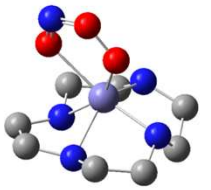
Computational Analysis of Nitric Oxide Dioxygenase Biomimicry with Non-heme Small Molecules



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Abstract: Nitric oxide (NO) is a gaseous, free-radical, 2° messenger with a half-life of 3-5 seconds.[1,2] Nitric oxide can be expressed in response to invading microbial species, cardiac vasodilation, or neuronal signaling.[2] Overexpression of the cytoprotective NO can lead to high concentrations of cytotoxic peroxynitrite ($OONO^-$), causing nitroxidative stress.[3,4] A counter to this is the biomimicry of Nitric Oxide Dioxygenase's (NOD) activity with water-soluble, non-heme macrocycles to convert NO to NO_3^-.[5] This mimicry was explored using Density Functional Theory (uM11/LANL2DZ) as well as Conformer-Rotamer Ensemble Sampling Tool (CREST). Current data shows that based on an energy screening of the macrocycles in water, mimicry is successful through a concerted mechanism (**Fig. 2**), but not through a sequential mechanism (**Fig. 3**) due to a high energy barrier (~26 kcal/mol). Additionally, preliminary results using an iron-cyclen complex shows that cis/trans geometry of the free reactive coordination sites may play a large role in biomimic's activity.

Background:

Nitric oxide is released by microglial cells as an immune response.

Microglial Cells

AB_{42} Plaques

Nitroxidative Stress!

Excess nitric oxide can cause nitroxidative stress, a potential etiology of Alzheimer's Disease.

Unhealthy Microglial Cells

Nature's Solution: Nitric Oxide Dioxygenase

A bacterial enzyme that has a critical reductase domain, and a flavo-hemoglobin-based active site.

NOD Heme Core

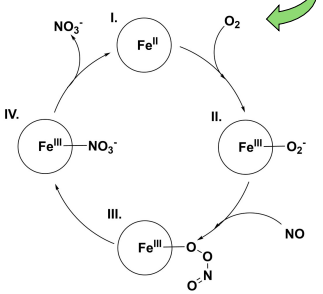
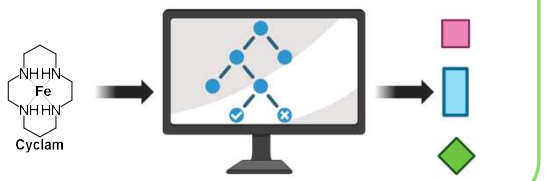
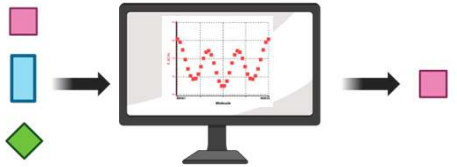


Fig 1. NOD Mechanism

1. Obtain Geometric Conformers using CREST:



2. Optimizing Best Conformers using DFT:



Computational Work-Flow

3. Develop Energy Diagrams for Analysis:

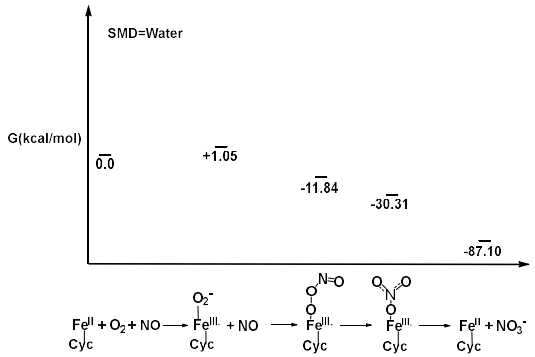


Fig 2. Concerted Energy Diagram Using Iron-Cyclam

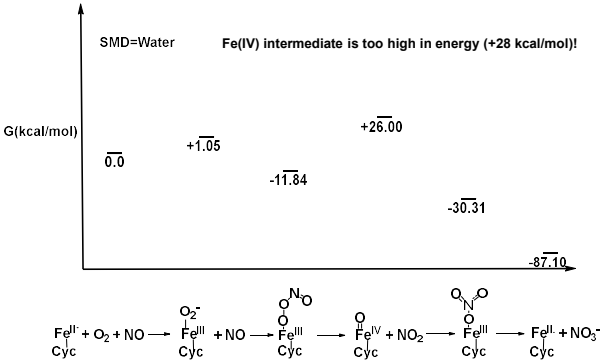
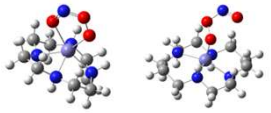


Fig 3. Sequential Energy Diagram Using Iron-Cyclam

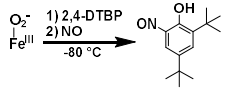
Conclusions:



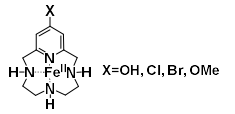
Cis Trans

- **Reaction overall proceeds exergonically, favoring a concerted pathway.**
- **The coordination position's (cis or trans) appear to play a role in stability of reaction pathway intermediates.**

Future Works:

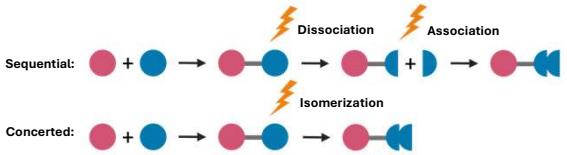


Will reactivity studies match theoretical results?



- **What are the transition state structures and energies?**
- **How would electron-donating and electron-withdrawing groups effect complex reactivity?**

Sequential vs. Concerted Mechanisms:

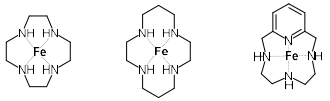


Macrocycles Tested:

Hypothesis: Can small, non-heme, water-soluble complexes mimic NOD?

If so, what is the mechanism?

What happens between steps III and IV?



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(1) Drew, B. *Ann. NY. Acad. Sci.* **2006.**
(2) Bryan, N. *Free Rad. Biol. Med.* **2007.**
(3) Beckman, J. *Am. Phys. Soc.* **1996.**
(4) Chu, H. *JACS* **2025.**
(5) Foo, K. *J. Med. Chem.* **2026.**