

# Guanine Oxidation, and Intra-Pair Proton Transfer and Non-Statistical Dissociation of Guanine-Cytosine Base Pair

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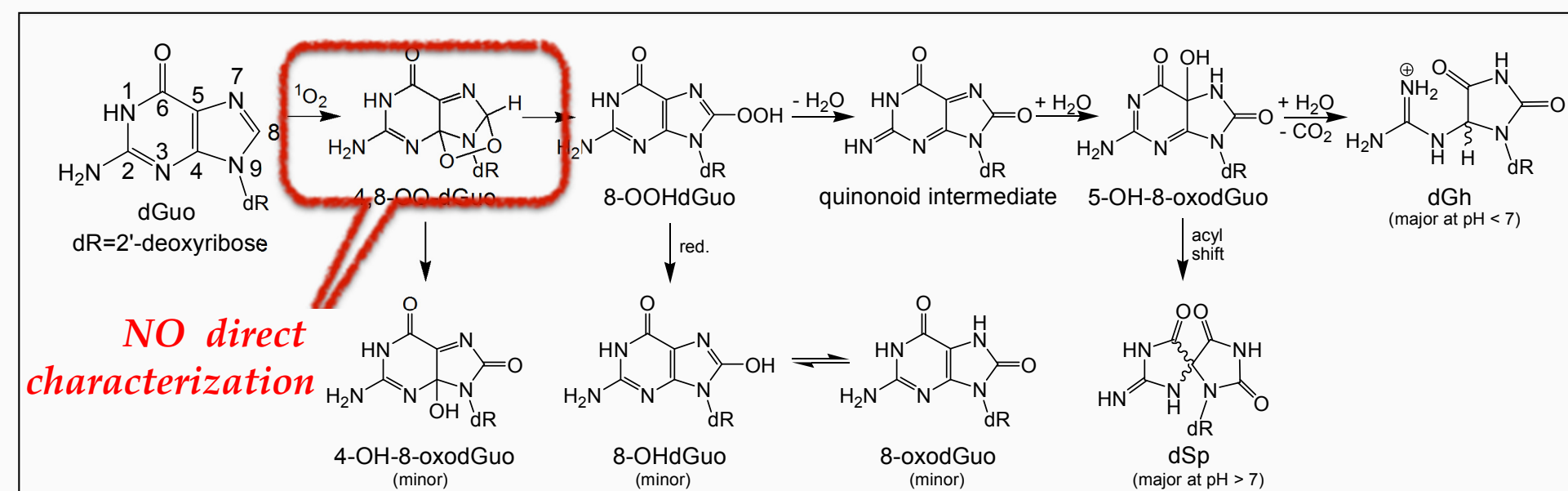
## I. Guanine oxidation mechanism and the questions we want to address

Guanine nucleobase is the exclusive DNA target for  $^1\text{O}_2$



- Genomic mutation
- DNA-protein cross-linking
- Lethality

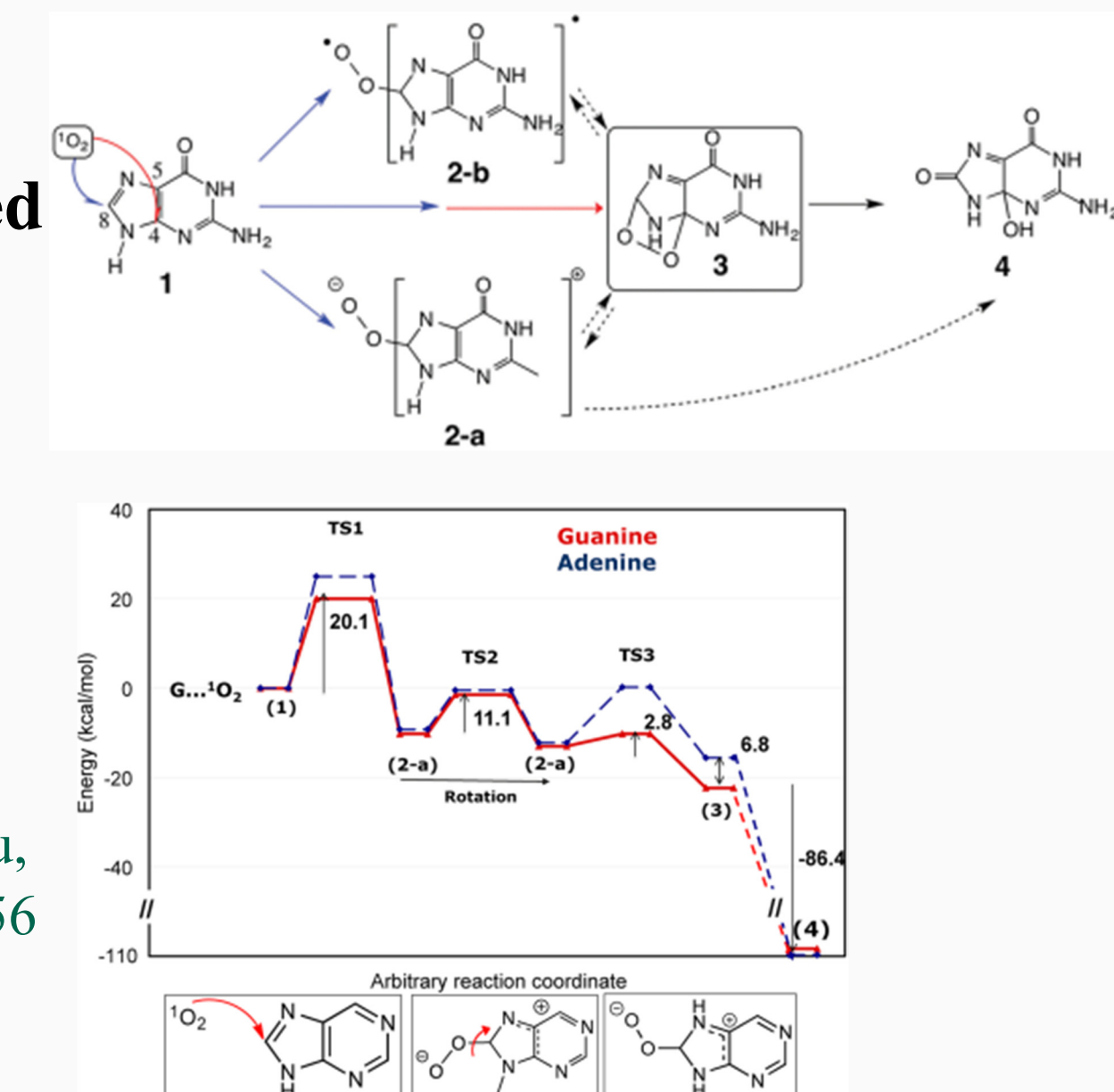
### Q1 Formation of transient endoperoxide?



The only evidence was from photooxidation of an 8-methyl substituted model guanosine compound at  $-78^\circ\text{C}$   
C. Sheu and C. Foote, *JACS*, 1993, **115**, 10446

### Q2 Concerted [4+2] cycloaddition across 4,8-bond OR stepwise addition initialized by 8-peroxide?

R Grüber, A Monari, E Dumont, *JPC A*, 2014, **118**, 11612

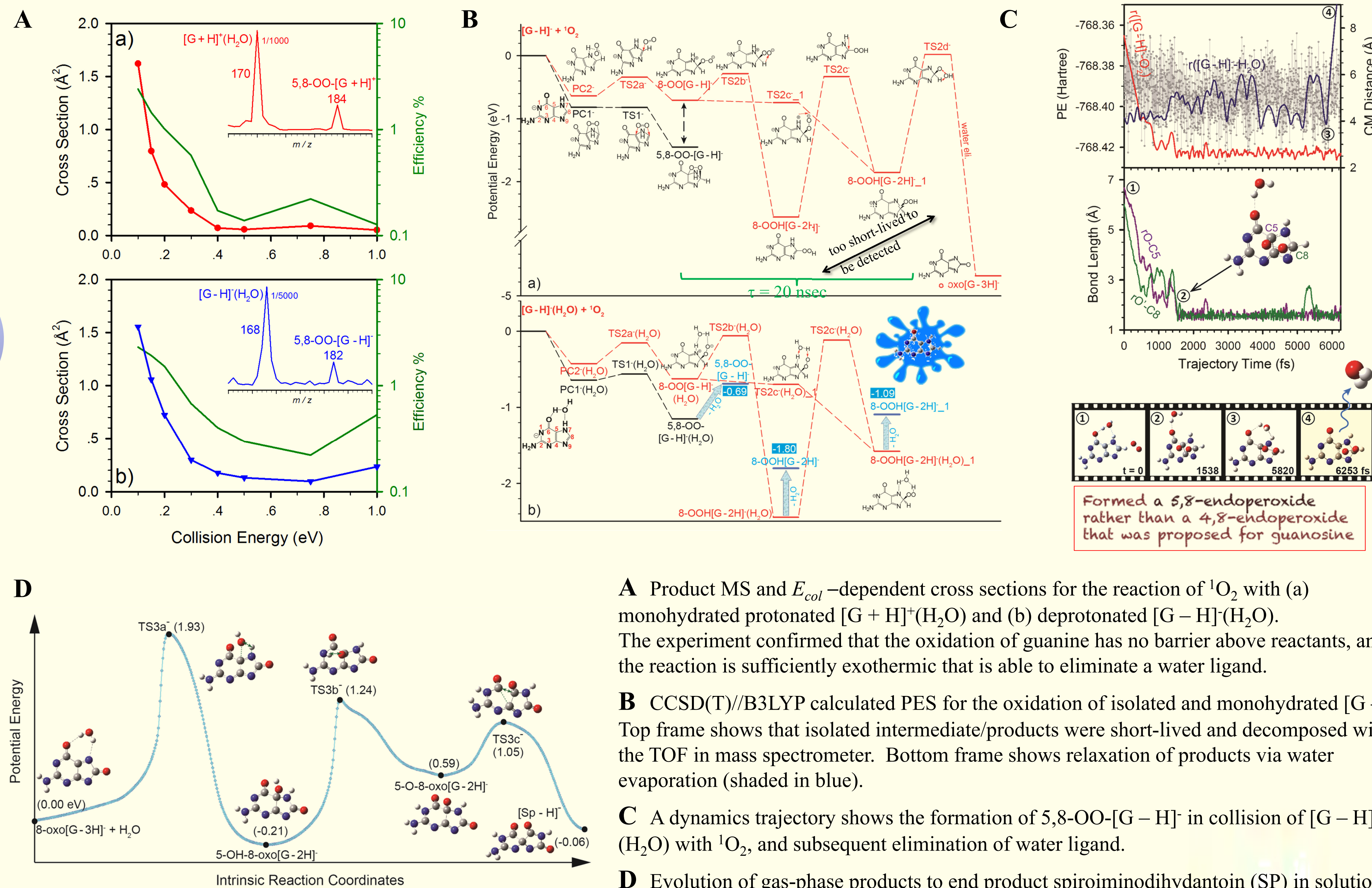
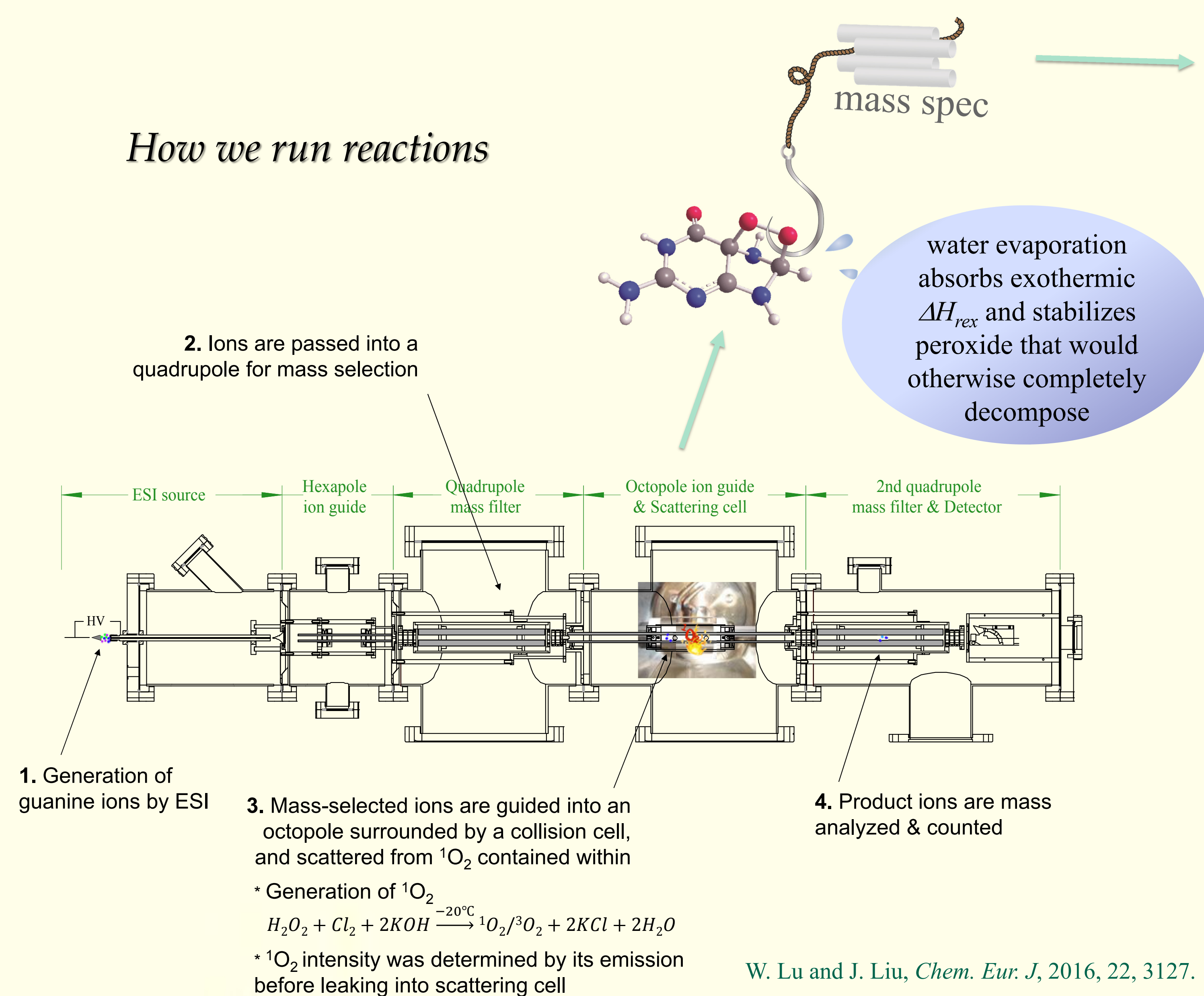


### Q3 An endothermic activation barrier for oxidation?

E Dumont, R Grüber, E Bignon, C Morell, Y Moreau, A Monari, J-L Ravanat, *Nucl. Acids Res.*, 2016, **44**, 56

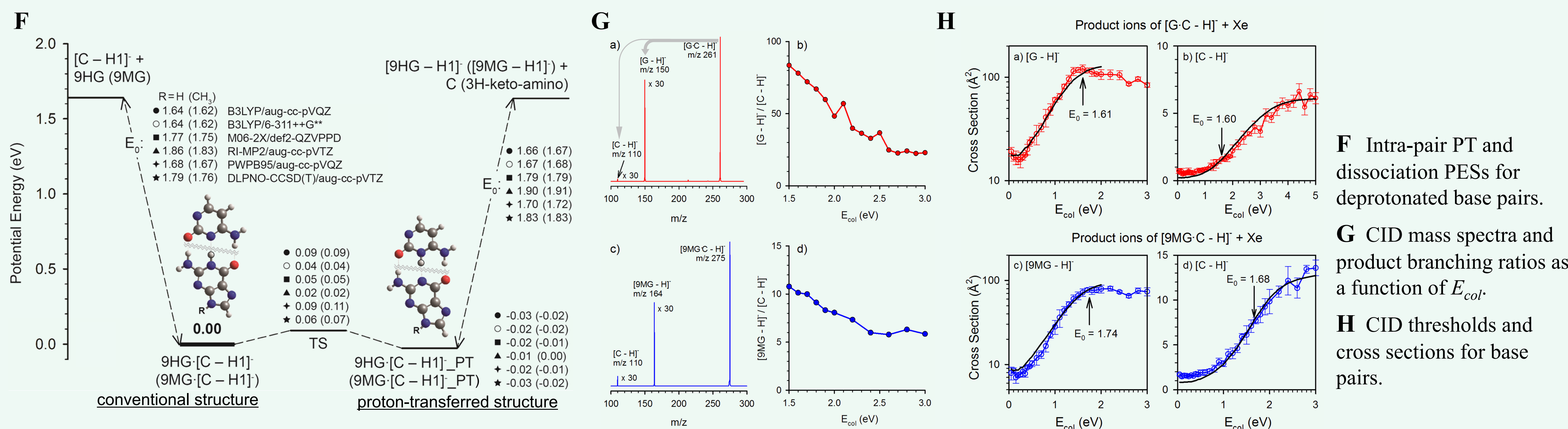
Capture transient oxidation intermediate in the gas phase using hydrated guanine ions as a target for  $^1\text{O}_2$

How we run reactions



## II. Intra-pair proton transfer and non-statistical kinetics of deprotonated [Guanine-Cytosine - H]- pair

- Deprotonation of base pairs is one consequence of ionizing radiation interacting with cells, occurring after dissociative electron attachment.
- Deprotonation of a nucleobase prompts intra-pair proton transfer  $\rightarrow$  Shift of actual deprotonation site & Structural perturbation



### I PT equilibrium constants ( $K_{PT}$ ), ratio of dissociation rate constants ( $k_{diss}$ ), and RRKM vs. Exp product branching

$E_{col}$ (eV)	$K_{PT}$	$k_{diss}(\text{conventional structure})/k_{diss}(\text{proton-transferred structure})$	Ratio of $[\text{G} - \text{H}]^- / [\text{C} - \text{H}]^-$
7HG-[C - H]- (population 62%)			
2.0	2.28	9.65	22.0
2.5	2.03	3.64	7.39
3.0	1.86	2.54	4.72
9HG-[C - H]- (population 38%)			
2.0	1.54	0.28	0.43
2.5	1.44	0.26	0.37
3.0	1.38	0.27	0.37
population-weighted average for [G-C - H]-			
2.0	-	-	13.8
2.5	-	-	4.6
3.0	-	-	3.1
9MG-[C - H]-			
2.0	1.27	0.10	0.13
2.5	1.22	0.17	0.21
3.0	1.18	0.22	0.26

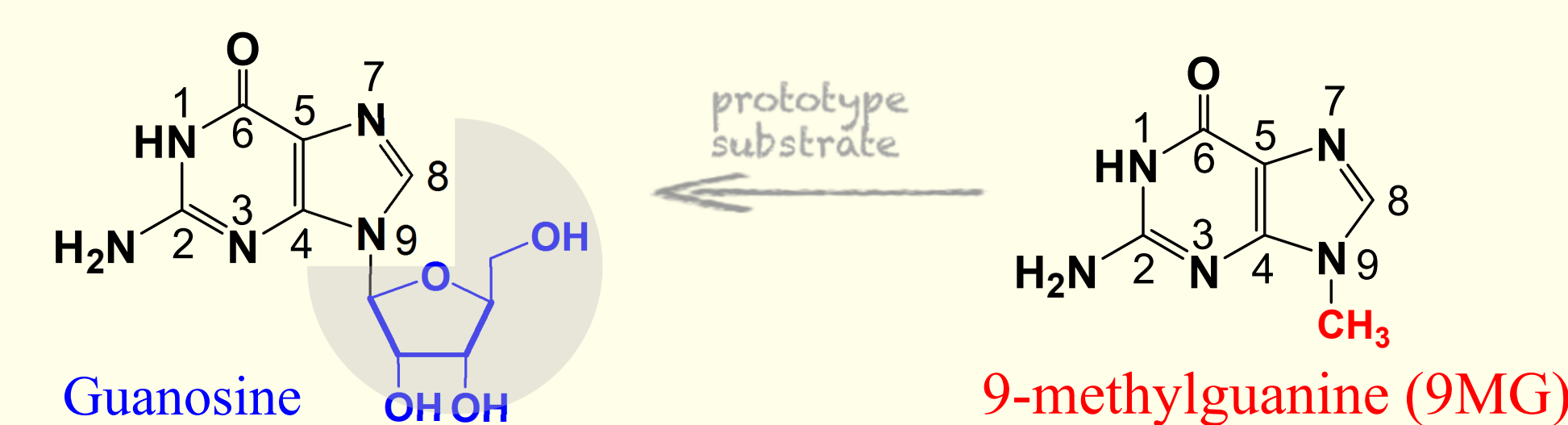
### Origin for non-statistical base-pair dissociation (?)

- 1) TS re-crossing for intra-pair PT was observed in trajectories  
TS geometries are twisted that bring about a dynamic bottleneck along the constrained configuration.
- 2) Location of a critical configuration that separates base pair and dissociation products  
Base pair dissociation has no reverse barrier and the location of the dividing surface depends on energy. We are trying a rigorous way to locate the critical configuration in reaction.
- 3) RRKM assumes that IVR renders the distribution of energy a random one. But CID may produce short time non-statistical fragmentation.

### On-going Work

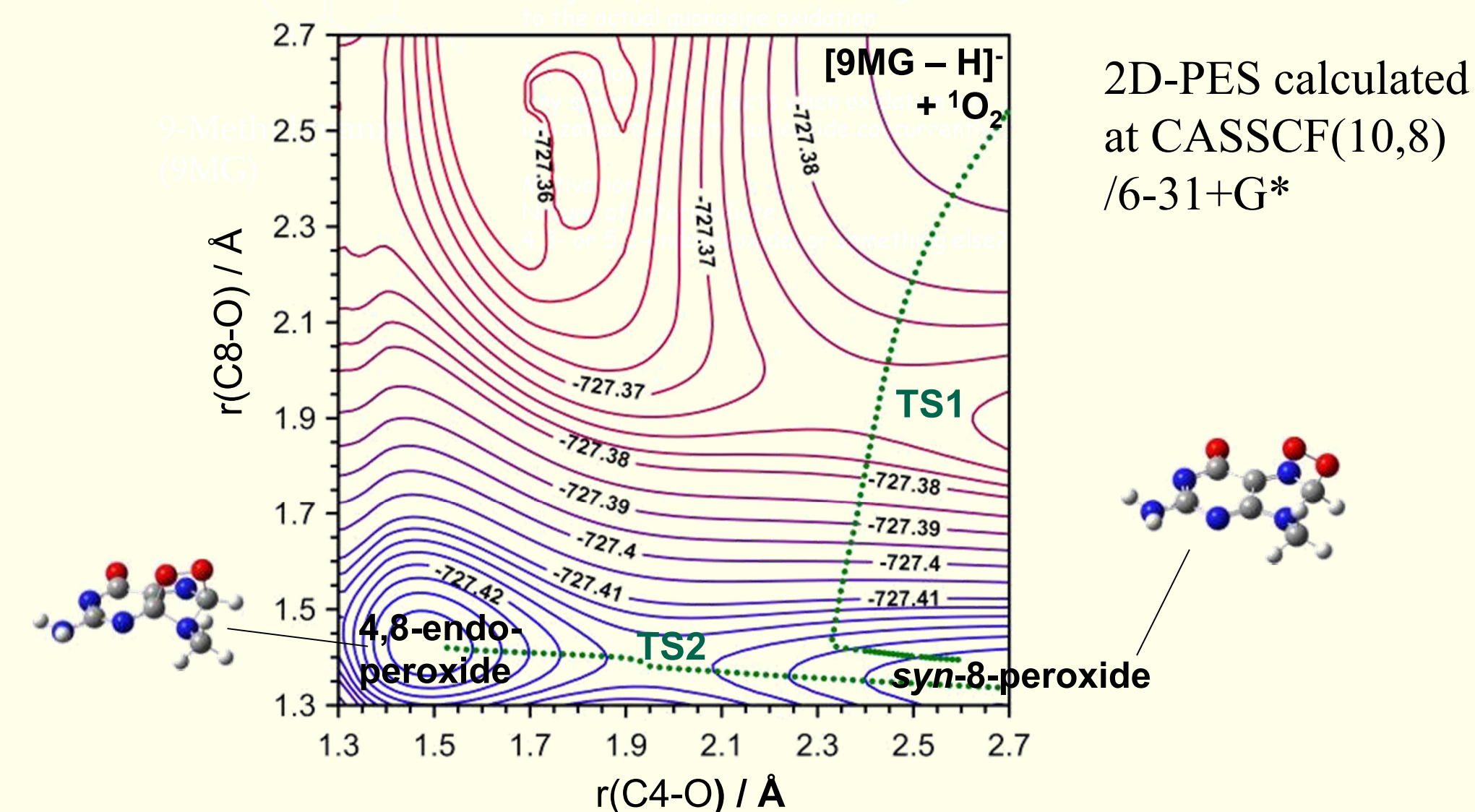
Trajectories are being propagated starting from both activated G-[C - H]- and its proton-transferred tautomer, and at the proton-transfer activation barrier.

### E $^1\text{O}_2$ oxidation of guanine nucleoside (A model study)



Oxidation of protonated  $[\text{9MG} + \text{H}]^+$  is similar to free guanine: reaction is mediated by a [4 + 2] cycloaddition leading to formation of 5,8-endoperoxide.

Oxidation of deprotonated  $[\text{9MG} - \text{H}]^-$  is different and proceeds *stepwise*, starting with a terminal peroxide that subsequently evolves to a 4,8-endoperoxide.



Implications for oxidation of guanosine Acidic and basic media may lead to different oxidation chemistries of guanosine, starting from initial stage.

W. Lu, H Teng, and J. Liu, *PCCP*, 2016, **18**, 15223.

### Acknowledgements

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W. Lu and J. Liu, *PCCP*, 2016, **18**, 32222.