Dynamics & Kinetics of $^{1}\text{O}_2$–Induced Guanine Nucleoside Oxidation:
A Combination of Potential Energy Surface, Kinetics Modeling, Dynamics Simulation & Guided-Ion-Beam Mass Spectrometry

Jianbo Liu
Department of Chemistry & Biochemistry
Queens College and the Graduate Center of the City University of New York
Singlet O$_2$ and DNA damage

Guanine is the exclusive DNA target for $^1$O$_2$

- Mutation such as G-C $\rightarrow$ A-T transversion
- DNA-protein cross-link
- Cell death
Guanine oxidation mechanism and questions


Q1 Reaction intermediate


Q2 Concerted OR stepwise O2 addition


Q3 Activation barrier and kinetics
A approach different than solution-phase photooxidation

Collisions of single biomolecule with $^{1}\text{O}_2$ in the gas phase

mass spectrometry
- products $m/z$ and structure by MS, MS$^2$
- capture transient intermediates
- intrinsic reactivity: energy dependence, activation barriers, etc.

computation
- electronic structure calculations
- reaction PES and statistical properties
- direct dynamics simulation
Guided-Ion-Beam Tandem Mass Spectrometer

1. Generation of biomolecular 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 \(^{1}\text{O}_2\) contained within

4. Product ions are m/z analyzed & counted

\[ \sigma = k / \nu_{\text{rel}} = \frac{I_{\text{product}}}{I_{\text{react}} \tan \theta} \frac{k_B T}{P_{\text{cell}} l_{\text{cell}}} \]

Y. Fang and J. Liu, JPC A. 2009, 113, 11250-11261
1. What we wanted to do first was to capture reaction intermediates
Protonated $[G + H]^+$

Deprotonated $[G - H]^{-}$

Ion-Molecule Collision within Ion Guide

products
RRKM analysis and implications

Estimate unimolecular $k$ using RRKM theory

$$k(E,J) = \frac{\sum_{k=J}^{J} G[E - E_0 - E_r(J,K)]}{h \sum_{k=J}^{J} N[E - E_r(J,K)]}$$

$t = 10 \mu s$ (time of flight)

$t = 20 \text{ ns}$

Potential Energy (eV)

$[\text{G-H} + 'O_2]$
Direct dynamics simulation of guanine ion-beam scattering

Form a 5,8-endoperoxide rather than a 4,8-endoperoxide that was proposed for neutral guanosine
Reactions of $^{1}$O$_{2}$ with [G + H]$^{+}$(H$_{2}$O) and [G - H]$^{-}$(H$_{2}$O)

Capture of transient endoperoxides via water evaporation cooling

Experimental assessment of the activation barrier associated with O$_{2}$ addition to guanine

2. More about O₂ addition mechanism: — A model study using 9MG

9-Methylguanine (9MG) has similar hydration, ionization, \( pK_a \) and reaction \( \Delta H \) as guanosine

Wenchao Lu, Huayu Teng, and J. Liu, *PCCP*, 2016, **18**, 15223-15234
pH-dependent $^{1}\text{O}_2$ addition

$[9\text{MG} + \text{H}]^{+}$ and $[\text{G} + \text{H}]^{+}$: a concerted cycloaddition to a 5,8-endoperoxide different than neutral guanosine which leads to a 4,8-endoperoxide
Switches to stepwise addition upon deprotonation

$[9\text{MG} - \text{H}^-] + ^1\text{O}_2$:
1) Different than neutral guanosine in a stepwise addition
2) Different than $[9\text{MG} + \text{H}]^+$ in $4,8$-OO-$[9\text{MG} - \text{H}^-]$ vs. $5,8$-OO-$9\text{MG} + \text{H}]^+$
3. From gas-phase dynamics to solution-phase kinetics and product distributions

Kinetics of $9\text{MG} + \text{^1O}_2$

$pH = 7$

$9\text{MSp}: (\text{gem}-9\text{Mdiol} + 9\text{MGh}) : 9\text{MGh}^{\text{ox}}$

<table>
<thead>
<tr>
<th></th>
<th>$9\text{MSp}$</th>
<th>$9\text{MGh}$</th>
<th>$9\text{MGh}^{\text{ox}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$pH = 7$</td>
<td>0.45</td>
<td>0.33</td>
<td>0.22</td>
</tr>
</tbody>
</table>

$pH = 10$

$9\text{MSp}: (\text{gem}-9\text{Mdiol} + 9\text{MGh}) : (9\text{MOG} + 9\text{MGh}^{\text{ox}})$

<table>
<thead>
<tr>
<th></th>
<th>$9\text{MSp}$</th>
<th>$9\text{MGh}$</th>
<th>$(9\text{MOG} + 9\text{MGh}^{\text{ox}})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$pH = 10$</td>
<td>0.72</td>
<td>0.09</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Solution-phase PES & kinetics

- Deprotonated guanine favors formation of Sp.
- Oxidation of protonated guanine is blocked by early-stage barriers.
- *Initial $^1O_2$ addition* is rate-limiting.
Oxidation rate constant

\[- \frac{d[9\text{MG} - H^-]}{dt} = k_1 [9\text{MG} - H^-][^{1}\text{O}_2]\]

\[\ln [9\text{MG} - H^-]_{\text{o}} \% = \frac{\text{product}_i}{\Sigma_i (\text{reactant} + \text{product}_i)} = -k_1 [^{1}\text{O}_2]_{\text{ave}} \cdot t\]

\[K_1 = 4.9 \times 10^7 \text{M}^{-1} \cdot \text{s}^{-1}\]

Summary

Guided by PES, kinetics & dynamics simulation

Gas-phase scattering probed early-stage dynamics & intermediates that is missing in condensed phase study

Solution-phase MS & spectroscopy measured late-stage kinetics & product distributions

<table>
<thead>
<tr>
<th>Gas phase</th>
<th>Aqueous solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹⁸O₂ addition</td>
<td>Intermediates</td>
</tr>
<tr>
<td>protonated</td>
<td>concerted</td>
</tr>
<tr>
<td>neutral</td>
<td>stepwise</td>
</tr>
<tr>
<td>deprotonated</td>
<td></td>
</tr>
</tbody>
</table>
Acknowledgements

Dr. Wenchao Lu
Yan Sun
Maida Tsai (collaborator, CUNY LGCC)
Wenjing Zhou
Bilal Karatash

CHE-1464171
Research Enhancement Funds
PSC Research Awards