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Review: Recent advances in the investigations of NO activation on cobalt and manganese porphyrins: a brief review

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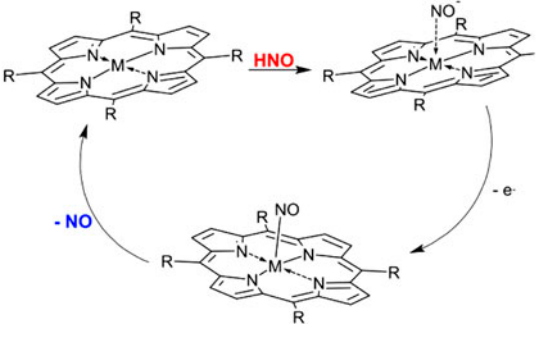

The results of recent research on interactions between cobalt and manganese porphyrins with nitric oxide species are summarized. The systems containing NO itself as well as its oxidized (nitrite) and reduced (nitroxyl) forms are discussed separately. Selected publications are primarily focused on the reaction mechanisms with respect to both biological systems and potential applications.

Cobalt and manganese porphyrins are known for their ability to activate small molecules. This is particularly important in the case of nitric oxide, whose role and mechanism of action in the redox biological systems have not yet been fully recognized. The goal of this article is to draw attention to some of the current trends of research in this area. The interactions involving NO itself and the primary products of its oxidation (nitrite) and reduction (nitroxyl) have been distinguished and separately discussed. The diversity of undertaken issues sheds light on both the expected behavior in biologically relevant systems as well as potential practical applications.

Keywords: Cobalt porphyrins; Manganese porphyrins; Nitric oxide; Mechanisms; Catalytic activity

Introduction

The chemistry of nitric oxide and its derivatives is particularly important for understanding various biological processes occurring in the human body. The identification of NO as an

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intermediate of endothelium-derived relaxation factor [1] triggered enormous interest among researchers throughout the world, which was the reason for the American Association for the Advancement of Science to confer NO the title of "molecule of the year" in 1992 [2].

Endogenous nitric oxide occurs as a product of L-arginine decomposition, the reaction catalyzed by the nitric oxide synthase and supported by the presence of molecular oxygen as well as many cellular cofactors [3]. Although most NO molecules are bound to iron(II) in the heme group of proteins or enzymes, the remaining part may interact with various cellular components or be transformed to even more reactive nitrogen species (RNS) or reactive nitrogen oxide species (RNOS) [4]. Moreover, NO itself can exist in different forms, which are convertible, depending on the redox character of the environment, because various forms may have various biomolecular targets and may react with them in different ways [4]. One such form is the nitroxyl, HNO/NO^-, which is the reduced form of NO and is isoelectronic with dioxygen. Despite the apparent similarities, it is suggested that the effects exerted by HNO on living organisms are distinct from those caused by nitric oxide [5]. Nitroxyl reacts with heme proteins and water-soluble ferric porphyrins to form ferrous nitrosyl derivatives [6, 7]. This is one expression of its unique chemical properties, such as spin-forbidden transition in acid–base equilibrium [8]:

$$^1\mathrm{HNO} \leftrightarrow {}^3\mathrm{NO}^- + \mathrm{H}^+, \quad pK_\mathrm{a} = 11.4 \tag{1}$$

With extremely low stability, HNO must be formed *in situ* from its endogenous or exogenous donors.

While HNO is a reduced form of nitric oxide, the nitrite ion, NO_2^-, is the result of its one-electron oxidation. Its biological versatility results from the fact that it can serve as both electron donor and acceptor [9]. Furthermore, NO_2^- is an ambident nucleophile [10], capable of binding to metal centers in several distinct ways.

In biological systems, the main targets for nitric oxide are iron porphyrins. Over the past dozen years, a number of reviews have been devoted to the mechanisms of the interactions occurring in such a system, taking into account both NO itself and its endogenous and exogenous donors [11–18]. The macrocyclic complexes of other redox active metals are also of interest in this respect, both natural, present in the human body and potentially able to interact with nitrogen oxides, and synthetic complexes which are useful for model studies. Particularly, noteworthy are cobalt and manganese complexes with the tetrapyrrole ligands. Vitamin B12 in its native and reduced form can be involved in tuning of the physiological action of nitric oxide *in vivo* playing a role of its biological scavenger [19, 20]. The complex structure of cobalamin which increases the probability of the interference from the background reactions encourages taking advantage of simpler model systems, based mainly on symmetric synthetic porphyrins [21].

Manganese porphyrins, especially those of Mn(II), are isoelectronic with respective iron (III) complexes. Therefore, their nitrosyl derivatives are considered good structural models for biologically relevant but kinetically unstable ferric-NO analogs [22]. This is particularly important in the case of manganese tetraarylporphyrins that can be related to cytochrome P-450 in terms of catalytic activity [23, 24].

We summarize the most important achievements in research on the reaction mechanisms occurring in systems containing cobalt and manganese porphyrins and various forms of nitric oxide that have been presented in the past few years. Diversity in the coordination forms as well as in the electron distribution within the products and intermediates make the

results of these studies important, not only from the point of view of bioinorganic chemistry but also chemical catalysis, especially mimicking natural processes.

Activation of NO on cobalt porphyrins

Nitric oxide

A dozen years ago, Wolak and van Eldik showed that nitric oxide can displace water in aquacobalamin (vitamin B_{12a}). The reaction takes place only at low pH and hence it cannot be observed under physiological conditions. Following the mechanism of reductive nitrosylation, it gives $Co^{II}Cbl(NO)$ as a final product which formally should be noted as $Co^{III}Cbl(NO^{-})$. The same product is observed in the reaction between reduced B_{12} and NO (scheme 1) [25].

Later Roncaroli and van Eldik demonstrated that Co(II) porphyrin complexes reveal similar affinity to NO, giving $Co^{II}P(NO)$ or $Co^{III}(III)(P(NO^{-})$ as products of the appropriate reaction [21]. Using three different cobalt(III) porphyrins, meso-tetra-(4-carboxyphenyl)-porphyrin (TCPP), meso-tetra-(4-sulfonatophenyl)-porphyrin (TPPS), and meso-tetra-(4-methyl-pyridyl)-porphyrin (TMPy), they showed that the number of intermediates occurring in the reaction pathway depends strongly on pH, whereas it is a single-step reaction in strongly acidic solutions, it becomes more complex at pH > 3.

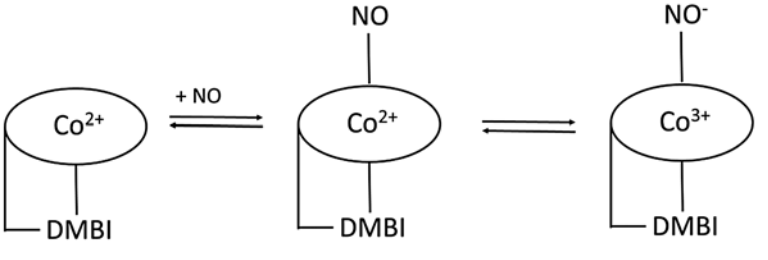
As indicated by the results of the detailed kinetic investigations, the rate-determining step of the latter reaction is substitution of water molecule by the first NO ligand (k_1 in equation 2).

$$\left[Co^{III}P(H_2O)_2\right]^n + NO \xrightarrow{k_1} \left[Co^{III}P(H_2O)(NO)\right]^n + H_2O \tag{2}$$

Substitution of remaining water molecule:

$$\left[Co^{III}P(H_2O)(NO)\right]^n + NO \xrightarrow{k_2} \left[Co^{III}P(NO)_2\right]^n + H_2O \tag{3}$$

is strongly facilitated due to the increase in electron density on the metal center for each considered Co(III) complex. Considerable complication is introduced with the presence of nitrite ions. Under such conditions, $Co^{III}P(NO)(H_2O)$ is destabilized, as NO_2^- substitutes nitric oxide molecule, forming a nitro complex, $Co^{III}P(NO_2^-)(H_2O)$. Such species was also recognized as an intermediate in the reaction of $Co^{III}P(H_2O)_2$ with NO_2^-. In solutions containing mixture of nitric oxide and nitrite, this species is accompanied by $Co^{III}P(NO_2^-)(NO)$ in the intermediate state. The latter complex decays to $Co^{III}P(NO^{-})$ and NO_2 via inner-sphere ligand-to-ligand electron transfer [21].



Scheme 1. The suggested mechanism of the reaction between B_{12r} and NO (according to [25]).

Additional structural information on the nitrosyl Co porphyrins was provided by Jaworska and Lodowski [26]. Based on DFT calculations, they pointed at a significant transfer of some electron density from the metal center toward NO ligand due to the donation from the doubly occupied d_{xy} orbital and a free electron pair on oxygen. The geometry of Co–N–O is distorted from linearity, which, to some extent, can be explained by the combination of single Co–N and double N–O bonds. Recently, the structural and energetic aspects of nitric oxide – Co(II) porphyrin interactions were discussed by Radoń from high-level theoretical calculations (DFT and DFT-D) [27]. According to his computations, binding of NO to Co(II) complex should be regarded as a simple radical recombination. Hence, the singlet ground state of the nitrosyl complex CoP(NO) can be associated with the ground state of the dissociation products, *viz.* ^{2}CoP + ^{2}NO.

High affinity of Co^{III}Ps toward nitric oxide can be adopted to biological conditions, under which they can play a role in the control of NO overproduction. In this regard, they exhibit some resemblance to iron porphyrins, with hemoglobin (Hb) being the most striking example, as it is involved in the active site of the nitric oxide dioxygenase (NOD). As long known, the reaction of HbO_2 with NO leads to the formation of nitrate and metHb. The intermediate of this dioxygenation reaction involves peroxynitrite coordinated to the metal [28–32]. Kurtikyan and co-workers showed that oxo-coboglobin (see figure 1) can mimic the enzymatic activity of NOD [33, 34]. $Co^{III}P(O_2)(NH_3)$ (figure 1) was synthesized by sequential treatment of microporous Co-porphyrin layers with NH_3 gas and O_2.

Two different isomeric forms of the nitrato complex were observed under nonstandard conditions. Sequential formation of various intermediate species can be observed on tuning the temperature within the range of 140–210 K (see scheme 2).

The last one, $Co(P)(\eta\text{-}ONO_2)(NH_3)$, is thermally unstable. At room temperature, the nitrate is substituted by NH_3 [34].

The NOD-mimicking complex, *viz.* $CoP(O_2)py$ was obtained in amorphous layers of four-coordinate CoP by sequential addition of small quantities of pyridine and dioxygen. In the presence of nitric oxide, $Co^{III}P(\eta\text{-}ONO_2)py$ is formed with $Co^{III}P(\eta\text{-}OONO)py$ being an intermediate accessible at low temperature, analogous to that observed in the reaction of $Co^{III}P(O_2)(NH_3)$. At room temperature, $Co^{III}(P)(\eta\text{-}ONO_2)py$ is transformed to $Co^{III}P(py)_2$, whereas at 200 K and under NO atmosphere, it can be converted to $Co^{III}P(NO_2)py$ (equation 4).

$$Co^{III}(P)\left(\eta^1 - ONO_2\right)py + NO \rightarrow Co^{III}(P)(NO_2)py + NO_2 \quad (4)$$

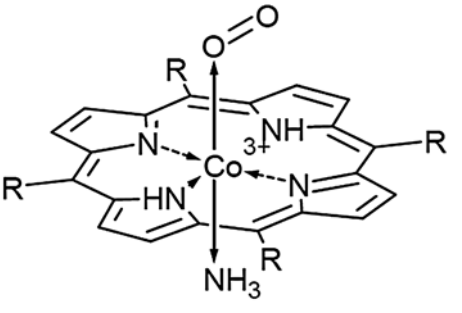
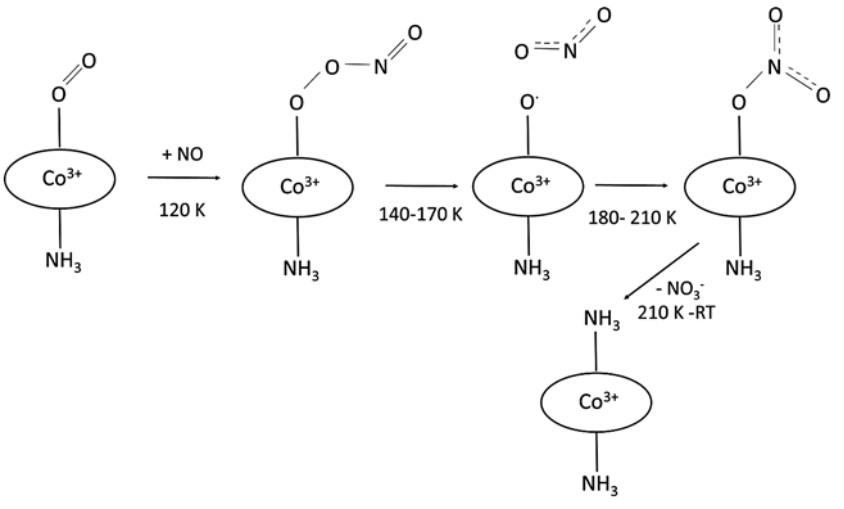


Figure 1. The structure of oxy-coboglobin.

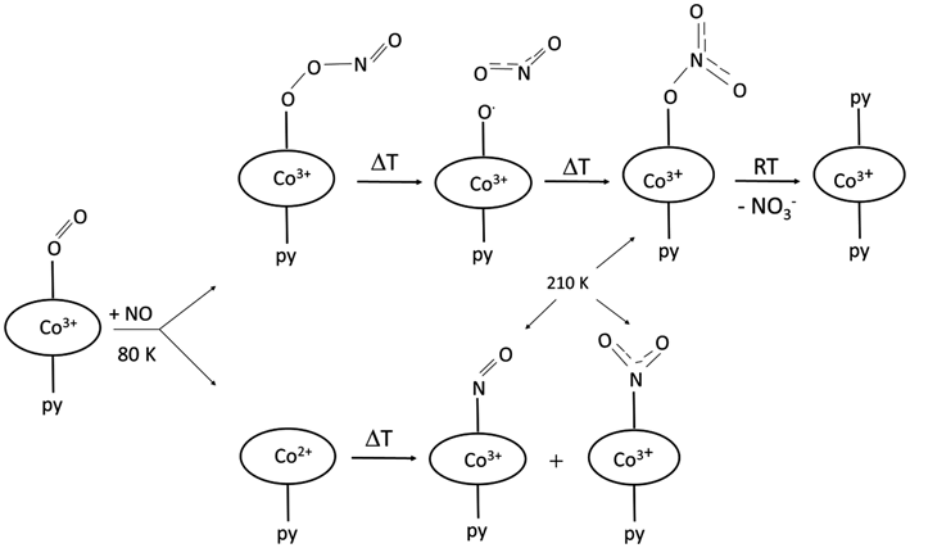


Scheme 2. Formation of peroxonitrite species on oxo-coboglobin as suggested by Kurtikyan *et al.* [34].

In contrast to the ammonia system, the axially coordinated O_2 in $Co^{III}(P)(O_2)py$ is labile and it can be released as a consequence of the electron transfer occurring in the presence of NO:

$$Co^{III}P(O_2)py \overset{+NO}{\rightarrow} Co^{II}Ppy + N_2O_3 + NO_2 \quad (5)$$

The five-coordinate species of cobalt(II) can bind either NO or NO_2 giving $Co^{III}P(NO)py$ or $Co^{III}P(NO_2)py$, respectively (compare scheme 3) [33].



Scheme 3. The reaction pathways occurring in oxo-coboglobin – NO system (according to Kurtikyan *et al.* [33]).

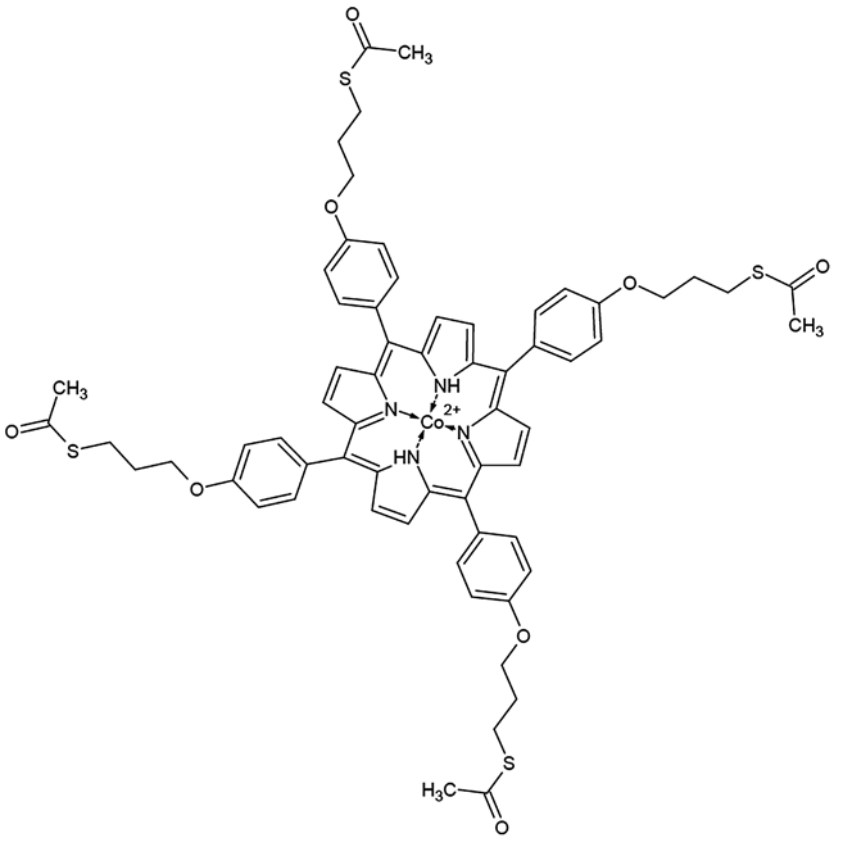


Figure 2. The structure of $Co^{II}TAPP$.

Using a high affinity of cobalt porphyrins for NO, Suarez and co-workers made attempts to extend the range of electrochemical sensors of nitric oxide [35]. Based on the well-known Malinski's model [36, 37], they proposed the use of cobalt(II) 5,10,15,20-tetrakis [3-(p-acetylthiopropoxy)phenyl]porphyrin, $Co^{II}TAPP$ (see figure 2), in the presence of a gold electrode.

It was confirmed that while the solution is purged with NO, the latter binds Co(II) thus leading to the formation of the complex which is formally $Co^{III}TAPP(NO^{-})$, as previously described by Roncaroli and van Eldik. Under applied conditions, NO remains completely inert toward $Co^{III}TAPP$ [21].

$$Co^{II}TAPP + NO \rightarrow Co^{III}TAPP(NO^{-}) \quad (6)$$

$$Co^{III}TAPP + NO \rightarrow \text{no reaction} \quad (7)$$

The use of a gold electrode introduces some complication into the system. When reaction (6) occurs in solution, no evidence was found for NO binding to the porphyrin adsorbed on the gold surface. This is presumably due to facilitation of the oxidation of gold-attached metalloporphyrin, and therefore only $Co^{III}TAPP$ species can be found on the surface of the

Table 1. The redox potentials of nitrosyl and nitrosyl-free complexes of CoP in solution and covalently attached to gold electrode [35].

Couple	Conditions	E (V)
$Co^{III}P \mid Co^{II}P$	Solution	+0.79
	Au electrode	+0.44
$Co^{III}P(NO^-) \mid Co^{II}P(NO^-)$	Solution	+0.89
	Au electrode	+0.86

electrode. The electrode-attached layer of $Co^{III}TAPP$ does not react with NO; however, it is possible to deposit $Co^{III}TAPP(NO^-)$ formed in reaction (6) in the solution.

More interesting findings were provided by the results of the electrochemical investigations, which showed that the redox potential of $[Co^{III}TAPP(NO)] \mid [Co^{II}TAPP(NO)]$ couple is significantly shifted by 0.4 V, with respect to the NO-free species, when the metalloporphyrin is attached to a gold electrode. In the case of dissolved cobalt complexes, the respective values are much closer to each other (compare table 1).

This can be explained, to some extent, by charge donation from the surface to the deposited macrocycle that stabilizes higher oxidation state of cobalt. Coordination of NO suppresses most of the effect and therefore there is no significant difference in the redox potential between $Co^{III}TAPP(NO)$ in solution and on the electrode. Such a significant shift of the redox potential measured on the $Co^{II}TAPP$-modified electrode determines its prospective usefulness in analytical assays of nitric oxide in solutions [35].

Nitrite ion

Investigations of the interactions between nitrite ions and tetrapyrrole complexes of Co(III) is of interest, as it is postulated that NO^- can be a substrate for cobalamin-catalyzed synthesis of nitroxyl [38]. Moreover, it introduces substantial complications to the kinetic studies on NO binding to metalloporphyrins in solution, as even trace quantities are competing for the axial position in the complex [39]. As shown by Roncaroli and van Eldik, substitution of water in $Co^{III}TPPS(H_2O)$ with NO_2^- is fast and accelerates with the replacement of the first ligand [21]. At pH 5, the second-order rate constant for the reaction:

$$\left[Co^{III}TPPS(H_2O)_2\right]^{3-} + NO_2^- \xrightarrow{k_1} \left[Co^{III}TPPS(NO_2)(H_2O)\right]^{4-} + H_2O \quad (8)$$

is $38.5 \pm 0.8\ s^{-1}\ M^{-1}$. The subsequent step:

$$\left[Co^{III}TPPS(NO_2)(H_2O)\right]^{4-} + NO_2^- \xrightarrow{k_2} \left[Co^{III}TPPS(NO_2)_2\right]^{5-} + H_2O \quad (9)$$

is much faster, as $k_2 = 3.4\ (\pm 0.6) \times s^{-1}\ M^{-1}$. This finding was explained in terms of the *trans*-labilization effect. In this particular case, the electron density on the metal center is increased with the first introduced nitrite ligand, giving it some Co(II) characters [21].

Another accelerating effect is observed when changing the reaction conditions to even more acidic. At pH 1, NO_2^- exists in solutions in a protonated form HNO_2. The nitrosylation rates for $Co^{III}TPPS(H_2O)_2$ and $Co^{III}TMPyP(H_2O)_2$ are noticeably higher than those determined at pH 5, thus pointing at acidic catalysis facilitating the dissociation step [21].

In the presence of NO, the $Co^{III}P(NO_2)(H_2O)$ can be converted to $Co^{III}P(NO^-)$ through inner-sphere electron transfer (equation 10). Under highly acidic conditions, $Co^{III}P(NO)(H_2O)$ appears as an intermediate, which further reacts with another NO molecule to produce the final product (equation 11) [21].

$$\left[Co^{III}TPPS(NO_2)(H_2O)\right]^{4-} + NO \rightarrow \left[Co^{III}TPPS(NO_2)(NO)\right]^{4-} + H_2O \quad (10)$$

$$\left[Co^{III}TPPS(NO_2)(NO)\right]^{4-} \rightarrow \left[Co^{III}TPPS(NO^-)\right]^{4-} + NO_2 \quad (11)$$

It can be expected that coordinated nitrite can be reduced to nitric oxide. Such activity is typical for some heme proteins belonging to the class of enzymes known as nitrite reductase (NiR) [40, 41]. Following this assumption, the Co(II)-substituted myoglobins, $Co^{II}Mbs$, were tested for potential formation of RNOS [42]. The research conducted in this direction faces another interesting issue, namely, the linkage isomerism in the complexes of metalloporphyrins with NO_x ligands. The possibility of occurrence of such a transformation was previously discussed on ruthenium porphyrins by Fomitchev *et al.* [43]. It appears from this work as well as from subsequent reports by Silaghi-Dumitrescu [44, 45], Xu et al. [46], Hoshino et al. [47], and Kudrik et al. [48, 49] that this effect is controlled by metal identity, oxidation state, and the macrocycle. As evident from results reported by Heinecke, nitrite ion binds $Co^{II}Mbs$ as ONO^-. Formation of O-nitrito complex, *viz.* $Co^{III}Mb(ONO^-)$, is accompanied by release of NO in the disproportionation reaction of two nitrite ions (equation 12):

$$Co^{II}Mb + 2NO_2^- + 2H^+ \rightarrow Co^{III}Mb(ONO^-) + NO + H_2O \quad (12)$$

The O-nitrito complex is observed also as the final product of $Co^{III}Mb$ reaction with nitrite ions. In the presence of excess dithionite, $Co^{III}Mb$ is reduced to $Co^{II}Mb$. The subsequent addition of NO_2^- results in the formation of $Co^{III}Mb(NO)$, as formulated by equation (13):

$$Co^{III}Mb + NO_2^- + S_2O_4^{2-} \rightarrow Co^{II}Mb(NO) \quad (13)$$

In this manner, it was proved that cobalt(II) substituted myoglobin possesses NiR activity, although much lower than its native form [42].

Silaghi-Dumitrescu and co-workers investigated the linkage isomerism of NO_x ligands on cytochrome cd1 NiR [44], Mb, Hb [50], and other iron and cobalt porphyrins [45]. The latter, involving Co in its higher stable oxidation state, are isoelectronic with ferrous heme. This analogy translates into similarity in the coordination preferences. Therefore, both Fe(II) and Co(III) porphyrins react with NO_2^- yielding thermodynamically stable N-adduct as a result of the transformation of metastable O-binding form [44, 45, 50]. Preferences of Co(III) with respect to the donor are retained in case of modifications of the macrocyclic ligand, as proved for both natural and synthetic complexes [46, 51].

Quite similar effect can be obtained electrochemically using Co(porphyrin)-modified electrodes [52]. The limitation for this process is imposed by the size of the interface and accessibility of high overpotentials. Calfumán and co-workers applied this method to explore the distribution of reaction products under mild conditions. They found that at neutral pH, reduction of nitrite is mediated by tetraruthenated Co(II) porphyrins ($Co^{II}TRP$), such as [Co^{II}μ-{meso-5,10,15,20-tetra(pyridyl)porphyrin} tetrakis{bis(bipyridine)(chloride) ruthenium(II)}]$(PF_6)_4$, adsorbed on glassy carbon (GC) or ITO electrodes and then

electrostatically assembled onto a Nafion (Nf) film. Under such conditions, nitrite was reduced at the potential of −0.66 V. The reduction current on GC/Nf/CoTRP-modified electrode is virtually independent of the rotation rate in the presence or absence of NO_2^-. The process can be explained by the CE mechanisms, according to which the electron transfer is directed by the propagation of charge into the Nf film. In this case, the chemical step, *viz.* formation of adduct between nitrite and macrocycle, was recognized as rate determining step (equation 14) [52].

$$\mathrm{Co(TRP)} \overset{e^-}{\leftrightarrow} [\mathrm{Co(TRP)}]_{red} \underset{slow}{\overset{+NO_2^- + e^-}{\longleftrightarrow}} \text{products} \tag{14}$$

Nitroxyl

Nitroxyl is another biologically relevant NO derivative whose activity is related to the interactions with heme proteins [53, 54]. Although its affinity for natural non-iron metalloporphyrins has not been confirmed in living matter, extensive studies involving complexes of different redox-active metal ions are conducted [8, 55–61], including Co^{2+} and Co^{3+} [21, 35, 58].

In 2010, Suarez *et al.* followed the reaction of Co^{II}TAPP with selected HNO donors, namely, sodium trioxodinitrate (Angeli's salt, AS) and toluenesulfohydroxamic acid (TSHA), in dichloromethane [35]. As evident from their spectroscopic measurements, there is no spontaneous reaction of nitroxyl with the complex of Co(II) in contrast to Co(III). The observed spectral changes gave evidence for HNO binding by Co^{III}TAPP and the formation of Co^{III}TAPP(NO^-) [35].

$$\mathrm{Co^{III}TAPP} + \mathrm{HNO} \rightarrow \mathrm{Co^{III}TAPP(NO^-)} + \mathrm{H^+} \tag{15}$$

Bearing in mind, the need for development of electrochemical techniques for HNO detection, similar experiments were performed using the metalloporphyrin deposited on the gold electrode. In these tests, the tetrapyrrole compounds were linked to the metal particles by four thiol groups in the side chains of the macrocycle. Such an approach allowed for a flat arrangement of the complex on the electrode, which facilitated the contact of cobalt ions with the solution. As a result of this combination, Co^{II}TAPP was oxidized to Co^{III}TAPP and a higher oxidation state of metal ion was stabilized by charge donation to the surface of gold. As mentioned above, such effect decreases the redox potential of the tetrapyrrole complex. This prepared system was subjected to reaction with HNO, which was monitored electrochemically. A significant shift of the measured redox potential for the porphyrin (from 0.40 to 0.83 V; compare table 1) indicated that nitroxyl binds cobalt ion to form Co^{III}TAPP (NO^-). It is different in NO-saturated solution, in which the reaction was not observed. Instead, under this condition, nitric oxide is able to interact with bare gold electrode. To avoid this background process, the surface was covered with cystamine rendering it inert to NO. This modification enabled Co^{III}TAPP-Au electrode to trap NO into Co^{III}TAPP(NO^-) (see equation 7). Subsequent oxidation of the complex to Co^{III}TAPP(NO) is followed by release of NO (see figure 3), thus completing the catalytic cycle, and thereby, confirming the possibility of using such a composite electrode in the selective determination of HNO in the presence of nitric oxide [35, 58]. This method was further characterized by satisfactory time resolution, manifested in direct response of the electrical pulse to the release of nitroxyl from its donor. Maximum intensity is reached after a few seconds and the measured value is proportional to the concentration of the donor [60].

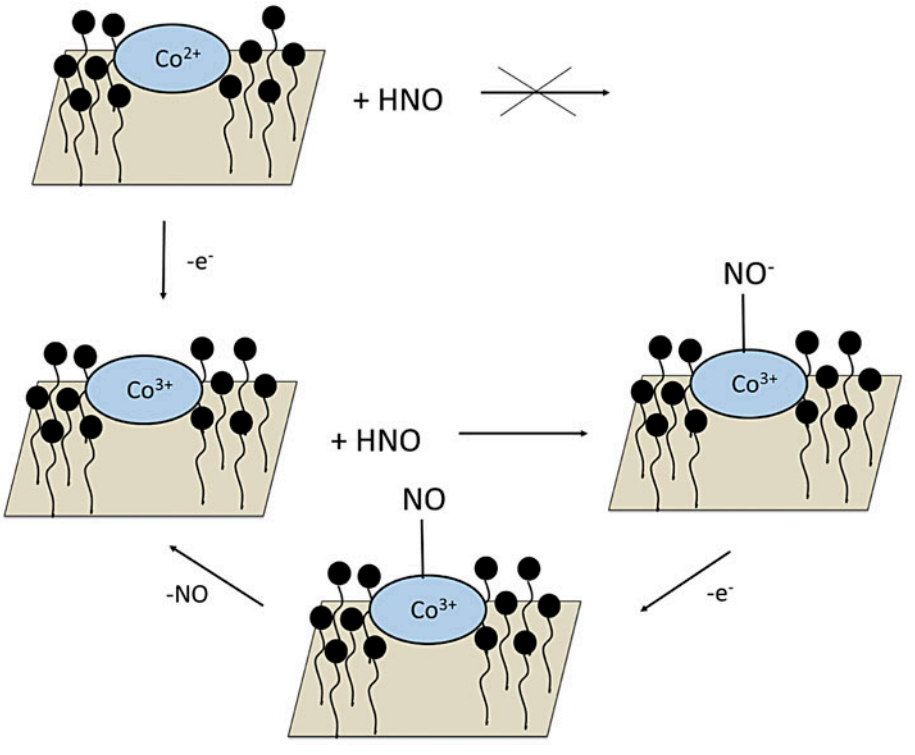


Figure 3. Schematic representation of the mechanism of electrochemical NO detection using Co^{III}P-Au electrode [8].

The stability of HNO in solution is considerably reduced, *inter alia*, by the presence of molecular oxygen [62]. It should be therefore assumed that O_2 will strongly interfere with analytical determination of nitroxyl. Therefore, attempts were made to estimate its impact on the utility of the electrochemical method. It has been shown that oxygen scavenges a large part of HNO generated in the solution; however, it does not prevent $Co^{III}TAPP(NO^{-})$ signal registration. Furthermore, the authors have provided convincing evidence that the other biologically relevant RNSs and ROSs, such as $NaNO_2$, NH_2OH, and H_2O_2, do not interact with the CoTAPP-modified electrode under aerobic or anaerobic conditions [60]. Finally, the preliminary biological tests demonstrated the possibility of the application of cobalt porphyrins in the electrochemical determination of HNO in tissues and cell cultures [8, 60].

Activation of NO on manganese porphyrins

Nitric oxide

Although the capability of transition metal complexes to induce the disproportionation of NO to N_2O and nitrites has long been known, to our knowledge, up to the beginning of this century, only one manganese compound has been reported in this respect. A few years earlier, Lippard and Franz studied the reaction between divalent tropocoronand Mn(THF)(TC-5,5) and NO [63]. They suggested that in the first step, a mononitrosyl complex

containing $\{Mn^{III}NO^{-}\}^{2+}$ moiety is formed; however, in excess NO, it is turned to [Mn (NO_2)(TC-5,5)] and N_2O gas comes out of solution (equations 16–18).

$$[Mn(THF)(TC-5,5)] + NO \rightarrow [Mn(NO)(TC-5,5)] \quad (16)$$

$$[Mn(NO)(TC-5,5)] + xNO \rightarrow \{Mn(NO_2)(NO)(TC-5,5)\} + N_2O + (x-4)NO \quad (17)$$

$$\{Mn(NO_2)(NO)(TC-5,5)\} \rightleftarrows [Mn(NO_2)(TC-5,5)] + NO \quad (18)$$

In 2004, Martirosyan *et al.* described the disproportionation of nitric oxide occurring at low temperature on sublimed layers of manganese(II) porphyrin [64]. This catalyst was prepared by the deposition of Mn^{II}TPP on CaF_2 or KBr plates using Mn^{II}TPP(pip) or Mn^{II}(TPP)(py) as starting material [65]. The obtained layers revealed microporosity, which enable selected ligands to percolate across the bulk. The reaction between sublimed layers of Mn^{II}TPP and pure NO gas was investigated using FTIR and UV–vis spectroscopy. Infrared spectra confirmed the formation of NO dimer and MnTPP(NO) as a result of MnTPP exposition to nitric oxide for 10 min at 100 K under high vacuum. Gradual heating of the sample (up to 130 K) caused a significant change in the spectrum, pointing at Mn^{III}TPP(NO)(ONO) and N_2O as new reaction products [64]. Further studies were carried out to clarify the mechanism of this transformation. Kurtikyan *et al.* investigated the reaction between amorphous Mn^{II}TPP layer and NO in a vacuum chamber at ambient temperature [66]. Under such conditions, two isomeric forms of MnTPP(NO) were distinguished as the reaction products. Recorded IR spectra contain two intense bands at 1739 and 1614 cm^{-1}. This was unexpected because the results of previous studies on analogous reactions involving Co^{II}TPP and Fe^{II}TPP layers showed clearly only a single NO band. It was suggested that double band recorded in the presence of manganese porphyrin reflects the dynamic equilibrium between two isomeric products, differing in the spatial orientation of coordinated NO. The transition is thermally reversible within wide temperature range of 20–293 K. Additionally, it was indicated that decreasing temperature favors the straightening of bent Mn–N–O species. More information was provided by DFT calculations that were carried out for various spin-state complexes with both linear and bent moieties involving N- or O-coordinated nitrosyl ligands. Optimized geometries and calculated vibrational frequencies predicted that the bent Mn–N–O species is a triplet state in contrast to the linear one, which is a singlet ground state (see figure 4) [66].

The issue of the interactions between manganese porphyrins and nitric oxide has become popular on the basis of theoretical methods. Taking advantage of *ab initio* molecular dynamics and the density functional theory, Leung and Medforth examined the $Mn^{II/III}$P–NO

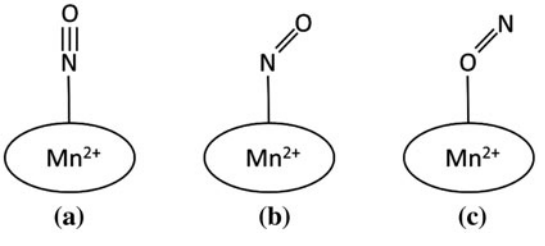


Figure 4. Linear (a), bent (b) and (c) structures of Mn^{II}P(NO) proposed by Kurtikyan *et al.* [66].

Table 2. Structural and energetic parameters for Mn–NO bonds obtained according to X-ray crystallography and DFT calculations [22, 67] determined experimentally for Mn^{II}TPP(NO) and theoretically for relative simplified porphyrin model.

Parameter	X-ray crystallography	DFT		
		PBE	DFT+U	B3LYP
Length of Mn–N_{NO} bond (Å)	1.641	1.617	1.91	1.89
Mn–N–O angle (°)	177.8	173.6	142.2	144.2
Mn(II) out-of-plane displacement (Å)	0.337	0.342	0.277	0.323
Preferred spin configuration (S)		0	1	1
NO binding energy (eV)		2.03	0.93	0.73

systems both in gas phase and in water [67]. One problem the authors had to deal with was prevision of the spin state of manganese porphyrin. In this respect, they provided important guidance regarding the methodology for tetrapyrrole Mn complexes. The practical application of DFT depends on the selection of the approximate exchange correlation functionals. The authors have shown that both types of used functionals, hybrid (B3LYP) and nonhybrid (such as PBE), may not be sufficient to accomplish this task [68, 69]. Despite B3LYP properly anticipating the high spin of a ground state of Mn^{II}P, its implementation is more expensive when applying periodic boundary requirements to condensed phase (liquid or metal surface). To avoid these problems, the modified DFT method involving screened Coulomb term, which increases repulsion between electrons in low pair of not completely filled d-electron orbital (so called DFT+U), was applied for manganese 3d electrons [70–72]. In all computations, manganese 3d orbitals were expanded on screened column '*U*' ($U = 4.2$) and exchange terms '*J*' ($J = 1.0$ eV). The reported values were selected to recreate high-spin/intermediate spin splittings for Mn^{II}P predicted by the B3LYP functional as well as the high spin for Mn^{III}P recognized experimentally. Nonhybrid functionals, such as PBE, were used to predict the spin state, bond lengths, and angles in Mn^{II}P(NO). All obtained values are in agreement with the X-ray structure determined for Mn^{II}TPP(NO) and several other manganese porphyrins (see table 2).

Moreover, PBE predictions demonstrated that the porphyrin ring is distorted and Mn(II) is displaced from the planar position. Both hybrid functionals (B3LYP) as well as DFT+U calculations are not fully in line with some experimental results. It applies, *inter alia*, to anticipation that $m = 1$ intermediate spin configuration is more stable than the low spin state [22, 73].

Similarly, Mn^{III}P(NO) system was investigated using PBE, B3LYP, DFT+U, and Gaussian calculations. Since the X-ray structure is, to our best knowledge, still not available for this complex, it remains impossible to evaluate the correctness of theoretical calculations. The latter forecasted that Mn^{III}P(NO) should have a low spin ($m = 1/2$) and short Mn–N_{NO} bond with linear Mn–N–O geometry. PBE predicts low spin structure, but with large Mn–NO binding energy of 1.30 eV. While PBE anticipated that the nitrosyl complex is more beneficial than the aqua complex, the DFT+U calculations showed the opposite result suggesting that NO can be substituted by H_2O in aqueous solutions of manganese(III) porphyrins.

Considerable attention was paid to the stability of the nitrosyl manganese porphyrins in water. AIMD simulations showed that NO dissociation is accompanied by water binding at the opposite side of the macrocycle. All these results demonstrated that none of the DFT or DFT+U functionals is versatile in modeling the NO complexes with metalloporphyrins [74].

The electronic structures, spectra, and binding energy of nitrosyl manganese porphyrins were considered by Jaworska and Lodowski [26]. Their DFT calculations showed that bond lengths, angles, and binding energies are in agreement with data obtained experimentally. In contrast to cobalt porphyrins, the geometry of Mn–N–O is linear. The binding of the nitrosyl ligand can be described as triply bonded Mn–N with one single N–O bond, with negative charge on the oxygen and positive charge on the nitrogen. However, a considerable charge shift to manganese should be expected, resulting from compensation of the energetically unfavorable charge separation inside the nitrosyl ligand by donation from free oxygen pairs. The calculated electronic spectra correlate well with experimental data except for the Soret band of $Mn^{II}P(NO)$, which is assigned with 0.3–0.5 eV higher energy than experimentally obtained data. Further computations by Radoń on NO binding to manganese (II) porphyrins shows that the formation of Mn–NO bond results in the spin state crossing, which is required to associate the low-spin ground state of the nitrosyl complex with the high-spin ground state of the dissociation products (^{6}MnP + ^{2}NO) [27].

Kalmar *et al.* reported the results of the experimental investigations of *in vitro* autoxidation of N-hydroxyurea (HU) catalyzed by Mn^{III}TTEG-2-PyP, a synthetic water soluble manganese(III) porphyrin (figure 5).

It is believed that this complex can mimic the activity of superoxide dismutase (SOD). The mechanism of the reaction was determined from the results of the kinetic studies performed at pH ranging from 9 to 12. The Mn^{III}TTEG-HU adduct was recognized as the first

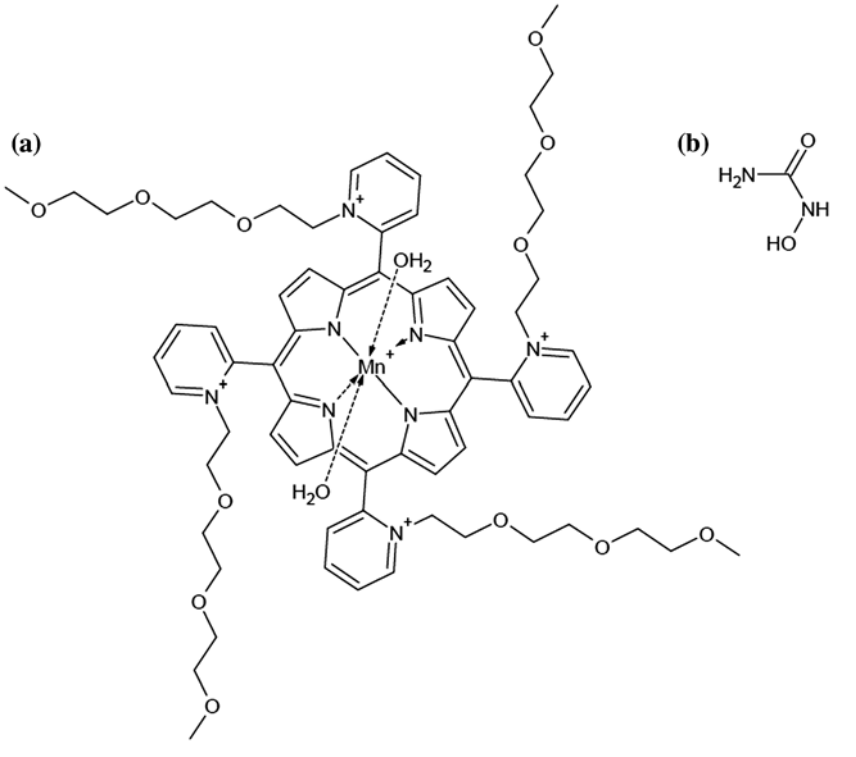


Figure 5. The structures of Mn^{III} TTEG (a) and hydroxyurea (b).

intermediate, which undergoes a rapid autoxidation resulting in the formation of {MnNO} moiety (see equations 19–22):

$$Mn^{III}P + HU \rightarrow (Mn^{III}P - HU) \quad (19)$$

$$2\left(Mn^{III}P - HU\right) + O_2 \rightarrow 2(Mn^{II}P - NO) \quad (20)$$

$$4\left(Mn^{II}P - NO\right) + O_2 \rightarrow 4Mn^{II}P + 4NO_2^- \quad (21)$$

$$Mn^{II}P + O_2 \rightarrow Mn^{III}P \quad (22)$$

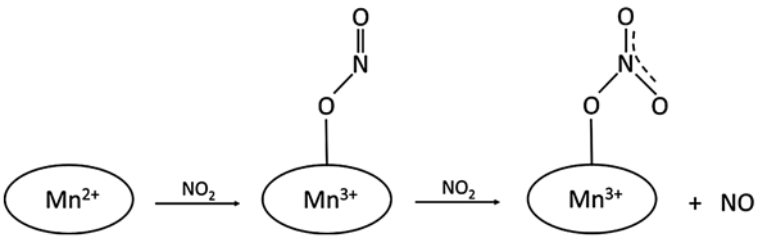
In the next step, Mn^{II}TTEG(NO) is transformed to Mn^{II}TTEG-2-PyP, while NO_2^- is released. In all these reactions, Mn^{III}TTEG acts as a catalyst. All products of reactions were identified and confirmed by ^{17}O-NMR, ESI-MS, IC, and UV–vis spectroscopy. Presented results proved that autoxidation is the alternative reaction leading to the formation of nitrosyl complex, whereas HU can be characterized as a new NO donor.

Nitrite ions

Kurtikyan *et al.* tested interactions between various NO_x and sublimed layers of manganese (II) porphyrin, *viz.* Mn^{II}TPP, in vacuum cryostats. According to the reported results, NO_2^- is ambidentate toward Mn(II), coordinating via oxygen, forming O-nitrito complex (M-ONO^-), or via nitrogen forming N-nitrito ("nitro") complex (M-NO_2^-). DFT calculations suggested that the energy of O-nitrito and N-nitrito complexes are comparable; however, the latter occurs more frequently and is quite typical for heme models and proteins [75]. The O-nitrito coordination of manganese porphyrins is quite unique, as only two five-coordinate Mn^{III}TPP(ONO) and six-coordinate Mn^{III}Mb(ONO) are known prior to Kurtikyan's work. The authors proposed sublimed porous layers of Mn^{III}TPP(ONO^-) as synthetic precursors of six-coordinate manganese complexes including different coordination modes of the nitrite ligands (i.e. Mn^{III}TPP(ONO^-)(NO_2^-)).

Due to the high sensitivity of manganese(II) porphyrins for O_2, the sublimed layers were prepared using more stable five-coordinate MnTPP(pip) and MnTPP(py) complexes. In order to produce the low-temperature sublimate, the sample was heated under vacuum ($p = 3 \times 10^{-5}$ Torr) to 470 K in the Knudsen cell forcing dissociation of the axial ligand. Subsequently, liquid nitrogen was poured into the cryostat and the Knudsen cell was heated to 510 K. At this temperature, Mn(TPP) sublimed onto the surface of the low-temperature substrate, which was KBr or CaF_2. It has been shown that the reaction between NO_2 gas and amorphous layers of Mn(TPP) pass through two different stages. Applying low pressure of NO_2 and short contact time, the reaction leads to the formation of five-coordinate O-nitrito complex, Mn^{III}TPP(ONO). Under elevated NO_2 pressure, it results in the formation of Mn^{III}TPP(NO_2) (see scheme 4). Both reaction products were identified and confirmed by electronic absorption spectra and FTIR spectroscopy.

The authors considered two possible pathways of the O-nitrito complex conversion to the O-nitrato complex. The first mechanism would involve oxygen transfer from free NO_2 to the nitrogen in Mn–O–N=O. The alternative scenario would engage the attack of NO_2 on coordinated oxygen to give Mn(η^1-ONO_2) accompanied by the displacement of NO molecule [75].



Scheme 4. Postulated mechanism of NO_2 activation on Mn^{II}(TPP) [79].

It should be emphasized that the formation of stable manganese complexes in their O-binding mode is unique, especially when compared with analogous complexes of iron and cobalt. The manganese porphyrins with NO_x ligands can, however, undergo linkage isomerism as highlighted by Xu [46] and previously announced by Hoshino [47]. The N-binding species, Mn(TPP)(NO_2), can appear as an intermediate in Mn^{III}(TPP)(ONO) recovery after its photoinduced dissociation in degassed toluene [46, 47].

Nitroxyl

Marti *et al.* investigated the effect of the manganese(III) porphyrin's charge on reactivity toward the nitroxyl donors. For this purpose, two selected macrocyclic Mn(III) complexes, *viz.* the cationic *meso*-tetrakis(N-ethylpyridinium-2-yl)porphyrin, (Mn^{III}TEPyP) and anionic *meso*-tetrakis(4-sulfonatophenyl)porphyrin, (Mn^{III}TPPS) were treated with AS and TSHA in aqueous solutions under argon in two phosphate buffers (pH = 7 and 10; see figure 6).

They found that the reaction between cationic Mn^{III}TEPyP and AS is completed in less than 1 min and leads to Mn^{II}TEPyP(NO), as indicated by a 33-nm shift in the Soret band in the UV–vis spectrum. Such product cannot be obtained when AS is replaced by the donor of nitric oxide, such as sodium nitroprusside or S-nitroso-N-acetylpenicillamine. To achieve the same product, the reaction with NO donor must be assisted by ascorbic acid, sodium dithionite, or some other reducing agent [59]. This requirement was previously indicated by Spasojevic *et al.*, who showed that reductive nitrosylation of cationic Mn(III) porphyrins is very slow when using NO gas in the presence of the reductant [76]. The mechanisms of the reductive nitrosylation of manganese(III) porphyrins are presented in scheme 5.

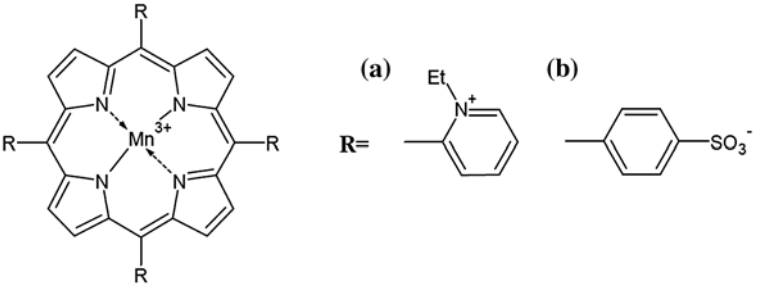
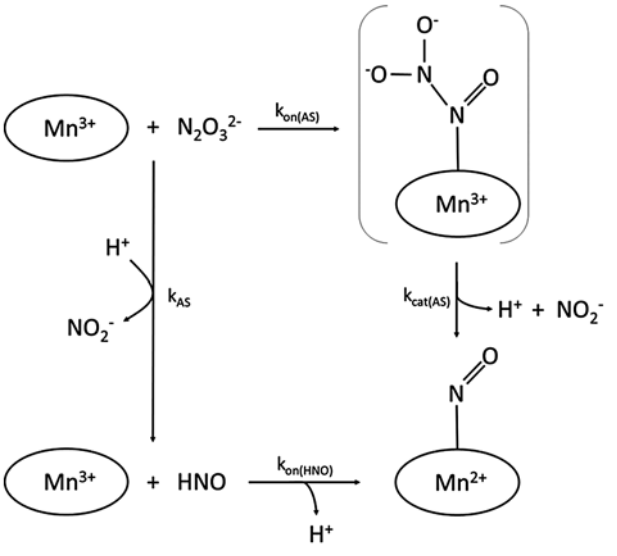


Figure 6. The structures of Mn^{III}TEPyP (a) and Mn^{III}TPPS (b).



Scheme 5. The catalytic activity of manganese(III) porphyrins toward nitroxyl donors-a mechanism postulated by Marti *et al.* [59].

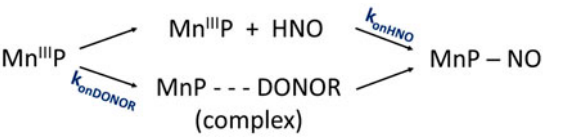
Kinetic studies on the reductive nitrosylation of Mn^{III}TEPyP with AS showed that the backward reaction is negligible under applied reaction conditions. It is somewhat different in the case of other HNO donors, *viz.* TSHA, whose reaction with manganese(III) porphyrin is reversible to some extent at neutral pH. Moreover, the HNO donor decomposes spontaneously at pH 7 with a half-life of 15 min, whereas the overall porphyrin-assisted reaction is approximately 1000 times faster, as its first-order rate constant ($k_{cat(AS)}$; see scheme 5) is $5 \times 10^{-}\ s^{-1}$ [6]. This result points at the catalytic effect of the macrocyclic compound in HNO release from Angeli's salt [6, 59]. Such activity is retained when changing to alkaline conditions (pH 10), under which AS occurs in its stable anionic form of $N_2O_3^{2-}$.

Analogous reactions were carried out in the presence of dioxygen. Although the formation of Mn^{II}TEPyP(NO) was confirmed, the aerobic conditions proved to be not preferable, as O_2 facilitates decomposition of the product.

In order to get deeper insight into the mechanism of Mn^{II}TEPyP(NO) formation, DFT calculations and simulations were performed using SIESTA code, which is recognized as suitable for biomolecules and heme models [77]. All computations were approximated to manganese(III) porphyrin in vacuum. The obtained results indicated that the only intermediate involving the nitroxyl donor linked to the Mn(III) center through oxygen is energetically unprivileged and therefore cannot be observed in the course of the reaction.

Similar investigations were performed using the complex of Mn(III) with anionic TPPS ligand. The reductive nitrosylation of this metalloporphyrin was observed only when a large excess of AS was applied. Moreover, the reaction yield is less than 2% at pH 10. The kinetic analysis showed that $\tau_{1/2}$ for the reaction at pH 7 is around 2 h, several times bigger than the respective value for the spontaneous decomposition of AS, thus pointing at the lack of catalytic activity of Mn^{III}TPPS toward the nitroxyl donor [59].

Recently, Doctorovich and co-workers published the report on their studies of AS and TSHA reactions with nine different manganese(III) porphyrins, both cationic and anionic.



Scheme 6. Suggested pathways of $Mn^{III}P$ reaction with HNO donors (according to [8]).

Their results are in fundamental agreement with the work of Marti. They lead to a conclusion that negatively charged manganese(III) porphyrins react at pH 7 with Angeli's salt and at pH 10 with the Piloty's acid, only in large excess of HNO donor. The reactions are slow and do not reveal linear relationship between the rate and the HNO donor concentration. This finding stands for that in the initial step, the nitroxyl is generated in the reaction mixture and subsequently it binds Mn(III) at its vacant coordination site. The reductive nitrosylation is considerably faster in the case of the cationic manganese(III) porphyrins. The reaction is first order with respect to nitroxyl donor concentration. Hence, its direct interaction with the metalloporphyrin is expected to take place prior to HNO release. The latter step is strongly facilitated when occurs from such an arrangement (see scheme 6).

On the basis of electrochemical measurements, the authors managed to determine the boundary redox potentials of the manganese(III) porphyrin for its catalytic activity toward the nitroxyl donors. They postulated that the metalloporphyrins with $E°_{Mn(III)|Mn(II)} > 100$ mV *versus* NHE are capable of accelerating the HNO release. In contrast, the negative redox potentials (<−160 mV) are characteristic for manganese(III) porphyrins that can take advantage only from free HNO species [78].

Conclusion

In this brief review, we have attempted to highlight the latest trends in the study of the interactions between the model tetrapyrrole complexes of cobalt and manganese and nitric oxide species. Presented achievements cover a variety of aspects, providing information, among other things, on the reaction mechanisms, structural details, activity of model biological enzyme systems, and the accuracy of the newly developed electrochemical analytical methods. Taking into account any additional factors, which are to be introduced by the transfer of these results to natural systems, such as vitamin B12, or functional catalyst systems, it becomes clear how wide the field of action is. Awareness of this makes us even more convinced that the NO molecule is fascinating despite the passage of nearly thirty years since the discovery of its importance for the functioning of the human body.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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