Mass Spectrometry Study of Histidine Oxidation by $^{1}\text{O}_2$:
from Gas-Phase Single Ions
through Water Clusters
to Aqueous Solution

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Biosystems
- Enzymatic or nonenzymatic
- Radical termination
- Energy transfer from protein-bound chromophores

- Progression of cell death
- Aging and diseases
- Photodynamic therapy

- Loss of amino acids in atmospheric aerosols
- Chemical markers
Photooxidation of Amino Acids

IN SOLUTION

Sensitizer & Light
(type II photosensitization)

\[ \text{competition with radical-mediated Reactions (type I photosensitization)} \]

\[ \text{pH} \]

solvent compositions

oxygen concentration

\[ \text{in solution} \]

\[ \text{in solution} \]

\[ \text{in solution} \]

\[ \text{in solution} \]
Our Approaches

1. GAS-PHASE REACTIONS of Amino Acid Ions with Clean $^1\text{O}_2$

- Distinguish intrinsic vs. external imposed properties of biomolecules
- Complemented by and compared with MD simulations

2. MICROSOLVATION of Amino Acid Reactant Ions in the Gas Phase

- Dynamical roles of hydrogen-bounded waters
How We Run Reactions of His Ions with $^{1}\text{O}_2$

1. Generation of His ions by ESI

2. Ions are passed into a quadrupole for mass selection

3. Mass-selected ions are guided into an octopole surrounded by a collision cell, and scattered from $^{1}\text{O}_2$.

4. Product ions are mass analyzed & counted.

Guided-Ion-Beam Tandem Mass Spectrometer
**Generation & Detection of $^{1}{O}_2$**

- Chemical $^{1}{O}_2$ generator

$$2H_2O_2 + Cl_2 + 2KOH \xrightarrow{-21^\circ C} ^1O_2/^{3}O_2 + 2KCl + 2H_2O$$

**Emission detection**

$$O_2(^1\Delta_g) \xrightarrow{\text{Emission}} O_2(^3\Sigma_g^-) + h\nu (1270 \text{ nm})$$
Gas-Phase Exp 1.
$^{1}O_2$ Oxidation of Protonated and Deprotonated His in the Gas Phase
Gas-Phase Exp 1.

$^{1}\text{O}_2$ Oxidation of Protonated and Deprotonated His in the Gas Phase

No oxidation products were observed.
Gas-phase isolated His cannot be oxidized by $^{1}\text{O}_2$
Why Is Gas-Phase Isolated His Non-Reactive?
Make Gas-Phase Experiments More Biologically Relevant

Use Hydrated Clusters to Approach Solution-Phase Oxidation Behaviors
Gas-Phase Exp 2. Reactions of $^{1}\text{O}_2$ with Hydrated HisH$^+$(H$_2$O)$_n$ and [His-H]$^-(\text{H}_2\text{O})_n$
Hydration effect: Suppression of Dissociative Pathways of Peroxide Intermediates by Water Cluster Dissociation
Dynamical Role of Water:
Direct Dynamics Trajectory of [His-H]-(H2O) + ^1O2 at $E_{col} = 0.1$ eV
Using Venus/Gaussian 09, w/ forces and Hessians calculated at B3LYP/4-31G*
Use Hydrated Clusters to Mimic pH-Dependence of Photooxidation

Photooxidation of His in solution

Reaction of hydrated His in the gas phase

Gas-phase solvated clusters provide a platform to elucidate intrinsic reactivity of biomolecules in vacuo. Can these results can be extrapolated to condensed phase?

I. B. C. Matheson and J. Lee, 
Exp 3: On-Line Reaction Monitoring of His + ^1O_2 (w/o sensitizers) in Aqueous Solution
UV-Vis Kinetics Analysis of His + $^{1}$O$_{2}$ in Aqueous Solution

Real-time UV-Vis Monitoring
On-Line ESI MS of His + $^1\text{O}_2$ in Aqueous solution

Time Profiles of Products

b) pH 10.4

m/z 186

161

323

154
Conclusions: Non-Reactivity in the Gas Phase

Peroxides in Water Clusters

pH-Dependence in Solution

- A common process: endoperoxide via [4+2] cycloaddition, and rearrange to hydroperoxide.
- Contrasting mechanisms of protonated vs. deprotonated His lead to pH dependence in solution

\[ \text{HisH}^+ + {^1}\text{O}_2 \xrightarrow{\text{gas phase}} 2,5\text{-endoperoxide} \xrightarrow{\text{ring-opening}} 5\text{-hydroperoxide} \xrightarrow{\text{in solution}} \text{stable hydrated imidazole} \]

vs.

\[ [\text{His-H}]^- + {^1}\text{O}_2 \xrightarrow{\text{gas phase}} 2,4\text{-endoperoxide} \xrightarrow{\text{ring-opening}} 2\text{-hydroperoxide} \xrightarrow{\text{in solution}} \text{hydrated imidazolone} \]  

\[ \rightarrow 6\alpha\text{-hydroxy-2-oxo-octahydro-pyrrolo[2,3-d] imidazole-5-carboxylate + His-His cross-linking.} \]

- Biological Implications

\[ pK_a \text{ (imidazole) 6.04, His exists in neutral/protonated/deprotonated forms at physiological pH} \]

\[ {^1}\text{O}_2 \text{ oxidation of the guanine moiety of DNA} \]
From Gas-Phase to Solution-Phase Dynamics

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