Kinetics and Mechanisms of Antithyroid Drug Methimazole via S-nitrosothiol Formation

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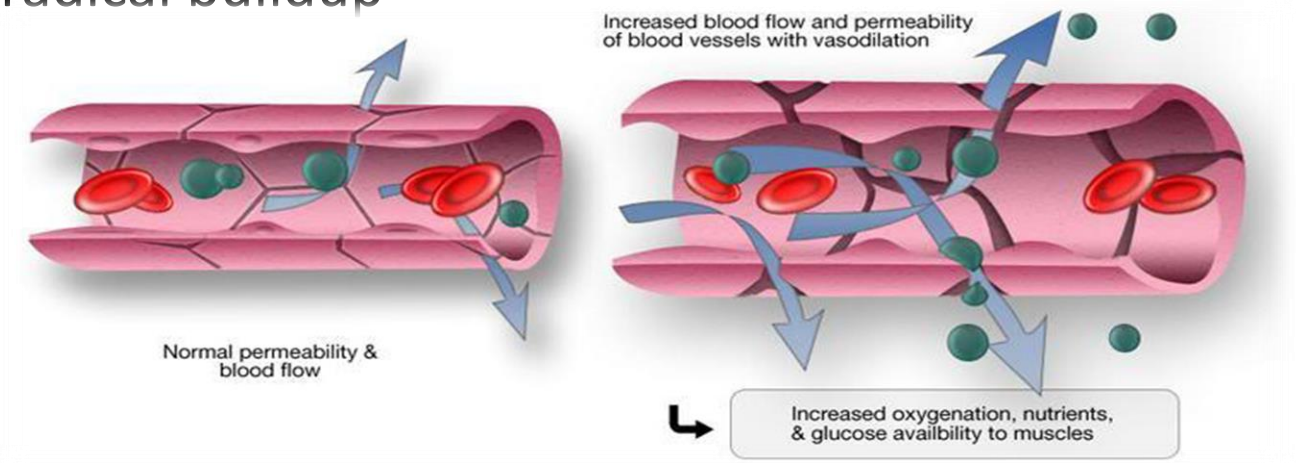
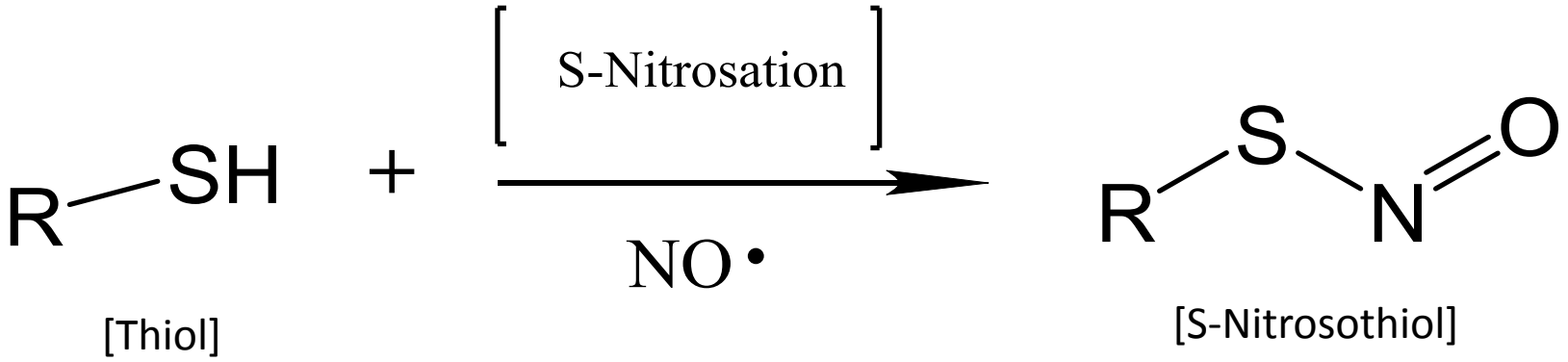
Importance of Nitric Oxide

- Research focus on nitrosating drugs to test nitric oxide carrying capacity throughout the body
  - Test if nitric oxide inhibits drug
- Regulatory system importance
  - Vasodilation
- Possible detrimental effects due to radical buildup

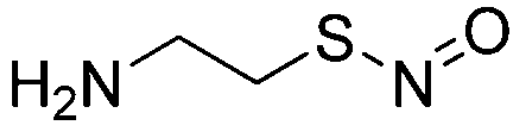


S-Nitrosothiols

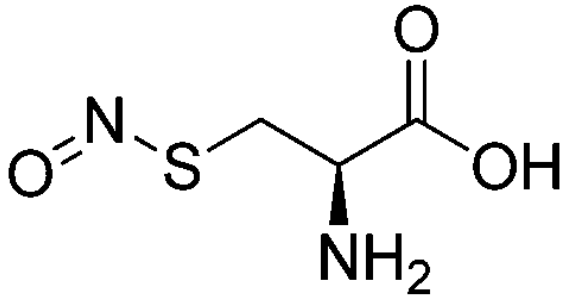


- Donor of nitrosonium ion NO+ and nitric oxide
- Notroso derivatives serve as signaling molecules

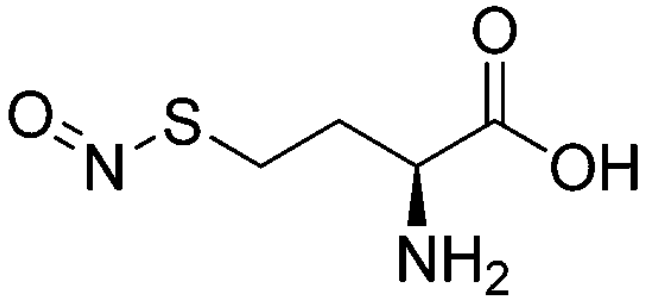
Nitric Oxide Carriers



S-nitrosocysteamine



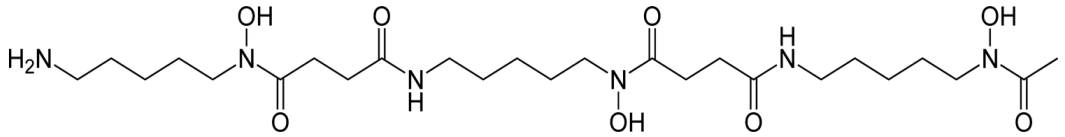
S-nitrosocysteine



S-nitrosohomocysteine

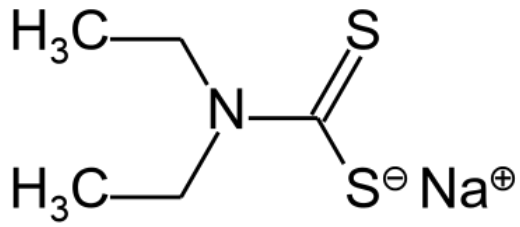
Selected Drugs for Nitrosation

DEFEROXAMINE



- Chelating agent - used as antidote for iron poisoning
- N-nitrosation of this compound has already been studied.

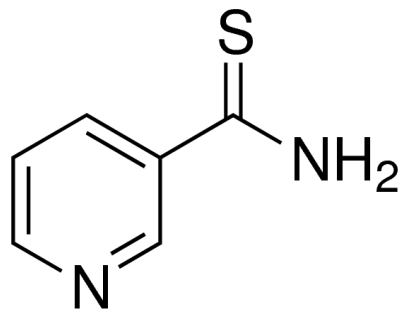
DIETHYLDITHIOCARBAMATE



- Chelates transition metals
- Antabuse
- No reaction observed

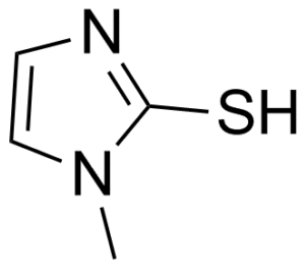
Selected Organosulfur Drugs for S-nitrosation

THIONICOTINAMIDE



- Chelating agent
- No reaction observed

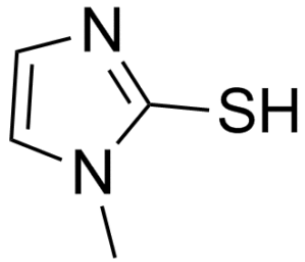
METHIMAZOLE



- Reaction observed

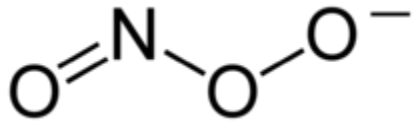
Methimazole Importance

- Used to treat hyperthyroidism
  - Inhibits thyroid gland from producing too much thyroid hormone



Nitrosating Compounds Used

PEROXYNITRITE



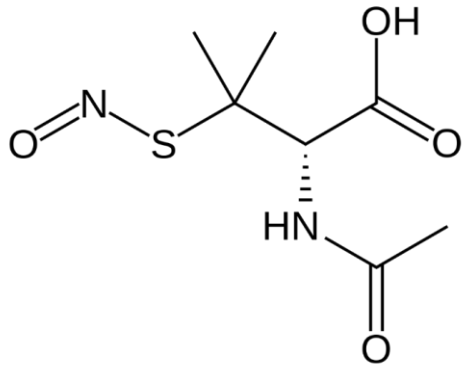
- Formed from nitric oxide and oxygenated hemoglobin
- Reactions carried out in basic conditions due to decomposition in acidic and neutral pH

SODIUM NITRITE

- Food preservative
- More stable than peroxynitrite
- Ability to react in a wider range of pH conditions

Nitrosating Compounds Used

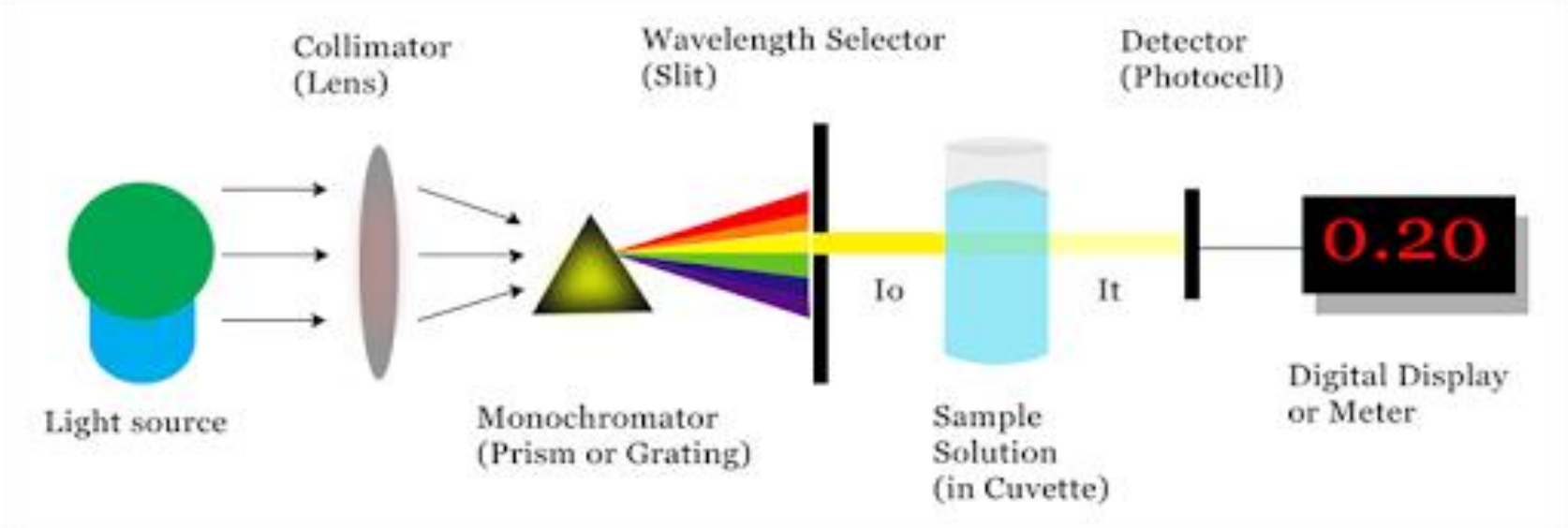
S-NITROSO-N-ACETYLPENICILLAMINE (SNAP)



- S-nitrosothiol
- Stable nitric oxide carrier

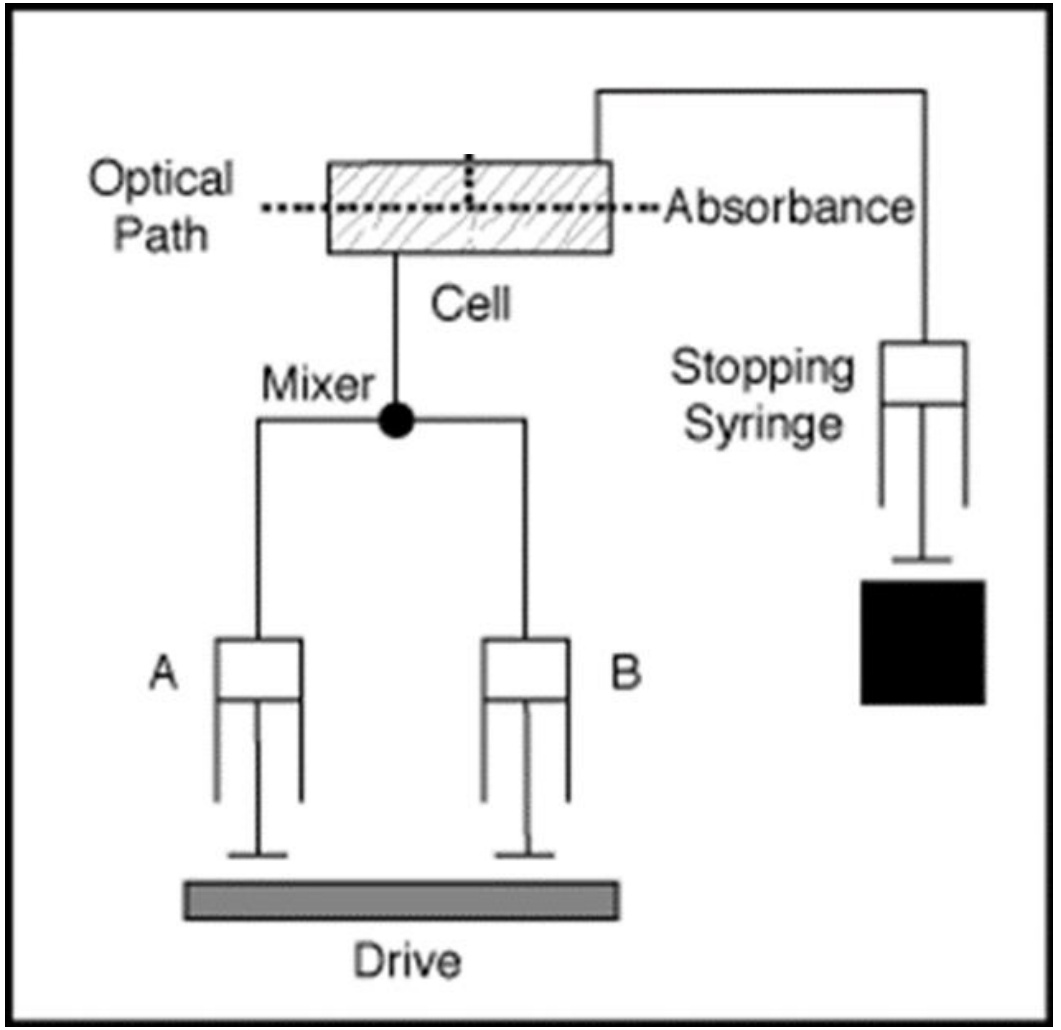
Instrumentation & Methods

UV-Vis Spectroscopy



Used to identify exact tracking wavelengths for each compound and product

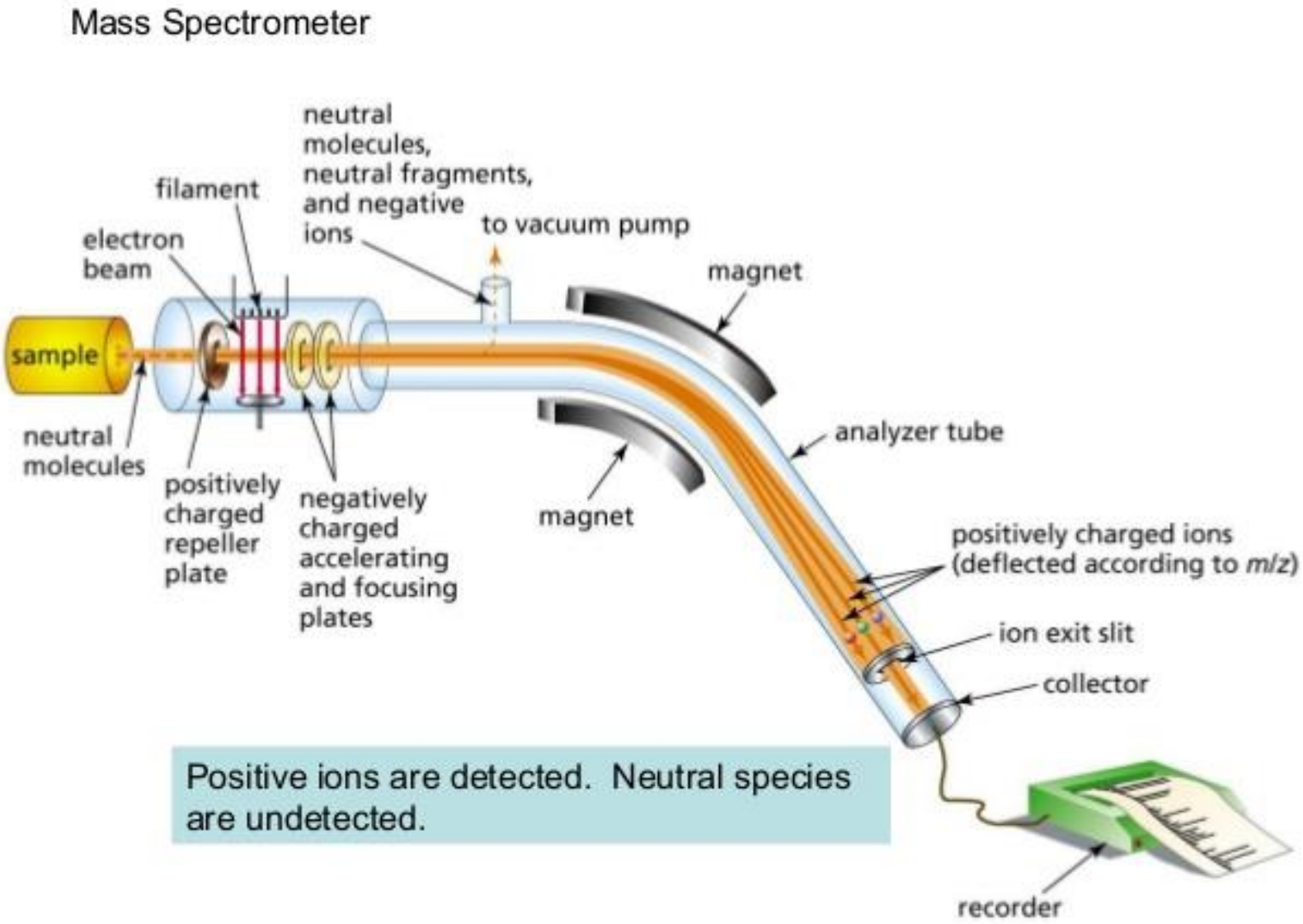
Stopped-flow Spectrometer



Used to track reaction kinetics at specific wavelengths

Liquid Chromatography-Mass Spectroscopy

- LC separates compounds based on polarity
- Mass spec gives molecular weight
- Used to determine compound and product structures

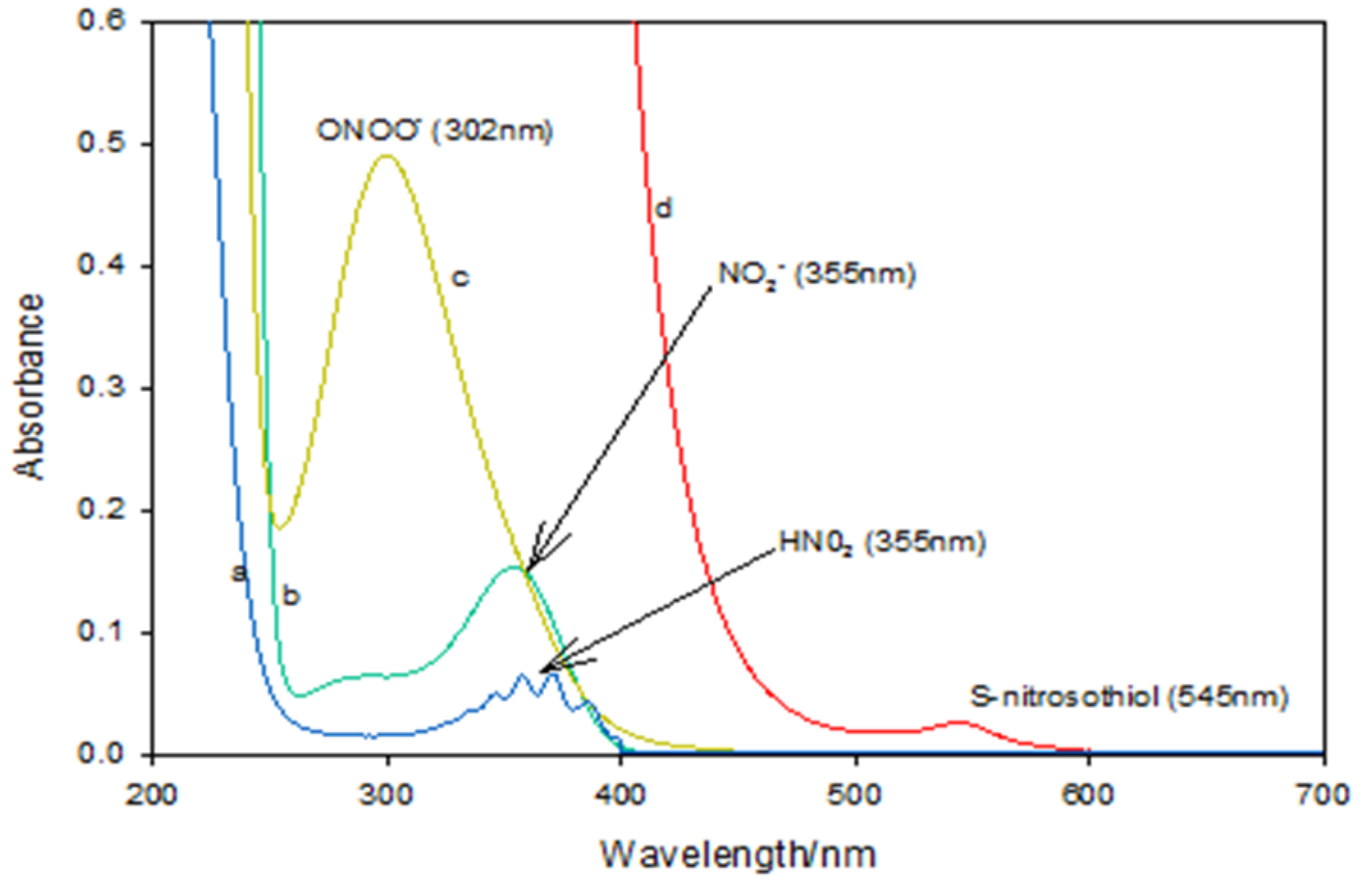


https://www.slideshare.net/ceutics1315/chap-14-mass-spec-39635178

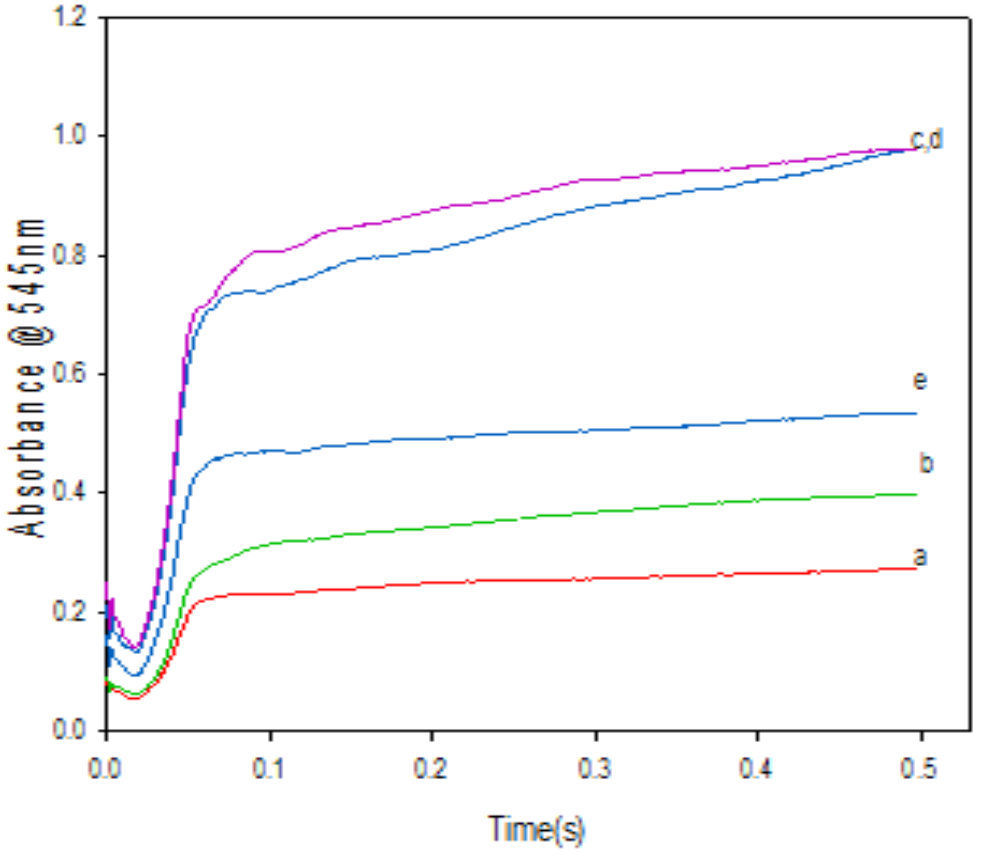
Portland State UNIVERSITY

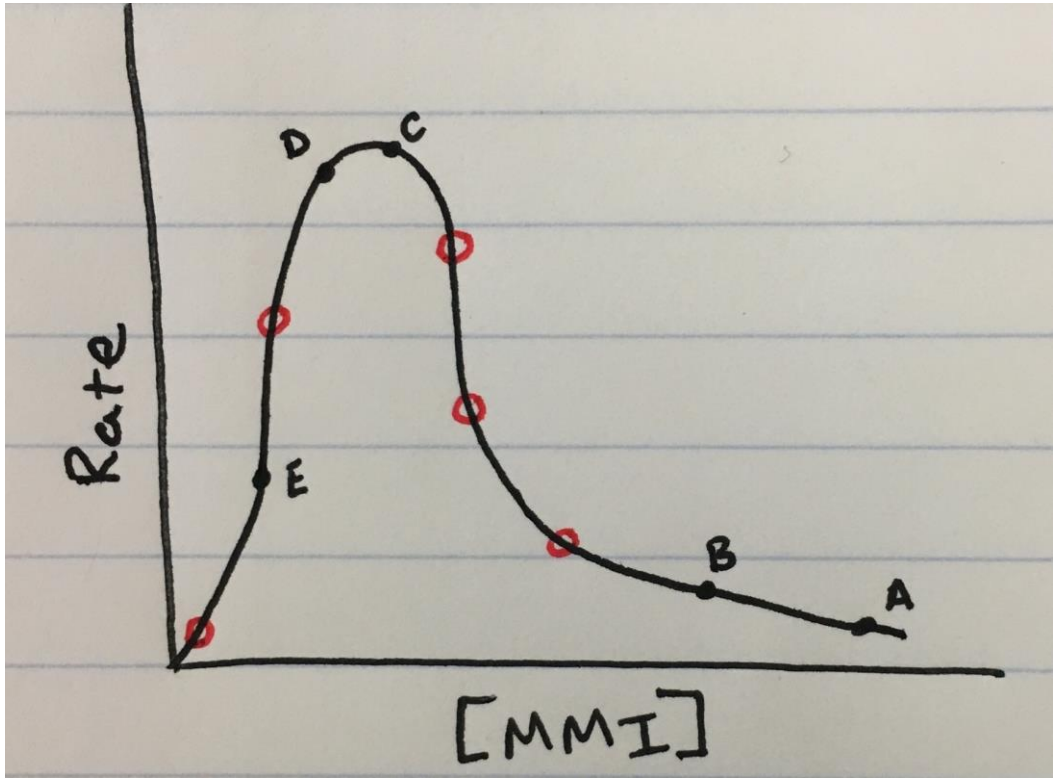
Results

UV-spectra of Studied Compounds

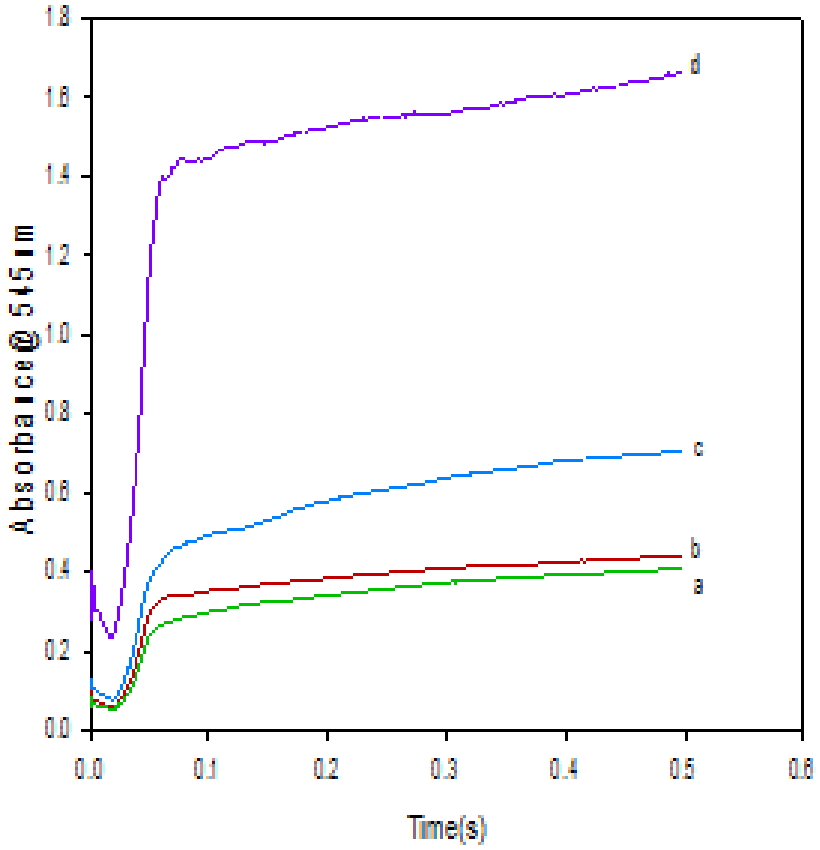


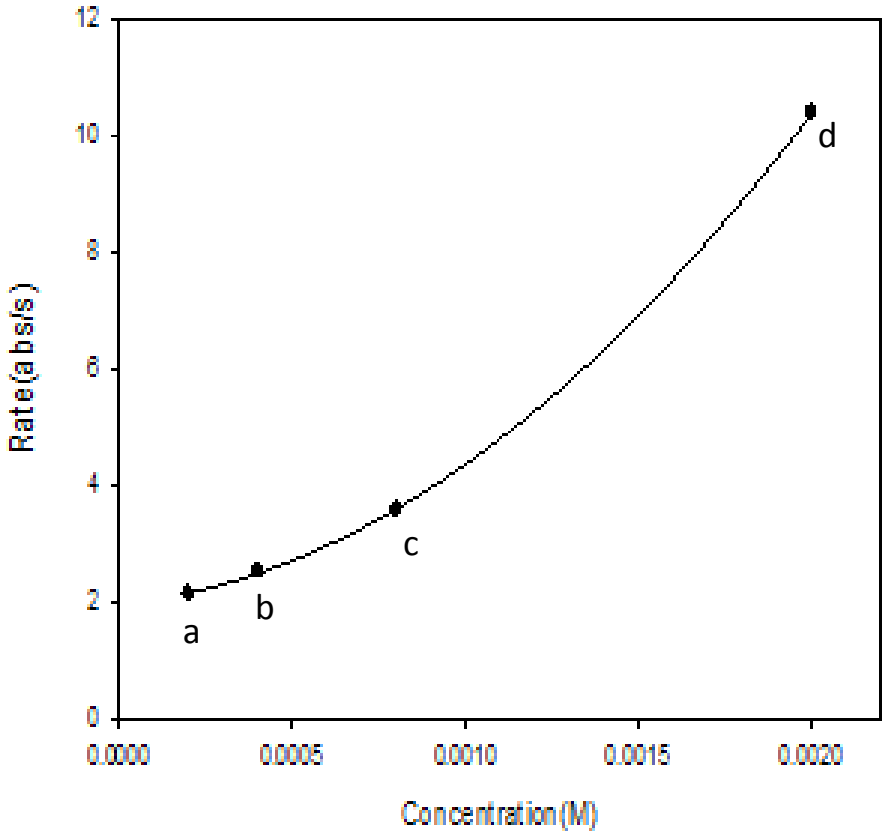
MMI Variation with SNAP



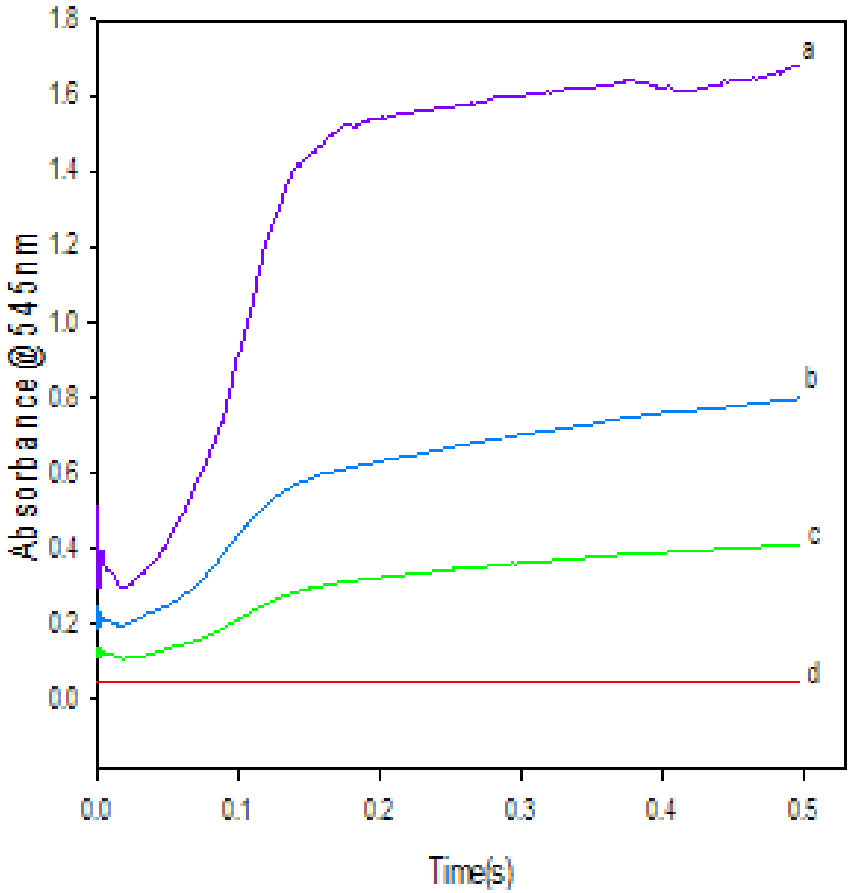


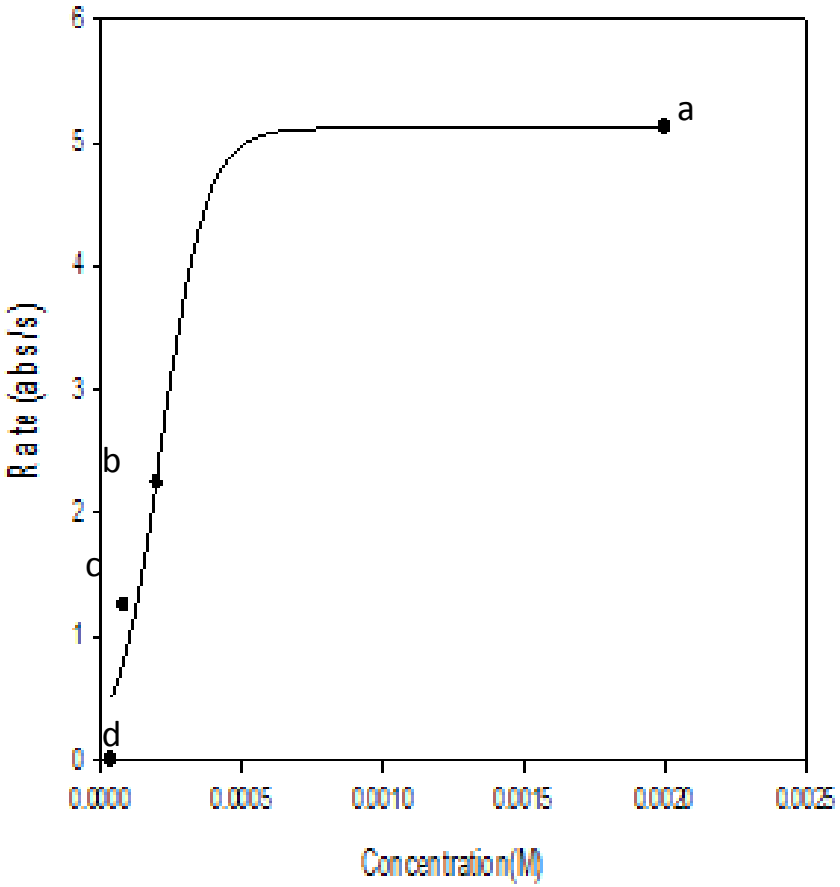
SNAP Variation with MMI



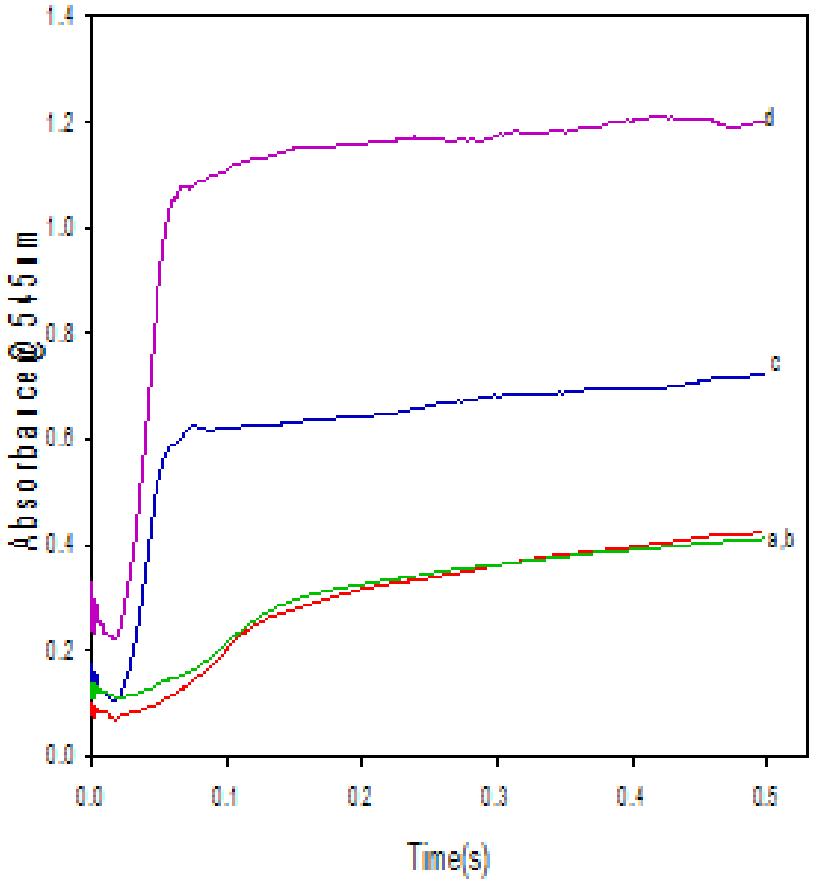


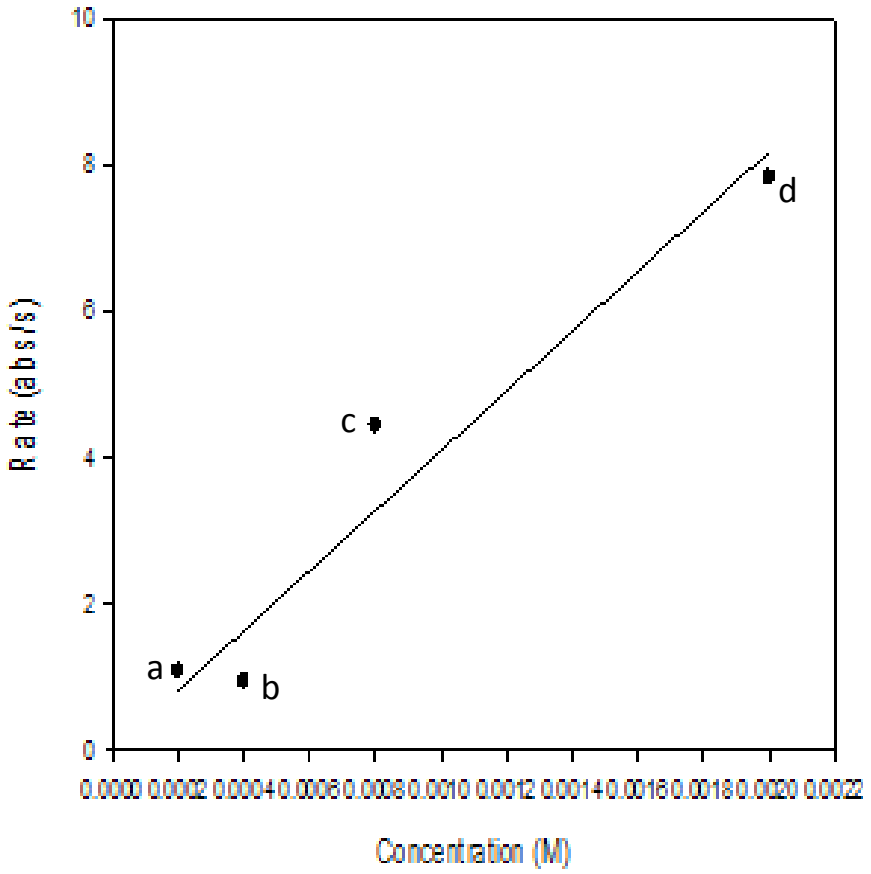
MMI Variation with Peroxynitrite



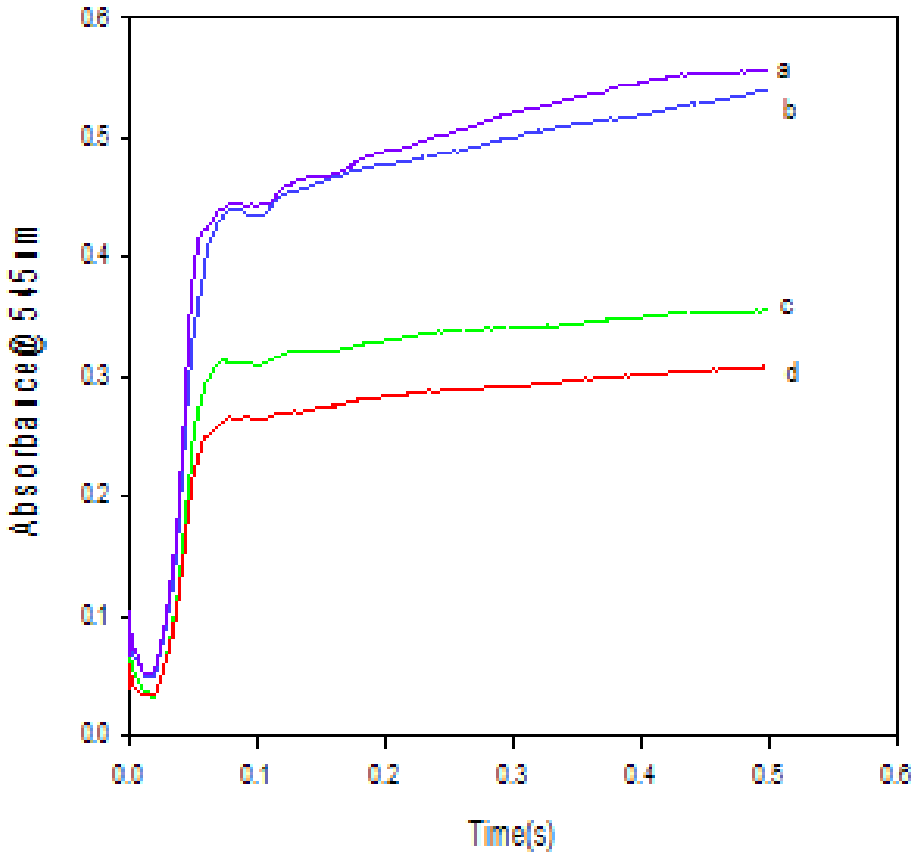


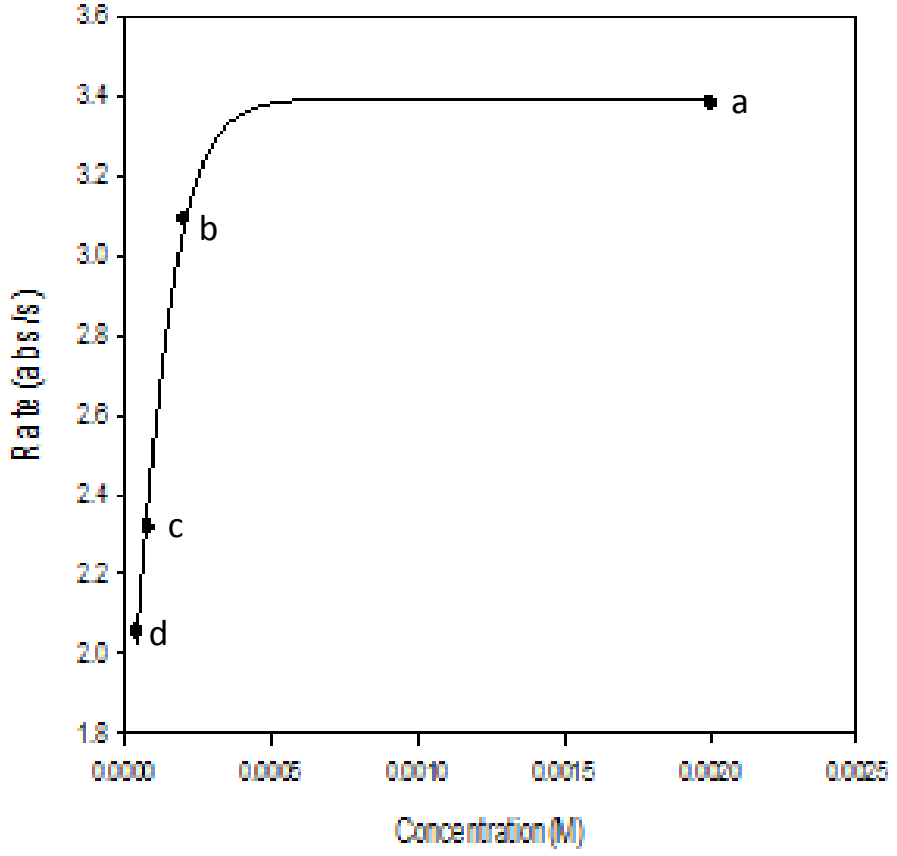
Peroxynitrite Variation with MMI



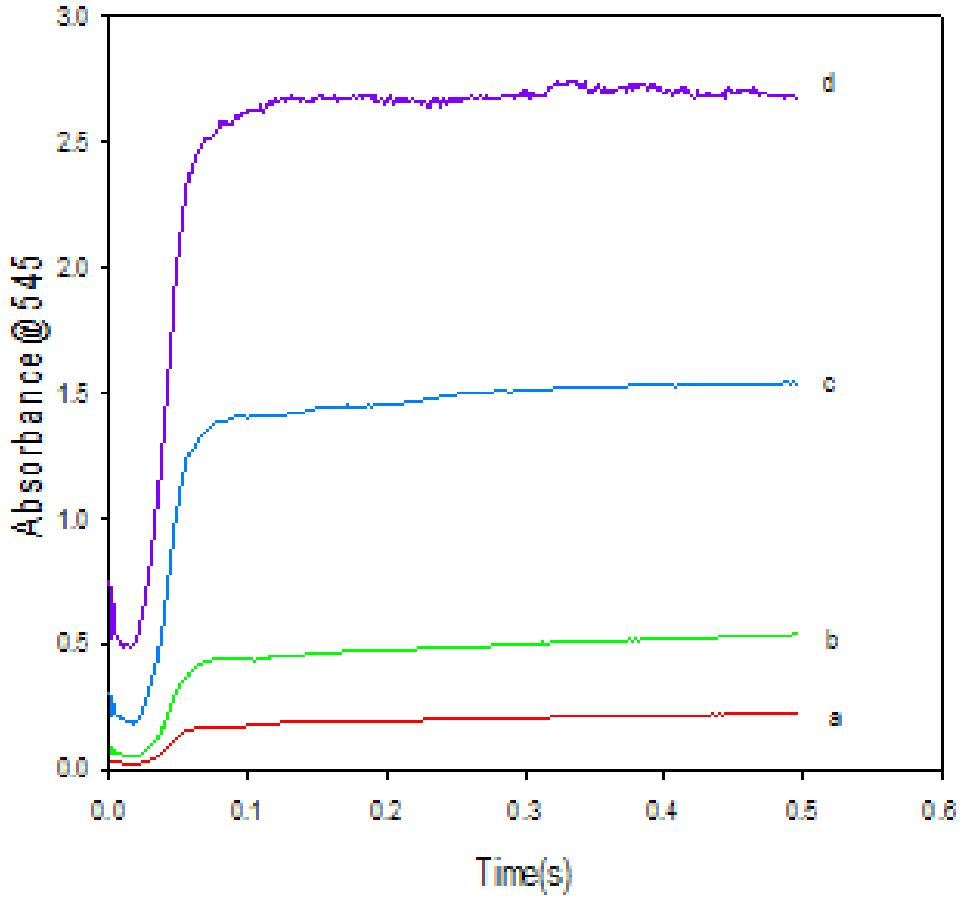


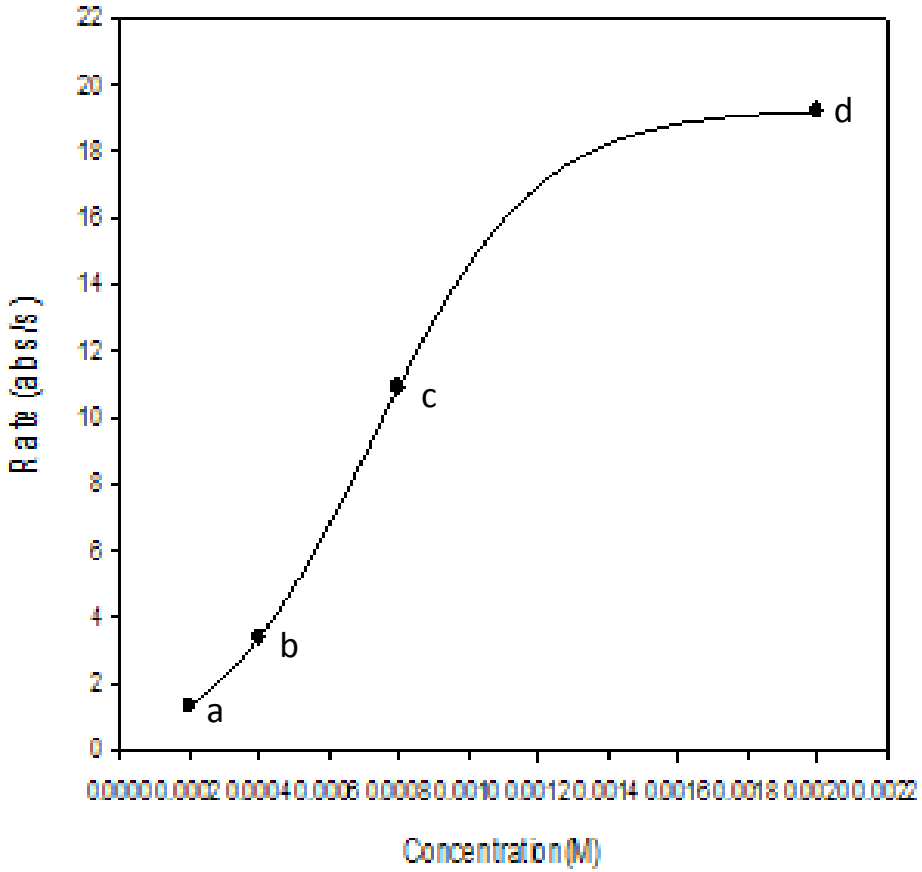
MMI Variation with Sodium Nitrite





Sodium Nitrite Variation with MMI





Future Work

- Continue to track more concentrations to fill out rate plots
- Complete LC-MS to confirm product formation

Acknowledgements

- REU Program
  - Emma Hovley
  - Dr. Erik Sanchez
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