

## Accepted Manuscript

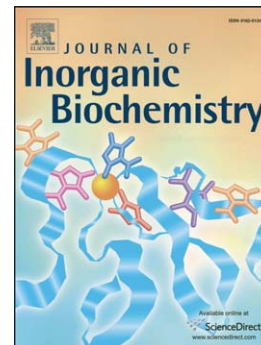
Theoretical investigation of the mechanism of nitroxyl decomposition in aqueous solution

Mauro Bringas, Jonathan Semelak, Ari Zeida, Dario A. Estrin

PII: S0162-0134(16)30179-9  
DOI: doi: [10.1016/j.jinorgbio.2016.06.016](https://doi.org/10.1016/j.jinorgbio.2016.06.016)  
Reference: JIB 10018

To appear in: *Journal of Inorganic Biochemistry*

Received date: 27 January 2016  
Revised date: 8 June 2016  
Accepted date: 14 June 2016



Please cite this article as: Mauro Bringas, Jonathan Semelak, Ari Zeida, Dario A. Estrin, Theoretical investigation of the mechanism of nitroxyl decomposition in aqueous solution, *Journal of Inorganic Biochemistry* (2016), doi: [10.1016/j.jinorgbio.2016.06.016](https://doi.org/10.1016/j.jinorgbio.2016.06.016)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

# Theoretical investigation of the mechanism of nitroxyl decomposition in aqueous solution

Mauro Bringas\*\*, Jonathan Semelak\*\*, Ari Zeida, Dario A. Estrin\*

*DQIAyQF, INQUIMAE-CONICET, FCEN UBA, Ciudad Universitaria, Pab. 2, CP 1428 Buenos Aires, Argentina*

## Abstract

Nitroxyl (HNO) is a species that has been proposed recently to play different roles in nitrosative stress processes. HNO decomposition in aqueous solution leading to N<sub>2</sub>O is a fast reaction that competes with many biochemical reactions in which HNO may be involved. Since molecular determinants of this reaction are still not fully understood, we present in this work an exhaustive analysis of the mechanism in terms of electronic-structure calculations as well as *state of the art* hybrid quantum mechanics/molecular mechanics molecular dynamics (QM/MM) simulations. We characterized the reaction mechanism and computed free energy profiles for the reaction steps using an umbrella sampling procedure. We propose a first dimerization step followed by an acid-base equilibria. Afterwards, the product is formed from two main pathways involving *cis*-hyponitrous acid (*cis*-HONNOH) and its conjugate basis as intermediate. Our calculations show preference for the anionic pathway under physiological conditions and allow us to rationalize the results in terms of a molecular description of specific interactions with the solvent. These interactions turn out to be determinant in the stabilization of transition states and, thereby, modifying the free energy barriers. We predict a strong pH-dependence of the overall kinetics of N<sub>2</sub>O formation, related with the fraction of reactive species available in solution. Finally, we suggest experimental procedures which could validate this mechanism.

Keywords: Nitroxyl, Reactive Nitrogen Species, Aqueous decomposition, Mechanism, QM/MM

## 1. Introduction

Nitroxyl (HNO) and its conjugate base (NO<sup>-</sup>) were added recently to the family of reactive nitrogen species (RNS). [1,2] Nitroxyl is a simple yet biologically relevant molecule. Even though it was discovered in the XIXth century, many aspects of its reactivity and its biochemical role are still controversial or not fully understood. [3] Historically, HNO was considered as a biologically active molecule because of studies related with cyanamide (H<sub>2</sub>NCN), which is used in alcoholism treatment. [4,5] Cyanamide reaction with catalases and peroxidases generates HNO, that reacts with a residue of cysteine (in thiolate form) in the active site of the aldehyde dehydrogenase, inhibiting it. This represents only one example among many of the high reactivity of HNO with thiolates (RS<sup>-</sup>). [6,7,8]

Nitroxyl's potential use in heart failure treatment makes it relevant in the field of pharmacology, as well as its vasodilator properties and its role in cellular metabolisms. [9,10]

Nitroxyl rapidly decomposes in aqueous solution generating nitrous oxide. [11] Due to its inherent reactivity and the need for *in situ* generation, the search of HNO donors and a better understanding of its chemical behavior have intensified considerably its biological interest.

(\*) Corresponding author: [dario@qi.fcen.uba.ar](mailto:dario@qi.fcen.uba.ar)

(\*\*) These authors made equal contributions.

Download English Version:

<https://daneshyari.com/en/article/7754564>

Download Persian Version:

<https://daneshyari.com/article/7754564>

[Daneshyari.com](https://daneshyari.com)