Air Pollutant Chemistry at the Air-Lung Interface: An Interdisciplinary Study

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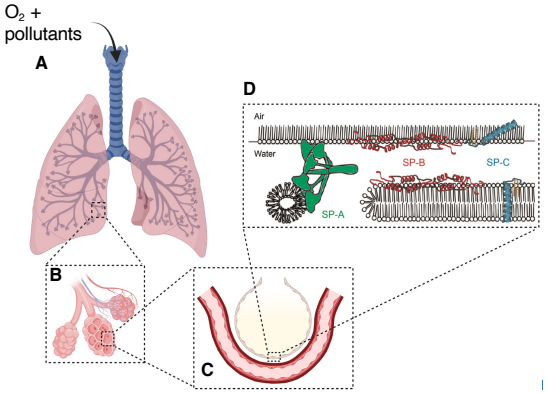
Objectives

This thesis built on biological approaches to modeling pulmonary surfactant by integrating atmospheric chemistry approaches to simulating the chemical reactivity of NO_2 at the air-lung interface. We aimed to answer the following questions: a) what is the **orientation** of inhaled atmospheric NO_2 with respect to biological molecules in surfactant, and b) based on this orientation, what **chemical transformations** does NO_2 undergo in this environment?

Background

- Nitrogen dioxide (NO_2) is a gaseous air pollutant and reactive nitrogen species. Exposure has been associated with respiratory disease, cardiovascular disease, and cancer, but the **mechanism of action underlying NO_2 toxicology remains uncertain**.
- Pulmonary surfactant (PS), the top layer of the lung lining fluid, is a complex mixture of lipids and proteins.[1] Situated at the **air-lung interface**, PS forms the first point of contact for inhaled atmospheric pollutants and therefore has been the subject of several investigations on the effect of foreign particles in the lung.

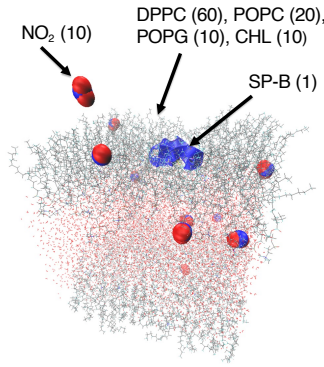


Pathway of air exchange in the lungs. Panel D is reprinted from Parra & Pérez-Gil (2015).[1]

- The effects of NO_2 on PS have not been experimentally tested, but exposing PS to reactive oxygen species has been shown to result in chemical modifications to lipids and proteins.
- These PS lipids and proteins have several functional groups which have been shown to react with NO_2 in other environments.
  - NO_2 can oxidize the **thiol functional group in cysteine** (Cys),[2] and although the **hydroxyl group on cholesterol** (CHL) is less acidic, a similar oxidation pathway has been shown computationally.[3]
- Furthermore, both thiol and hydroxyl oxidation reactions have been observed to accelerate at air-water interfaces such as PS. Water has been shown to act as a catalyst at these aqueous interfaces, an effect known as "**on-water catalysis**."[4]
- To our knowledge, only one study has investigated the effect of atmospheric pollutants on PS using computational methods, and the methodology did not allow consideration of chemical reactivity.[5]

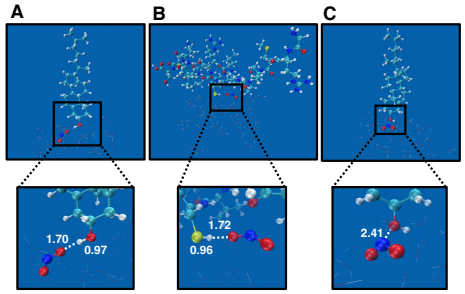
Methods

Molecular dynamics (MD) simulations



PS was modeled using a bilayer separated by a water slab in a 6.5x6.5x8.5 nm^3 box. Simulations were run in GROMACS for 200 ns.

Ab initio MD (AIMD) simulations

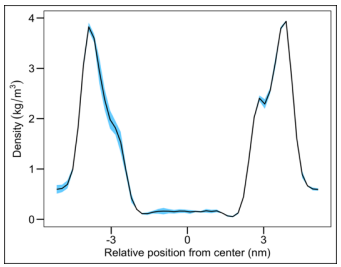


Three reactions were probed using a scaled-down version of our MD model: A) hydrogen abstraction from CHL, B) hydrogen abstraction from Cys, and C) nucleophilic attack by CHL. The air-water interface was modeled using a water slab (1.5x1.5x0.75 nm^3). Simulations were run using CP2K with Plumed plug-in packages and the metadynamics method.

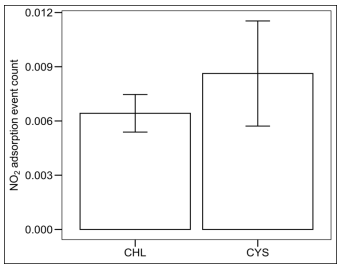
Results

MD simulations: Adsorption analysis

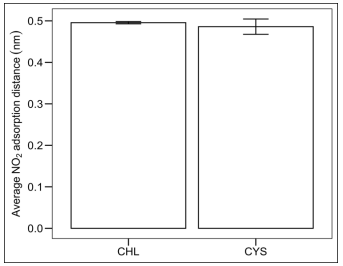
NO_2 mass density profile



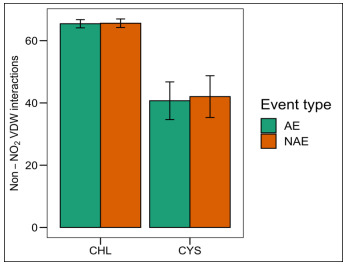
Number of adsorption events



Adsorption distance



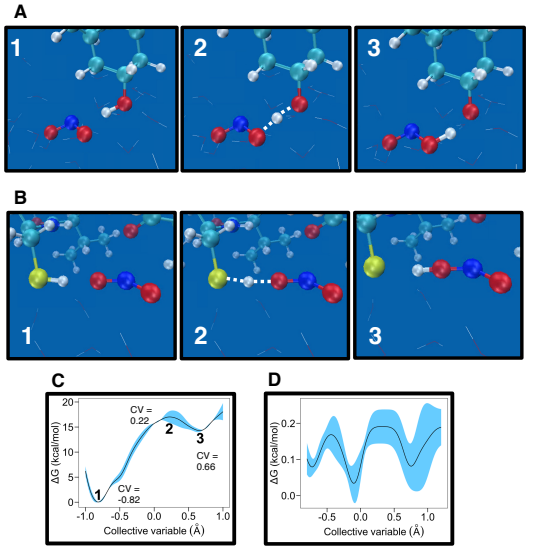
Interactions with non-NO_2 atoms



NO_2 molecules adopted a symmetric bimodal distribution during the simulations, preferentially locating in and around the lipid layers. Adsorption of NO_2 on CHL and Cys was equally likely and equally strong as measured by distance and number of non-NO_2 interactions broken.

Results

AIMD simulations: Free energy analysis



Hydrogen abstraction by NO_2 from both CHL hydroxyl (A) and Cys thiol (B) was observed, yielding HONO(+) and alkoxy or thiolate anions, respectively. Only the Cys thiol pathway was found to be energetically spontaneous (C, D).

Conclusions

- Our simulations established the preferential distribution of NO_2 in the lipid layer of PS near functional groups such as CHL and Cys, suggesting the possibility of chemical reactions occurring.
- Given the comparable strength of adsorption for both functional groups, our AIMD simulations suggest that hydrogen abstraction by Cys thiol in PS is a more favorable process.
- Future work should explore the health implications of HONO(+) and of the functional group modifications observed to yield additional insight into the molecular mechanism by which NO_2 impacts health.

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References 1. Parra, E., & Pérez-Gil, J. (2015). Composition, structure and mechanical properties define performance of pulmonary surfactant membranes and films. *Chemistry and Physics of Lipids, 185*, 153–175.
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