Singlet O_2 Oxidation Dynamics of 8-Bromoguanine Radical Cations using Guided-Ion-Beam Tandem Mass Spectrometry

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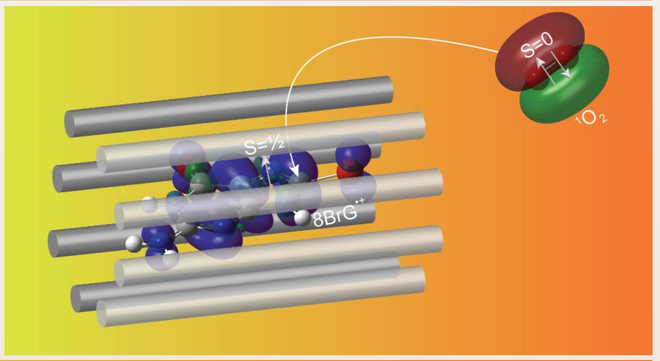
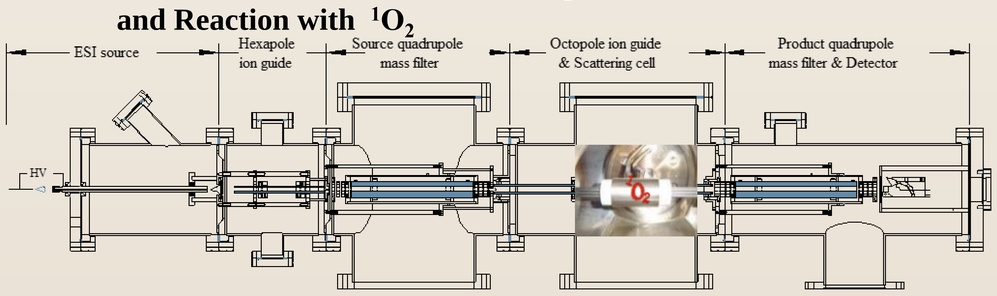
Introduction

- Guanine, the preferred target in DNA for bromination by reactive halogen species (RHS), forms the mutagenic lesion 8-Bromoguanine (8BrG)
- Biological significance of oxidatively generated radical cations of 8-Bromoguanine ($8BrG^{\bullet+}$) and 8-Bromoguanosine ($8BrGuo^{\bullet+}$) by the lowest electronically excited singlet O_2 ($a^1\Delta_g$):
  - ❖ Chronic inflammation and Cancer
  - ❖ DNA strand breaks, DNA-protein crosslinks, mutation and apoptosis
  - ❖ Biomarker for oxidative and halogenative stress within cells and tissues
  - ❖ Singlet O_2–based photodynamic therapy in cancer treatment
  - ❖ Brominated nucleotides are considered potential radiosensitizers in radiotherapy



Instrumentation & Experiment

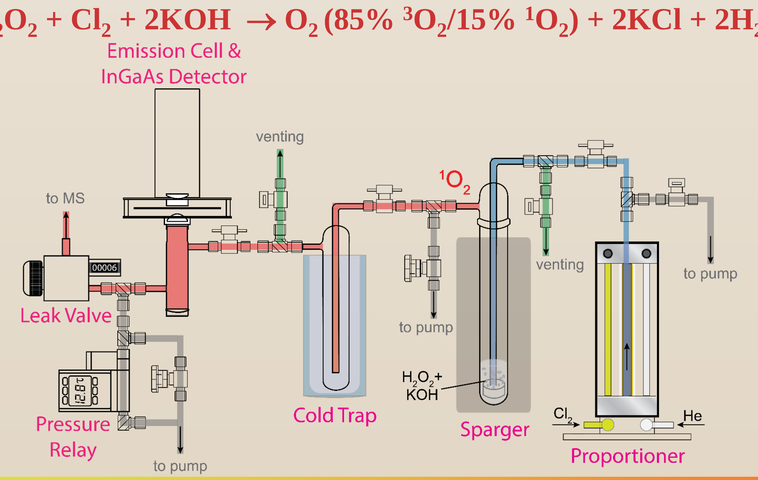
I. Guided-Ion-Beam Tandem Mass Spectrometer for Generation of $8BrG^{\bullet+}$ and Reaction with $^1O_2$



$[Cu^{II}(8BrG)_3]^{\bullet 2+} \rightarrow [Cu^{I}(8BrG)_2]^{+} + 8BrG^{\bullet+}$

II. Generation and Detection of $^1O_2$ Before Leaking into the Scattering Cell of the Mass Spectrometer

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



Theoretical Methods

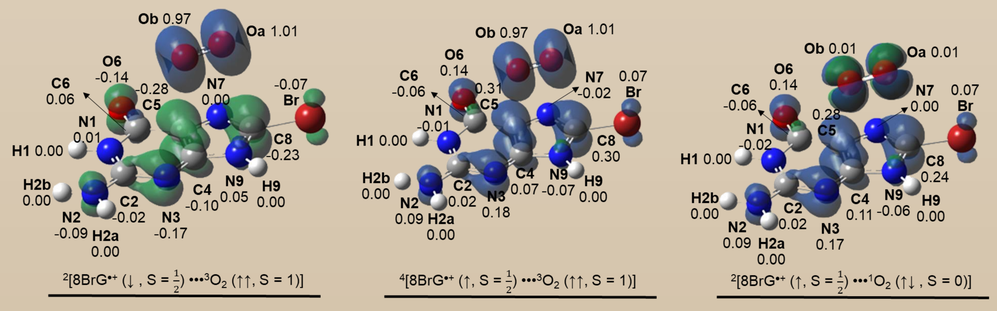
The calculation of the reaction potential energy surface for $8BrG^{\bullet+}$ with $^1O_2$ is challenging due to multiconfigurational wavefunctions originating from the mixed open- and closed-shell character of $^1O_2$, and spin contamination in transition states and products

I. Approximately Spin Projected DFT

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

$$\langle\hat{S}^2\rangle^{BS}_{exact} = \frac{N^\alpha - N^\beta}{2}\left(\frac{N^\alpha - N^\beta}{2} + 1\right)$$

E^{BS}: energy for broken-symmetry state
$\langle\hat{S}^2\rangle^{BS}$: spin angular momentum for broken-symmetry state
E^{HS}: energy for high-spin state
$\langle\hat{S}^2\rangle^{HS}$: spin angular momentum operator for high-spin state
N^α: number of alpha electrons
N^β: number of beta electrons



II. Coupled-Cluster Theory

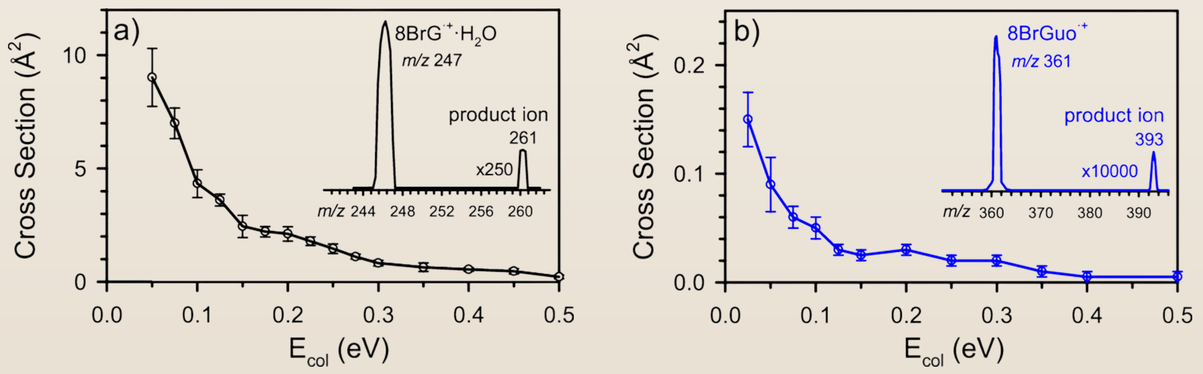
DLPNO-CCSD(T) coupled with the aug-cc-pVTZ basis set was employed to assess the spin contamination in the reaction structures using the T1 diagnostic; it was also considered the gold standard of quantum chemistry due to its accuracy comparable to experiments (in the absence of spin contamination)

III. CASPT2

Energies of the DFT optimized reaction structures were recalculated using the multireference active space self-consistent field method CASPT2/6-31G**. It adds dynamic correlation to the complete active space self-consistent field (CASSCF) wavefunction using the second order perturbation theory

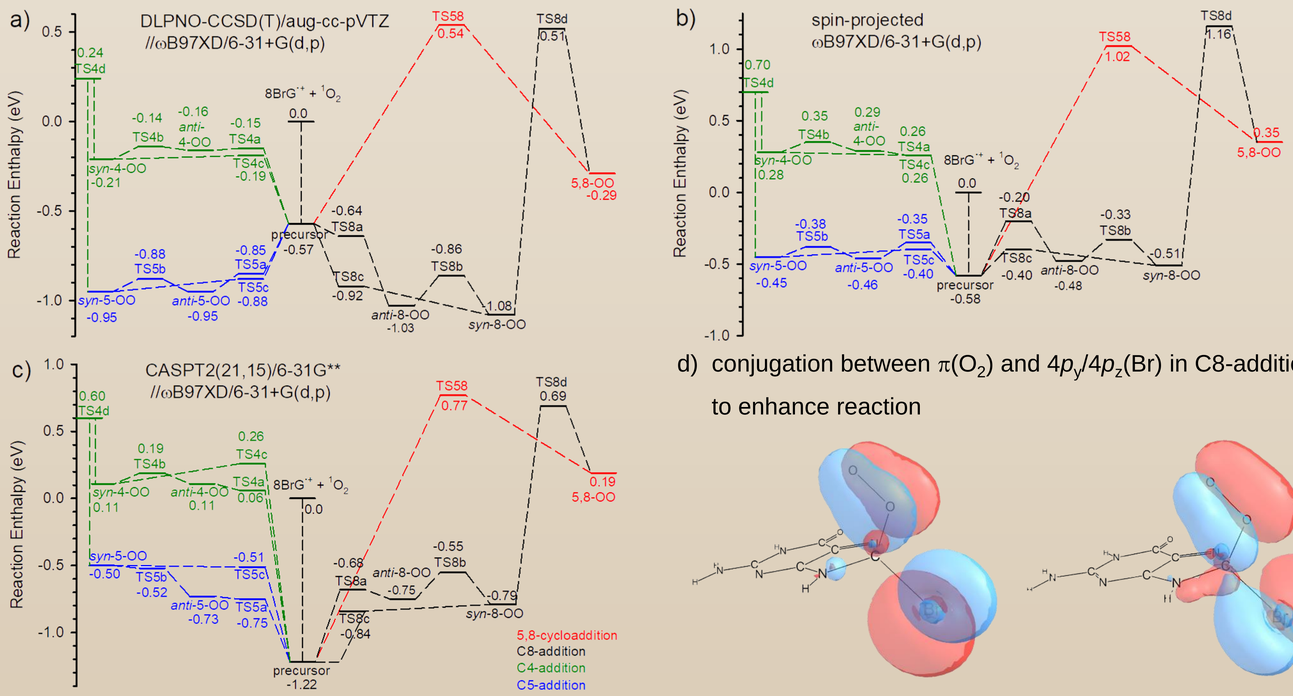
Results

I. Reaction Products and Cross Sections for $^1O_2$ with $8BrG^{\bullet+}$ and $8BrGuo^{\bullet+}$



- Reaction is exothermic and has no activation barriers above starting reactants
- The reactivity of $8BrG^{\bullet+}$ is 5-fold higher than that of the unsubstituted guanine ($G^{\bullet+}$)
  - The reaction efficiency of $8BrG^{\bullet+}$ is 9.5% at E_{col} = 0.05 eV and decreases to 3% at 0.4 eV
  - The reaction efficiency of $G^{\bullet+}$ is 2% at E_{col} = 0.05 eV and decreases to 1.4% at 0.1 eV

II. Reaction Potential Energy Surface of $^1O_2$ with $8BrG^{\bullet+}$ at different levels of theory



d) conjugation between $\pi(O_2)$ and $4p_y/4p_z$(Br) in C8-addition to enhance reaction

Among the different computational methods used in the PES calculations, the CASPT2(21,15) theory provided the best description and agreement with experimental data

Conclusions

➢In the reaction of $^1O_2$ with $8BrG^{\bullet+}$/$8BrGuo^{\bullet+}$, the product cross section increases with decreasing E_{col}. It indicates that the reaction is exothermic

➢The most energetically favorable reaction pathways for $8BrG^{\bullet+}$ + $^1O_2$ are the C5-O_2 and C8-O_2

Acknowledgements

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References

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