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Forum Article

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Preface for Small-Molecule Activation: From Biological Principles to Energy Applications. Part 2: Small Molecules Related to the Global Nitrogen Cycle

Nicolai Lehnert*,† and Jonas C. Peters*,‡

†Department of Chemistry, The University of Michigan, 930 N. University, Ann Arbor, Michigan 48109, United States

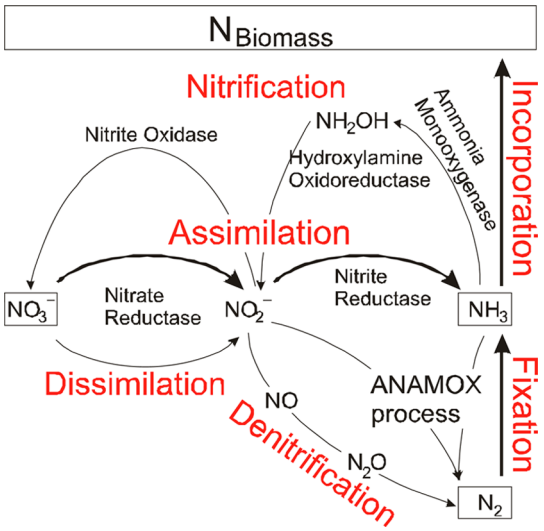
‡Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

The nitrogen cycle is among the most significant biogeochemical cycles on Earth because nitrogen is an essential nutrient for all forms of life.[1] The largest contributor of nitrogen in the cycle is atmospheric dinitrogen (N_2), which is generally unavailable to plants by direct assimilation. Hence, access to fixed forms of nitrogen constitutes in many cases the most limiting factor for plant growth. This is in sharp contrast to carbon, which is easily taken up by plants from the atmosphere by fixing gaseous carbon dioxide (CO_2). The availability of nitrogen (and water) hence limits the ability to produce sufficient crops to feed our planet's growing population.

The second most important reservoir for nitrogen is nitrate (NO_3^-) in the form of inorganic minerals and fertilizers; this is the form of nitrogen that is easily assimilated by plants and microbes that live in soil and water. The key role of the nitrogen cycle for food and biofuel production in agriculture, pollution, and atmospheric chemistry is widely recognized. The National Science Foundation recently underscored this recognition by launching the "Innovations at the Nexus of Food, Energy, and Water Systems (INFEWS)" program. The nitrogen cycle is a key component at the heart of this new initiative.[2]

Scheme 1 summarizes the key chemical processes of the nitrogen cycle in soil and water.[3] The major **reductive nitrogen pathways** utilized by organisms are nitrogen fixation, assimilation, and denitrification. The key **oxidative process** that counters these reductive processes is bacterial nitrification, which leads to the depletion of free ammonia from the soil. Because all of these processes are closely intertwined, a better understanding of the dynamic interaction between these reductive and oxidative pathways is required to optimize fertilization, plant growth, and crop production, while at the same time depressing nitrogen loss from the soil.

Scheme 1. Overview of the Most Important Chemical Processes in Soil and Water in the Nitrogen Cycle



This *Inorganic Chemistry* Forum highlights recent contributions in the area of chemistry and biochemistry that further our understanding of the mechanisms of important enzymes in the nitrogen cycle, especially nitrogenases, nitrite and NO reductases (NORs), and ammonia monooxygenases. In addition, many contributions describe efforts to create synthetic catalysts that can mimic important reactions in the nitrogen cycle, not only to clarify important mechanistic questions but also to generate synthetic catalysts that could someday form the basis for industrial applications in nitrogen fixation, NO_x degradation, and water purification.

CONTRIBUTIONS IN THE AREA OF NITROGEN FIXATION

Nitrogen fixation is the process by which atmospheric nitrogen is converted to a bioavailable form; it is essential to sustaining all life on this planet.[4] Global population growth, which exploded in the 20th century, drove the widespread deployment of industrial fertilizer production (the Haber−Bosch process), a remarkable technological achievement that enables the global agriculture industry to feed billions of people each day. The scale of this industrial process is daunting: approximately 140 million metric tons of ammonia are produced annually, accounting for about half of all nitrogen fixed globally and significant global energy (∼2%) and natural gas (∼4%) consumption.[4a] Environmental consequences from fertilizer production and use are severe,[5] including heavy CO_2 emissions, surface and groundwater pollution from runoff, eutrophication of freshwater systems, and massive killing of aquatic organisms in coastal regions that comprise so-called dead zones due to depleted oxygen. Given the importance of nitrogen fixation to global food production, developing environmentally sustainable ways to make fertilizer and deploy

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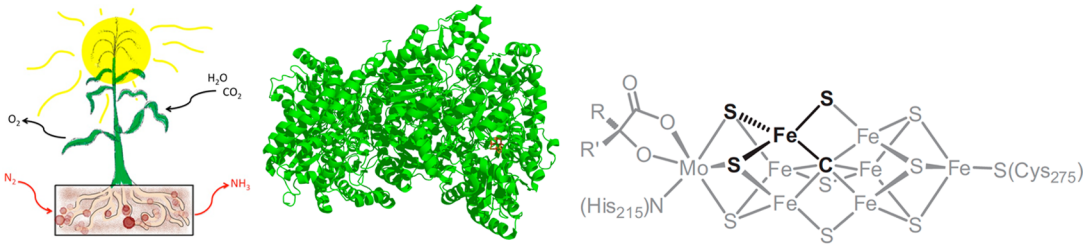

$$N_2 + 8\,H^+ + 16\,MgATP + 8\,e^- \rightarrow 2\,NH_3 + H_2 + 16\,MgADP + 16\,P_i$$

Figure 1. (left) Depiction of the nitrogen-fixing bacteria within the root nodules (brown circles) of a plant. (middle) X-ray crystal structure of the MoFe-protein of FeMo-nitrogenase, highlighting (right) the catalytic FeMoco.

it is a worthy goal. Toward this end, inorganic chemists continue to seek answers to fundamental questions, in particular with respect to (1) the mechanistic understanding of biological nitrogen fixation at the atomic level and (2) the design of more efficient synthetic catalysts and sustainable fertilizer production technologies.

In contrast to the Haber–Bosch process, which operates between 150 and 350 atm of pressure and 350 and 600 °C,[4a] certain microorganisms can fix nitrogen (N_2) under ambient conditions, using extensive ATP hydrolysis to power the reaction (Figure 1). Housed within any given nitrogen-fixing organism are a conserved set of proteins—the nitrogenase enzymes—that bind and convert N_2 to NH_3. Nitrogenases require iron as an essential transition metal, and can—but are not required to—contain molybdenum (MoFe-nitrogenase) or vanadium (VFe-nitrogenase).[6] MoFe-nitrogenase has been best studied and has been structurally characterized in its resting state.[7] This enzyme consists of an Fe-protein that delivers reducing equivalents and a MoFe-protein. The latter contains the unique M-cluster ($MoFe_7S_9C$-homocitrate), an inorganic FeMo cofactor (FeMoco) that mediates the catalytic bond-breaking and -making steps (Figure 1). Inorganic chemists have long puzzled over how this cofactor works[8] and, in collaboration with biochemists, biologists, and spectroscopists, have tried to solve this conundrum for more than 4 decades.[6,9]

The synthetic modeling community placed an early emphasis on molybdenum model systems because MoFe-nitrogenase was the first to be purified and because low-valent inorganic molybdenum complexes were known to bind N_2 and facilitate its protonation to release NH_3 in near-quantitative yield.[8a,10] Yet, it was not until just over a decade ago that a comparatively well-defined molecular catalyst, featuring molybdenum as the active metal site, was shown to facilitate a modest degree of N_2 reduction catalysis under ambient conditions.[11]

More recently, biochemical and spectroscopic evidence has shifted the focus to iron as the biologically active N_2-binding site within the cofactor.[9a] This emphasis is perhaps not surprising given that iron is the only transition element known to be essential to nitrogenase function.[6b,10] Revision of the FeMoco structure to include an interstitial light atom at its center[7b] that has now been firmly assigned as a carbide (C^{4-})[7a,12] has helped to facilitate designs for iron model studies.[11d,13] The remaining prima facia challenge facing our community is to learn, unambiguously, how nature fixates N_2. Such knowledge will facilitate the future design of synthetic nitrogen-fixing catalysts that may ultimately offer a complementary technology to the Haber–Bosch process.

This Forum issue features selected articles related to the design of comparatively well-defined transition-metal systems for the activation and functionalization of N_2. It opens with a timely overview of catalytic systems for nitrogen fixation emphasizing molecular catalysts, where the principles of catalysis may be probed most readily. In this review, Nishibayashi provides a brief summary of the decades of work undertaken in the 20th century to prepare and study well-defined inorganic complexes capable of binding, activating, and mediating the conversion of N_2 to NH_3.[14] He then moves on to discuss the latest developments in functional catalysts for N_2-to-NH_3 conversion, where the most promising in-roads have been made with the biologically relevant metals molybdenum and iron. Catalytic N_2 functionalizations to products such as $N(SiMe_3)_3$ have also been discovered for these metals (and also cobalt) in recent years, as discussed.

Chatt and Hidai's early work with Mo–N_2 complexes in the context of N_2 protonation/derivatization and NH_3 release[8a,15] provide the conceptual framework for future catalytic studies using molybdenum. The first bona fide molecular catalyst that converted N_2 to NH_3 was discovered by Yandulov and Schrock in 2003 and employed molybdenum as the active metal.[11a] This tris(amido)amine "[$Mo^{HIPT}N_3N$]" molybdenum system continues to be a subject of study because it is thought to be mechanistically well-defined and many experimental parameters can be explored. It is in this context that Neese and Tuczek contribute to this Forum, undertaking detailed theoretical studies using modern density functional theory methods regarding the free reaction enthalpy profile by which [$Mo^{HIPT}N_3N$] mediates N_2-to-NH_3 conversion.[16] While a complete theoretical picture for the energetics of this Schrock cycle emerges in this study, the energetics of the specific protonation steps remain uncertain and provide motivation for the application of improved theoretical methods.

Iron is the only transition metal ubiquitous to all nitrogenases, and its likely role as the site of N_2 binding and reduction at the active-site cofactors of nitrogenases is gaining appreciation. While the discovery of molecular iron catalysts that mediate N_2-to-NH_3 conversion has shifted the thinking that molybdenum may be special/unique in its ability to do so,[8b,d] the elucidation of molecular transition-metal catalysts not known to be biologically active for this transformation remains a challenge. It is in this context that Peters and co-workers report in this Forum on comparative reactivity studies of Co–N_2 and Fe–N_2 complexes that exhibit modest competence as catalysts for N_2-to-NH_3 conversion at low temperatures in an ethereal solution.[17] The structure/function studies described provide insight into some of the factors that are important in observing productive N_2-to-NH_3 functionalization and underscore that a metal that is not biologically

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relevant, in this case cobalt, can, nonetheless, afford a viable molecular catalyst.

Progress toward the discovery of nitrogen-fixing catalysts requires the introduction of new catalyst architectures in addition to exploring familiar architectures with different active-site metals. Lu and Gagliardi's contribution in this Forum describes an elegant combined approach wherein a binucleating scaffold enables the preparation of trigonal-bipyramidal Co−N_2 complexes that include a second metal (e.g., aluminum, vanadium, chromium, or cobalt) at an axial site opposite the N_2 ligand.[18] These scaffolds offer the possibility of systematically tuning the electronic structure at the Co−N_2 subunit through variation of the supporting metal. It remains to be determined how such variation may alter the reactivity profiles of the activated N_2 ligand, but the observed ranges of redox potentials and ν(NN) stretching frequencies as the supporting metal is varied suggest that fascinating reactivity differences may be uncovered in the future.

Bimetallic complexes for N_2 activation are well-known and in many instances are thermodynamically favored relative to their monomeric, terminally bound counterparts. Such bridged systems often lead to significant activation of the N_2 unit, although this does not typically correlate with more desirable reactivity patterns in terms of N_2 functionalization.[19] In this Forum, Fryzuk and Masuda introduce a new and highly activated $Fe_2(\mu\text{-}N_2)$ system supported by a strongly electron-donating iminophosphorane ligand.[20] This system is of fundamental interest and has been thoroughly characterized, showing that, akin to the original $[Fe(nacnac^{tBu})]_2(\mu\text{-}N_2)$,[15b] it can be best described by two high-spin iron(II) centers and an N_2^{2-} ligand in the bridge.

Recent attention also has focused on the preparation of trimetallic scaffolds that can mediate nitrogen reduction.[21] The cluster nature of the FeMoco of MoFe-nitrogenase provides ample motivation for preparing such systems, wherein cooperative reactivity can, in principle, enable multielectron reductive transformations with transition-metal centers that need only engage in one-electron redox steps. Murray has pursued this idea with an elegant ligand scaffold that ties three β-diketiminato ligands into a 3-fold symmetric ligand cage that houses three iron centers.[21] The study published by Murray in this Forum issue describes a nitride (N^{3-}) stabilized by three iron centers. While the nitride is delivered via an azide source, mechanistic context is drawn with respect to the previous N_2 reductive study that led to NH^{2-} bridging subunits on this scaffold.[22]

Finally, metrics for N−H bond strengths and pKa's are fundamental to nitrogen fixation catalyst design and mechanistic considerations. Using a square planar Ir scaffold, Schneider and de Bruin contribute a study to this Forum that focuses on proton, electron, and H-atom transfer steps to a TM-coordinated NH_x ligand (X = 0 − 3).[42] Their study is interesting in the context of terminal nitride reduction to NH_3 and shows that a terminal Ir(NH) species features a weak N−H bond that is prone to facile disproportionation.

CONTRIBUTIONS IN THE AREA OF NO_X INTERCONVERSIONS

Compared to the extensive studies on nitrogenases and corresponding model systems, biochemical, spectroscopic, and synthetic modeling studies on other enzymes relevant to the nitrogen cycle are less developed. Our mechanistic understanding of these enzymes is correspondingly less advanced. Yet, these other processes in the nitrogen cycle, as shown in Scheme 1, are of critical importance because they play key roles for the actual nitrogen uptake and incorporation into biomass by plants (assimilation). They also determine to a large degree the fate of nitrogen fertilizers once deployed on agricultural soil. In fact, the vast majority (~80%) of total nitrogen used to produce food is lost to the environment,[23] in large part due to the fact that crops recover only 30−50% of nitrogen supplied as fertilizer![24]

Nitrogen assimilation in plants is a complex process that involves nitrate transporters/receptors that sense and uptake nitrogen from the soil, as well as a set of enzymes involved in nitrate reduction and assimilation into organic forms. In order for NO_3^- to be incorporated into biomass, reduction to NH_3 by nitrogen-assimilating enzymes is necessary. These enzymes facilitate the reduction of NO_3^- to NH_3 via a process that involves the intermediate production of nitrite (NO_2^-), as shown in Scheme 1. The key step in the assimilation process is the direct, six-electron reduction of nitrite to ammonia, which is catalyzed by assimilatory nitrite reductases. These unique enzymes contain a siroheme in the active site that is directly linked to a [4Fe4S] cluster.[25] Despite the central importance of these enzymes for plant growth and their unique active-site structure, the mechanism of these enzymes on a molecular level remains largely unknown. These enzymes are also challenging targets for bioinorganic modeling studies because of the lability of the sulfide/thiolate bridge between the heme and the [4Fe4S] cluster in synthetic model systems that lack the stabilizing protein matrix.[26] It is worth noting that nitrogen assimilation is *the* most energy-intensive biochemical pathway in plants, requiring the equivalent of 12 ATPs to assimilate one molecule of nitrate into glutamine.[27]

The inefficient nitrogen use by crop plants, as described above, has resulted in the overfertilization of agricultural soils, which, in turn, results in the large-scale transformation of the nitrogen fertilizer into nitrous oxide; N_2O is now the third most important greenhouse gas. In fact, the 100-year global warming potential of N_2O is 300 times larger than that of CO_2. This transformation is mediated by denitrifying bacteria and fungi that live in soil and seawater. These microbes use nitrate as an alternative electron acceptor for anaerobic respiration. Dissimilatory denitrification is a complex process that requires a large number of enzymes in order to facilitate the stepwise reduction of NO_3^- to dinitrogen (bacteria) and nitrous oxide (fungi). In the former case, a large percentage of N_2O is also lost to the atmosphere because of the fact that N_2O is a very weak ligand to transition metals.[28] Hence, dissimilatory denitrification is largely responsible for the breakdown of inorganic fertilizers in soil and seawater, leading to the large-scale generation of the greenhouse gas nitrous oxide.

Each step in dissimilatory denitrification is catalyzed by different enzyme families, as indicated in Scheme 1. Of particular interest in this process are NORs,[29] which are directly responsible for N_2O generation. In denitrifying bacteria, these enzymes are evolutionarily related to cytochrome *c* oxidases and contain a unique heme/nonheme iron active site.[30] Curiously, the fungal enzyme is completely unrelated and belongs to the cytochrome P450 enzyme family.[31] However, despite many recent efforts in the literature, much work is still required to fully elucidate the molecular mechanisms of these enzymes.[32] In particular, the mechanism of NO reduction by bacterial NORs has remained elusive, and

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the role of the nonheme iron center for catalysis has been a matter of intense discussion in the literature.[33]

In 2010, Nicolai Lehnert (University of Michigan) and Robert Scheidt (University of Notre Dame) coedited an *Inorganic Chemistry* Forum on nitric oxide entitled "The Coordination Chemistry of Nitric Oxide and Its Significance for Metabolism, Signaling and Toxicity in Biology". This earlier collection of articles highlights research on NO_x interconversions, with significance for the global nitrogen cycle and the biologically relevant functions of NO and its derivatives.[34] The present Forum extends the previous one by specifically focusing on catalytic processes that interconvert NO_x species, in particular nitrite, NO, N_2O, and HNO, and how this relates to the nitrogen cycle. The paper by Bykov and Neese reviews their recent computational studies on the mechanism of dissimilatory multiheme cytochrome *c* nitrite reductase (ccNIR), which is capable of the direct, six-electron reduction of nitrite to NO.[35] The paper presents a detailed analysis of the molecular mechanism of this important reaction using quantum-chemical calculations. These results not only elucidate the mechanism of ccNIRs but also provide a mechanistic blueprint for other assimilatory nitrite reductases that are of key importance for the assimilation of nitrogen-containing fertilizers by plants as described above. Another important class of dissimilatory enzymes are bacterial and fungal NORs, which are key enzymes in dissimilatory denitrification that are ultimately responsible for the generation and release of the important greenhouse gas N_2O into the atmosphere.[32] The paper by Sage, Lu, and co-workers summarizes their recent efforts to model the heme/nonheme iron active site of bacterial NORs, and to elucidate the detailed molecular mechanism of these enzymes.[36] Here, Lu's group uses an active-site model, designed into the myoglobin (Mb) active site, to explore the reactivity of the heme/nonheme diiron center with NO. A particular focus of the paper is the electronic structure and the possible role of the nonheme iron center for catalysis. Critical intermediates in the reaction mechanism of denitrifying and scavenging NORs are hyponitrite complexes. The paper by Wright and Hayton reviews the structures, spectroscopic and electronic properties, and reactivities of transition-metal hyponitrite complexes, which is of direct mechanistic relevance for NO coupling and N_2O formation in all NORs.[37] The paper by Marti, Doctorovich, and co-workers discusses the conversion of NO into HNO by important antioxidants like phenolates, thiols, ascorbate, Vitamin E, etc.[38] Although HNO has been proposed as a signaling molecule in biological systems, it has for the longest time been unclear if and how HNO could be produced in vivo. These results demonstrate that HNO can be straightforwardly produced by the simple inner-sphere, one-electron reduction of NO.

The contribution by Harrop and co-workers[39] is focused on the reaction of Fe− and Co−NO complexes in the $\{MNO\}^{6/7/8}$ redox states (following the Enemark−Feltham notation, where the exponent corresponds to the number of valence electrons)[40] with thiols. Typical products of these reactions are unstable nitrosothiol complexes (as was first observed for sodium nitroprusside), Roussin's red ester [in the case of dinitrosyl iron complexes (DNICs)], and DNICs in the case of nonheme iron nitroxyl complexes. The biological significance of these reactions is further discussed. Along those lines, the paper by Ivanovic-Burmazovic, Filipovic, and co-workers explores how NO and H_2S, two signaling molecules in mammals, could "cross-talk" and modulate each other's activity.[41] Here, the potential role of perthionitrite ($SSNO^-$) as an important biological source of NO is evaluated. The results presented in this paper show that $SSNO^-$ decomposes readily in the presence of light, water, or acid, with concomitant formation of elemental sulfur and HNO, and, hence, it is unlikely that this species could have a role as a signaling molecule and NO reservoir in mammals. It could, however, play a role for the formation of HSNO and HNO.

We hope you enjoy reading the fine contributions in this second part of the Forum on Small Molecule Activation.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: lehnertn@umich.edu.

*E-mail: jpeters@caltech.edu.

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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