Singlet O_2 Oxidation of 8-Oxo-2´-deoxyguanosine Radical Cation Using Guided-Ion Beam Tandem Mass Spectrometry and Multi-reference Computational Methods

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Motivation

Nucleosides	Oxidation Potential (E° vs. NHE), V	Ionization Energy (eV)
8-oxo-2′-deoxyguanosine (OG)	0.58 - 0.74	6.38
Guanosine (Guo)	1.29	7.13
Adenosine (Ado)	1.42	8.27
Deoxycytidine (Cyd)	1.60	8.66
Thymidine (dT)	1.70	8.82

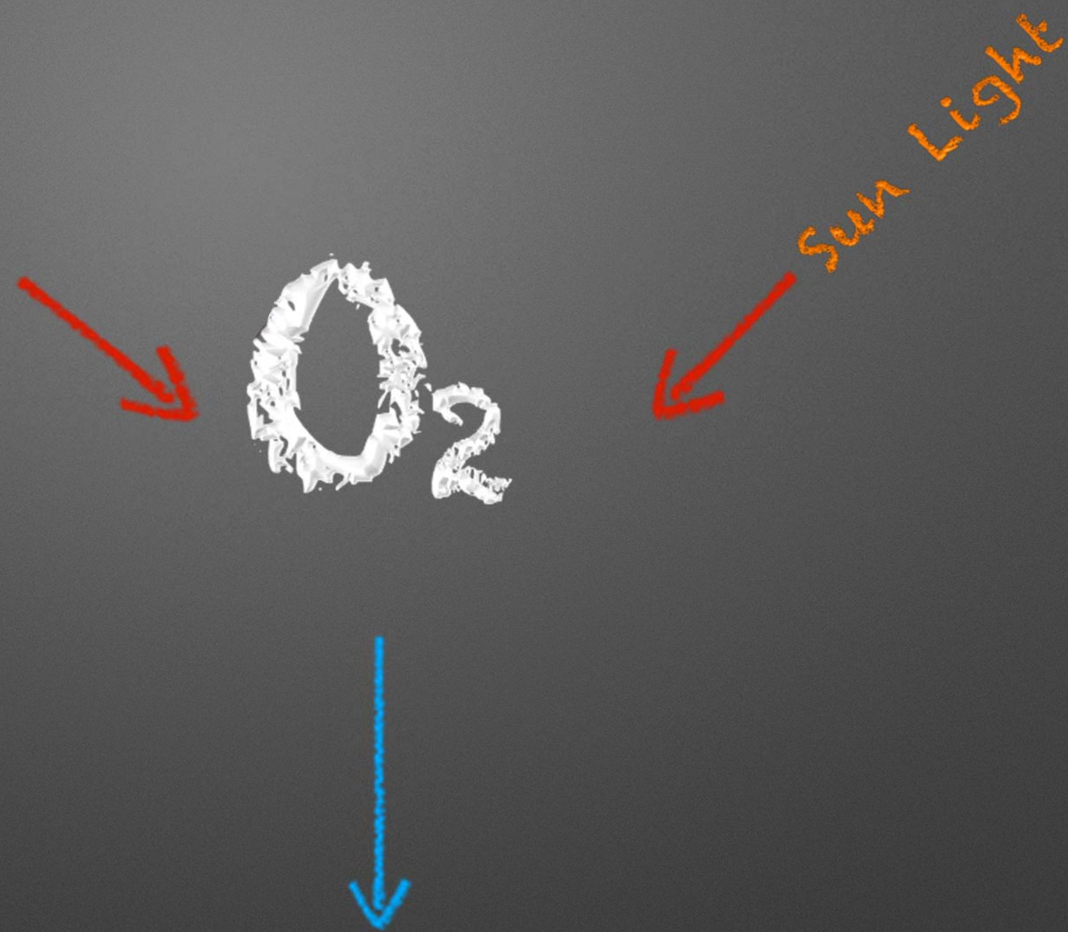
- Guanosine is the exclusive DNA target for $^1O_2$ ($a^1\Delta_g$), photo-oxidation and ionizing radiation.
- OG is the oxidized guanine product is and it is used as a common biomarker.

Yanagawa, H.; Ogawa, Y.; Ueno, M., *J. Biol. Chem.* **1992,** *267*, 13320-6.
Steenken, S.; Jovanovic, S. V., *J. Am. Chem. Soc.* **1997,** *119*, 617-618.
Zhou, J.; Kostko, O.; Nicolas, C.; Tang, X.; Belau, L.; de Vries, M. S.; Ahmed, M., *J. Phys. Chem. A* **2009,** *113*, 4829-4832.
Schwell, M.; Hochlaf, M., *Top. Curr. Chem.* **2015,** *355*, 155-208.

$^1O_2$ as Reactive Oxygen Species

Biosystems

- ➢ Enzymatic/nonenzymatic
- ➢ An oxidizer



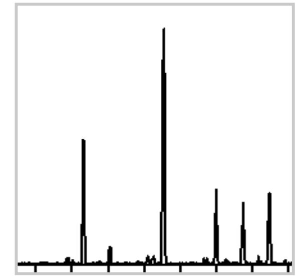
- Progression of cell death
- Mutation, ageing and diseases
- Cancer treatment

Foote, Christopher S. *Accounts of Chemical Research* 1.4 (1968): 104-110.

Instrumentation

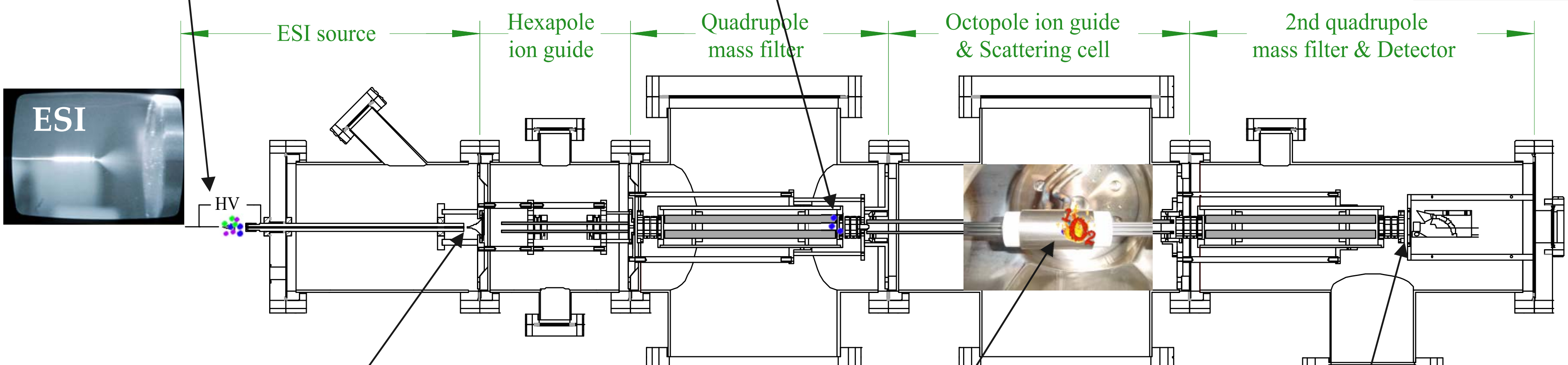
Guided-Ion-Beam Tandem Mass Spectrometer

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



3. Ions are passed into a quadrupole for mass selection

1. Generation of $[Cu^{II}(9MOG)_{3-n}]^{\bullet 2+}$ complex by ESI

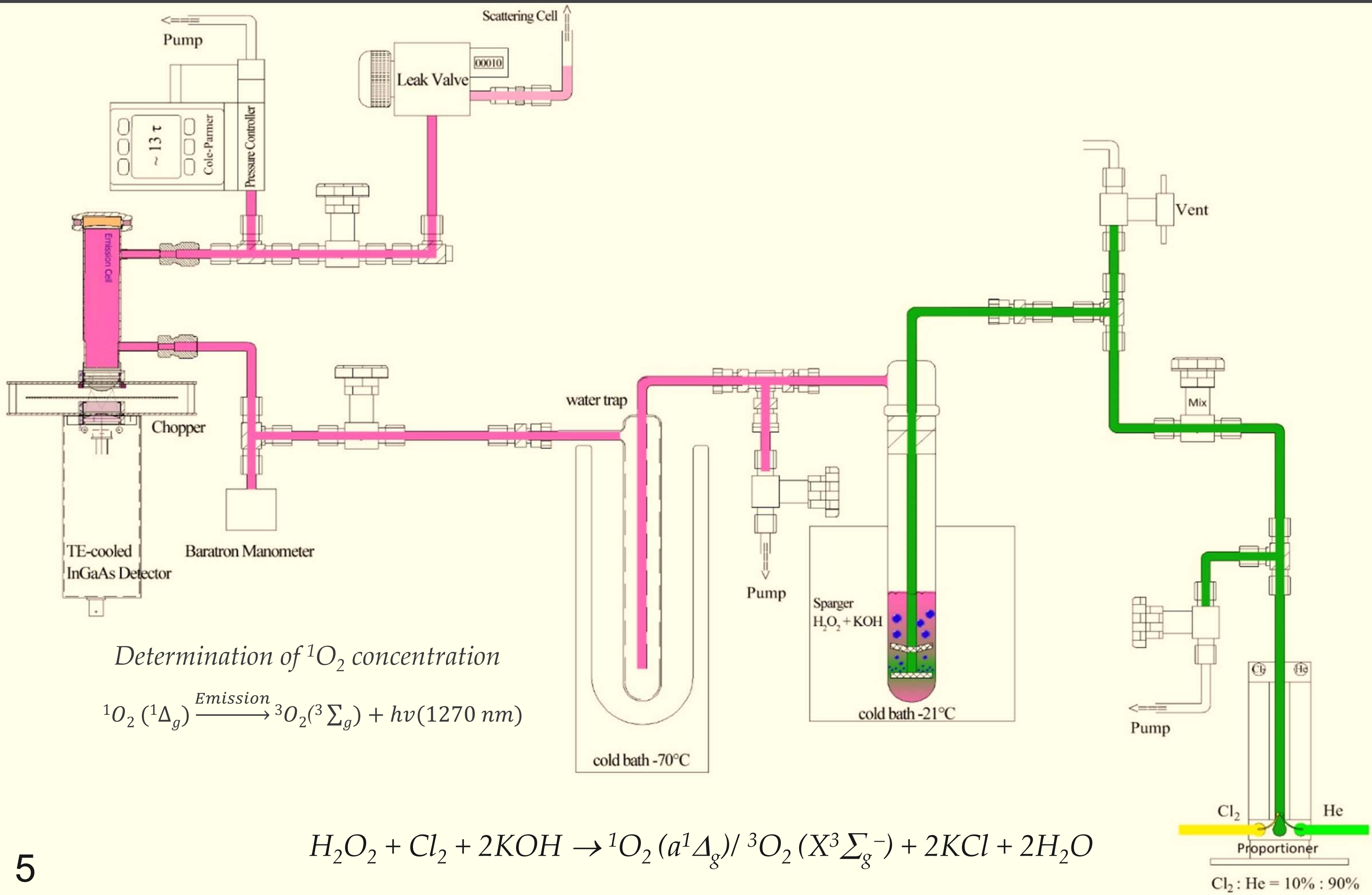


2. The complex $[Cu^{II}(9MOG)_{3-n}]^{\bullet 2+}$ undergoes redox separation to produce $9MOG^{\bullet +}$.

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

5. Product ions are mass analyzed & counted

$^1O_2$ Generation



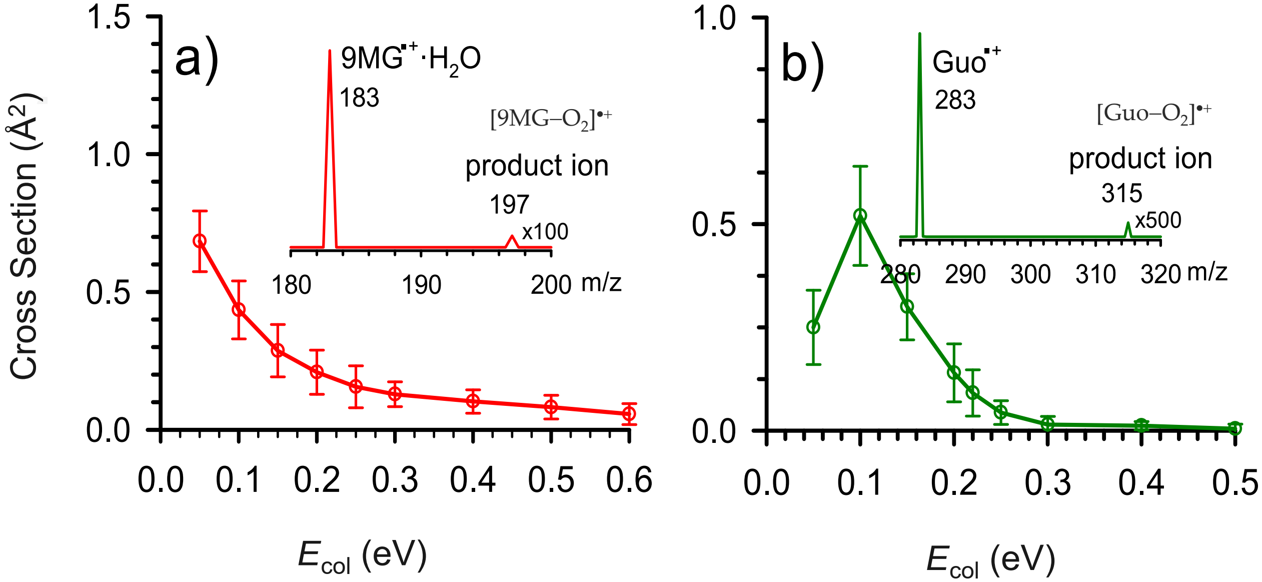
Determination of $^1O_2$ concentration

$$^1O_2\,(^1\Delta_g) \xrightarrow{Emission} {}^3O_2(^3\Sigma_g) + h\nu(1270\,nm)$$

$$H_2O_2 + Cl_2 + 2KOH \rightarrow {}^1O_2\,(a^1\Delta_g)/\,{}^3O_2\,(X^3\Sigma_g^-) + 2KCl + 2H_2O$$

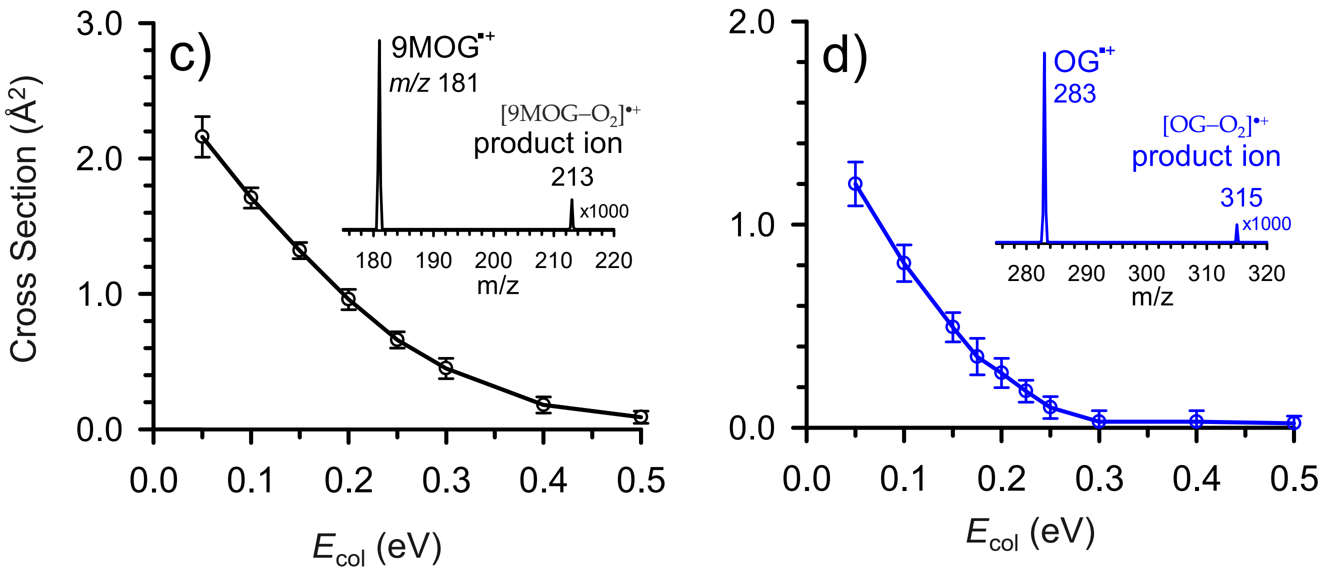
Reaction Product Cross Section and Energy Dependence

Singlet O_2 reaction with $9MG^{\bullet+}$



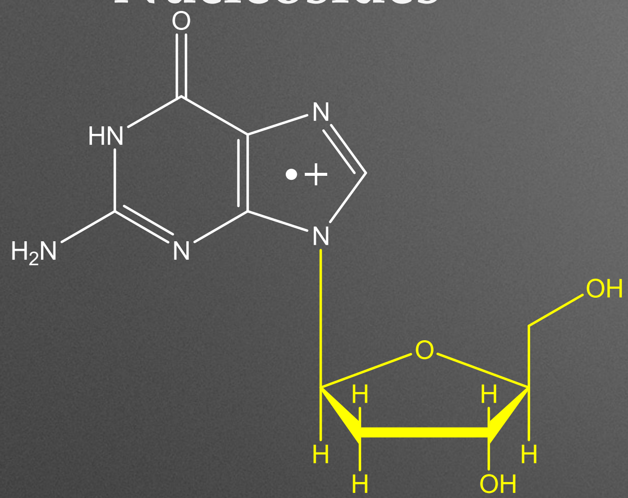
- Exothermic reactions
- Reaction heat release is more than the product hydration energy

Singlet O_2 reaction with $9MOG^{\bullet+}$

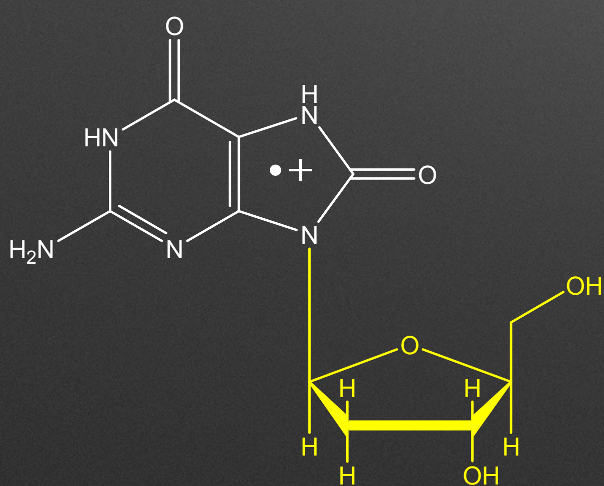


Computational Modeling

Nucleosides



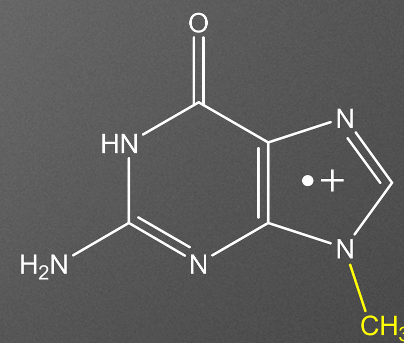
Guanosine ($Guo^{\bullet+}$)



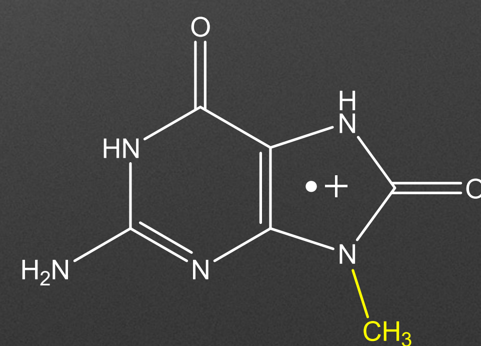
8-oxo-2′-deoxyguanosine ($OG^{\bullet+}$)

prototype substrate

Nucleobases



9-methyl-guanine ($9MG^{\bullet+}$)

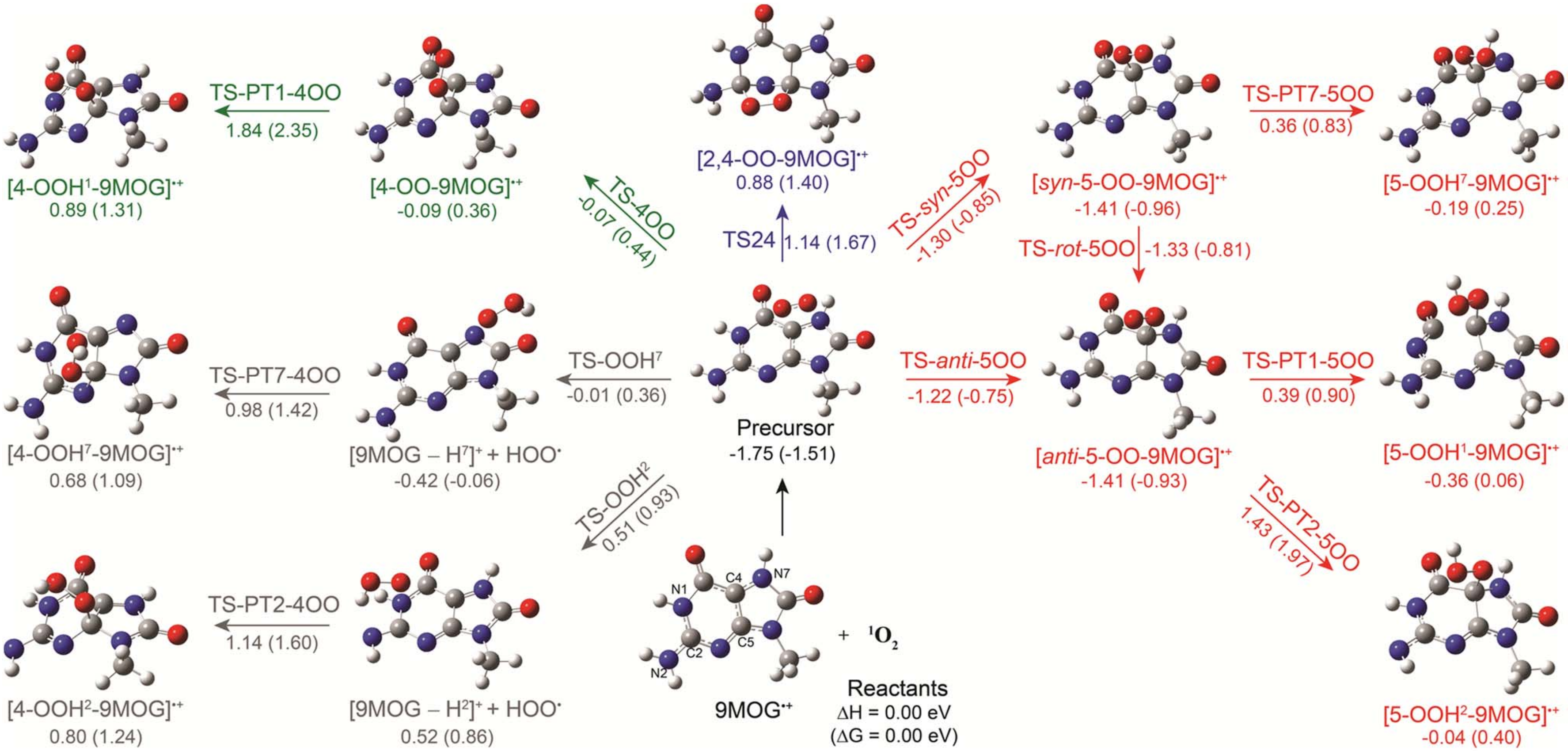


9-methyl-8-oxoguanine ($9MOG^{\bullet+}$)

Iteration 1

Single reference

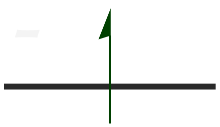
Density Functional Theory ωB97XD/6–31+G(d,p)



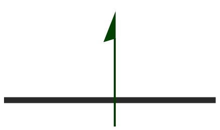
Computational Modeling and Challenges

1. Spin contamination of $^1O_2$ from $^3O_2$

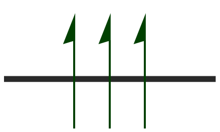
2. Doublet-Quartet Mixing



$^1O_2$ (↑↓) ---- $9MOG^{\bullet +}$ (↑) *doublet 2*



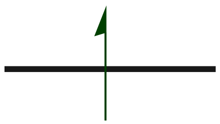
$^3O_2$ (↑↑) ---- $9MOG^{\bullet +}$ (↓) *doublet 1*



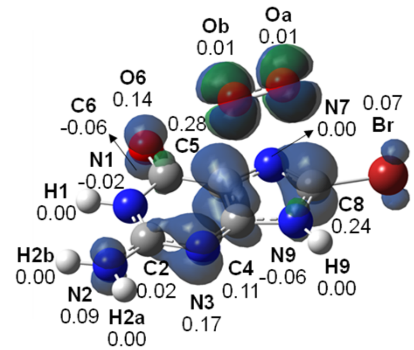
$^3O_2$ (↑↑) ---- $9MOG^{\bullet +}$ (↑) *quartet*

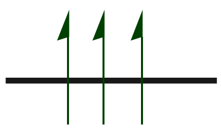
} *degenerate*

Yamaguchi's approximate spin projection

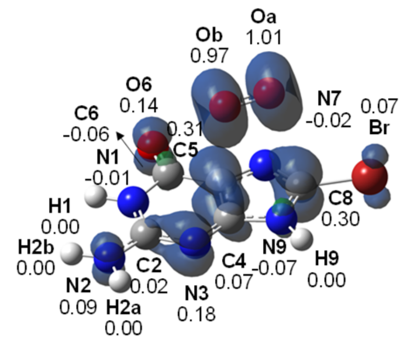


$^{2}[8BrG^{\bullet+}\ (\uparrow,\ S = \frac{1}{2}) \bullet\bullet\bullet {}^{1}O_2\ (\uparrow\downarrow\ ,\ S = 0)]$





$^{4}[8BrG^{\bullet+}\ (\uparrow,\ S = \frac{1}{2}) \bullet\bullet\bullet {}^{3}O_2\ (\uparrow\uparrow,\ S = 1)]$



$$\boldsymbol{E} = \frac{\langle \hat{S}^2 \rangle^{HS} - \langle \hat{S}^2 \rangle^{BS}_{exact}}{\langle \hat{S}^2 \rangle^{HS} - \langle \hat{S}^2 \rangle^{BS}} \boldsymbol{E}^{BS} - \frac{\langle \hat{S}^2 \rangle^{HS} - \langle \hat{S}^2 \rangle^{BS}_{exact}}{\langle \hat{S}^2 \rangle^{HS} - \langle \hat{S}^2 \rangle^{BS}} \boldsymbol{E}^{HS}$$

$$\langle \hat{S}^2 \rangle^{HS}_{exact} = \frac{N^{\alpha} - N^{\beta}}{2} + 1$$

E^{BS} = the computed total energy for a target broken-symmetry state

$\langle \hat{S}^2 \rangle^{BS}$ = the expectation value of the total spin angular momentum

E^{HS} & $\langle \hat{S}^2 \rangle^{HS}$ = the counterparts for the corresponding high-spin state

N^{α} & N^{β} = the number of alpha and beta electrons
BS & HS = the singlet and triplet for $^{1}O_2$ and doublet and quartet for O_2 adducts.

Benny, J., Saito, T., Moe, M.M. and Liu, J., *The Journal of Physical Chemistry A*. 2021, 126, 68-79.

Iteration 2

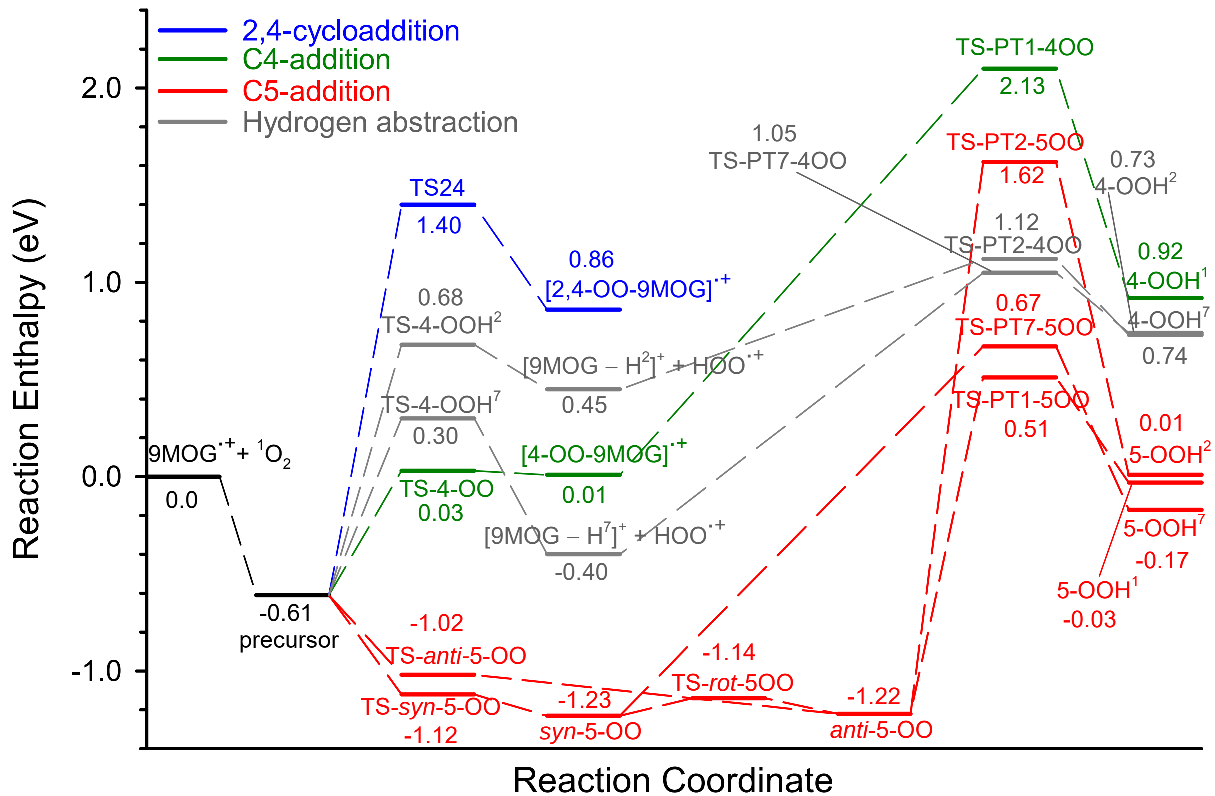
Single reference

Coupled-Cluster Single-, Double- and perturbative Triple excitations (CCSD(T))

➢Tolerate mild spin contamination

➢T1 diagnostic: measure of multireference effects

<0.02 closed shell, <0.03 radicals



Iteration 3

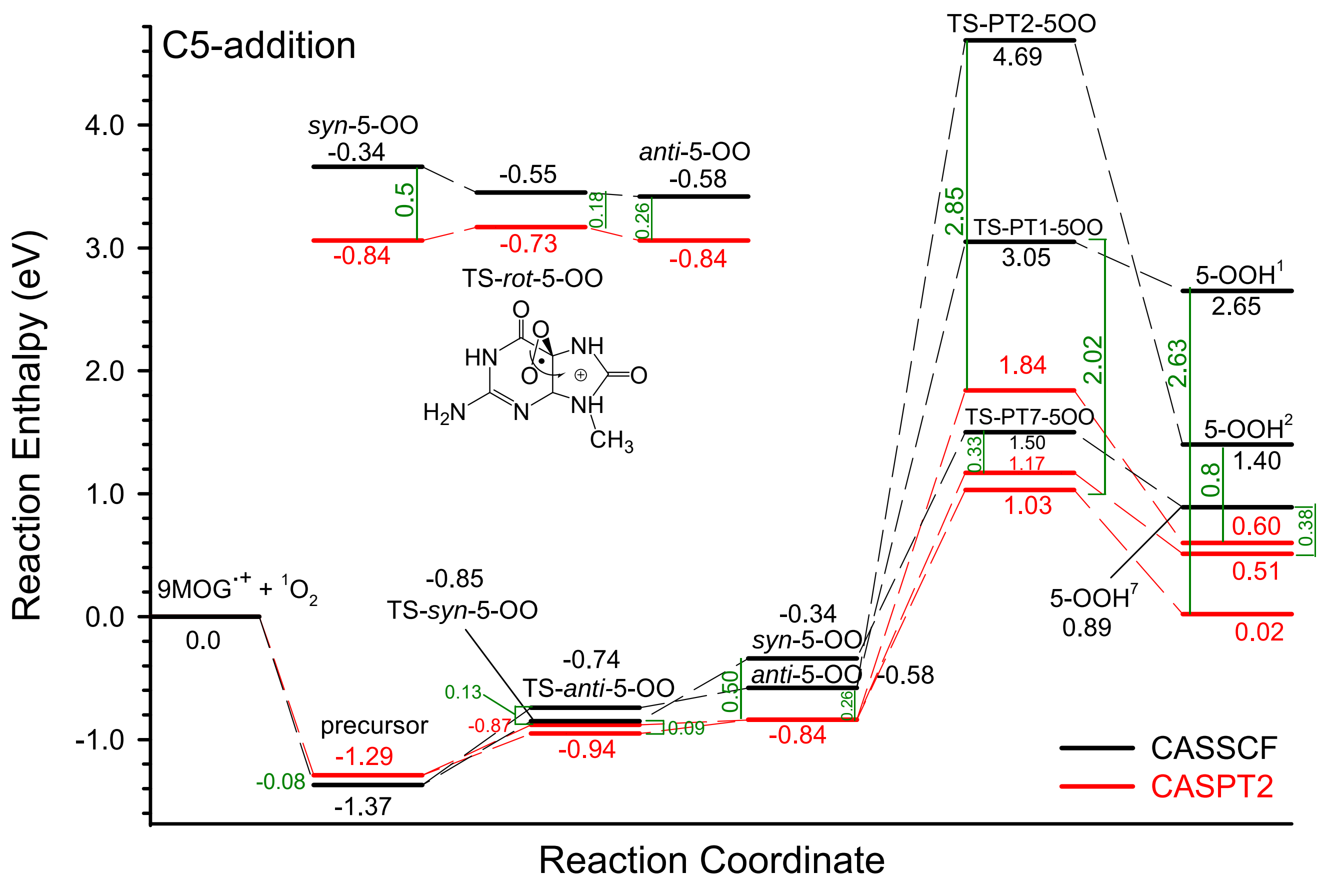
Multireference

Complete active space self-consistent field (CASSCF)

- ➢Multiconfigurational method
- ➢Insufficient dynamic treatment

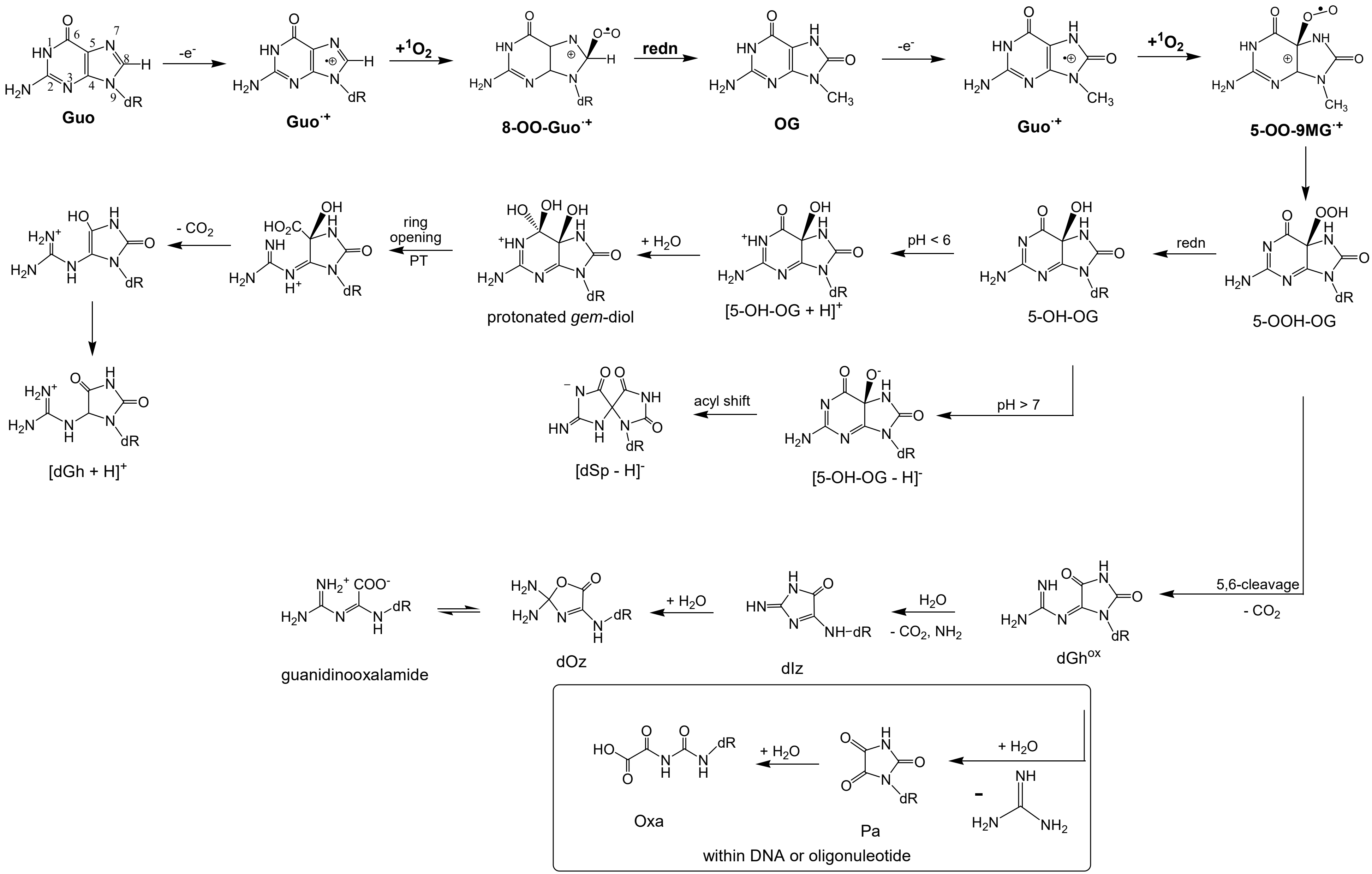
Complete active space 2nd perturbation theory (CASPT2)

- ➢ CASSCF multiconfigurational method
- ➢Additional 2nd perturbation for dynamic treatment.



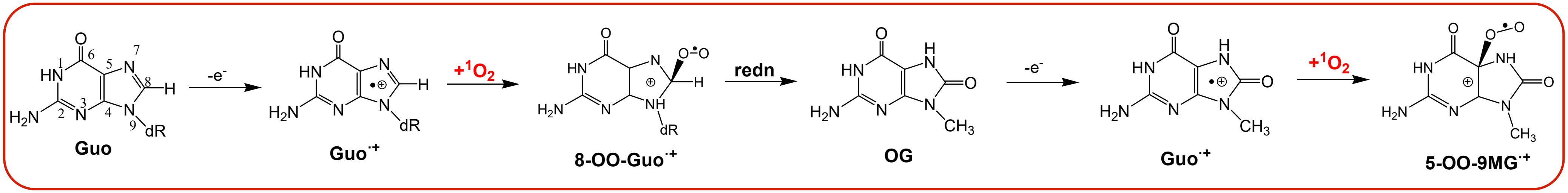
Summary

1. Complex mechanistic reaction pathway and biological significance



Summary

2. Understanding the chemistry of DNA damage and their rate limiting transient states.



3. Technological Advantages

Gas-phase Mass Spectrometer

- No spontaneous deprotonation

$$G^{\bullet +} \not\rightarrow [G - H]^{\bullet} + H^{+}$$

- Longer $^{1}O_2$ lifetime

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- Dr. Toru Saito (Hiroshima City University, Japan)

Project Participants

- Dr. Yan Sun
- Jonathan Benny (**Ph.D. Student**)
- Wenjing Zhou (**Ph.D. Student**)

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