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Ph.D. DISSERTATION DEFENSE

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Title:	Computational Studies of Metal-Mediated Biological Reactions and Interactions for Important Nitrogen-Containing Species
Chairperson:	Dr. Yong Zhang, Department of Chemistry and Chemical Biology, School of Engineering and Sciences
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ABSTRACT

Nitrogen is a fundamental component of biomolecules essential for the structure and function of living organisms. Nitrogen-containing species play critical roles in various scientific, biological, pharmacological, and environmental contexts. Understanding the diverse functions and behaviors of these compounds is crucial in advancing fields ranging from biomedicine to environmental science. This work includes four detailed quantum chemical studies that collectively contribute to our understanding of metal-mediated reactions and interactions involving essential nitrogen-containing species.

As the one-electron-reduced derivative of the well-known signaling molecule, nitric oxide (NO), nitroxyl (HNO) exhibits unique properties in regulating biological and pharmacological activities. The first study investigates a newly introduced mixed thia/aza Cu complex and its favorable reactivity towards nitroxyl (HNO) and the mechanistic origins that leads to its reusability as a biosensor. The computational studies not only revealed the structural and electronic details for improved reactivity, but also elucidates the previously unclear reaction pathway of the subsequent conformation change, a crucial factor for achieving reusable use. The findings will facilitate the design of efficient and recyclable HNO sensors.

Nitric oxide plays important role as a signaling molecule for cardiovascular regulation, immune response, neurotransmission, and other physiological processes. As a signaling molecule, its concentration needs to be regulated. bacNORs utilize di-Fe heme/non-heme active site to convert the toxic NO to N_2O. Studying the mechanisms of NORs with biomimetic metal complexes is exciting as the chemical process has significant biological and environmental importance. In the second study, the focus shifts to studying the unprecedented one-electron pathway of NO to N_2O conversion via both Fe and Co heme systems, in contrast to the two-electron native enzymatic

pathway. The quantum chemical investigation provides mechanistic insights into the novel reaction features and explains the more favorable experimental reactivity in Fe heme system. This knowledge holds promise for the development of chemical agents in degrading toxic NO in various situations.

Nitrosoarenes (ArNOs) are toxic metabolic intermediates that interact directly with heme proteins to alter their functions. The biological functions of ArNOs are closely related to their interactions with the Fe centers, but the factors to determine its preferential binding are unknown. The computational study offers a deeper understanding of the binding mode preference of nitrosoarene to iron heme porphyrin, unraveling key coordination information about the interactions that affect biological functions at the molecular level. The research findings offer valuable information for designing targeted pharmaceutical interventions and catalysts in medicinal chemistry.

Finally, the fourth study focuses on the tethering of a nitrile inhibitors to the iron heme porphyrin, which can be applied in targeted cancer therapies and other diseases. The detailed computational investigation provided explanations to the preferential factors for high binding affinities of the nitrile inhibitors. These insights contribute to discovering and designing small molecule tethers that can bind selectively with heme proteins for potential treatments including cancer, fungal infection, HIV, hypertension, etc.

The comprehensive computational study provides new perspectives on the metal mediated biological reactions and interactions involving nitrogen-containing species, offering new avenues for innovation in various scientific disciplines.