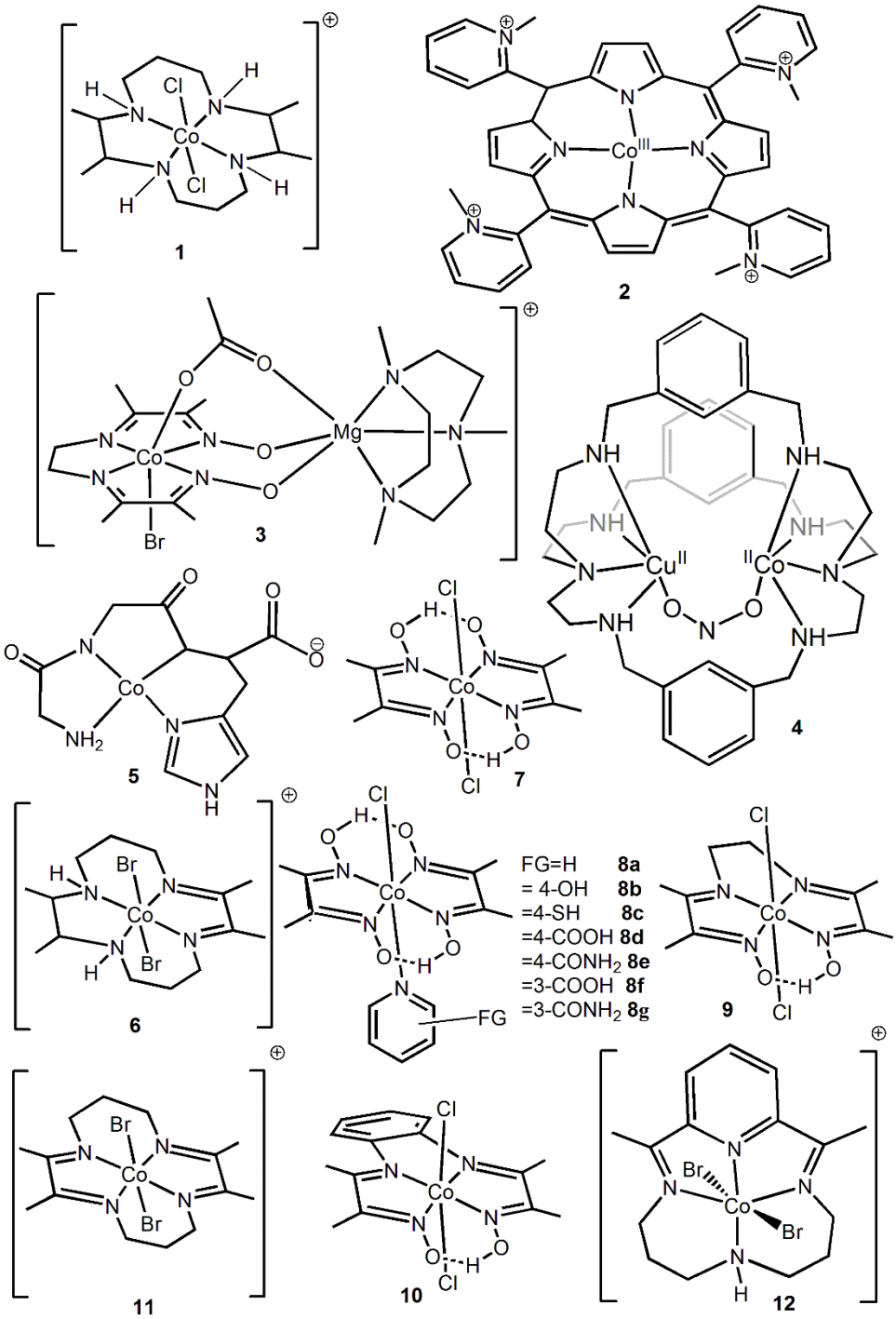


Figure 6 Reported molecular Co-catalysts for nitrite reduction

A recent investigation of an analog of cyclam possessing an unsaturated α-diimine ligand framework, $[Co(DIM)Br_2]^+$(Catalyst **6**, Figure 6) (DIM=2,3-dimethyl-1,4,8,11-tetraazacyclotetradeca-1,3-diene) was shown to electrocatalyticallyreduce nitrate as well as nitrite with good efficiency [68]. The nitrite reduction was reported to happen via the in-situ formation of six coordinated $[Co(DIM)(NO_2)_2]^+$ complex in aqueous solution [69].This complex was reduced by two electrons: one-electron reduction was coupled with NO_2^- ligand loss, the additional single-electron reduction led to form Co^{II}–DIM(-I), which could reversibly bind NO_2^-. The investigation revealed the critical importance of the macrocycle N–H groups to electrocatalysis. Intramolecular proton transfer from an amine group of the macrocycle to a nitro ligand promoted the N–O bond cleavage of the nitro ligand with the formation of intermediate and H_2O. These results demonstrated that complexes with redox active ligands and/or proton shuttles also tend to facilitate catalytic NO_2^- reduction. Here the amine proton involved in intramolecular protonation of the coordinated nitrite. Thus, the intramolecular proton transfer from ligand backbone seems to be crucial for such electrocatalystic reduction. Meanwhile cobaloximes (catalysts **7**, **8**, **9**, **10**, Figure 6.) were also demonstrated as a

bioinspired molecular platform for exclusive ammonia synthesis via electrocatalytic NO_2^- reduction with 98-99% faradaic efficiency (FE) under nearly neutral conditions where the mechanistic studies illustrated that cobaloximes furnished effective binding with NO_2^- along with continuous, rapid $6e^-/8H^+$ transfer with an intramolecular hydrogen bonding framework [70]. It is important to note that sometimes external proton shuttles can also provide such functionality that is what reported for $[Co(TIM)Br_2]^+$(Catalyst **11**, Figure 6.) (TIM = 2,4,9,10-tetramethyl-1,4,8,11-tetraazacyclodec-1,3,8,10-tetraene). Here the ligand TIM with no amine proton was found to be inactive towards nitrite reduction in unbuffered solution but became an excellent catalyst in phosphate buffer to form hydroxylamine and ammonia [71]. Here the phosphate served as a source of proton during the reduction process (**Figure 8**).

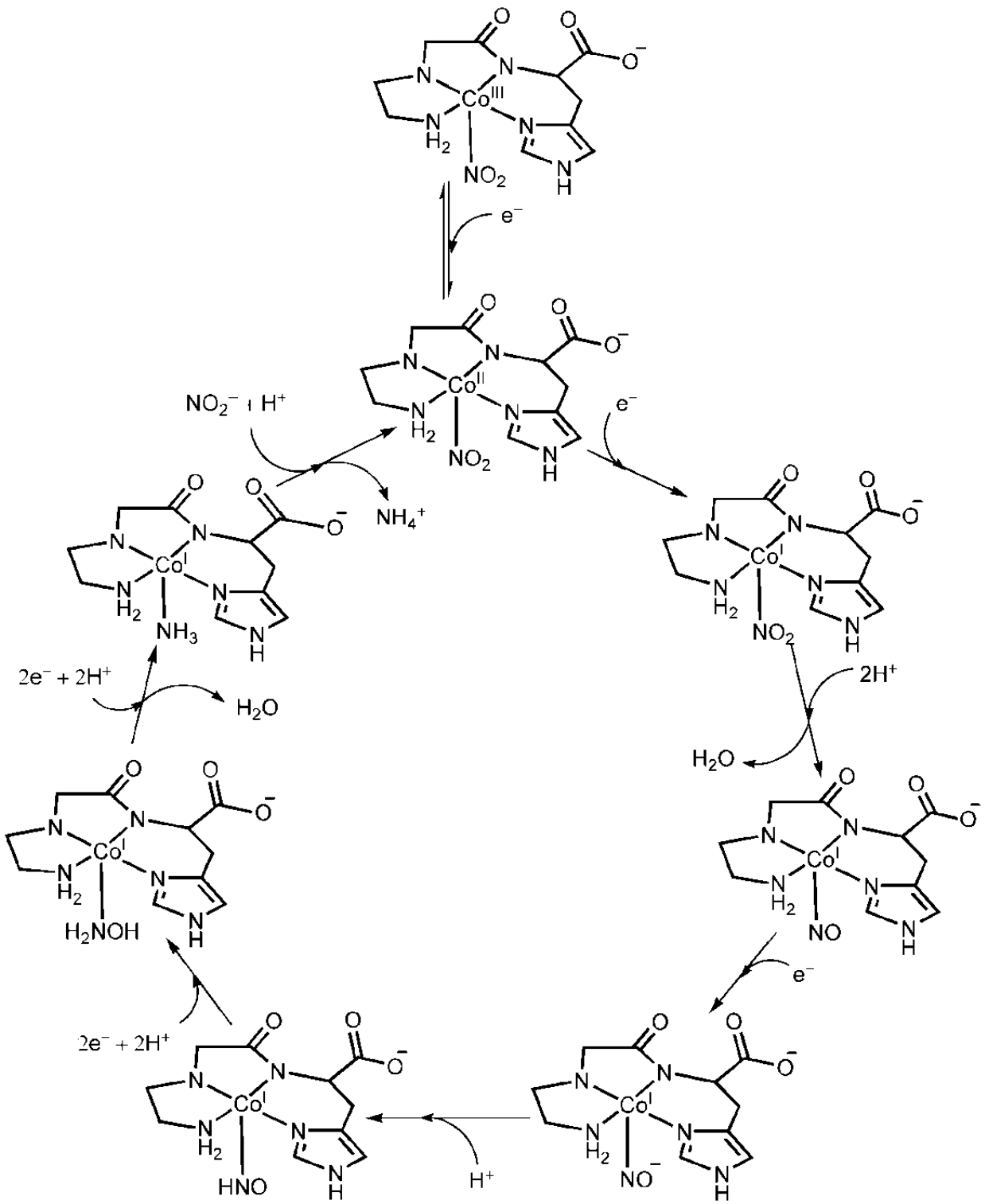


Figure7 Proposed catalytic cycle for reduction of nitrite to ammonia by Co-GGH complex (Catalyst **5**) [67]

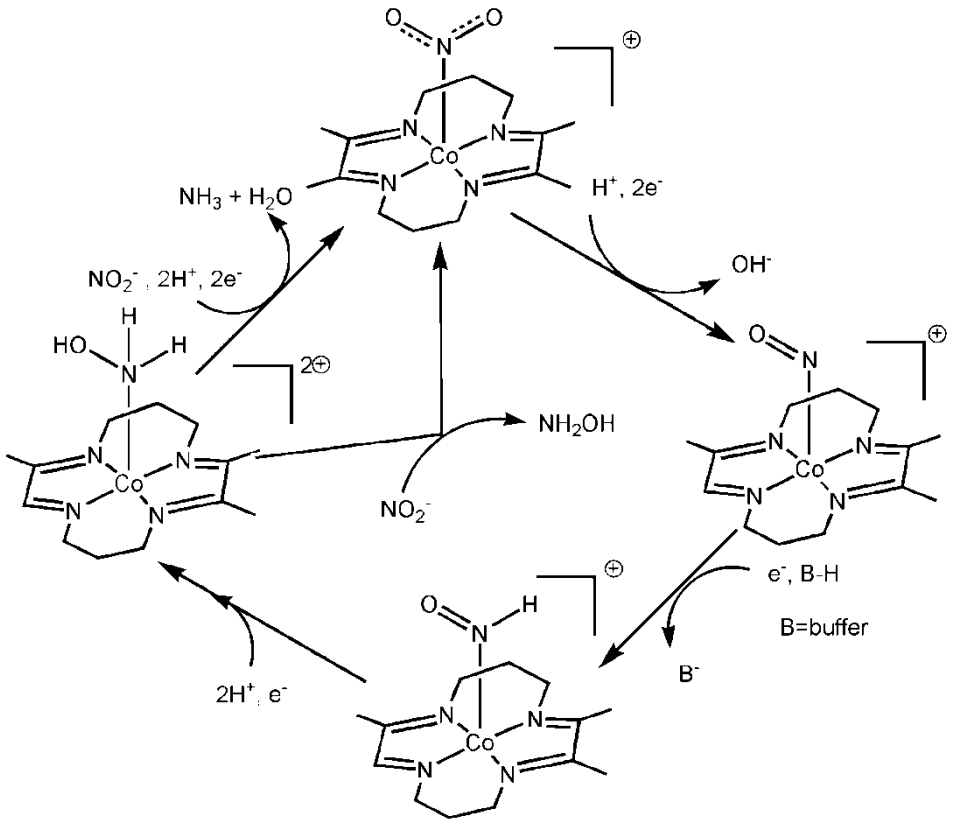


Figure 8 Buffer assisted nitrite reduction by $[Co(TIM)Br_2]^+$ (catalyst **12**) at neutral pH

All these studies together suggest a list a ligand design criterion for an active molecular electrocatalyst for nitrite reduction. A ligand having macrocycle with a combination of redox non-innocent character, possible proton shuttles and flexibility is most likely create a coordination environment that is active towards nitrite reduction. A recent report of Co^{III} complex, $[Co(CR)Br_2]^+$(Catalyst **12**, Figure 6) where the ligand CR (2,12-dimethyl-3,7,11,17-tetraazabicyclo-[11.3.1]-heptadeca-1(17),2,11,13,15-pentaene), possess all the above criteria also found to facilitate electrocatalytic reduction of nitrite and nitrate. The complex $[Co(CR)Br_2]^+$reduce nitrite under acidic (pH=6.40) condition to yield ammonium with 88% FE and it appeared that the complex underwent two Co-centered reduction steps to Co^I followed by a ligand reduction to activate catalysis at -1.46 V vs. SCE [72, 74]. Addition of buffer to the system enhances rate of electrocatalysis and the buffering agents were found to influence the selectivity of the product and longevity of the catalyst [73].

Challenges and future perspectives

To attain TON and TOF required for large scale applications, long-term stability and augmented reactivity of the catalysts areof fundamental importance. Endeavours on both pursuing new catalysts and modifying existing catalysts have made this goal much closer. To explore new catalyst strategic ligand design plays a crucial role. As we have learned throughout this report, for both natural and artificial nitrite reduction proton shuttles are vital. Proton shuttles facilitate proton transfer; maintain proton balance at the active site, supporting proton coupled electron transfer (PCET) mechanism. Without efficient proton source nitrite reduction would be much slower or even impossible under physiological and laboratory condition. As discussed in this account, the redox non-innocence and proton responsive site in the ligand framework have shown very positive effects in this regard. Incorporating these factors into the ligand scaffold can enable PCET, redox, and pH-dependent lability. All these phenomena are vital for lowering the overpotential of nitrite or nitrate reduction.

Conclusion

Activity, selectivity, efficiency and stability are the key parameters for exploring effective electrocatalyst for practical application. Molecular catalyst has the advantages of a clear structure, uniform distribution of active sites, and adjustable coordination environment, which is ideal model for studying catalytic mechanism. As we have summarised in this account, there are now multiple reports of cobalt-based molecular systems for electrocatalytic NO_2^- reduction

and it is notable that all of these electrocatalysts operate with a relatively large overpotential (>1 V). Mechanistically, this large overpotential can be attributed in part to the need for the N−O bond cleavage to occur by two-electron steps. Nitrite reduction with cobalt centre hence requires the catalyst to be reduced from Co^{III} or Co^{II} to the formally Co^{I} oxidation state. In the case of redox innocent ligands the onset potential for electrocatalysis is therefore dictated by the potential required to access Co^{I}. While the ability of redox non-innocent ligands to store electrons makes access to the equivalent redox state in these complexes more accessible, relatively cathodic potentials are still required. Mechanistic investigations on the reported catalytic systems implicate few critical features of the ligand scaffold in facilitating the electrocatalytic activity: (1) as in the case of many important biological reactions NO_2^-reduction occur by managing the proton and electron flow at the enzyme active site and for this to happen smoothly, the ligand backbone has to be redox-active or redox non-innocent, which allows electrons to be stored on the ligand, thereby promoting the reduction steps; (2) for macrocyclic ligand the flexibility is certainly a valuable requirement which allows for *cis*-coordination of the substrate; (3) the presence of proton-responsive site, which facilitate intramolecular protonation of the substrate and (4) hemilability at the ligand site is sometimes very crucial to create an open coordination site at which the reactivity can occur. To be specific for cobalt catalyst, the ligand that better stabilize the formally Co(I) state in aqueous solution will allow for nitrite reduction electrocatalysis with smaller overpotentials. Thus a single ligand scaffold having all these requirements may provide us an efficient turnover.

Conflicts of interest

The author declare that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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