# Singlet Oxygenation and Base-Pair Dissociation of 9-Methyl-8-Oxoguanine−1-Methyl-Cytosine Radical Cation [9MOG·1MC]•+

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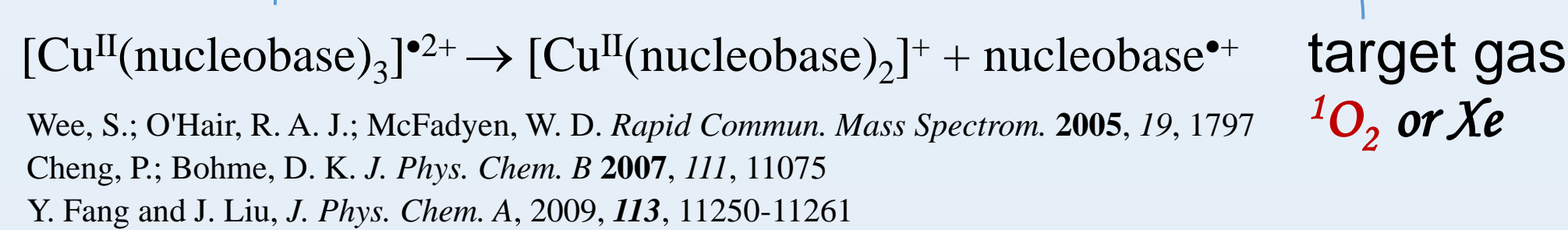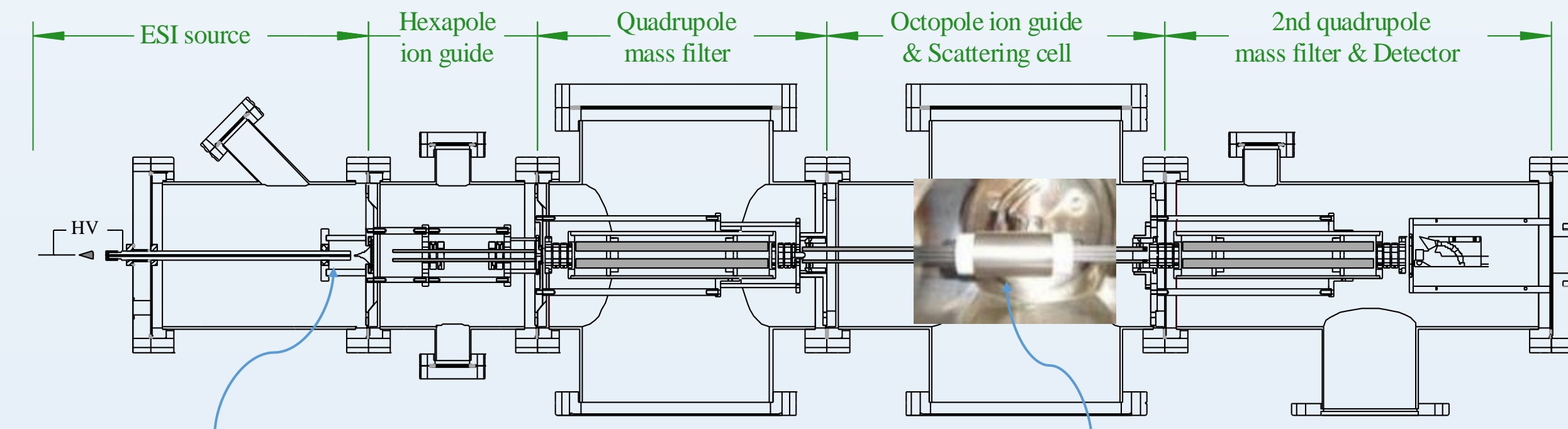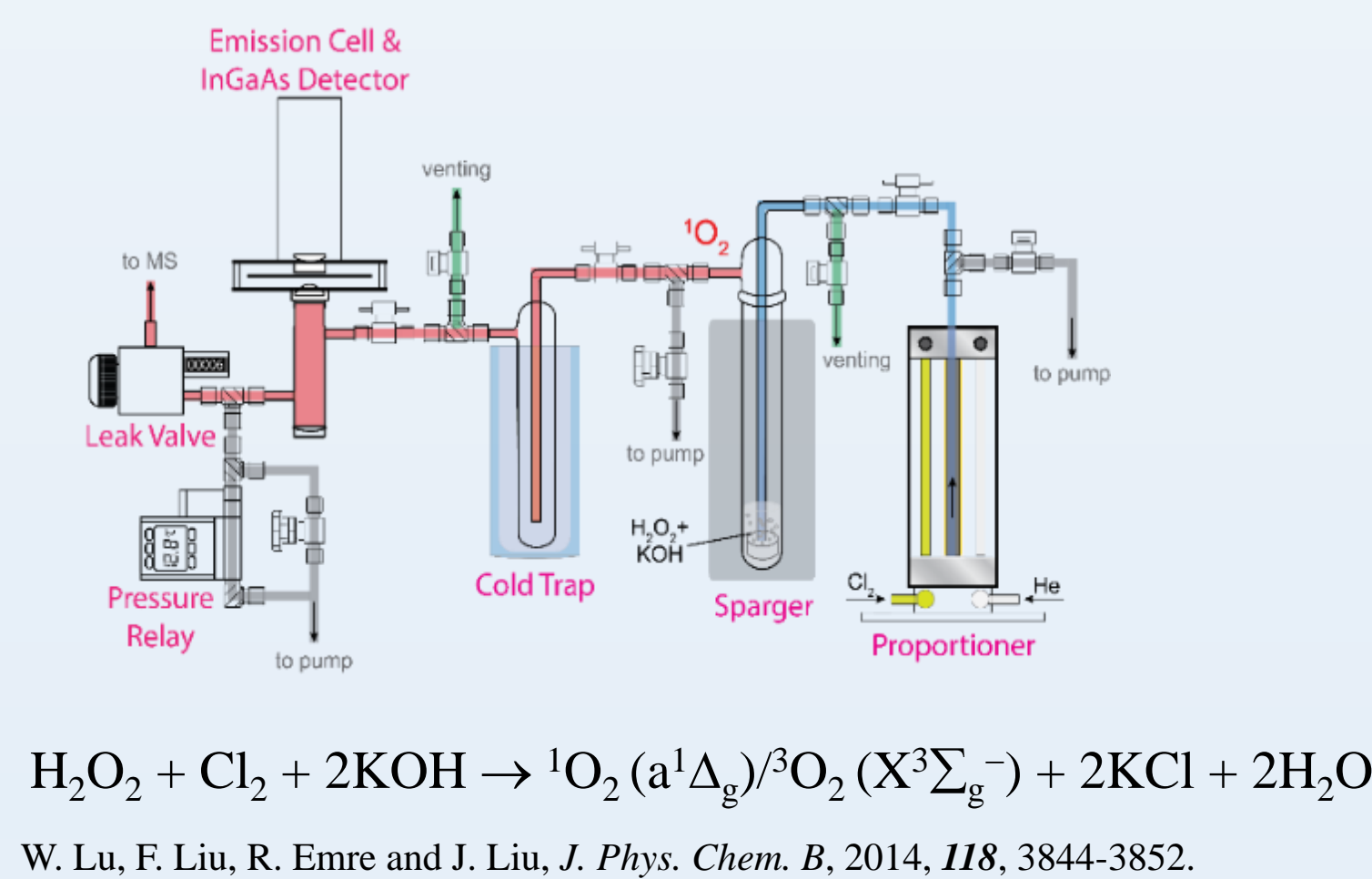
## Introduction

➢ Guanosine is susceptible to oxidative stress in biological systems, producing 8-oxo-7,8-dihydroguanosine (OG) as one of the major products. OG has an even lower oxidation potential than that of guanosine, leading to facile formation of radical cation OG•+ in subsequent oxidatively generated DNA lesions.

➢ OG adopts an *anti*-conformation when pairing with cytidine, following a Watson-Crick (WC)-type base-pairing motif. The presence of OG·C in base pair can lead to OG·A transversion if unrepaired during replication [Y. Nakabeppu, *Int. J. Mol. Sci.* **2014**, 15, 12543].

➢ Synergistic ionizing radiation and singlet O₂ [a¹Δg] oxidation of OG·C have implications on the radiotherapy and photodynamic therapy for cancer treatment; moreover, singlet oxygenation and ionization may affect intra-base pair proton transfer (PT) and dissociation of the OG·C base pair

## Instrumentation and Experiment

**Formation and reaction of [OG·C]•+ in the gas phase using ESI guided-ion beam tandem mass spectrometer**



[Cuᴵᴵ(nucleobase)₃]•²⁺ → [Cuᴵᴵ(nucleobase)₂]⁺ + nucleobase•+   **target gas  ¹O₂ or Xe**

Wee, S.; O'Hair, R. A. J.; McFadyen, W. D. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 1797
Cheng, P.; Bohme, D. K. *J. Phys. Chem. B* **2007**, *111*, 11075
Y. Fang and J. Liu, *J. Phys. Chem. A*, 2009, *113*, 11250-11261

**Chemical generation of ¹O₂ and detection using near IR emission**



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

W. Lu, F. Liu, R. Emre and J. Liu, *J. Phys. Chem. B*, 2014, *118*, 3844-3852.

## Experimental Results and Theoretical Modeling of a Base-Pair Model System [9MOG·1MC]•+

### 1. Identification of conventional and PT conformers of [9MOG·1MC]•+ and dissociation kinetics by tandem CID MS
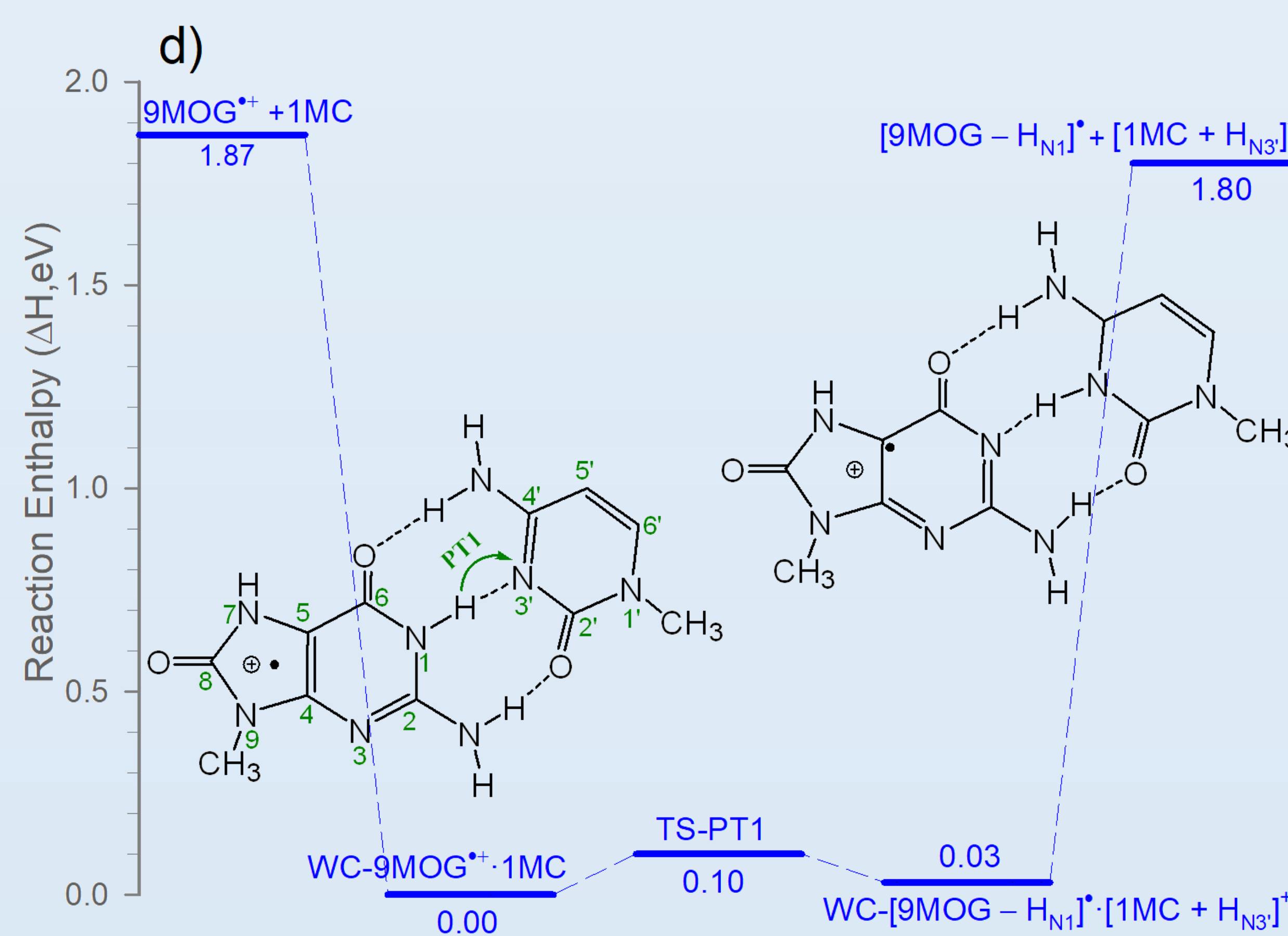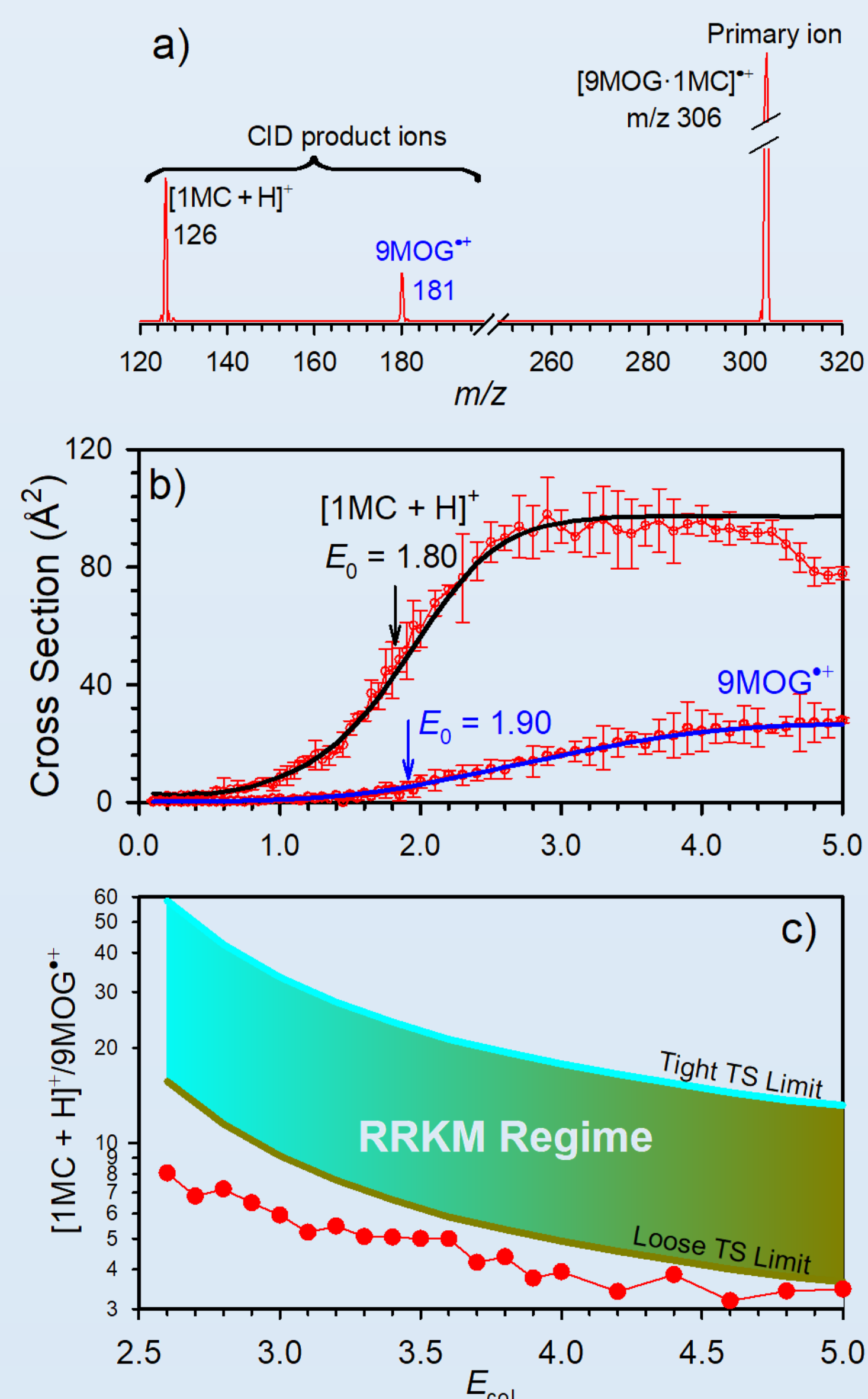


CID of the 9MOG•+·1MC ⇌ [9MOG − Hₙ₁]•·[1MC + Hₙ₃·]⁺ equilibrium ensemble with Xe: a) product ion mass spectrum, b) product ion cross sections, c) comparison of product ion ratio with RRKM predications, and d) dissociation PES for 9MOG•+·1MC and its PT conformer, calculated at DLPNO-CCSD(T)/aug-cc-pVQZ//ωB97XD/6-311++G**, including 298 K thermal corrections.

### 2. Singlet oxygenation of [9MOG·1MC]•+ : Ion-molecule reaction measurements and PES modeling
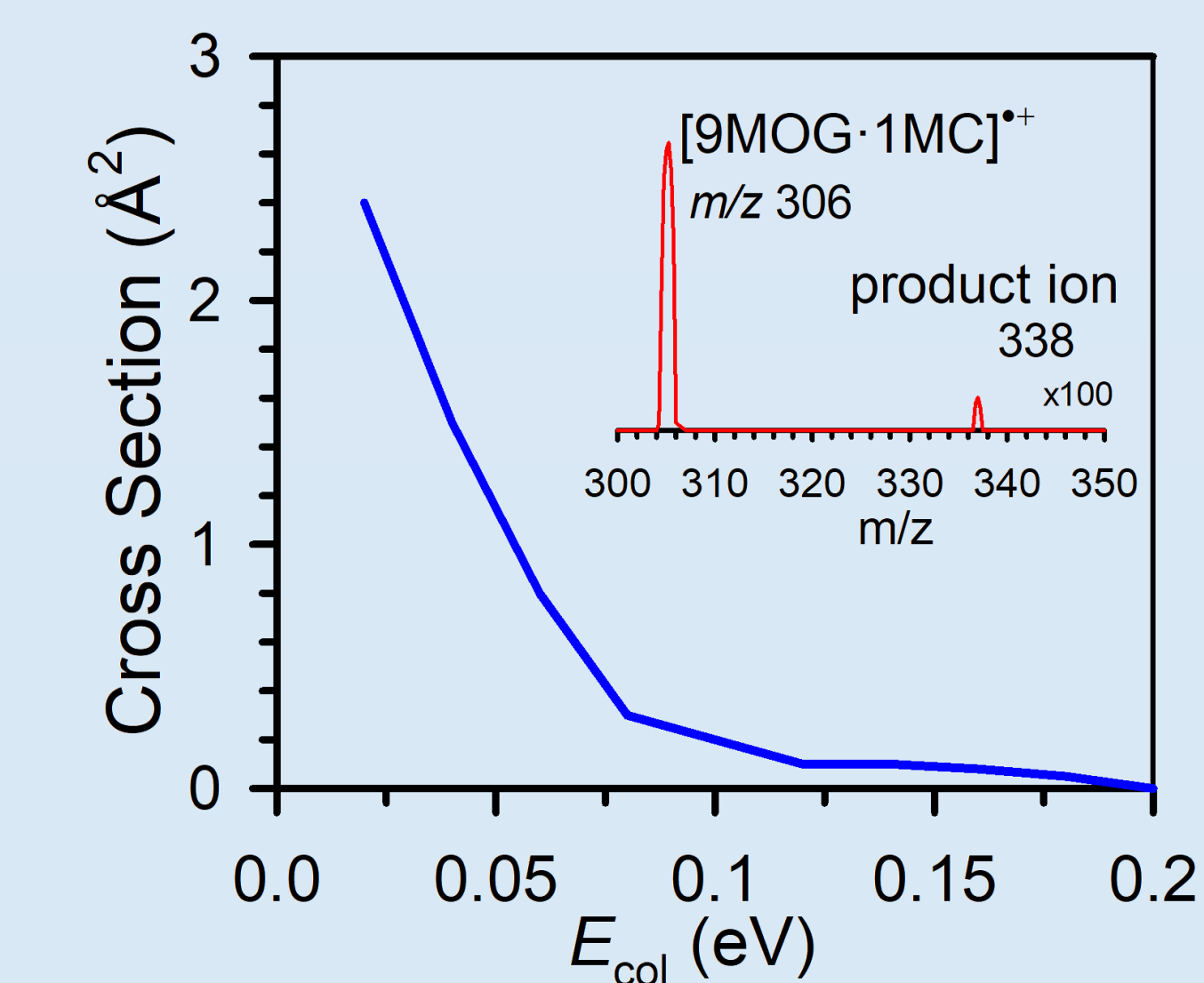


Product ion and cross section of ¹O₂ + [9MOG·1MC]•+ Inset show a product ion mass spectrum at Ecol = 0.02 eV.
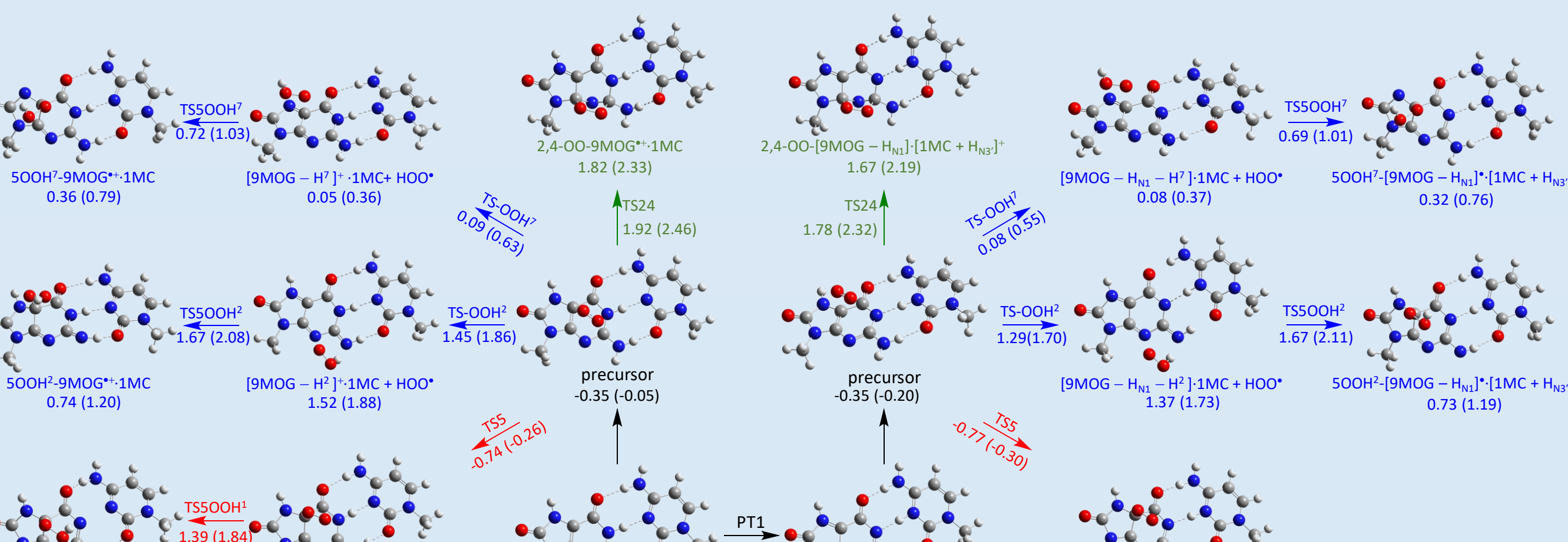
Various ¹O₂ oxidation pathways of 9MOG•+·1MC and [9MOG − Hₙ₁]•·[1MC + Hₙ₃·]⁺ calculated at approximately spin-projected ωB97XD/6-31+G**, including 298 K thermal corrections.

### PES for C5-O₂ addition and H-abstraction at N7, constructed using approximately spin-projected ωB97XD/6-31+G** and CASPT2/6-31G**

— eliminate spin-contamination and account for multireferential characters (mixing of doublet and quartet) for doublet radical + ¹O₂
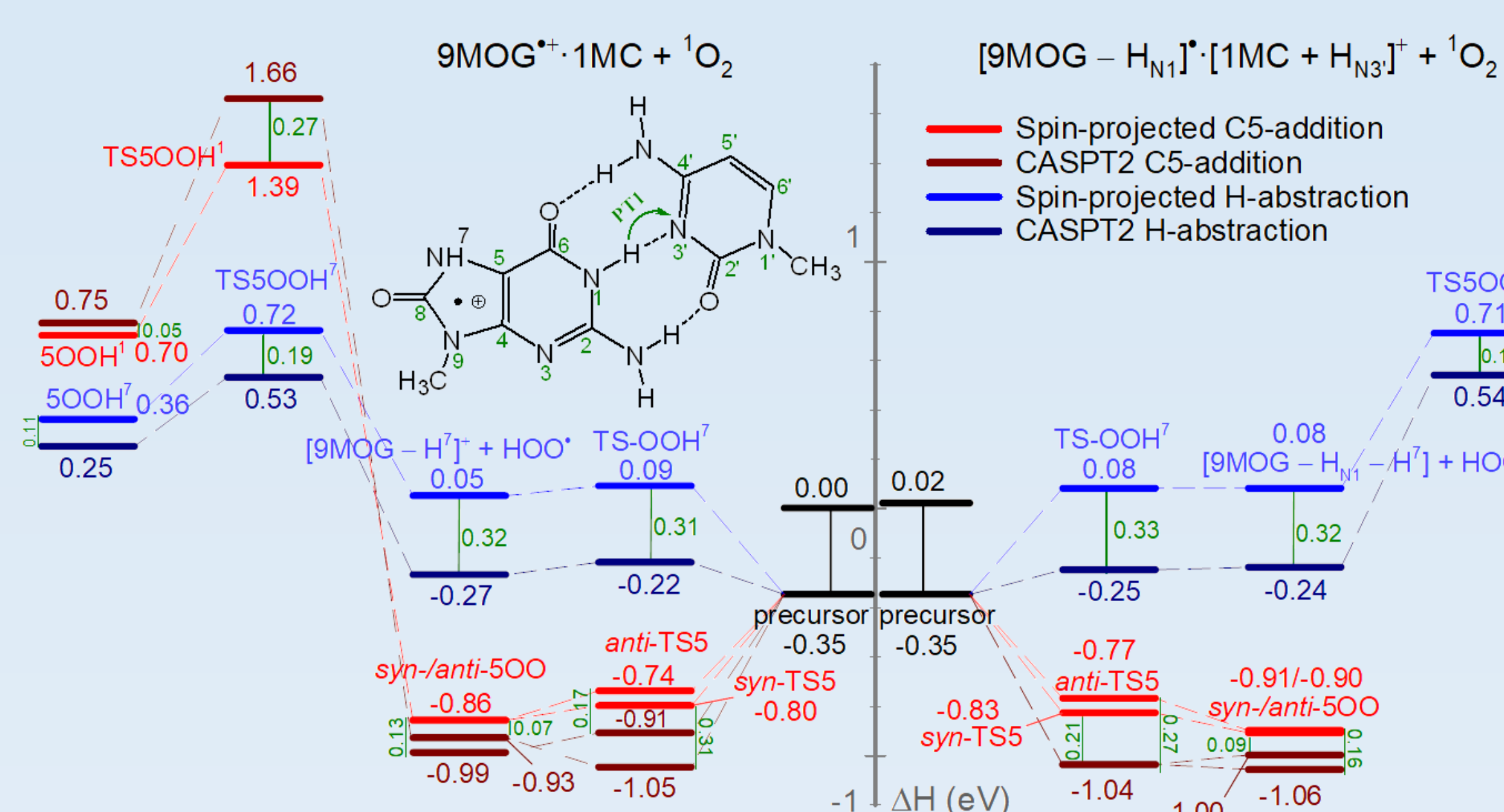


Energy differences of the two levels of theory are illustrated in green color.

**Approximate spin projection (AP) method**

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

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

$E^{BS}$    energy for broken-symmetry state
$E^{HS}$    energy for high-spin state
$\langle \hat{S}^2 \rangle$    average value of the total spin angular momentum operator
$N^\alpha$ and $N^\beta$    numbers of alpha and beta electrons

T. Saito, et.al, *J. Phys. Chem. A*, 2010, *114*, 7967-7974
J. Benny, T. Saito, M M. Moe and J. Liu, *J. Phys. Chem. A*, 2022, *126*, 68-79
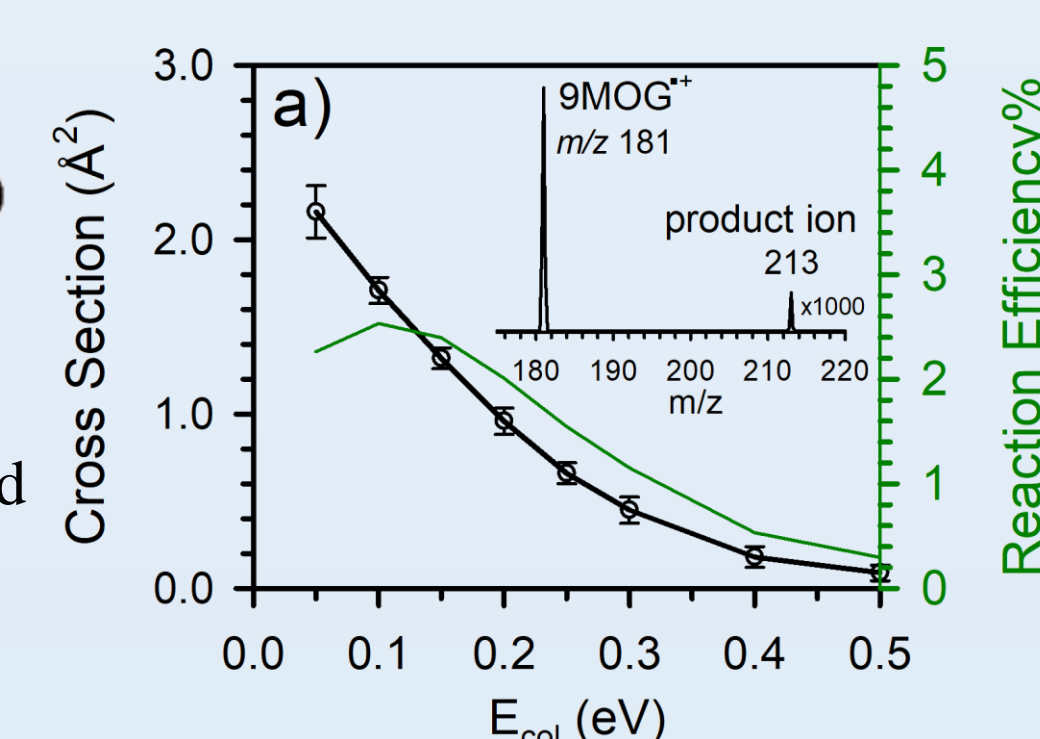
**CASPT2**

Add dynamic correlation using second order perturbation theory with the CASSCF wavefunction as the reference

A composite CASPT2/DFT approach was able to produce correct PESs for many ¹O₂ reactions
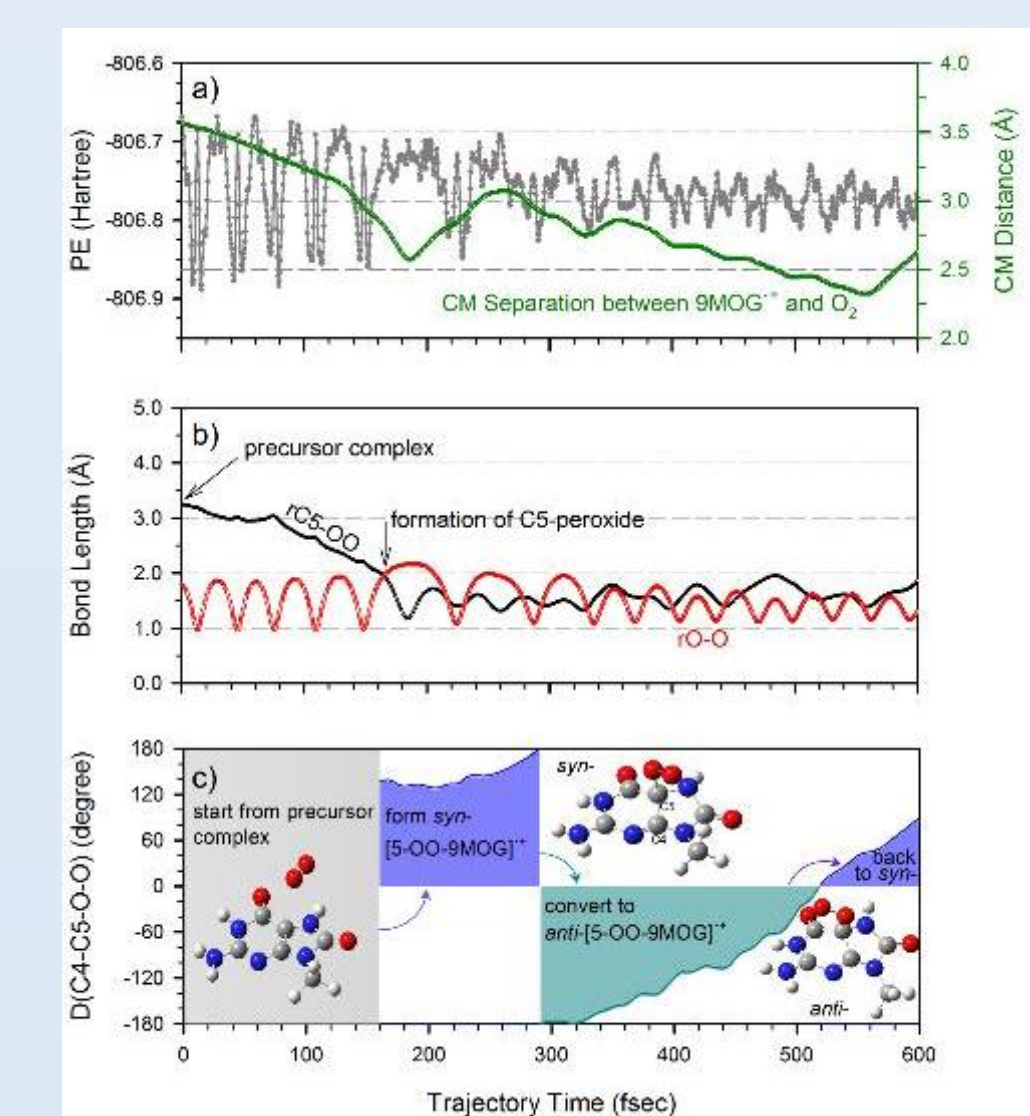
## Comparison to ¹O₂ with the 9MOG•+ monomer
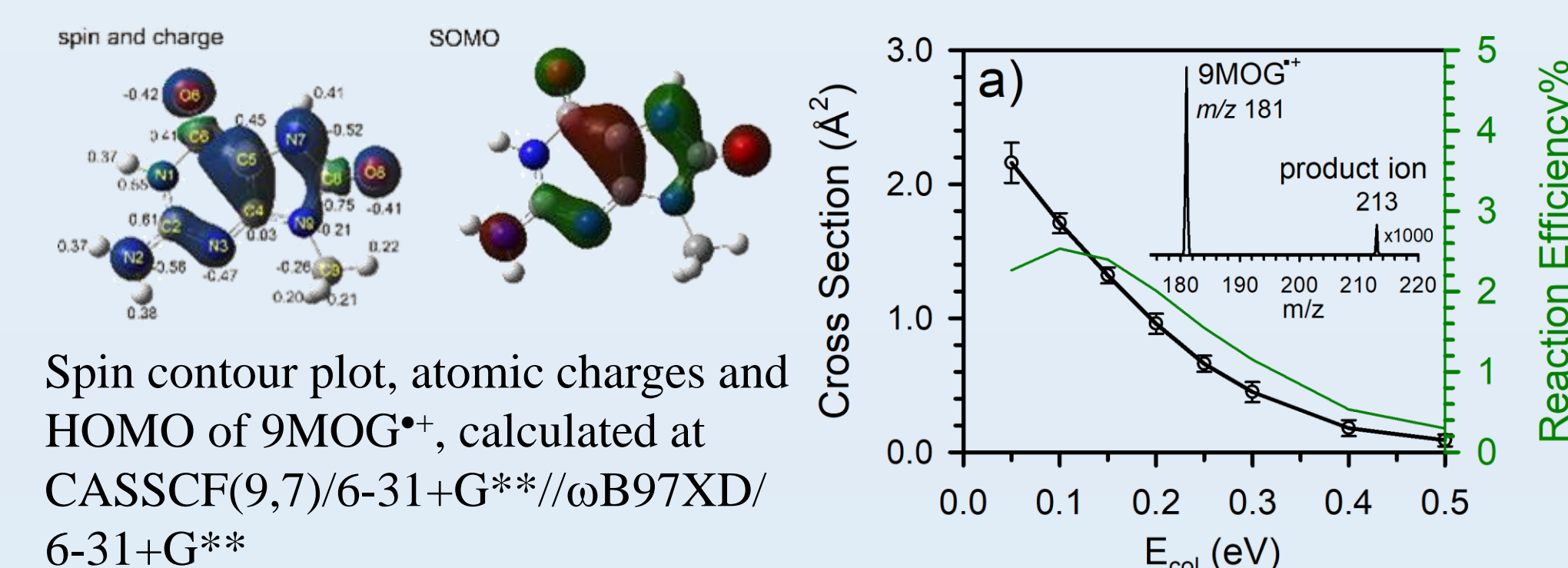


Spin contour plot, atomic charges and HOMO of 9MOG•+, calculated at CASSCF(9,7)/6-31+G**//ωB97XD/6-31+G**

Product cross sections and reaction efficiencies (right axis) for the ¹O₂ reaction with 9MOG•+. Inset shows product ion mass spectrum at Ecol = 0.05 eV.

The most probable product is [5-OO-9MOG]•+ as revealed by dynamics simulations of 9MOG•+ with ¹O₂ at Ecol = 0.05 eV. (a) Variations in potential energy and in the center-of-mass distance between the collision partners, (b) changes of reactive bond lengths, and © interconversion between *syn*- and *anti*-[5-OO-9MOG]•+.
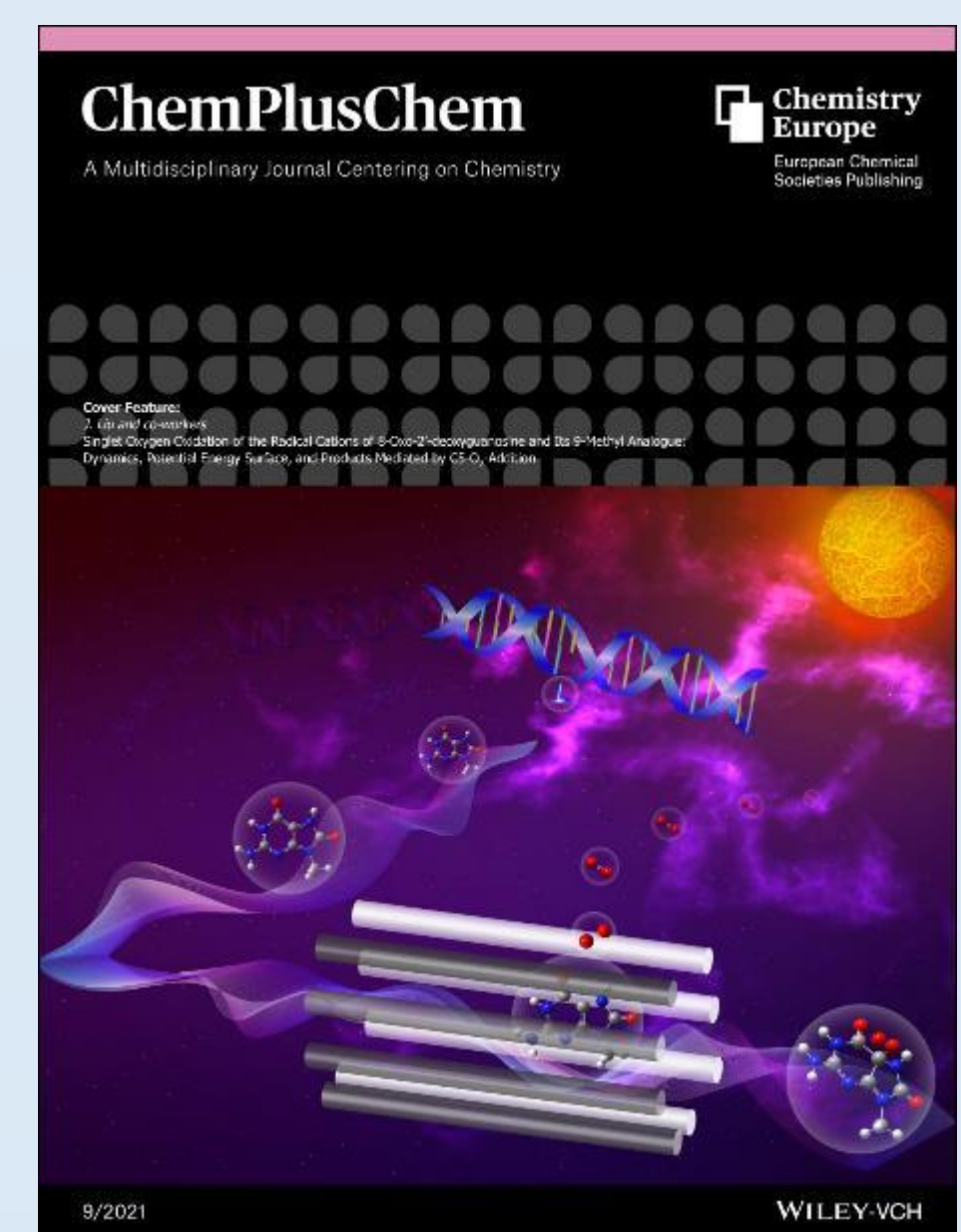
## Conclusions

The present work has assessed the chemistry of ¹O₂ with a 9MOG nucleobase in a radical cation vs. a dehydrogenated neutral radical and either as an isolated monomer or paired with cytosine within a Watson−Crick base pair:

• 9MOG•+, 9MOG•+·1MC and its PT conformer were formed in the gas phase by electrospray of Cuᴵᴵ-nucleobase complex to the gas phase followed by redox-separation of the complex to nucleobase radical cation and Cuᴵ.

• The two base-pair isomers (a conventional 9MOG•+·1MC and a PT structure [9MOG − Hₙ₁]•·[1MC + Hₙ₃·]⁺ ) were distinguished by CID mass spectra, and their dissociation product ratios deviate from a statistical RRKM predictions by factor of 2.

• 9MOG•+·1MC and [9MOG − Hₙ₁]•·[1MC + Hₙ₃·]⁺ follow the same reaction pathways with ¹O₂, except for the lack of 5OOH¹ and H-abstraction in the PT conformer. Their most probable product channels correspond to an exothermic C5-O₂ adduct, followed by H-abstraction at N7, both of which have no activation barriers above reactants.

• Singlet oxygenation slightly lowers the energies of the PT base-pair structure in the oxidation products.

• The 9MOG radical within a WC base pair maintains the same reactivity with ¹O₂ as the isolated single 9MOG•+

• Approximately spin projection and CASPT2 have effectively removed spin-contamination in the multireferential PES of doublet radical with ¹O₂. The CASPT2-calcaued reaction energies are generally 0.05 − 0.3 eV lower than the spin-projected DFT energies, except for 5OOH¹ for which the CASPT2 energy is 0.05 − 0.27 eV higher.

## Acknowledgements