Dynamics & Kinetics of $^1O_2$–Induced Guanine Nucleoside Oxidation:

A Combination of Potential Energy Surface, Kinetics Modeling, Dynamics Simulation & Guided-Ion-Beam Mass Spectrometry

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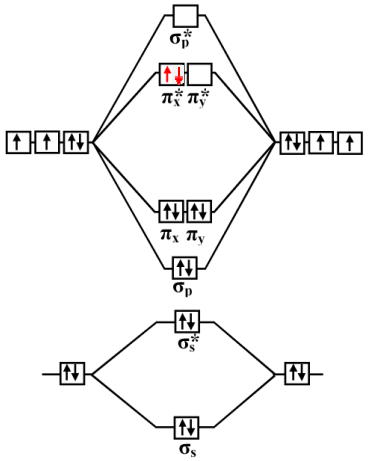
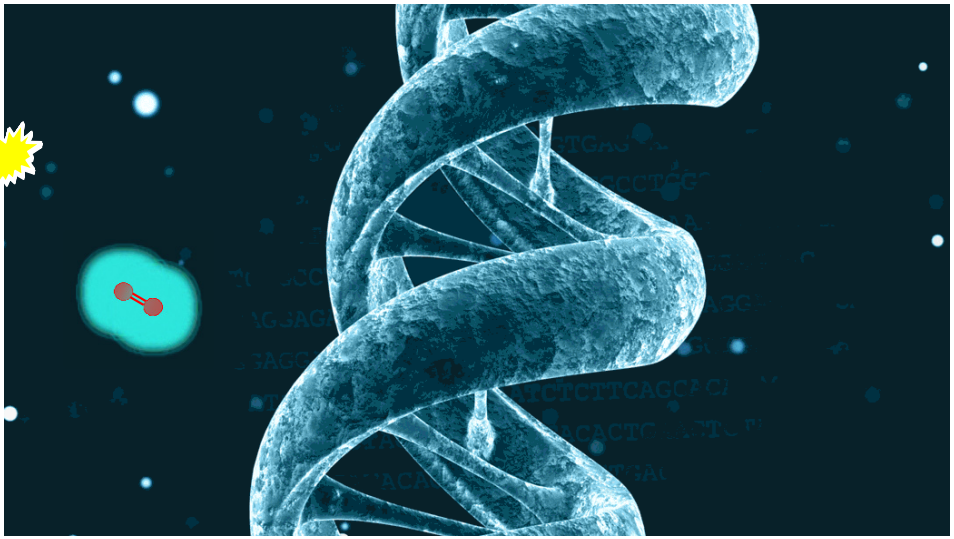
Singlet O_2 and DNA damage



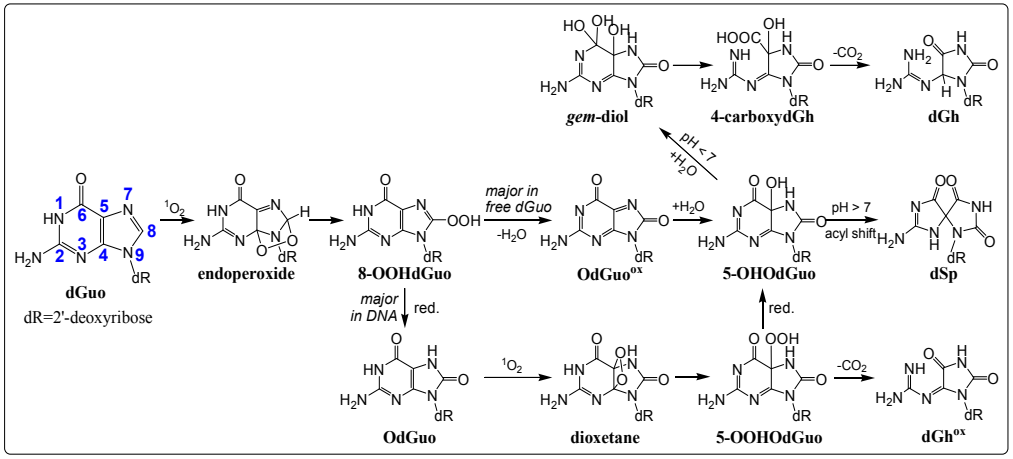


https://nasa.tumblr.com/post/151016092994/why-sequencing-dna-in-space-is-a-big-deal

Guanine is the exclusive DNA target for $^1O_2$

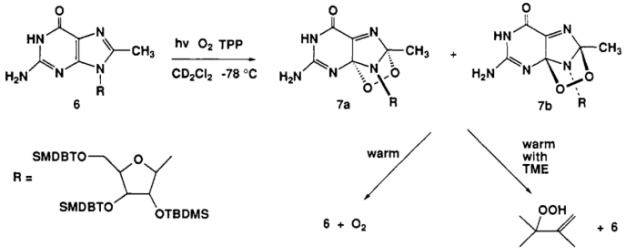
- Mutation such as G-C → A-T transversion
- DNA-protein cross-link
- Cell death

Guanine oxidation mechanism and questions



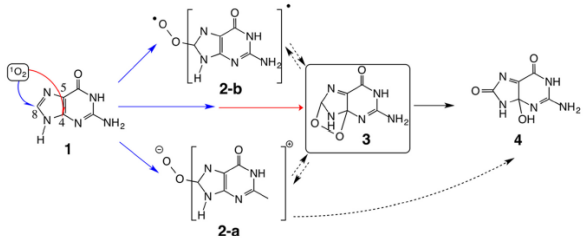
(1) Sheu, C.; Foote, C. S. *J. Am. Chem. Soc.* **1993,** *115*, 10446-10447; (2) Ye, Y.; Muller, J. G.; Luo, W.; Mayne, C. L.; Shallop, A. J.; Jones, R. A.; Burrows, C. J. *J. Am. Chem. Soc.* **2003,** *125*, 13926-13927; (3) McCallum, J. E. B.; Kuniyoshi, C. Y.; Foote, C. S. *J. Am. Chem. Soc.* **2004,** *126*, 16777-16782; (4) Cadet, J.; Ravanat, J.-L.; Martinez, G. R.; Medeiros, M. H. G.; Mascio, P. D. *Photochem. Photobiol.* **2006,** *82*, 1219-1225;(5) Neeley, W. L.; Essigmann, J. M. *Chem. Res. Toxicol.* **2006,** *19*, 491-505; (6) Fleming, A. M.; Burrows, C. J. *Free Radic. Biol. Med.* **2017,** *107*, 35-52.

Q1 Reaction intermediate



NMR of photooxidation of a model compound at -78 °C , C. Sheu and C. Foote, *JACS*, 1993, 115, 10446

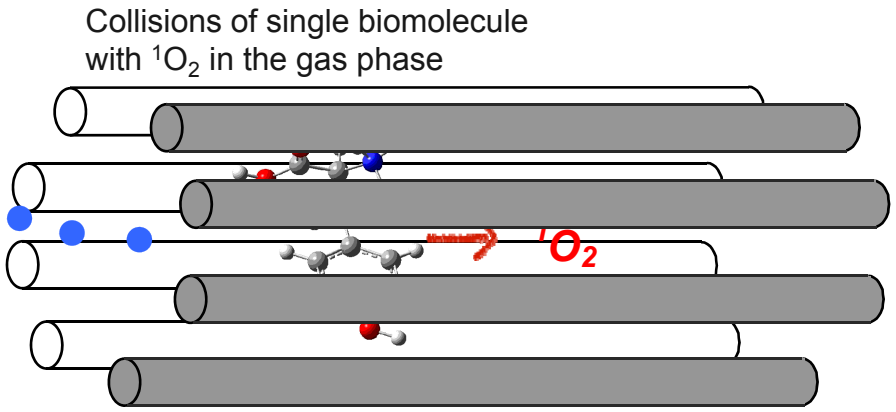
Q2 Concerted ***OR*** stepwise O_2 addition



R Grüber, A Monari, E. Dumont, *JPC A,* 2014, 118, 11612

Q3 Activation barrier and kinetics

A approach different than solution-phase photooxidation



mass spectrometry

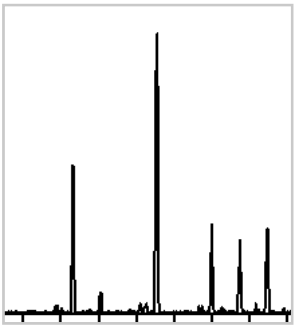
- products *m/z and* structure by MS, MS^2
- capture transient intermediates
- intrinsic reactivity: energy dependence, activation barriers, etc.

computation

- electronic structure calculations
- reaction PES and statistical properties
- direct dynamics simulation

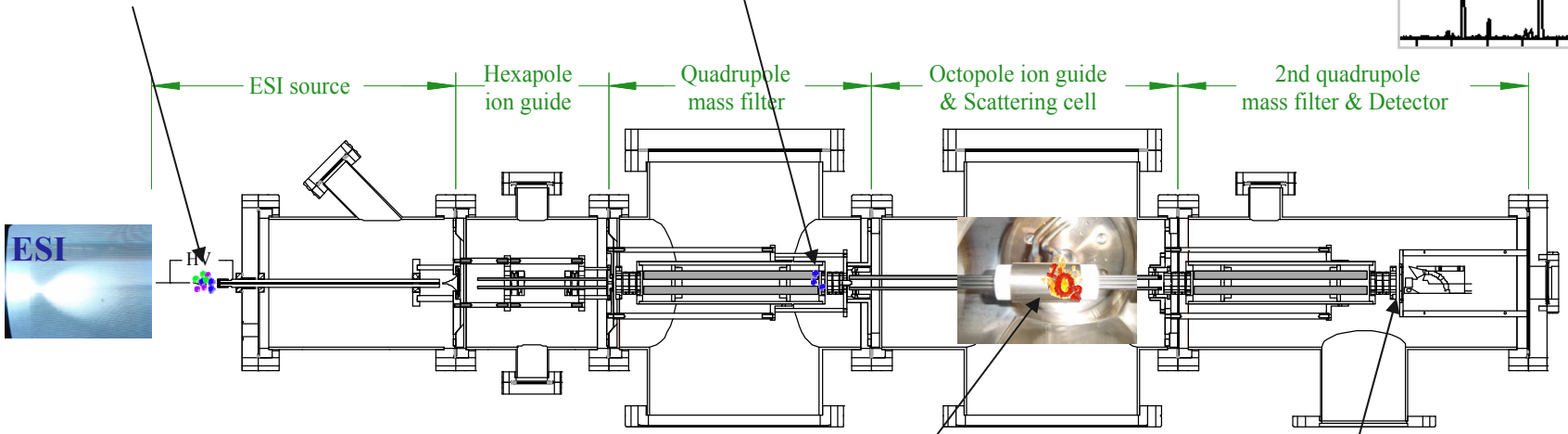
Guided-Ion-Beam Tandem Mass Spectrometer

$$\sigma = k / v_{rel} = \frac{I_{product} k_B T}{I_{reac\,tant} P_{cell} l_{cell}}$$



1. Generation of biomolecular ions by ESI

2. Ions are passed into a quadrupole for mass selection

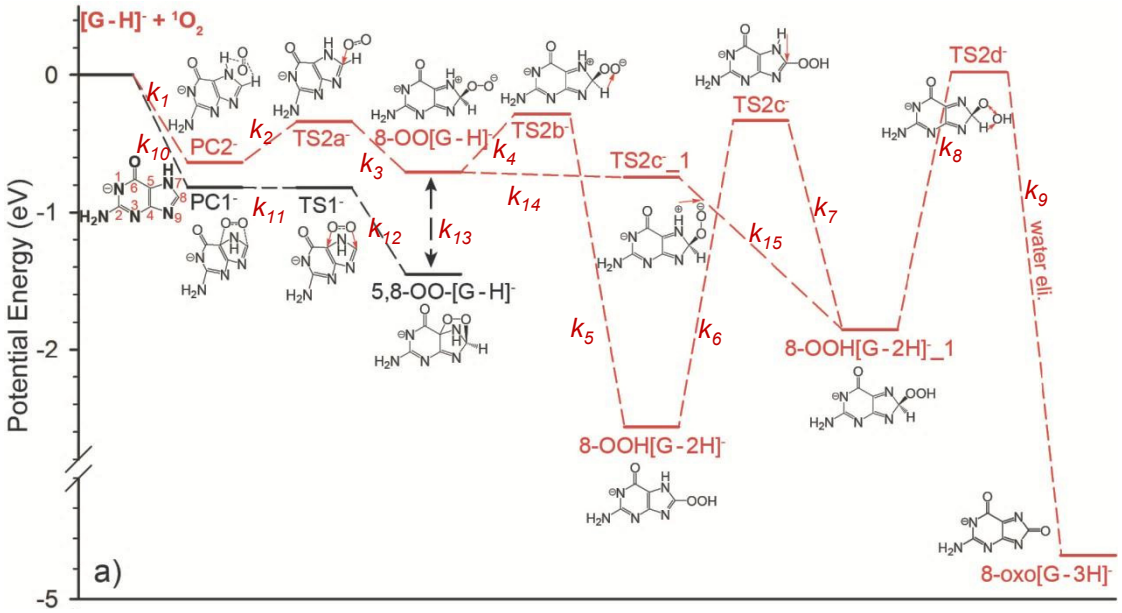


3. Mass-selected ions are guided into an octopole surrounded by a collision cell, and scattered from $^1O_2$ contained within

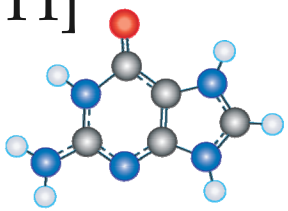
4. Product ions are m/z analyzed & counted

Y. Fang and J. Liu, *JPC A*. 2009, 113, 11250-11261

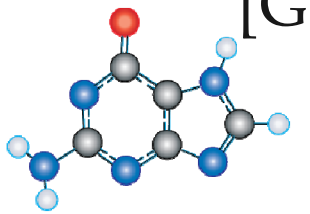
1. What we wanted to do first was to capture reaction intermediates

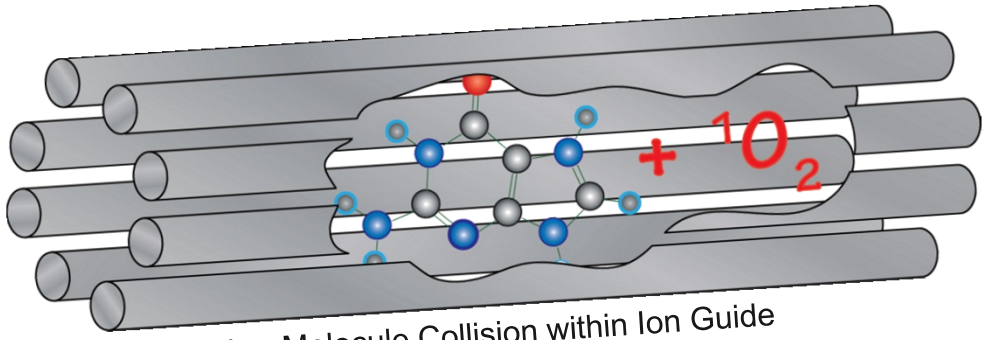


Protonated
$[G + H]^+$



Deprotonated
$[G - H]^-$

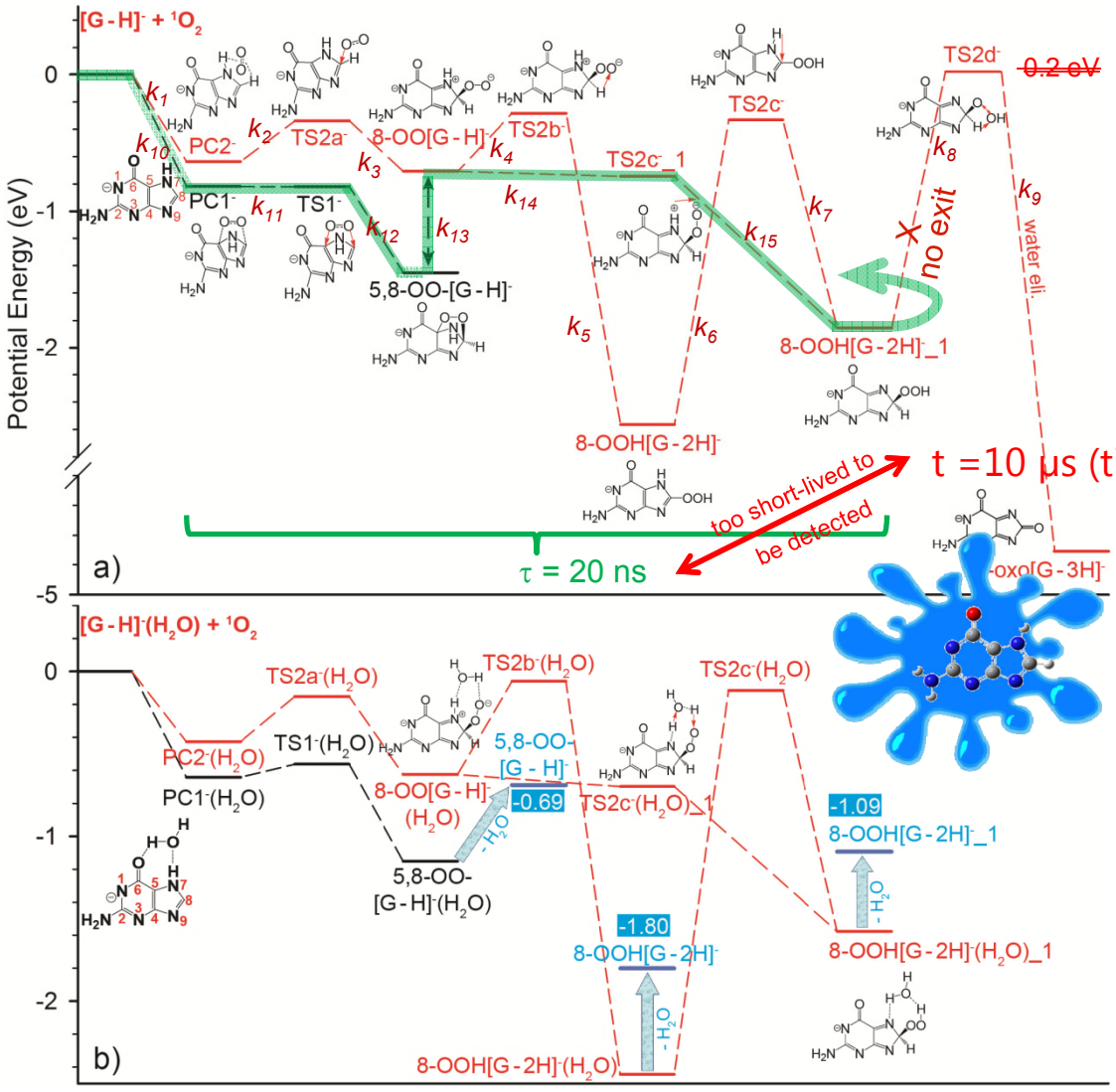




Ion-Molecule Collision within Ion Guide

products

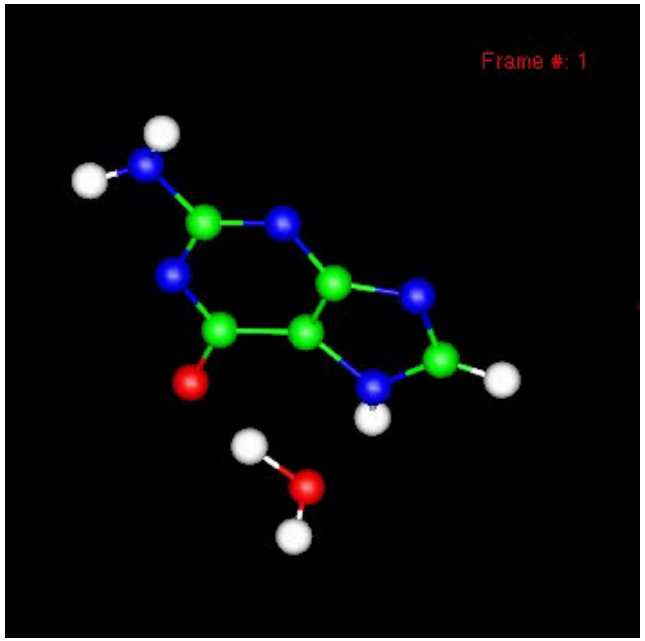
RRKM analysis and implications



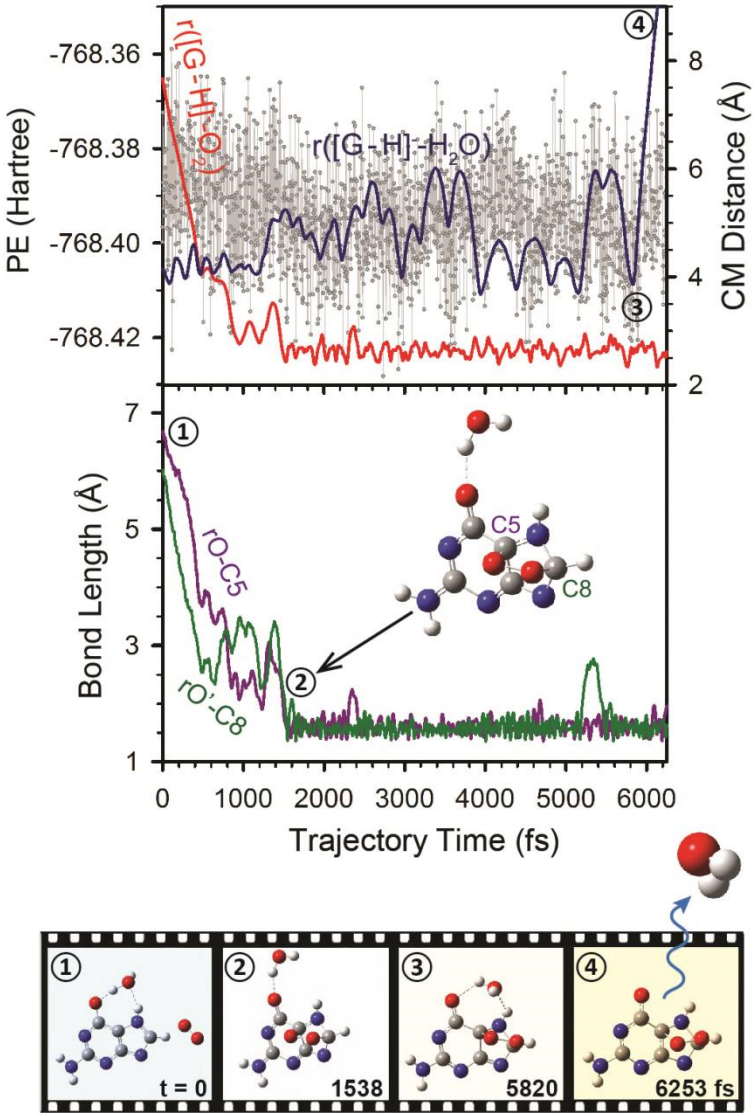
Estimate unimolecular *k* using *RRKM* theory

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

Direct dynamics simulation of guanine ion-beam scattering

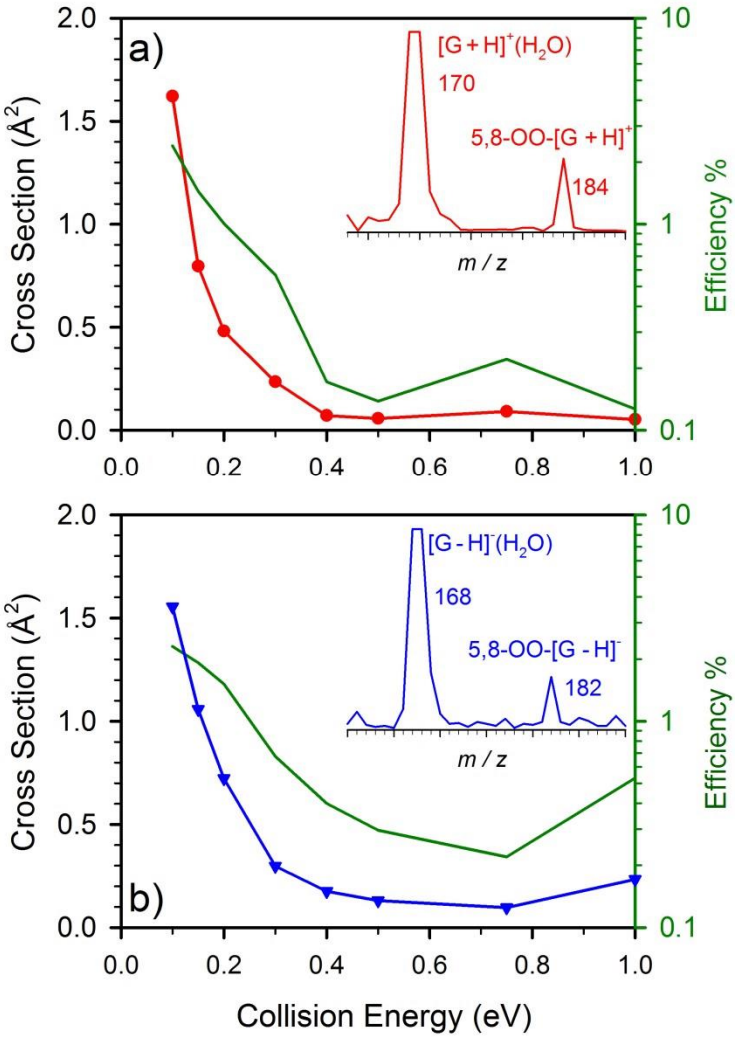


simulated at B3LYP/6-31G*



→ Form a *5,8-endoperoxide* rather than a 4,8-endoperoxide that was proposed for neutral guanosine

Reactions of $^1O_2$ with $[G + H]^+(H_2O)$ and $[G - H]^-(H_2O)$



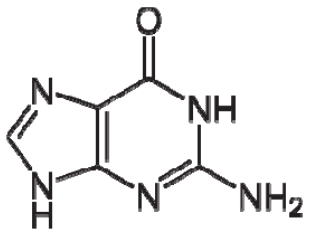
→ Capture of transient endoperoxides via water evaporation cooling

→ Experimental assessment of the activation barrier associated with O_2 addition to guanine

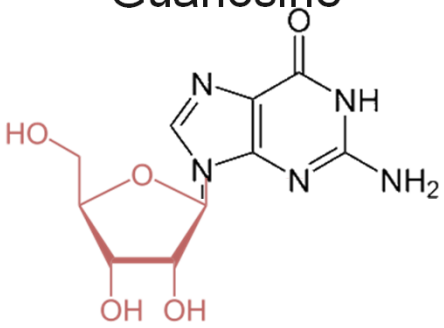
Wenchao Lu and J. Liu, *Chem. Eur. J.*, 2016, 22, 3127-3138

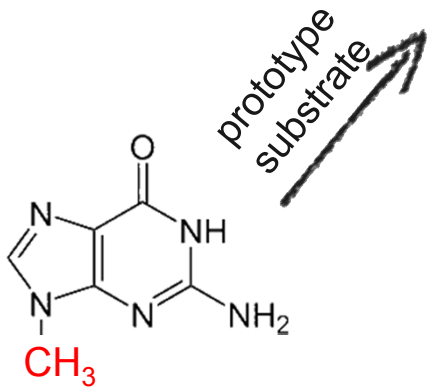
2. More about O_2 addition mechanism: — A model study using 9MG

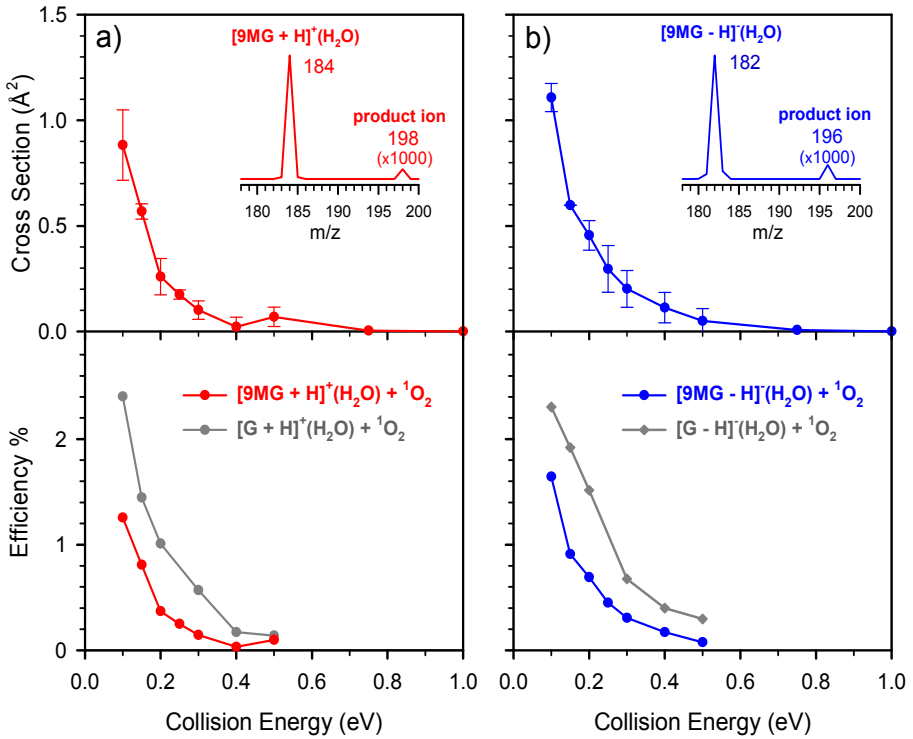
Guanine base



Guanosine



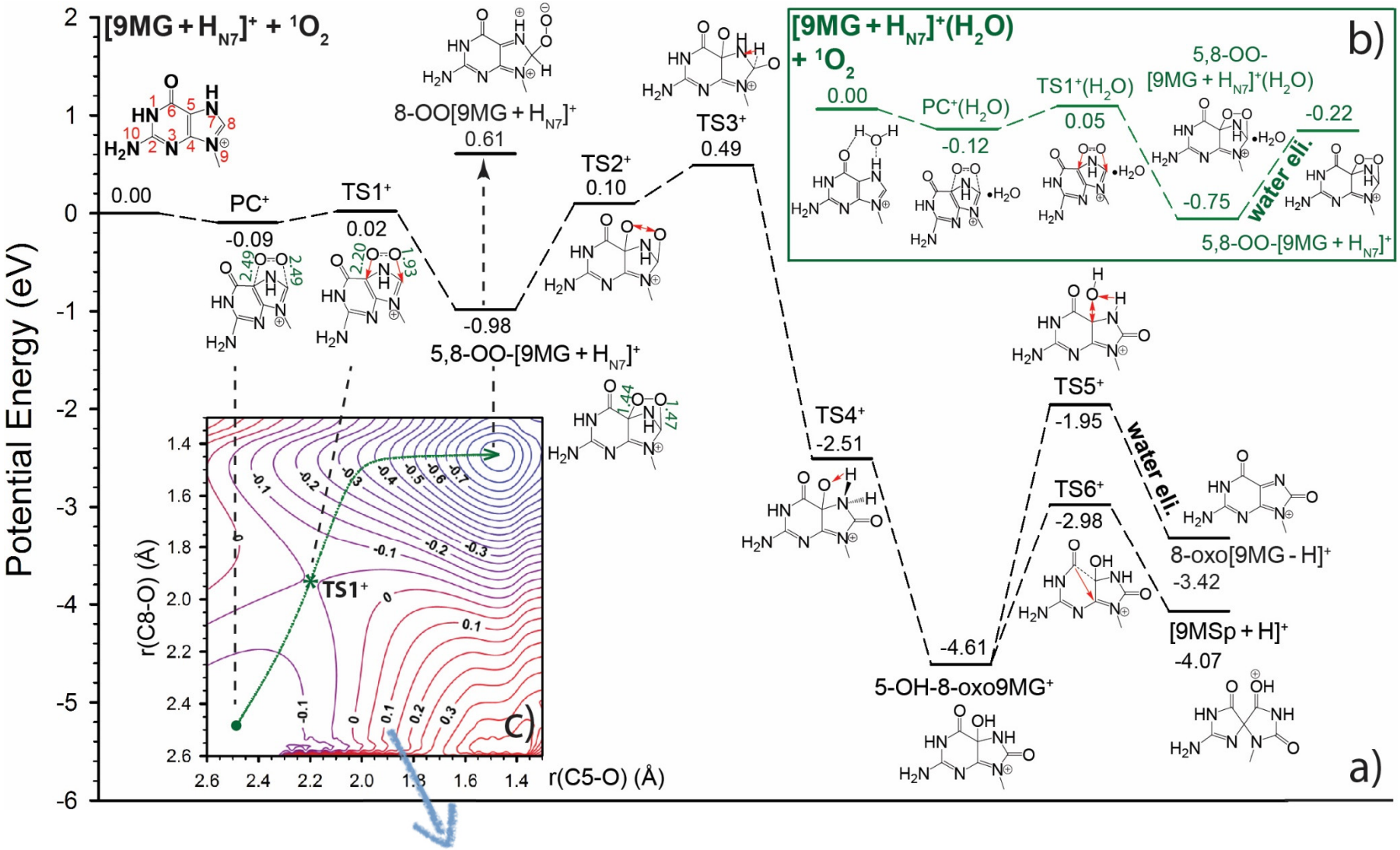




9-Methylguanine (9MG) has similar hydration, ionization, pK_a and reaction ΔH as guanosine

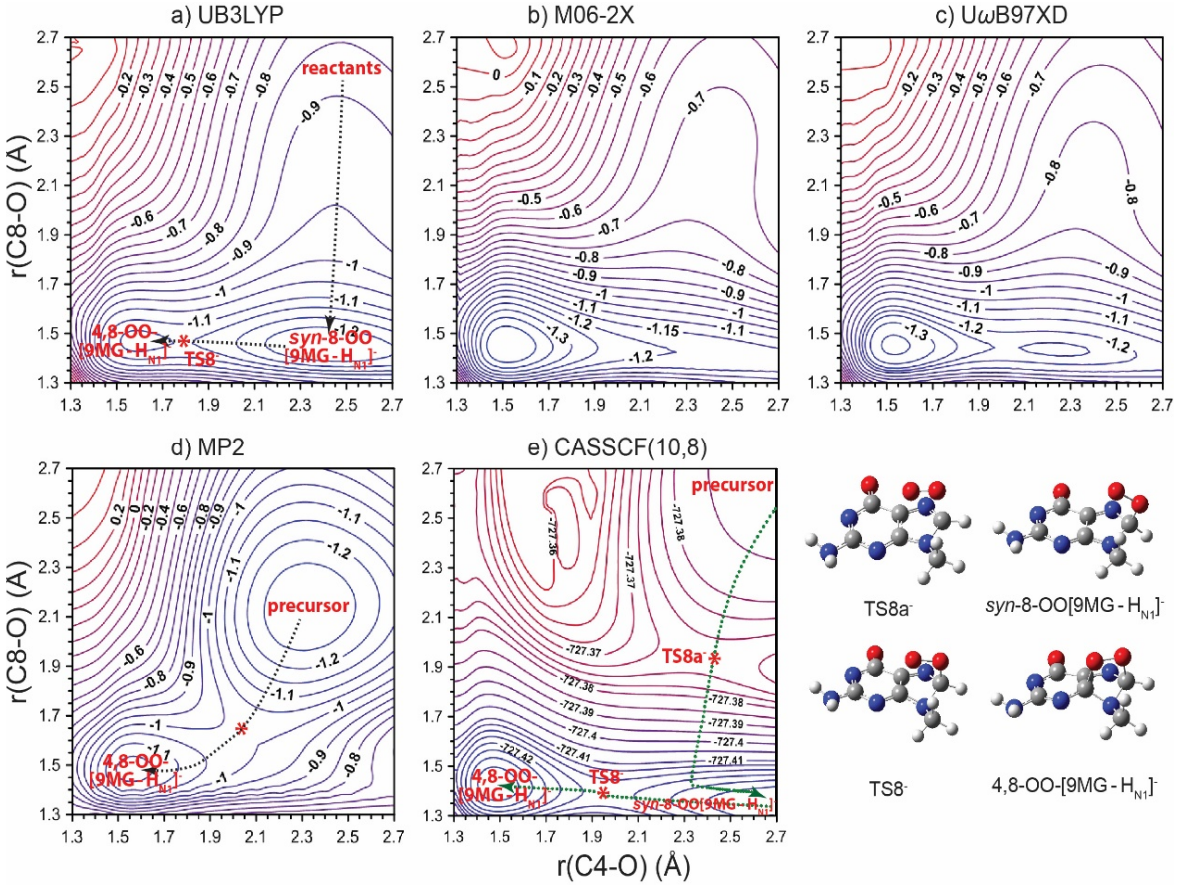
Wenchao Lu, Huayu Teng, and J. Liu, *PCCP*, 2016, **18**, 15223-15234

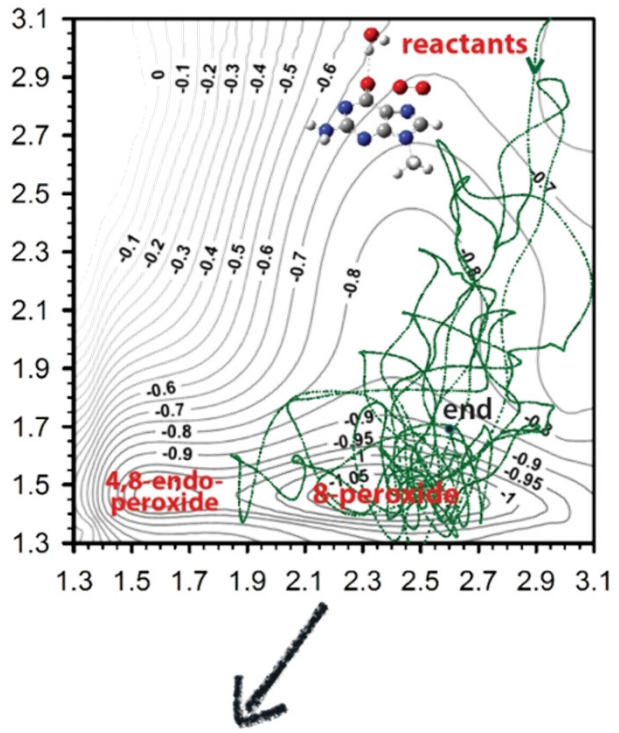
pH-dependent $^1O_2$ addition



[9MG + H]$^+$ and [G + H]$^+$: a concerted cycloaddition to a 5,8-endoperoxide different than neutral guanosine which leads to a 4,8-endoperoixde

Switches to stepwise addition upon deprotonation

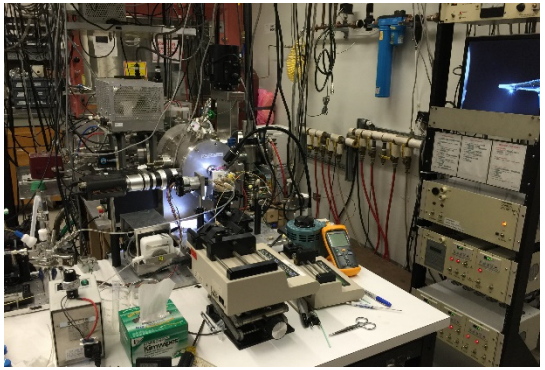


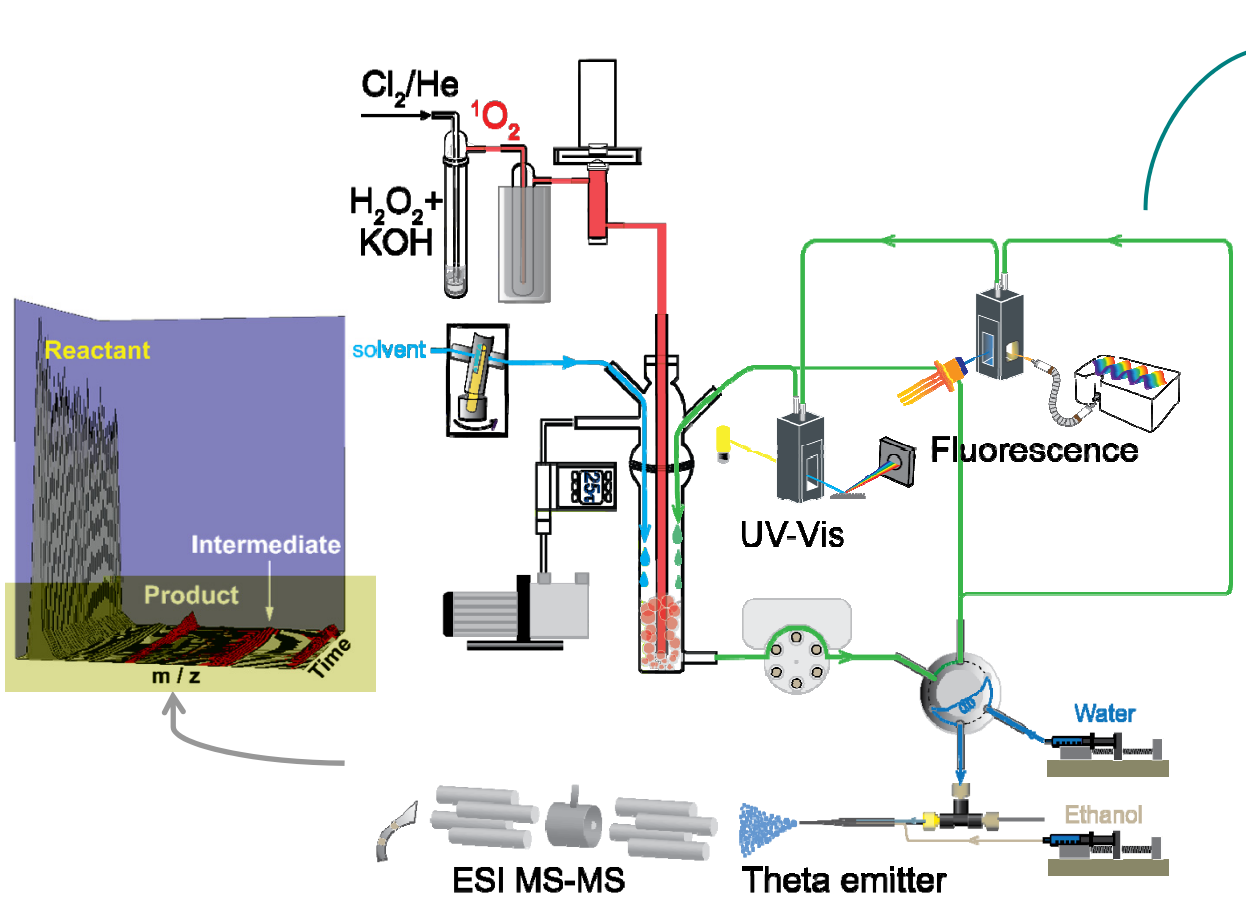


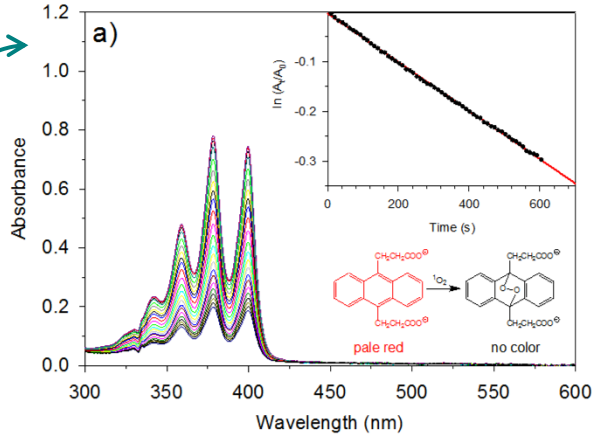
$[9MG - H]^- + {}^1O_2$:

1) Different than neutral guanosine in a stepwise addition
2) Different than $[9MG + H]^+$ in 4,8-OO-$[9MG - H]^-$ vs. 5,8-OO-$9MG + H]^+$

3. From gas-phase dynamics to solution-phase kinetics and product distributions







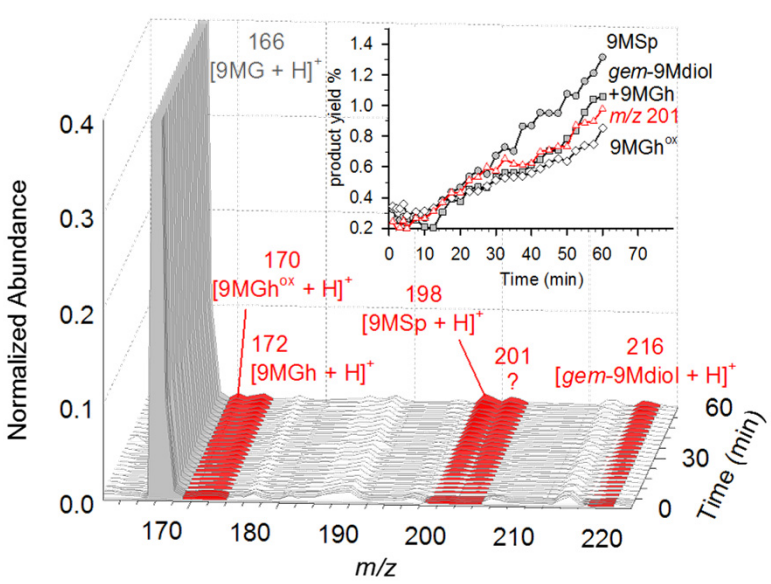
Fangwei Liu, Wenchao Lu, Vincent Yin, and J. Liu, *J. Am. Soc. Mass. Spec.*, 2016, 27, 59-72.

Kinetics of 9MG + $^1O_2$

pH = 7

9MSp : (*gem*-9Mdiol + 9MGh) : 9MGh^{ox}

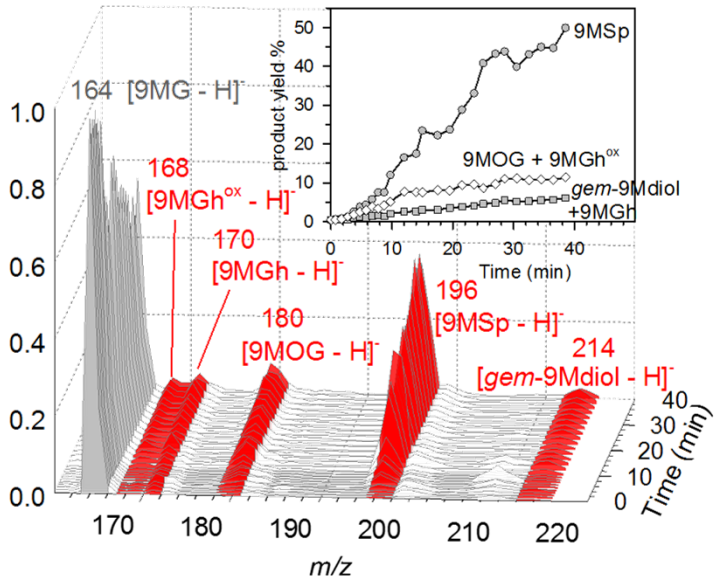
0.45 0.33 0.22



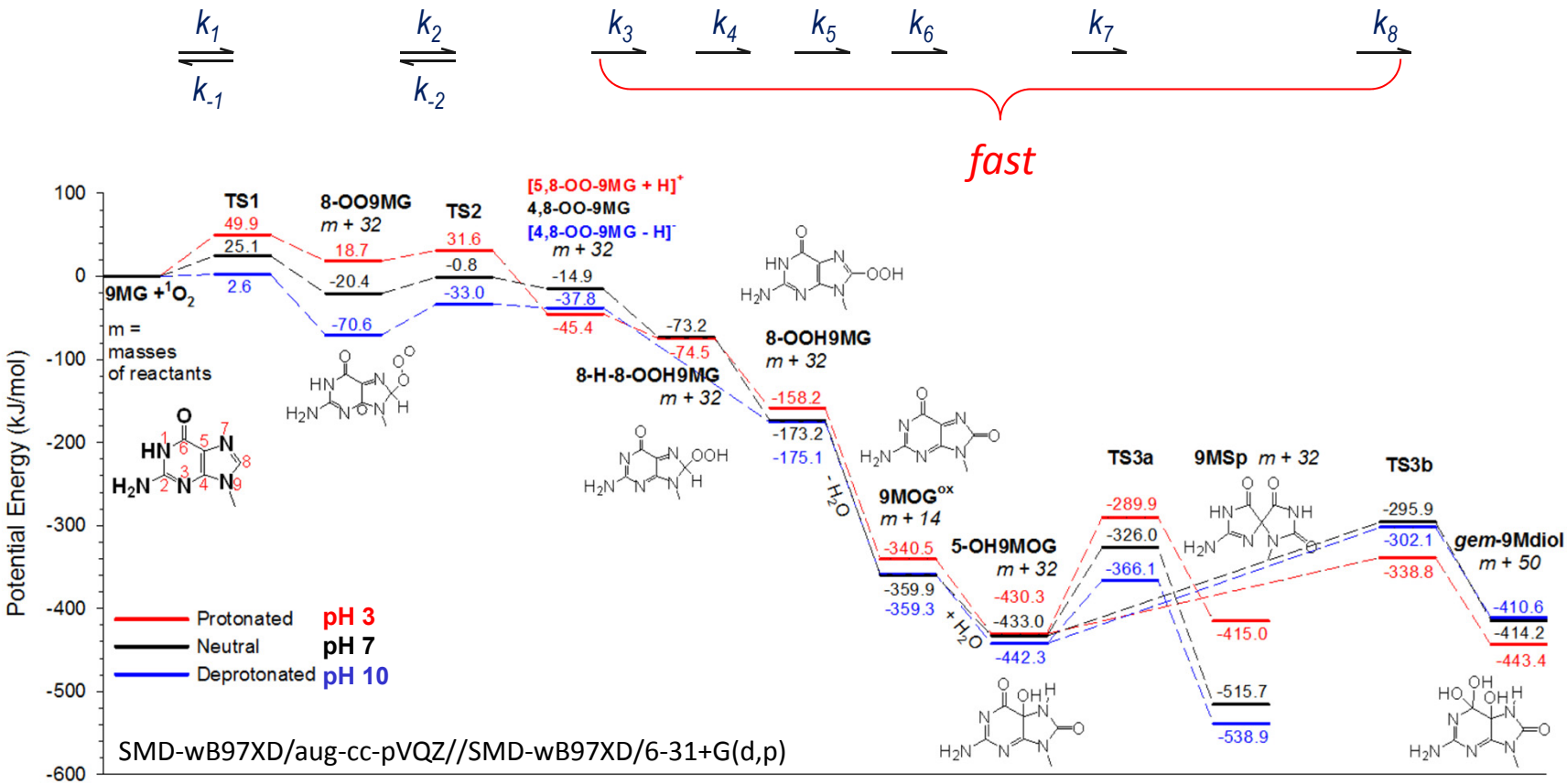
pH = 10

9MSp : (*gem*-9Mdiol + 9MGh) : (9MOG + 9MGh^{ox})

0.72 0.09 0.19



Solution-phase PES & kinetics

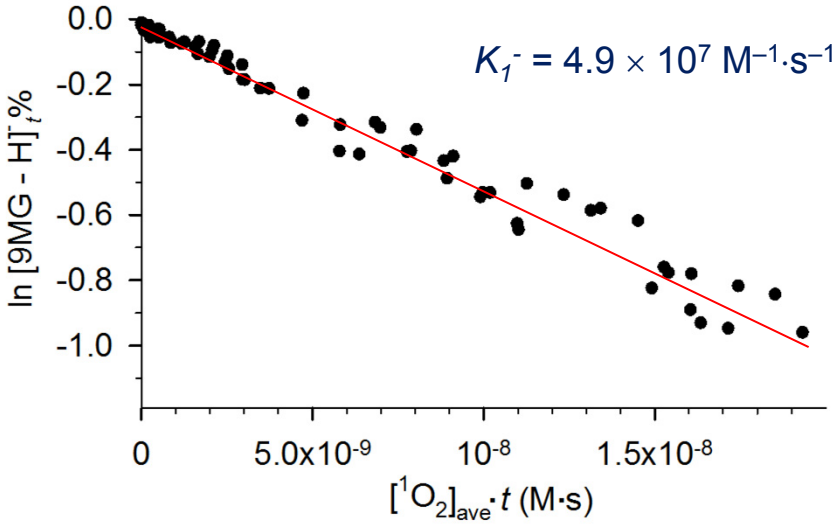


- Deprotonated guanine favors formation of Sp.
- Oxidation of protonated guanine is blocked by early-stage barriers.
- *Initial $^1O_2$ addition* is rate-limiting.

Oxidation rate constant

$$-\frac{\mathrm{d}[[9\mathrm{MG}-\mathrm{H}]^-]}{\mathrm{d}t} = k_1^-[[9\mathrm{MG}-\mathrm{H}]^-][^1\mathrm{O}_2]$$

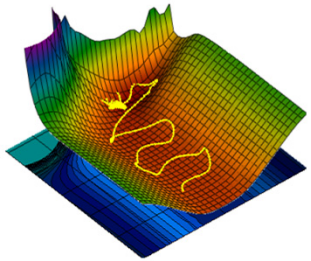
$$ln\,[9\mathrm{MG}-\mathrm{H}]^-_t\% = \frac{product_i}{\Sigma_i\,(reactant + product_i)} = -k_1^-[^1\mathrm{O}_2]_{\mathrm{ave}}\cdot t$$



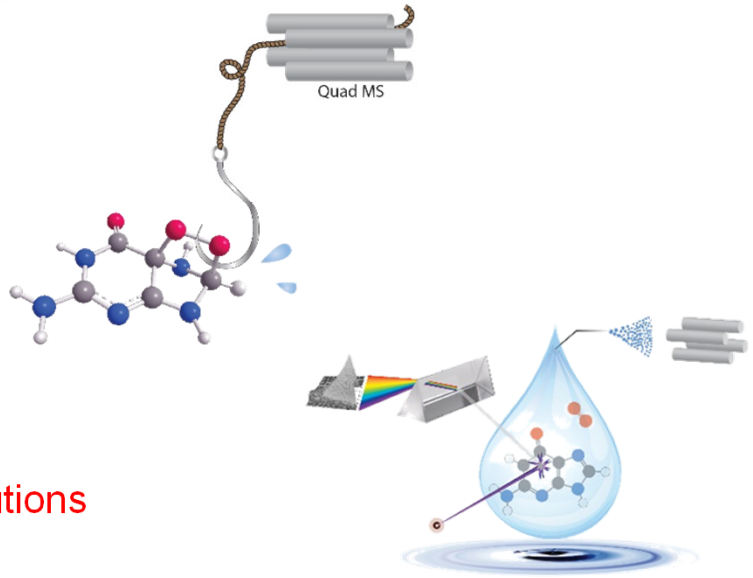
Wenchao Lu, Yan Sun, Wenjing Zhou, and J Liu, *JPC B,* 2018, **122**, 40-53

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

Gas phase				Aqueous solution		
	$^1O_2$ addition	**Intermediates**	**Efficiency**		**End products**	**k_1**
protonated	concerted	5,8-endoperoxide	1.3%	**pH 3**	none	—
neutral	stepwise	4,8-endoperoxide	—	**pH 7**	9MSp, gem-9Mdiol, 9MGh, 9MGh^{ox}	1.2×10^6 $M^{-1}{\cdot}s^{-1}$
deprotonated			1.7%	**pH 10**	9MSp, gem-9Mdiol, 9MGh, 9MGh^{ox}, 9MOG	4.6×10^7 $M^{-1}{\cdot}s^{-1}$

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Yan Sun
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Bilal Karatash

CHE-1464171

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