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Preface for the Inorganic Chemistry Forum: The Coordination Chemistry of Nitric Oxide and Its Significance for Metabolism, Signaling, and Toxicity in Biology

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Since the discovery that the toxic molecule nitric oxide (nitrogen monoxide, NO) is synthesized in mammals, including humans, for the purpose of signaling and immune defense in the 1980s,[1] research on the physiologically important transformations of NO and its oxidized and reduced relatives, generally termed NO_x, has exploded. These include, in particular, nitrite (NO_2^-), peroxynitrite ($ONOO^-$), nitrogen dioxide (NO_2), and dinitrogen trioxide (N_2O_3) on the oxidized side and nitroxyl (NO^-) and its acid HNO, hyponitrite ($N_2O_2^{2-}$), and nitrosothiols (RS-NO) on the reduced side. All these species along with NO itself have been invoked in various physiologically important processes, either as signaling agents (HNO, NO_2^-, RS-NO), as intermediates of the transformations of NO (NO_2^-, $ONOO^-$, NO_2, $N_2O_2^{2-}$), as mobile NO "transporters" (N_2O_3, RS-NO), or as byproducts formed under oxidative stress (NO_2, $ONOO^-$). In fact, NO is a double-edged sword in biological systems. NO is suitable as a signaling molecule, because it is a freely diffusible radical with a relatively long lifetime *in vivo* and an extraordinarily high affinity to ferrous heme, which makes it detectable by the mammalian NO receptor, soluble guanylate cyclase (sGC), in the process of cardiovascular or neuronal signaling in subnanomolar concentrations. On the other hand, the immune system (for example, macrophages) produces up to micromolar concentrations of NO, which, in chronic inflammations, under septic shock, or in other disease states like diabetes, becomes detrimental. NO itself is toxic (*vide infra*) and, in the presence dioxygen (O_2) or superoxide (O_2^-), can further be oxidized to NO_2 or $ONOO^-$, which are very strong oxidizing agents that damage DNA, proteins, cell walls, and so forth. It is therefore very important for the well-being of mammals that the concentration of free NO is tightly regulated, and the mechanisms for these processes are currently heavily investigated.[2−4]

Many of the important biological functions of NO, including its biosynthesis, detection (in signaling), transport, and detoxification are mediated by heme proteins. Additional important metal sites involved in NO function and/or toxicity are found in copper and iron−sulfur proteins. This *Inorganic Chemistry* Forum is therefore focused on the fundamental coordination chemistry of NO with transition metal centers, characteristic of these proteins, in particular (but not limited to) heme proteins and corresponding model complexes. This Forum comprises 10 articles that reflect the breadth of current research conducted in this area, reaching from fundamental structural and spectroscopic studies of transition metal NO and NO_x complexes all the way to the imaging of NO *in vivo* and the biological chemistry of its relative, HNO.

Nitric oxide is a fascinating diatomic radical in the context of coordination chemistry due to its notorious noninnocent behavior in transition metal complexes. For example, NO adducts of ferrous iron complexes could have electronic structures that vary all the way from an Fe(I)-NO^+ to an Fe(III)-NO^- extreme with the Fe(II)-NO(radical) case being intermediate. This distinction is significant, as it can be expected that NO^+, NO(radical), and NO^- will show very different reactivities. However, characterizing the exact electronic structures of transition metal nitrosyls has been difficult, which led to the establishment of the famous Enemark-Feltham notation that allows for a general classification of transition metal nitrosyls without the need to define an exact electronic structure.[5] Another complication of the coordination chemistry of NO is that many transition metal complexes catalyze the oxidative or reductive transformation of NO into other NO_x species, most prominently nitrite, nitrate (NO_3^-), hyponitrite, nitrous oxide (N_2O), or HNO. A Latimer diagram that presents redox potentials for important nitrogen species is shown in Figure 1. To this date, nitrosyl complexes have been prepared for the majority of transition metal ions.[6]

The kinetics of NO and NO_x binding to ferrous and ferric heme sites, including the discussion of the relevant activation parameters, is presented in Peter Ford's (University of California at Santa Barbara) contribution. This also includes an overview of the interaction of NO with ferric hemes in the presence of base, leading to reductive nitrosylation and

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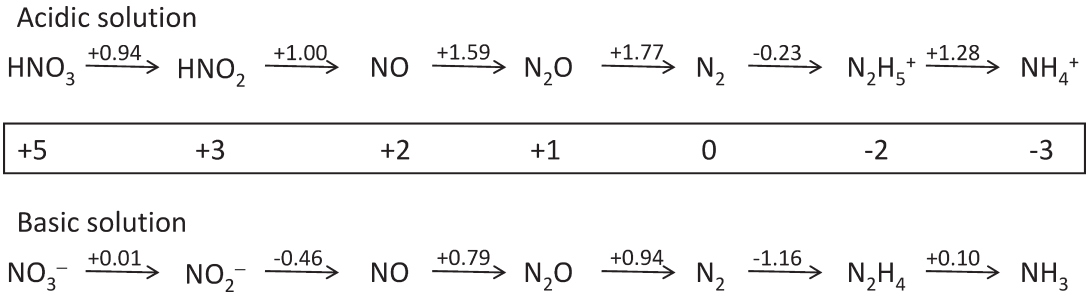

Figure 1. Latimer diagram of nitrogen oxides in acidic and basic solution.

generation of ferrous heme-nitrosyls. Structural aspects of the latter complexes are highlighted in the paper by Robert Scheidt (University of Notre Dame) and Timothy Sage (Northeastern University) and their co-workers for corresponding model complexes, whereas the article by George Richter-Addo (University of Oklahoma) and co-workers presents structures of ferrous NO and ferric NO_2^- adducts of hemoglobin (Hb) and myoglobin (Mb). The basic spectroscopic properties of ferrous and ferric heme-nitrosyls are summarized in the paper by Nicolai Lehnert (University of Michigan) and co-workers. On the basis of these data and in correlation with density functional theory (DFT) calculations, detailed electronic-structural descriptions of heme-nitrosyls, in particular as a function of the *trans* ligand to NO, have been derived and are also reviewed in Lehnert's paper. How these electronic properties of ferrous and ferric heme-nitrosyls relate to their function in biological systems is further discussed. The vibrational dynamics of ferrous nitrosyl porphyrins are further elucidated in the contribution by Scheidt and Sage. Finally, the linkage isomers of NO, usually generated photochemically at low temperature, are described in the contribution by Richter-Addo.

The biologically relevant transformations of NO can be subdivided into oxidative and reductive processes. NO dioxygenation (NOD), that is, the reaction of oxy-Hb/Mb with NO, is of central importance for the control of the concentration of free NO in blood and tissue. Kinetic and mechanistic data of this reaction and related processes are presented in the contribution by John Groves (Princeton University) and his co-worker. This reaction generates nitrate via a proposed peroxynitrite intermediate. The article by Groves focuses on the biological chemistry of peroxynitrite, the exact mechanism of its generation, and the potential cytotoxic roles of this strongly oxidizing species, which is also generated by activated macrophages. Further insight into NOD chemistry, in particular with respect to the potential role of copper proteins for peroxynitrite generation, is provided in the contribution by Kenneth Karlin (Johns Hopkins University) and co-workers. The physiologically available nitrite ion can also interact with deoxy- or met-Hb/Mb. As discussed in Ford's paper, deoxy-Hb/Mb can reduce nitrite to NO, analogous to heme cd_1 nitrite reductase (NIR) in denitrifying bacteria. This reaction constitutes an alternative pathway for the generation of NO *in vivo* besides NO synthase.[7,8] On the other hand, ferric hemes can activate nitrite, for example, for O-atom transfer or potentially the formation of N_2O_3 by reaction with NO, as presented in Ford's contribution. Nitrite binding to met-Hb is further investigated in detail in the original research paper by David Singel (Montana State University) and Jonathan Stamler (Duke University) and their co-worker.

NO reductases (NOR) catalyze the important reduction of NO to nitrous oxide (N_2O), which is another major pathway (besides NOD) for the detoxification of NO in biology. This reaction is also observed for a number of cytochrome c oxidases (CCOs). The contribution by Karlin provides a concise summary of this area, including model complex studies by the authors' and other laboratories. In this reaction, a dinuclear (heme/nonheme for NORs and heme/copper for CCOs), bridging hyponitrite intermediate has been proposed. The articles by Richter-Addo and Karlin further review the available hyponitrite complexes with respect to their structures, spectroscopic properties, and reactivities and how this relates to the proposed NO reduction mechanisms of NORs and CCOs.

In mammals, the primary NO receptor is soluble guanylate cyclase as mentioned above.[9] Possible mechanisms of sGC activation are discussed in Ford's article. In addition, the paper by Lehnert shows, based on experimentally calibrated electronic structure descriptions, how the σ *trans* effect of NO labilizes the proximal Fe(II)-His bond, leading to the formation of a five-coordinate ferrous heme-nitrosyl complex as the first step in the activation of sGC. The interaction of sGC with HNO is also discussed (*vide infra*). Besides the role of NO in cardiovascular and neuronal signaling mediated by sGC, recent results show that certain transcription factors also contain heme-based gas sensor subunits. In particular, Per-Arnt-Sim (PAS) domains are known to bind cofactors and serve as sensors that monitor environmental changes, for example, electrochemical potential (redox-sensitive) or gas concentrations. Combined with a DNA-binding module, these PAS proteins function as transcription factors that are activated by changes in the PAS domain. The original research paper by Kenton Rodgers (North Dakota State University) and co-workers presents the spectroscopic characterization of the PAS-A sensor domain of the mammalian circadian protein CLOCK, including binding studies with the diatomics CO and NO. The results show that NO could be the target for PAS-based sensing in CLOCK. Another interesting aspect is the sensing of hypoxic conditions by red blood cells, leading to the release of NO to induce vasodilation and, hence, an increase in blood flow to hypoxic tissue. This aspect is addressed in Ford's and Singel's and Stamler's contributions. Finally, the paper by Patrick Farmer (Baylor University) and Katrina Miranda (University of Arizona) and co-workers describes the interaction of HNO with heme

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proteins, including the potential activation of sGC by this one-electron reduced NO relative, and its reaction with thiols. This paper also summarizes the known properties of the HNO adducts of deoxy-Mb and other heme proteins and of a corresponding nitroprusside-based model complex.

As mentioned above, NO is a highly toxic molecule, for example, due to its ability to inhibit heme proteins. The contribution by Stephen Lippard (Massachusetts Institute of Technology) and co-workers highlights another important aspect of NO toxicity: the degradation of iron−sulfur clusters, leading to the generation of mononuclear dinitrosyl iron complexes (DNICs). Here, biomimetic approaches are discussed that allow for a detailed analysis of the mechanisms of the iron−sulfur cluster breakdown. The detrimental oxidative chemistry of peroxynitrite, generated from the reaction of NO with free or heme-bound superoxide, and of NO_2 is described in Groves' article. This paper also reviews the ability of iron and manganese porphyrins to act as highly effective (metal-based) drugs for the destruction of peroxynitrite *in vivo*, which treats a number of corresponding pathological conditions, for example, diabetic neuropathy. A final highlight of the Forum is the application of copper-based fluorescent agents for the imaging of NO in live cells, as described in Lippard's article. These sensors constitute the necessary tool to study the functions of NO in the brain in response to different external stimuli. This includes the exact signal transduction mechanisms in neurons and the underlying causes of NO-related pathologies like amyotrophic lateral sclerosis (ALS). Application of these sensors to monitor NO production in pathogens like *Bacillus anthracis* is also demonstrated.

In summary, this *Inorganic Chemistry* Forum on Nitric Oxide summarizes the most recent findings with respect to the coordination chemistry of NO and corresponding NO_x derivatives and highlights the biological significance of these species. Since the biological chemistry of these compounds is mostly mediated by transition metal ions, the basic understanding of their coordination chemistry is key to arrive at a detailed picture of their generation, transformation, regulation, and detoxification in biological systems.