

Dynamics for singlet oxygen addition to guanine and 9-methylguanine: About the initial stage of guanine nucleoside oxidation

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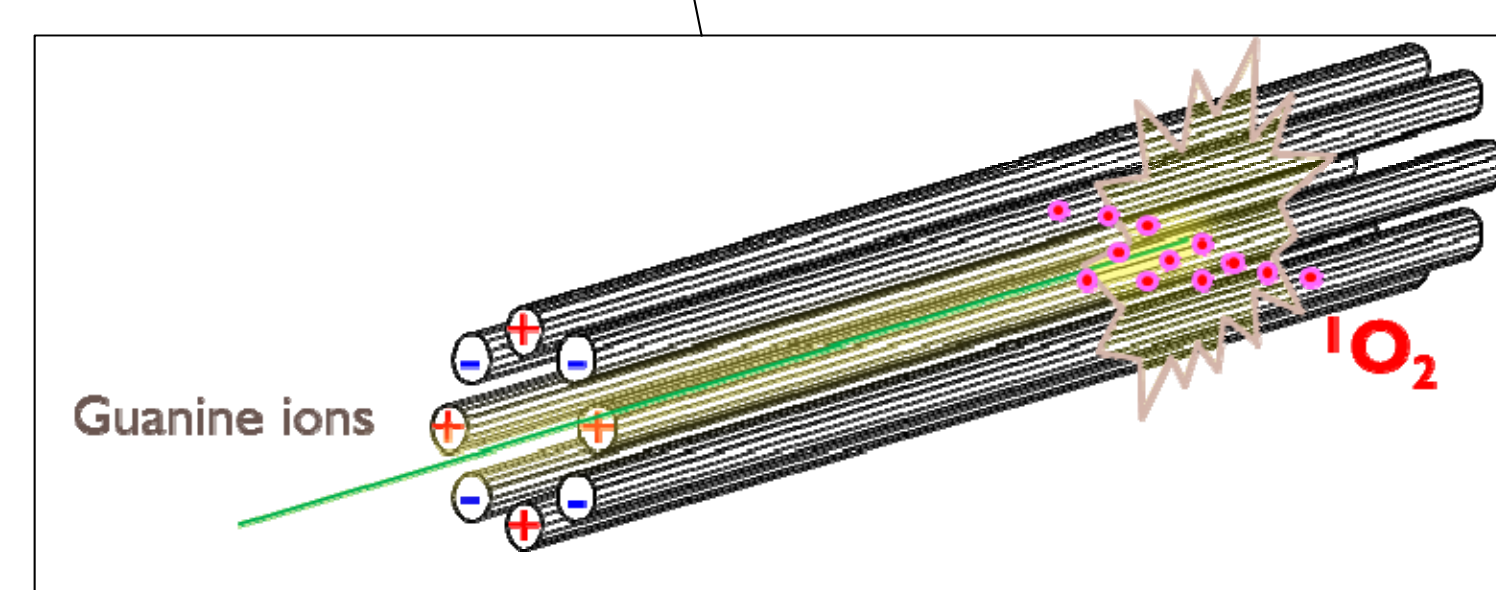
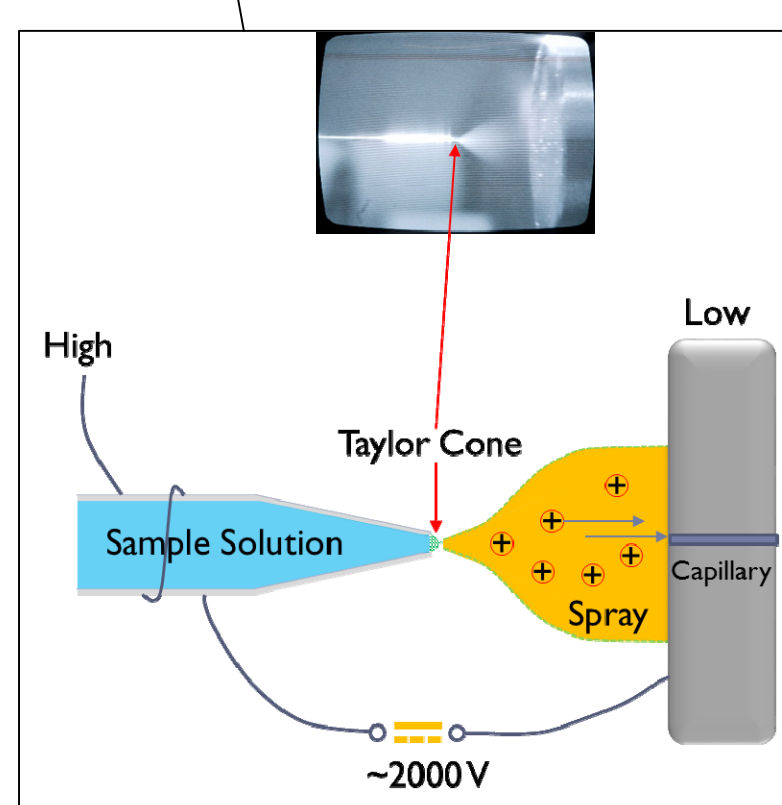
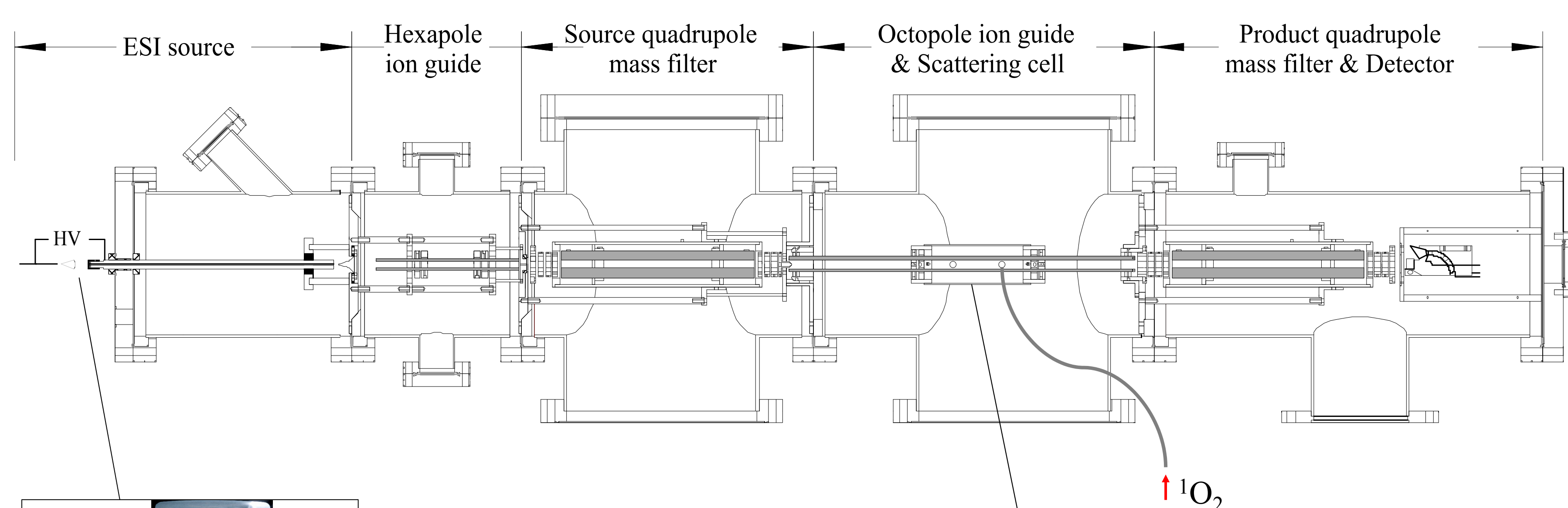
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Introduction

- The chemistry of singlet oxygen toward the guanine base of DNA is highly relevant to DNA lesion, mutation, cell death and pathological conditions. The reaction is assumed to initiate via [4+2] *Diels-Alder* addition to endoperoxide structure, but so far, there is no evidence showing endoperoxide intermediate was directly detected in native guanine or guanosine even down to -100 °C.
- Gas-phase ion-molecule scattering mass spectrometry was used to capture unstable endoperoxides in the collisions of singlet oxygen with dry/hydrated guanine ions (protonated and deprotonated) at ambient temperature. Molecular quantum calculation, kinetic modeling and dynamics simulations are conducted to further investigate various aspects of endoperoxide formation and transformation, including guanine ionization, hydration, ion-molecule collision energy as well as the N9-substitution.

Instrumentation and Methodology

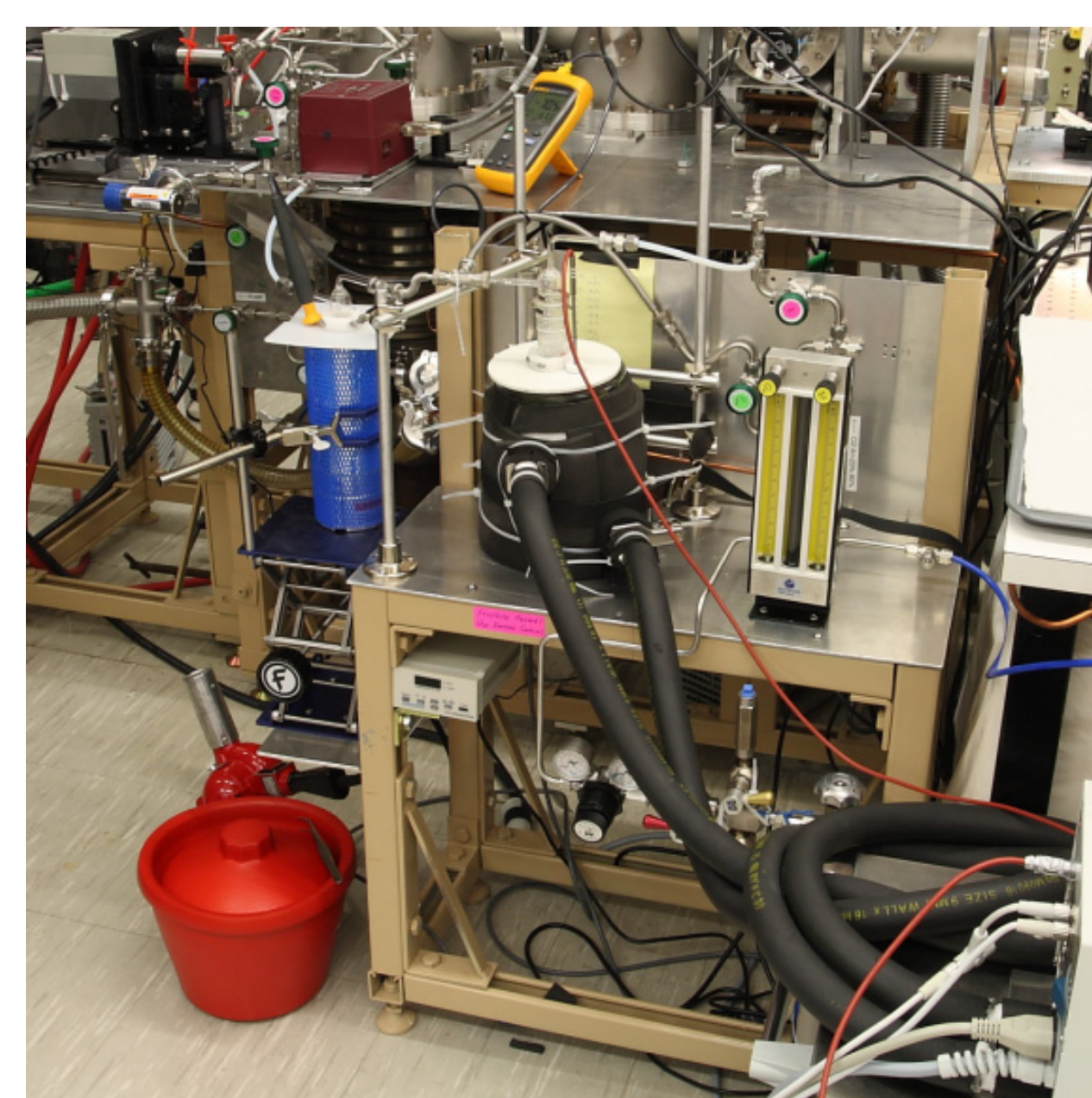
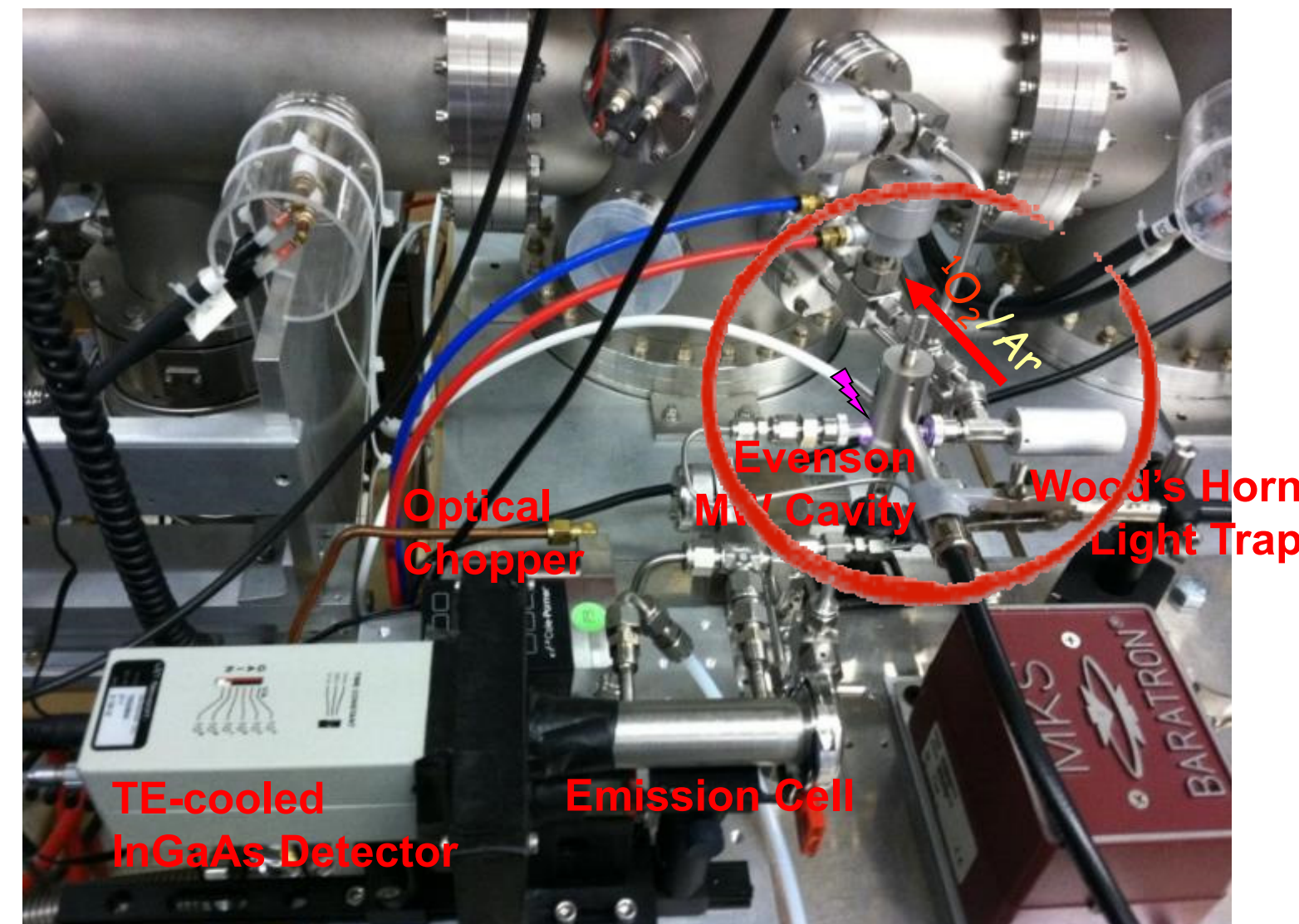
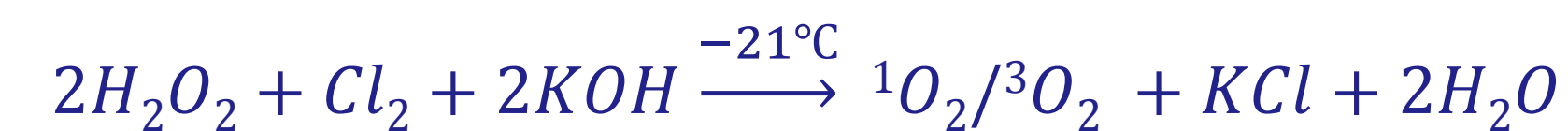
- Guided-ion-beam tandem mass spectrometer



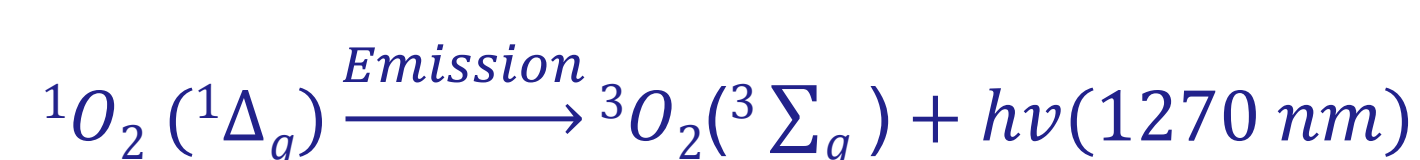
- ¹O₂ Generator and detection system

- Microwave discharge $3O_2 \xrightarrow{MW} {}^1O_2 ({}^1\Delta_g)$

- Chemical ¹O₂ generator



- Determination of ¹O₂ concentration

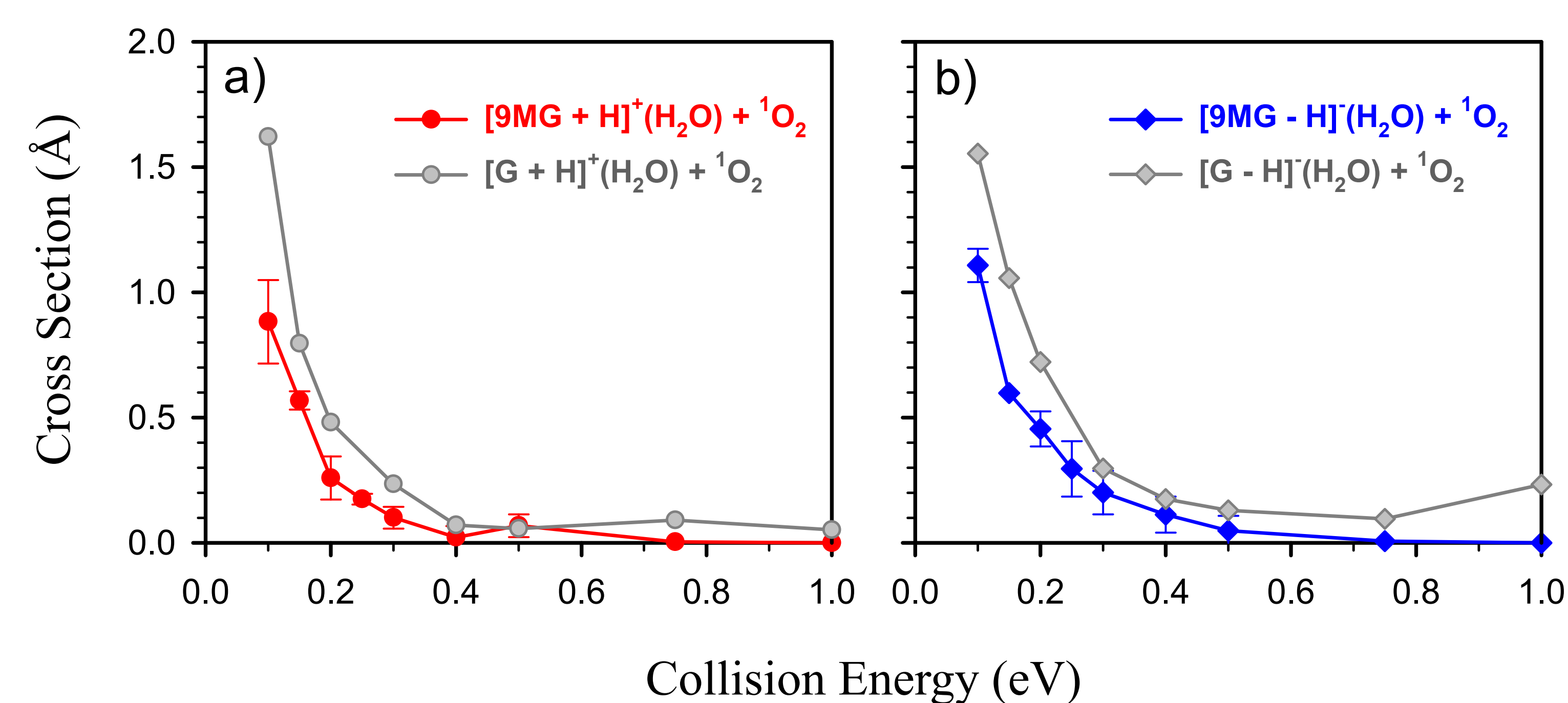


- Quantum chemical calculation

All the jobs are done using Gaussian 09 D.01. Various methods, ranging from DFT to post-HF, and multiconfigurational method are used for geometry optimization, transition state searching, PES and IRC scan. Stability of wavefunctions were checked. Direct dynamic simulations were carried out at $E_{col} = 0.1$ eV in B3LYP/6-31G* using Venus Software interfaced with Gaussian 09.

Results

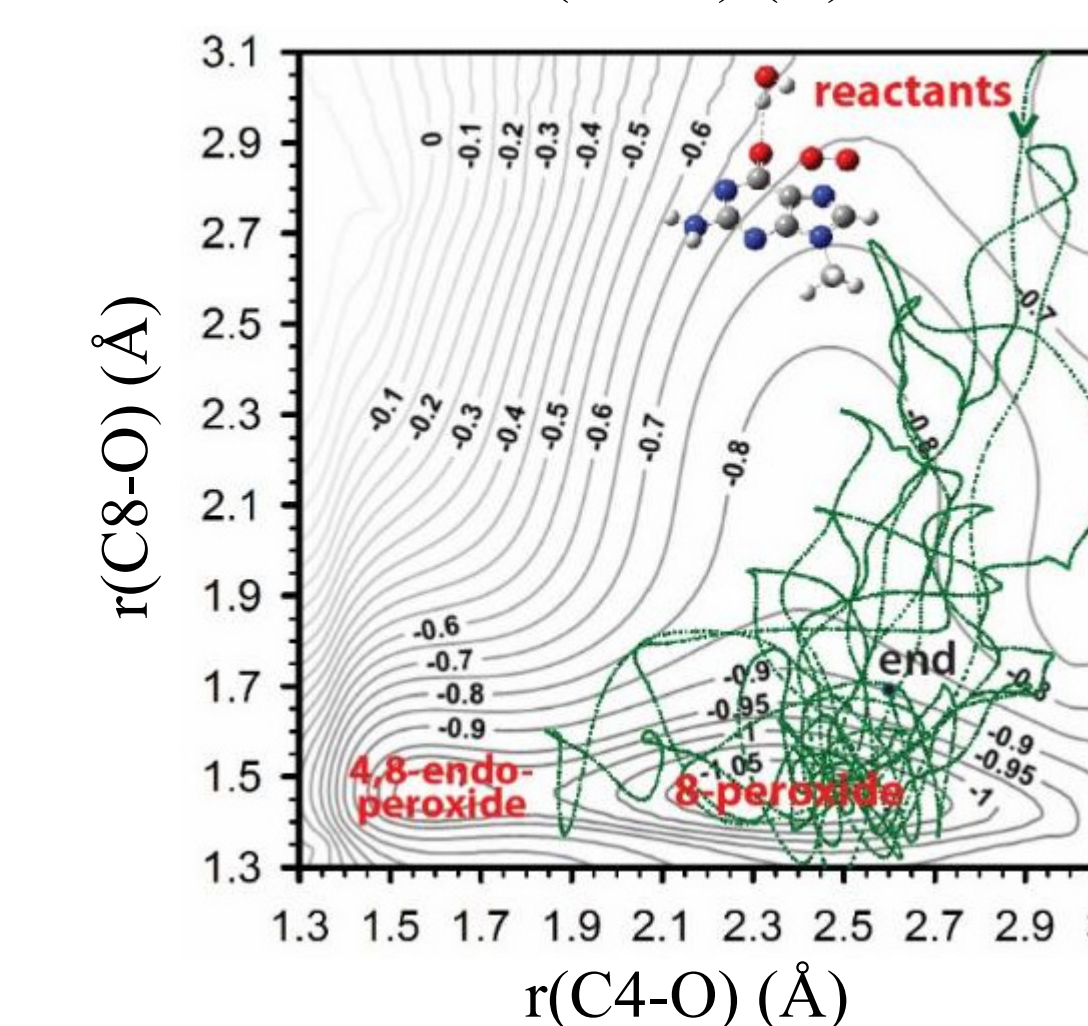
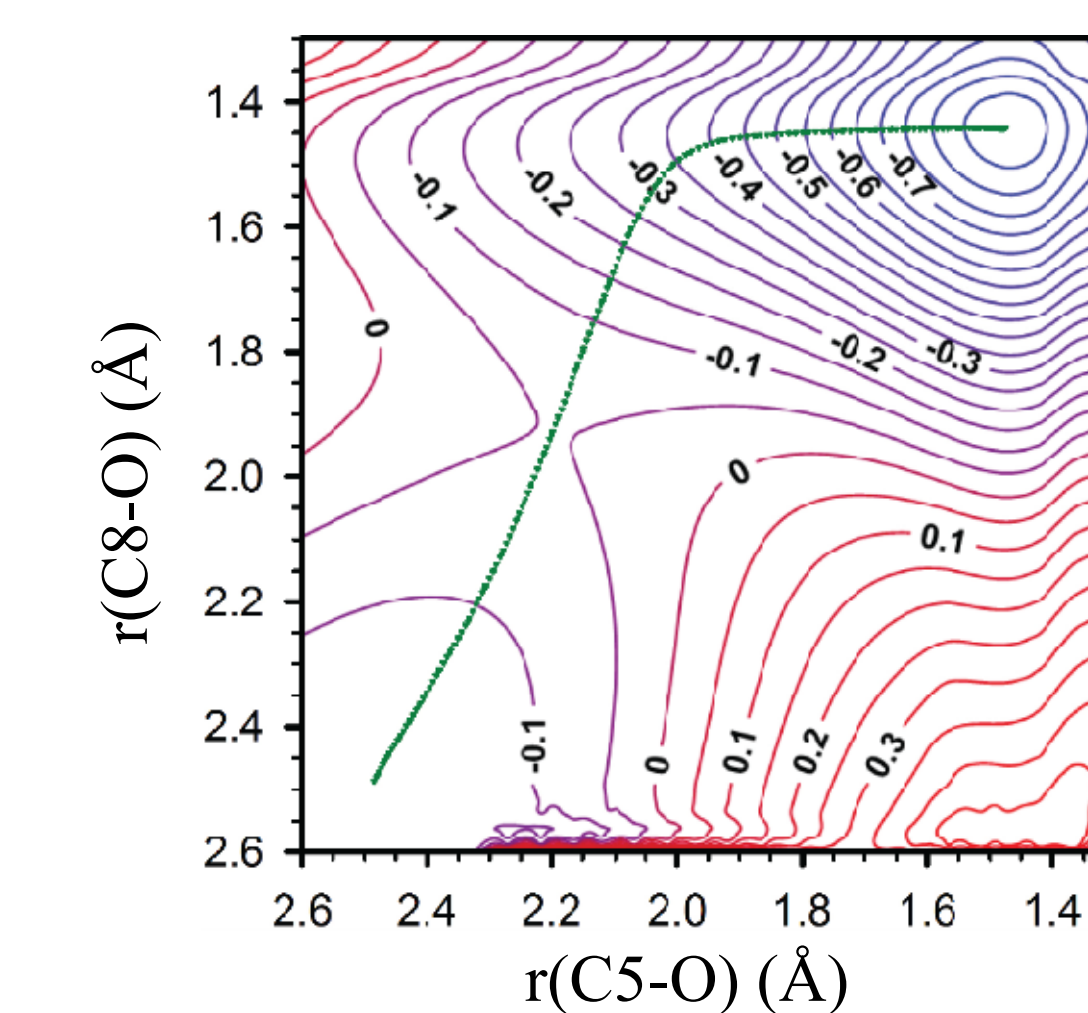
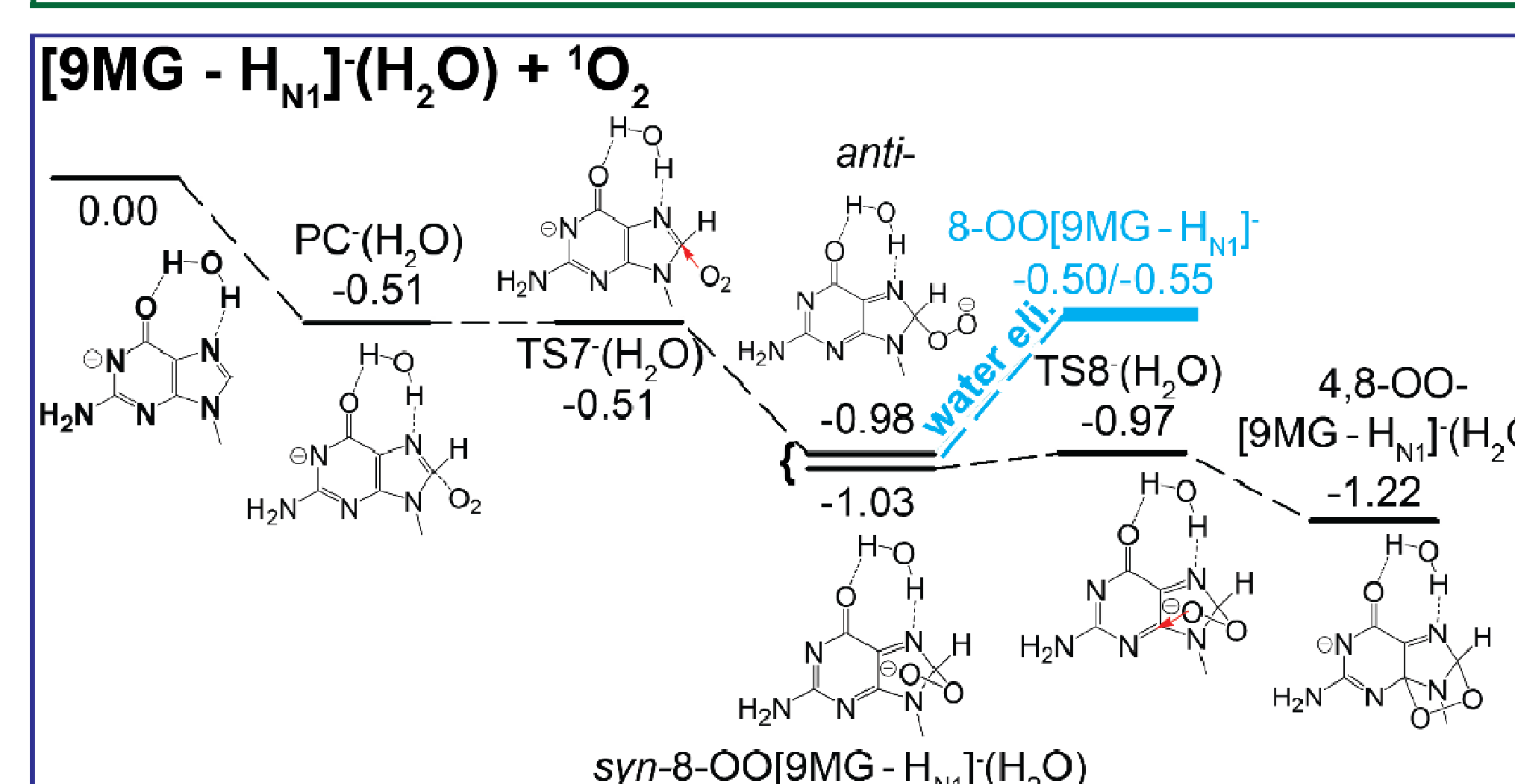
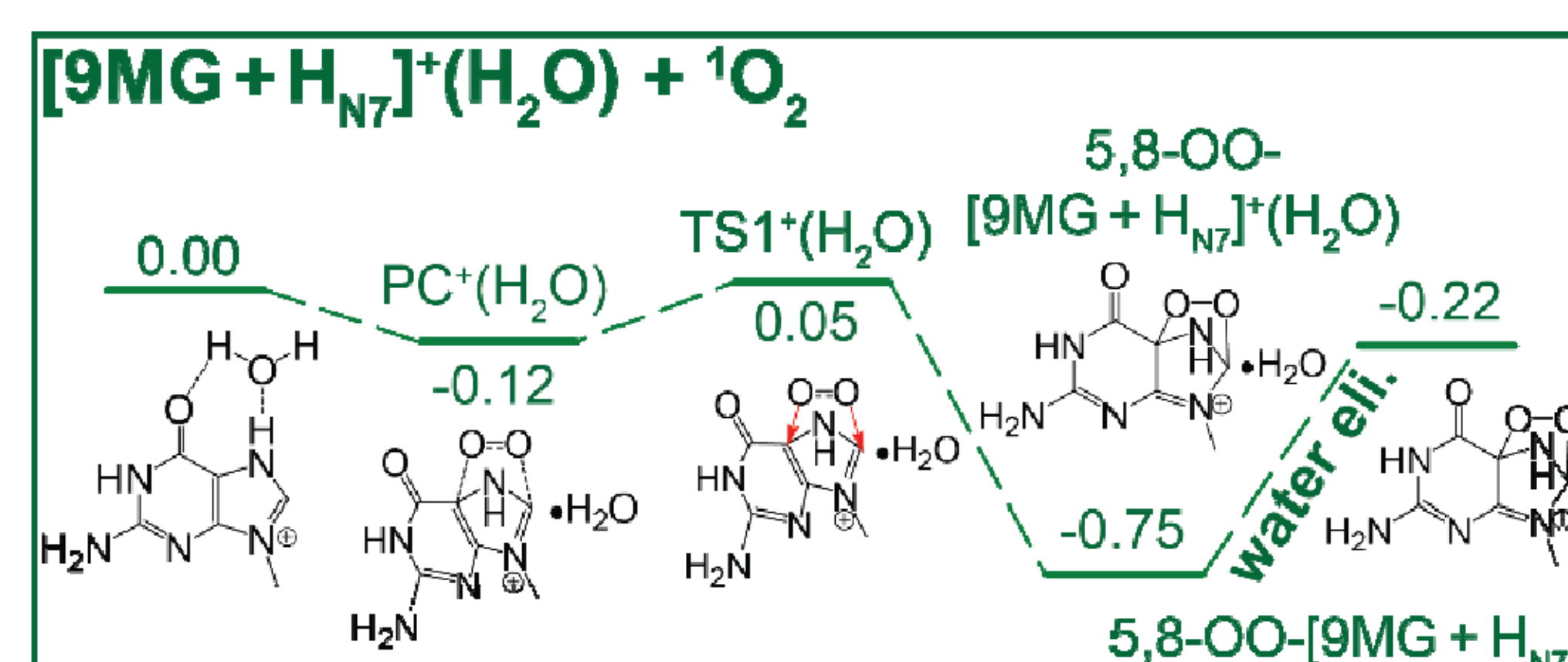
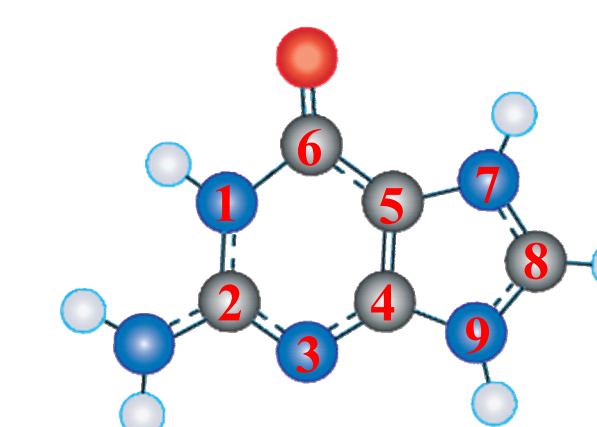
- Cross section measurements



Dry guanine and 9-methylguanine ions are non-reactive toward ¹O₂ addition. Hydrated ions are reactive, and the only pathway is addition of ¹O₂ followed by releasing H₂O. Reaction efficiency of 9MG ions (a prototype of guanosine) is inhibited compared with G ions. All these are exothermic, indicating there would be no reaction barriers.

- More insights from calculation

Dry G and 9MG ions	No reactions. Energy barrier located.
[G + H] ⁺ (H ₂ O)	Concerted addition. 5,8-endoperoxide. Then -H ₂ O
[G - H] ⁺ (H ₂ O)	Concerted addition. 5,8-endoperoxide. Then -H ₂ O
[9MG + H] ⁺ (H ₂ O)	Concerted addition. 5,8-endoperoxide. Then -H ₂ O
[9MG - H] ⁺ (H ₂ O)	Stepwise. 4,8-endoperoxide and/or 8-peroxide. Then -H ₂ O



Conclusions

- Hydrated guanine ions provide a platform to investigate the endoperoxide intermediates, which are not stable both in gas phase (due to the high internal energy) and in solution (due to the subsequent secondary reactions). Electronic structure calculations and quasi-classical direct dynamics trajectory simulations provide supportive insights for a better understanding of reaction mechanisms.

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References

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