Effects of Intra-Base Pair Proton Transfer on Dissociation and Singlet Oxygenation of 9-Methyl-8-Oxoguanine–1-Methyl-Cytosine Base-Pair Radical Cations [9MOG·1MC]•+

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Biological Relevance of OG$^{\bullet+}$

➢ Both G$^{\bullet+}$ and G$^{\bullet+}$ form readily under oxidative stress in cells.

| species	$E°$ (vs. NHE, V)	species	AIP (eV)	
			gas phase	solution
8-oxoguanosine (OG)	0.74[1]	8-oxoguanine	6.93[2]	
	↕ 0.55		↕ 0.75	
guanosine (G)	1.29[3]	guanine	7.68[4]	4.42[5]
adenosine (A)	1.42[3]	adenine	8.26[4a, 6]	4.81[5]
deoxycytidine (C)	1.6[3]	cytosine	8.66[4a, 6]	4.91[5]
thymidine (T)	1.7[3]	thymine	8.82[4a, 7]	5.05[5]
		PO_4^{3-}	unstable	8.4 (vertical)[8]
		HPO_4^{2-}	unstable	8.9[8]
		$H_2PO_4^-$	4.57[9]	9.5[8]
		deoxyribose		9.4-9.7[8b, 10]

[1] S. Steenken, et al., *J. Am. Chem. Soc.* **2000**, *122*, 2373.
[2] F. Prat, et al., *J. Am. Chem. Soc.* **1998**, *120*, 845.
[3] a) S. Steenken, et al, *J. Am. Chem. Soc.* **1997**, *119*, 617;
    b) C. J. Burrows, J. G. Muller, *Chem. Rev.* **1998**, *98*, 1109.
[4] a) M. Schwell, et al, *Top. Curr. Chem.* **2015**, *355*, 155;
    b) J. Zhou, et al., *J. Phys. Chem. A* **2009**, *113*, 4829.
[5] C. E. Crespo-Hernández, et al., *J. Phys. Chem. A* **2004**, *108*, 6373.
[6] D. Touboul, et al., *J. Chem. Phys.* **2013**, *138*, 094203.
[7] H.-W. Jochims, et al., *Chem. Phys.* **2005**, *314*, 263.
[8] a) E. Pluharova, et al., *J. Phys. Chem. B* **2012**, *116*, 13254;
    b) C. A. Schroeder, et al., *J. Am. Chem. Soc.* **2015**, *137*, 201.
[9] X.-B. Wang, et al, *J. Phys. Chem. A* **2001**, *105*, 10468.
[10] L. P. Candeias, et al. *J. Am. Chem. Soc.* **1992**, *114*, 699.

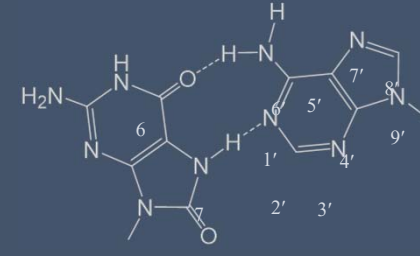➢ Guanine radical cation G$^{\bullet+}$ is the precursor of OG
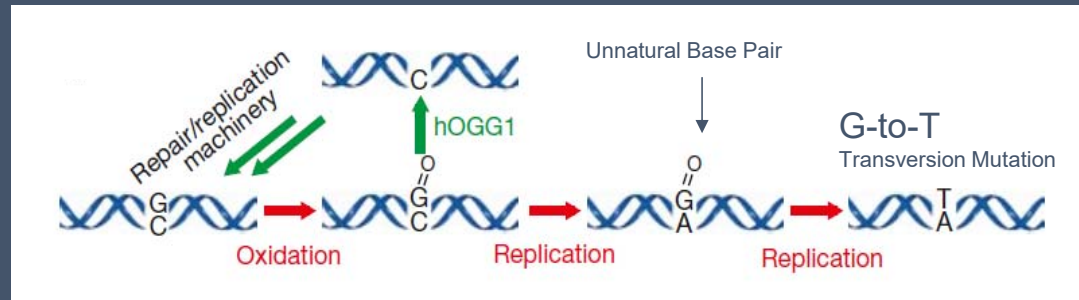
OG-containing Base Pairs in DNA
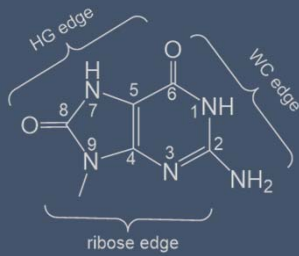
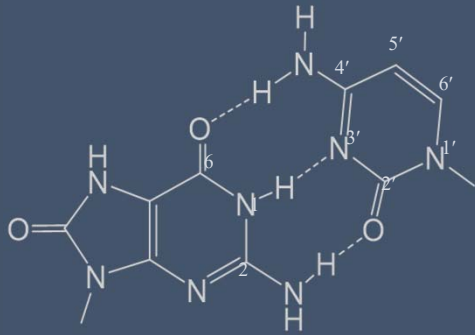L. A. Lipscomb, et al., *PNAS* **1995**, *92*, 719
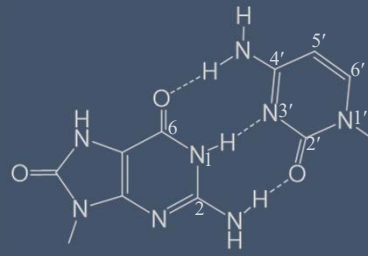
Watson-Crick OG·C

Hoogsteen OG·A

S. D. Bruner, et al., *Nature*, **2000**, *403*, 859

**In what context we examined
the dissociation and singlet oxygenation of [OG·C]$^{\bullet+}$**

Watson-Crick OG·C

The synergistic damage of the OG·C mismatch pair, if not repaired, upon the attack of **ionizing radiation** **and** **reactive oxygen species (ROS)** **simultaneously**

Practical interest: Explore addictive effects of combining **ionizing radiation-based radiotherapy** **and** **singlet O$_2$-based photodynamic therapy** **in cancer treatment.**

Experimental Approaches for G$^{\bullet+}$/OG$^{\bullet+}$ Chemistry

Photolysis/radiolysis in solution

Ionization of Purine Nucleosides and Nucleotides and Their Components by 193-nm Laser Photolysis in Aqueous Solution: Model Studies for Oxidative Damage of DNA[1]

L. P. Candeias and S. Steenken*

Contribution from the Max-Planck-Institut für Strahlenchemie, D-4330 Mülheim, Germany.
Received July 1, 1991. Revised Manuscript Received September 9, 1991.

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Article

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Lifetimes and Reaction Pathways of Guanine Radical Cations and Neutral Guanine Radicals in an Oligonucleotide in Aqueous Solutions

Yekaterina Rokhlenko, Nicholas E. Geacintov, and Vladimir Shafirovich*

Chemistry Department, New York University, 31 Washington Place, New York, New York 10003-5180, United States

J. Phys. Chem. B 2006, 110, 24171–24180   24171

The Guanine Cation Radical: Investigation of Deprotonation States by ESR and DFT

Amitava Adhikary,* Anil Kumar, David Becker, and Michael D. Sevilla*

Department of Chemistry, Oakland University, Rochester, Michigan 48309
Received: July 11, 2006; In Final Form: September 12, 2006

THE JOURNAL OF PHYSICAL CHEMISTRY Letters

Letter

pubs.acs.org/JPCL

Proton Transfer of Guanine Radical Cations Studied by Time-Resolved Resonance Raman Spectroscopy Combined with Pulse Radiolysis

Jungkweon Choi,*†‡ Cheolhee Yang,‡§ Mamoru Fujitsuka,† Sachiko Tojo,† Hyocheol Ihee,‡§ and Tetsuro Majima*†

†The Institute of Scientific and Industrial Research (SANKEN), Osaka University, Mihogaoka 8-1, Ibaraki, Osaka 567-0047, Japan
‡Center for Nanomaterials and Chemical Reactions, Institute for Basic Science (IBS), Daejeon 305-701, Republic of Korea
§Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Republic of Korea

Formation of radical cations in the gas phase via collision-induced intramolecular electron transfer and dissociation of copper complex

$$[Cu^{II}G_3]^{\bullet 2+} \xrightarrow{redox\ separation} G[Cu^{II}G_2]^+ + G^{\bullet+}$$

Tuning the gas phase redox properties of copper(ii) ternary complexes of terpyridines to control the formation of nucleobase radical cations† ‡ §

Adrian K. Y. Lam,[abc] Brendan F. Abrahams,[a] Martin J. Grannas,[a] W. David McFadyen[*a] and Richard A. J. O'Hair[*abc]

J. Phys. Chem. B 2007, 111, 11075–11082   11075

Gas-Phase Formation of Radical Cations of Monomers and Dimers of Guanosine by Collision-Induced Dissociation of Cu(II)–Guanosine Complexes

Ping Cheng and Diethard K. Bohme*

Department of Chemistry, Centre for Research in Mass Spectrometry and Centre for Research in Earth and Space Science, York University, Toronto, Ontario, Canada, M3J 1P3
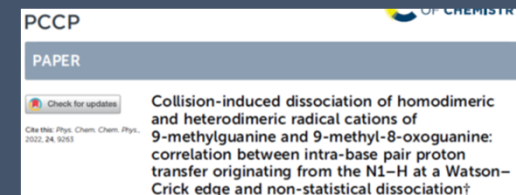Received: March 9, 2007; In Final Form: July 6, 2007

THE JOURNAL OF PHYSICAL CHEMISTRY A

pubs.acs.org/JPCA

Article

Dynamics and Multiconfiguration Potential Energy Surface for the Singlet O$_2$ Reactions with Radical Cations of Guanine, 9-Methylguanine, 2'-Deoxyguanosine, and Guanosine

Published as part of The Journal of Physical Chemistry virtual special issue "Cheuk-Yiu Ng Festschrift".

Yan Sun, Midas Tsai, May Myat Moe, and Jianbo Liu*

Cite This: J. Phys. Chem. A 2021, 125, 1564–1576   Read Online

PCCP

PAPER

Check for updates

Cite this: Phys. Chem. Chem. Phys., 2022, 24, 9263

Collision-induced dissociation of homodimeric and heterodimeric radical cations of 9-methylguanine and 9-methyl-8-oxoguanine: correlation between intra-base pair proton transfer originating from the N1–H at a Watson–Crick edge and non-statistical dissociation†

- What was actually measured in solution: neutral [G – H]$^\bullet$ and OG$^{\bullet+}$/[G – H]$^\bullet$

$$G \xrightarrow{radiolysis} G^{\bullet+}(pk_a = 3.9) \xrightarrow{deprotonation} [G - H_{N1}]^\bullet + H^+$$

- Radical cations formed in the DNA duplex retain more cationic character than would isolated radical and they persist sufficiently long to react with ROS and RNS.
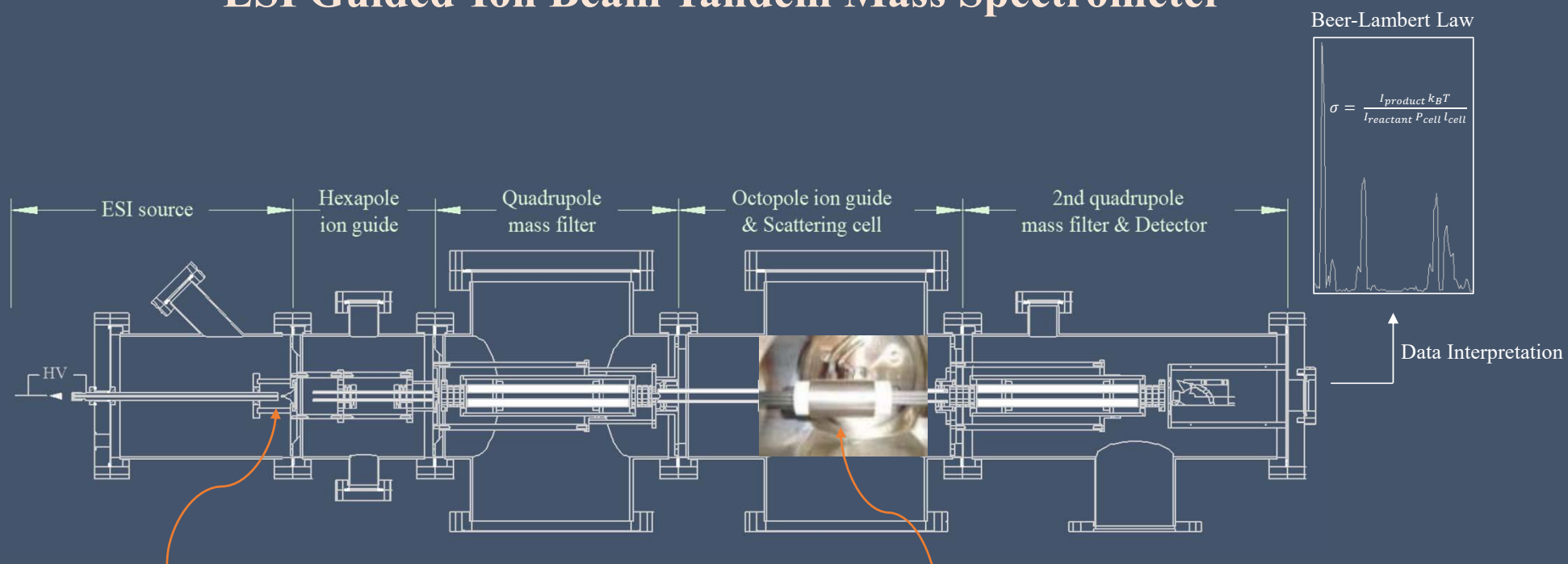- Warrant the measurement of radical cation reactivity directly

ESI Guided-Ion Beam Tandem Mass Spectrometer

Beer-Lambert Law

$$\sigma = \frac{I_{product}\, k_B T}{I_{reactant}\, P_{cell}\, l_{cell}}$$

Data Interpretation

ESI source — Hexapole ion guide — Quadrupole mass filter — Octopole ion guide & Scattering cell — 2nd quadrupole mass filter & Detector

HV

target gas
$^1O_2$ or Xe

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

$[Cu^{II}(9MOG\cdot1MC)_3]^{\bullet 2+} \rightarrow [Cu^I(9MOG\cdot1MC)_2]^+$ and $[9MOG\cdot1MC]^{\bullet +}$

9MOG: 9-methyl-8-oxoguanine to mimic 8-oxoguanosine
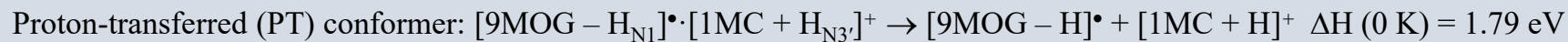
1MC: 1-methycytosine to mimic cytidine

6

Exp # 1: Intra-Base Pair PT of [9MOG·1MC]$^{•+}$
explored using collision-induced dissociation (CID) tandem MS

9MOG$^{•+}$·1MC

[9MOG − H$_{N1}$]$^{•}$·[1MC + H$_{N3'}$]$^{+}$

Relative population = 62%

38%
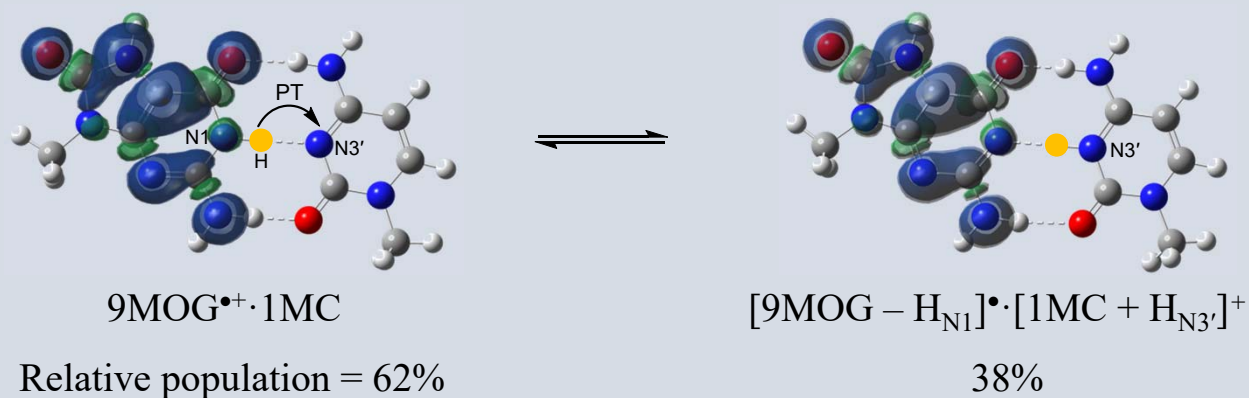
Thermodynamics Equilibrium of

9MOG$^{•+}$·1MC $\rightleftharpoons$ [9MOG − H$_{N1}$]$^{•}$·[1MC + H$_{N3'}$]$^{+}$

Conventional conformer: 9MOG$^{•+}$·1MC $\rightarrow$ 9MOG$^{•+}$ + 1MC ΔH (0 K) = 1.87 eV

Proton-transferred (PT) conformer: [9MOG − H$_{N1}$]$^{•}$·[1MC + H$_{N3'}$]$^{+}$ $\rightarrow$ [9MOG − H]$^{•}$ + [1MC + H]$^{+}$ ΔH (0 K) = 1.79 eV

Insight into Kinetics of [9MOG·1MC]$^{•+}$ Dissociation in Xe CID

$[9MOG - H_{N1}]^{•} \cdot [1MC + H_{N3'}]^{+}$ (PT) $\rightarrow$ $[9MOG - H]^{•}$ + $[1MC + H]^{+}$ $\gg$ $9MOG^{•+} \cdot 1MC$ (conventional) $\rightarrow$ $9MOG^{•+}$ + 1MC
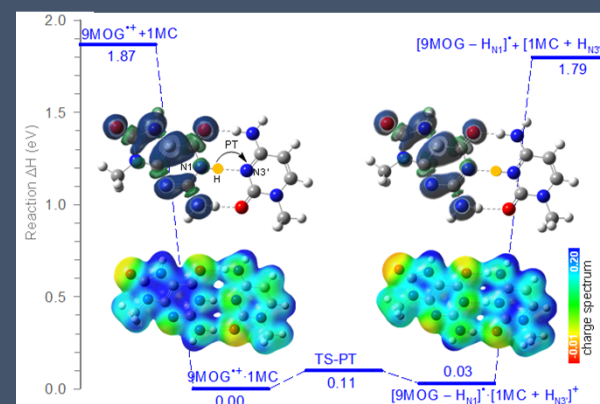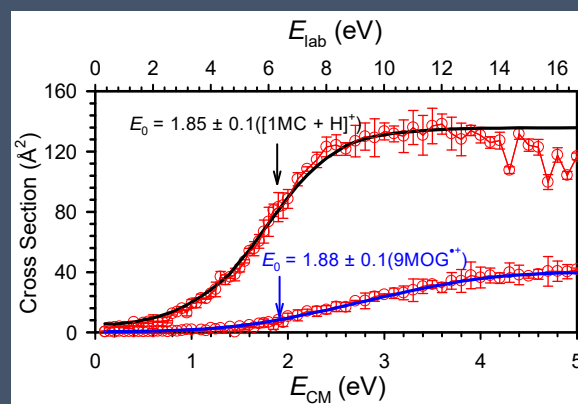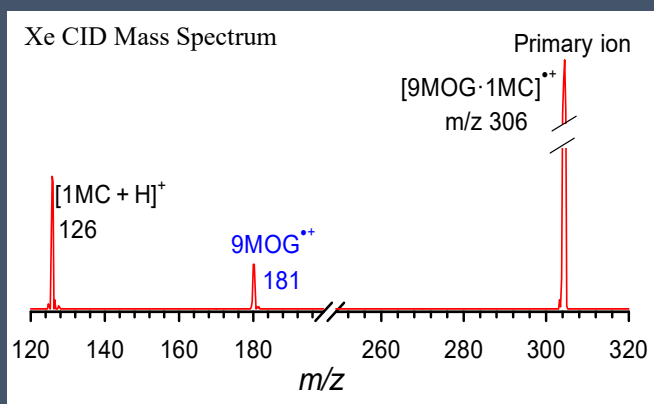
Implicated that   i) the population of PT conformer > conventional conformer upon collisional activation

       or   ii) the dissociation rate $k_{PT} > k_{conventional}$
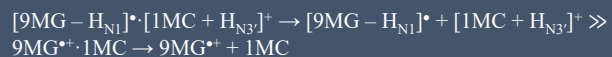
       or   iii) both i and ii

Non-Statistical Dissociation: A Characteristic Behavior of WC Base Pairs (?)

accompanied with an intra-base pair PT originating from N-H at the WC-edge

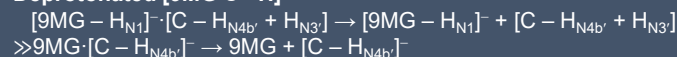### Kinetics modeling in statistical theory framework
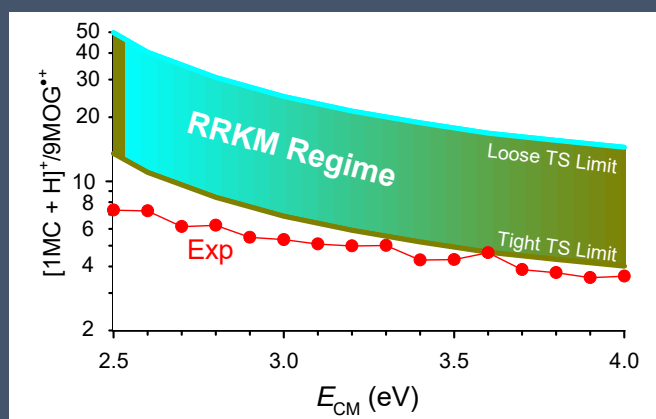
- ➤ RRKM assumption: energy is randomized and distributed statistically among all energetically accessible states at TS

- ➤ Dissociation: no reverse barrier, tight and loose TS were assumed based on base pair and product probabilities
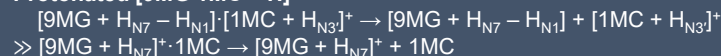
$[9MG - H_{N1}]^\bullet \cdot [1MC + H_{N3'}]^+ \rightarrow [9MG - H_{N1}]^\bullet + [1MC + H_{N3'}]^+ \gg$
$9MG^{\bullet+} \cdot 1MC \rightarrow 9MG^{\bullet+} + 1MC$

Previous findings of non-statistical CID in other WC-base pairs

Deprotonated [9MG·C - H]⁺
$[9MG - H_{N1}]^- \cdot [C - H_{N4b'} + H_{N3'}] \rightarrow [9MG - H_{N1}]^- + [C - H_{N4b'} + H_{N3'}]$
$\gg 9MG \cdot [C - H_{N4b'}]^- \rightarrow 9MG + [C - H_{N4b'}]^-$

PCCP., 2016, **18**, 32222
PCCP., 2017, **19**, 30616

Protonated [9MG·1MC + H]⁺
$[9MG + H_{N7} - H_{N1}] \cdot [1MC + H_{N3'}]^+ \rightarrow [9MG + H_{N7} - H_{N1}] + [1MC + H_{N3'}]^+$
$\gg [9MG + H_{N7}]^+ \cdot 1MC \rightarrow [9MG + H_{N7}]^+ + 1MC$

PCCP., 2020, **22**, 24986

[9MG·9MG]•⁺ and [9MG·9MOG]•⁺
$[9MOG - H_{N1}]^\bullet \cdot [9MG + H_{N7}]^+ \rightarrow [9MOG - H_{N1}]^\bullet + [9MG + H_{N7}]^+$
$\gg 9MOG^{\bullet+} \cdot 9MG \rightarrow 9MOG^{\bullet+} + 9MG$

PCCP, 2022, **24**, 9263
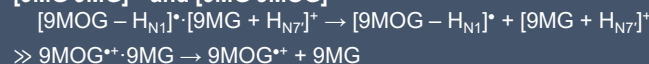
[9MG·1MC]•⁺
$[9MG - H_{N1}]^\bullet \cdot [1MC + H_{N3'}]^+ \rightarrow [9MOG - H_{N1}]^\bullet + [1MC + H_{N3'}]^+$
$\gg 9MG^{\bullet+} \cdot 1MC \rightarrow 9MG^{\bullet+} + 1MC$
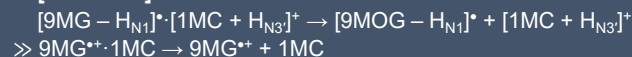
PCCP, 2020, **22**, 14875
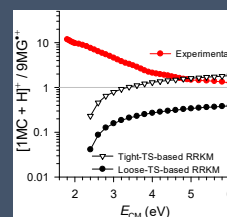
On the contrary, HG-base pair is statistical

Protonated HG-[9MG·1MC + H]⁺

PCCP, 2021, **23**, 9365

9

Exp 2: Singlet O$_2$ Oxidation of [9MOG·1MC]$^{•+}$

$^3O_2$ (X$^3\Sigma_g^-$) $^1O_2$ (a$^1\Delta_g$)

➢ Singlet O$_2$ can be generated by non-enzymatic (photochemical, thermal, chemical) or enzymatic activation of O$_2$

➢ The lowest electronically excited molecular O$_2$ (a$^1\Delta_g$)

➢ As a strong oxidant, it readily oxidizes cellular components; within DNA, $^1O_2$ exclusively target at guanine/8-oxoguanine due to their lower oxidation potentials **Consequences**: cell death, ageing and diseases

➢ **Implication**: photodynamic therapy (to destroy cancer cells)

➢ Photosensitization is the *conventional way* to generate singlet O$_2$ and conduct oxidation in solution phase

➢ The present work, on the other hand, studied the reaction of [9MOG·1MC]$^{•+}$ with pure $^1O_2$ in the gas phase, without interferences that may exist in solution
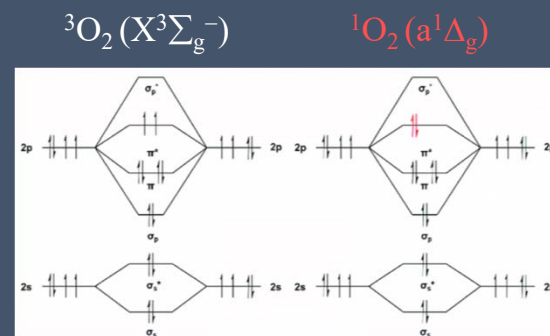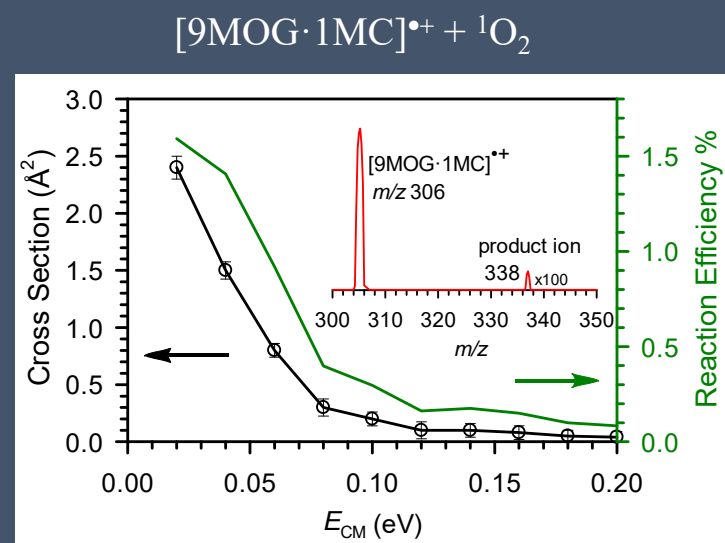
Chemical Generation of $^1O_2$ and Ion-Molecule Reaction

$$H_2O_2 + Cl_2 + 2KOH \rightarrow \, ^1O_2\,(15\%)/^3O_2\,(85\%) + 2KCl + 2H_2O$$
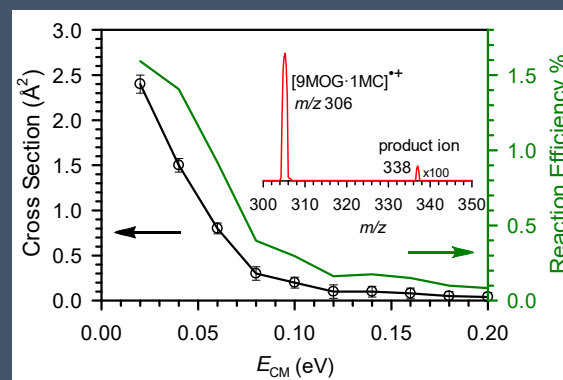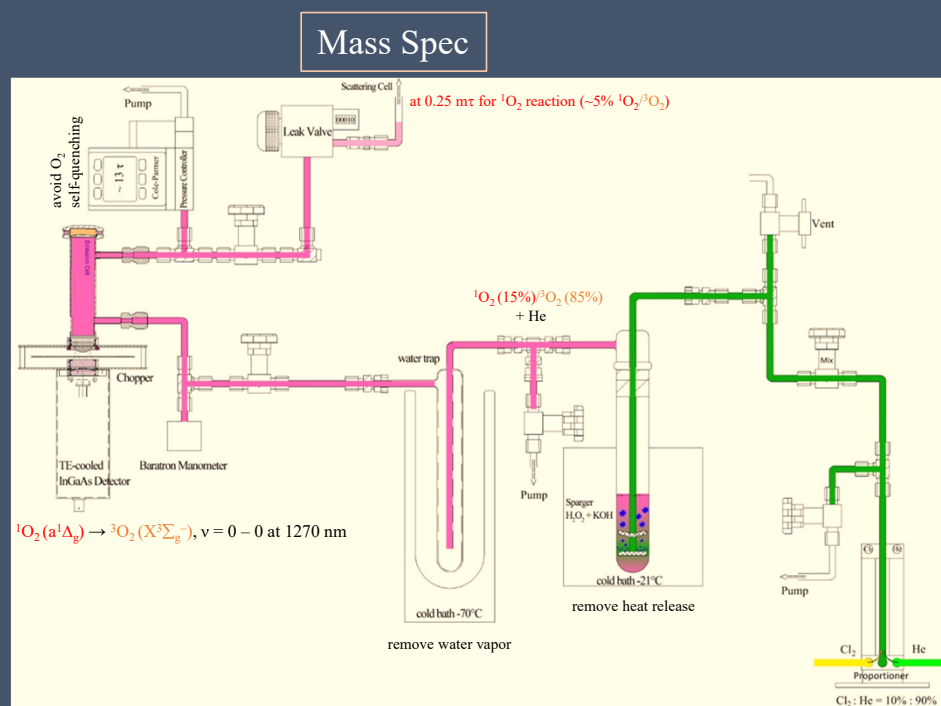
Mass Spec

Product ion and cross section of $^1O_2$ + [9MOG·1MC]•+. Inset show a product ion mass spectra at E_{CM} = 0.02 eV.

- Energy-dependence suggests an exothermic ion-molecule reaction.
- The cross section decreases as increasing E_{CM}
- Maximum of 2.4 Å^2 at the lowest E_{CM}, minimum at the highest energies
- Maximum reaction efficiency of $^1O_2$ with [9MOG·1MC]•+ is ~ 1.6% at 0.02 eV
- The efficiency become negligible above 0.1 eV

A. Midey, I. Dotan, A. A. Viggiano, *J. Phys. Chem. A* **2008**, *112*, 3040
A. A. Viggiano, A. Midey, N. Eyet, V. M. Bierbaum, J. Troe, *J. Chem. Phys.* **2009**, *131*, 094303
Y. Fang, F. Liu, A. Bennett, S. Ara, J. Liu, *J. Phys. Chem. B* **2011**, *115*, 2671-2682

Reaction Products and Cross Section of 9MOG$^{•+}$ vs. [9MOG·1MC]$^{•+}$

$9MOG^{•+} + {}^1O_2$

$[9MOG·1MC]^{•+} + {}^1O_2$
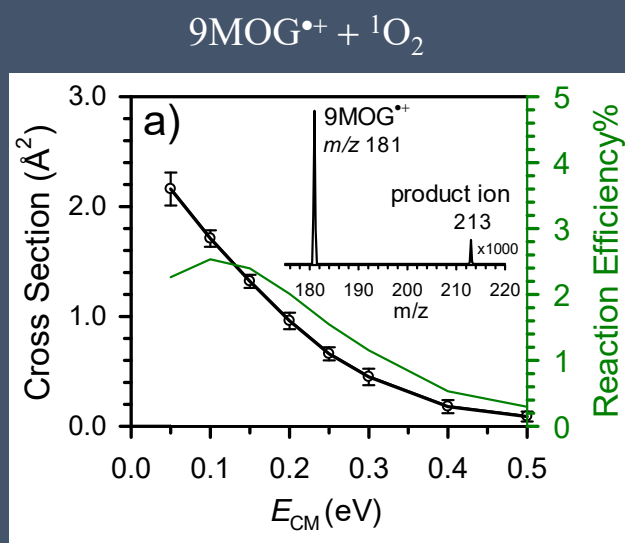
The reactivity to 9MOG$^{•+}$ monomer toward singlet O$_2$ is a factor of 2 higher than that of the base pair

The equilibrium of 9MOG$^{\bullet+}\cdot$1MC $\rightleftharpoons$ [9MOG – H$_{N1}$]$^{\bullet}\cdot$[1MC + H$_{N3'}$]$^+$ brings about two different forms of 9MOG radicals

Approximately spin-projected DFT, DLPNO-CCSD(T), CASPT2 & NEVPT2 computations of

9MOG$^{\bullet+}$ vs   [9MOG – H]$^{\bullet}$

9MOG$^{\bullet+}$ vs   9MOG$^{\bullet+}\cdot$1MC

[9MOG – H]$^{\bullet}$ vs   [9MOG – H$_{N1}$]$^{\bullet}\cdot$[1MC + H$_{N3'}$]$^+$

9MOG$^{\bullet+}\cdot$1MC   vs   [9MOG – H$_{N1}$]$^{\bullet}\cdot$[1MC + H$_{N3'}$]$^+$

In all cases, C5-O$_2$ addition is the most favorable, followed by H-abstraction at N7

13

Conclusions

Non-statistical CID product ion ration of $[9MOG \cdot 1MC]^{\bullet+}$, that provides insight into the intra-base pair PT reaction of $9MOG^{\bullet+} \cdot 1MC \rightleftharpoons [9MOG - H_{N1}]^{\bullet} \cdot [1MC + H_{N3'}]^{+}$

The same the PT leads to two different radical forms of 9MOG in the reactions with $^1O_2$.
The base-pair context effect on singlet oxygenation is first reflected in
the reduced reactivity of $9MOG^{\bullet+}$ within the base pair;

The neutral radical presents more favorable reaction energetics than the radical cation,
both in an isolated monomer or within a base pair

The relative reactivity toward $^1O_2$ is
$[9MOG - H]^{\bullet} > 9MOG^{\bullet+} > [9MOG - H_{N1}]^{\bullet} \cdot [1MC + H_{N3'}]^{+} \geq 9MOG^{\bullet+} \cdot 1MC$
- Effect of intra-base pair PT
- Effect of base pairing
- Electrostatic effect
- Effect on base-pairing energy

14

Acknowledgements

PhD students

May Mya Moe
Jonathan Benny
Wenjing Zhou

Collaborator

Prof. Midas Tsai
(LaGuardia Community College)

Special thanks to Dr. Bernhard Lippert (University of Dortmund, Germany) for providing 9MOG as a gift

Singlet O$_2$ Oxidation of OG and Its Derivatives

16