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Remarkable Sensitivity of the Prospective Photodynamic Therapy Agent 6-Selenoguanine to pH

Collin Merrick
Case Western Reserve University

Sean J. Hoehn
Case Western Reserve University, sxh905@case.edu

Luis A. Ortiz-Rodríguez
Case Western Reserve University

Sarah Krul
Case Western Reserve University

Carlos E. Crespo-Hernández
Case Western Reserve University, cxc302@case.edu

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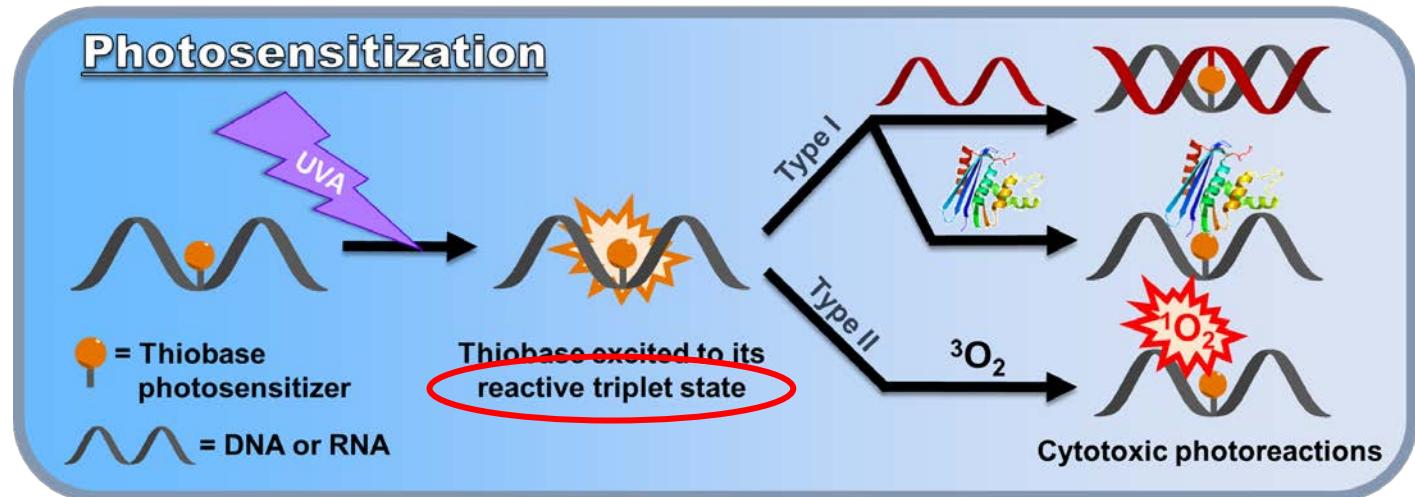
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Remarkable Sensitivity of the Prospective Photodynamic Therapy Agent 6-Selenoguanine to pH

Collin Merrick, Sean J. Hoehn, Luis A. Ortiz-Rodríguez, Sarah Krul and Carlos E. Crespo-Hernández*
Department of Chemistry, Case Western Reserve University
10900 Euclid Ave Cleveland, OH 44106

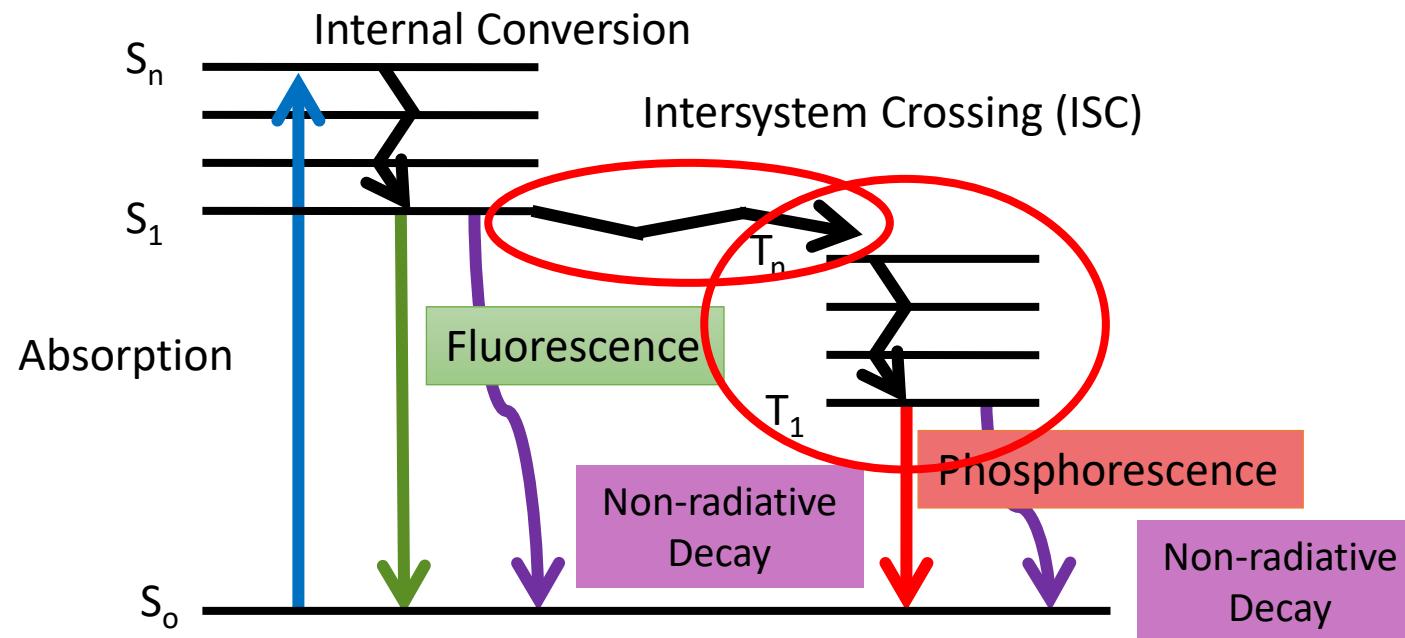
Photodynamic Therapy

- Utilizes UVA irradiation to cause localized cell death
- Treatment option for several medical conditions



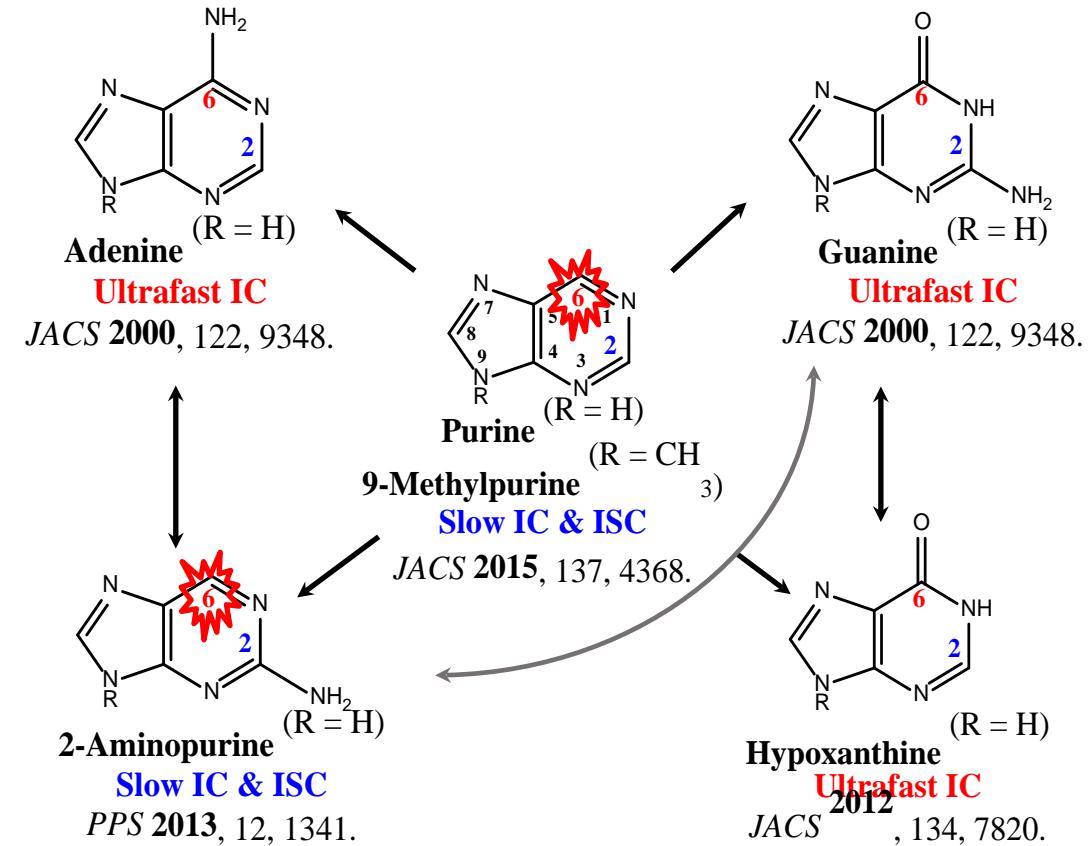
Ashwood, B.; Pollum, M.; Crespo-Hernández, C. E. Photochemical and Photodynamical Properties of Sulfur-Substituted Nucleic Acid Bases,. *Photochem. Photobiol.* **2019**, 95 (1), 33–58.

Excitation and Relaxation



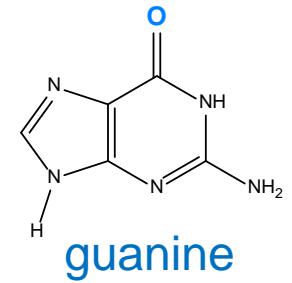
Functionalization Controls Relaxation Mechanisms

- Changing functional groups changes relaxation pathways
 - Only certain combinations of functional groups result in reactive triplet states

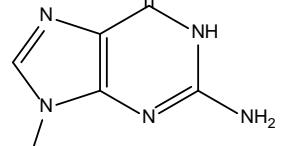


Crespo-Hernández, C. E.; Martínez-Fernández, L.; Rauer, C.; Reichardt, C.; Mai, S.; Pollum, M.; Marquetand, P.; González, L.; Corral, I. Electronic and Structural Elements That Regulate the Excited-State Dynamics in Purine Nucleobase Derivatives. *J. Am. Chem. Soc.* 2015, 137 (13), 4368–4381.

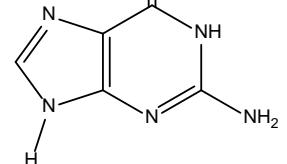
Heavy Atom Substitution



guanine



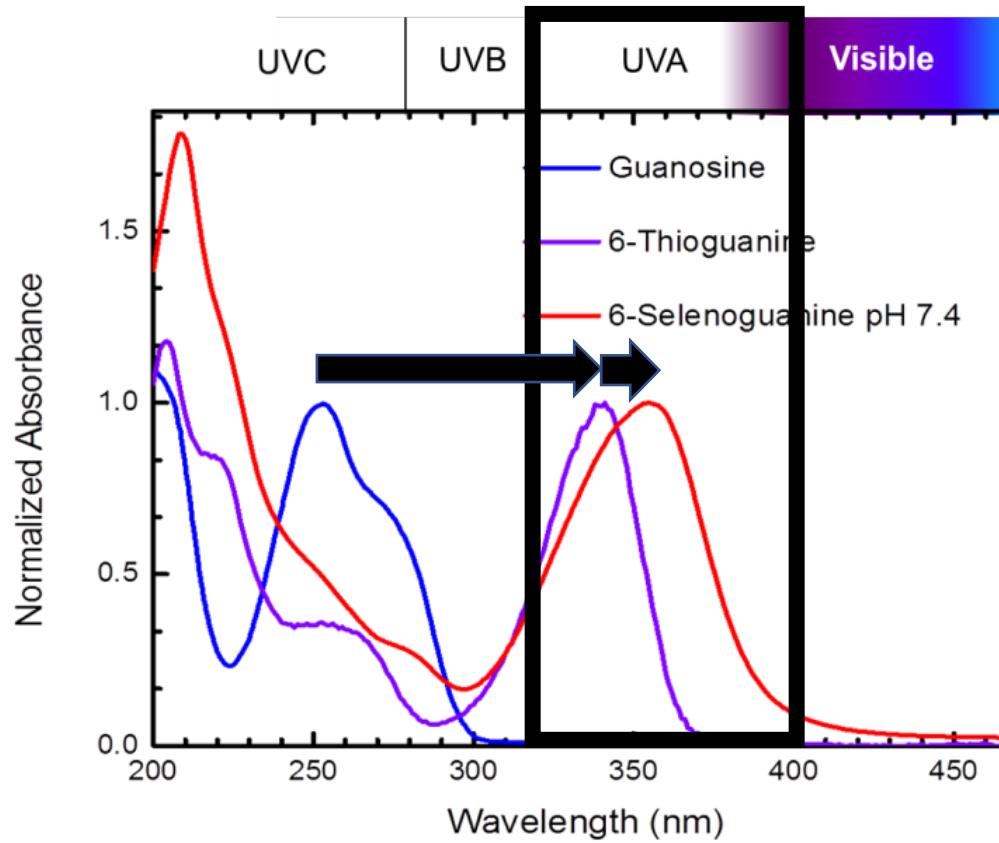
6-thioguanine



6-selenoguanine

A vertical column from the periodic table highlighting group 6A (Oxygen, Sulfur, Selenium, Tellurium, Polonium, Livermorium). The table includes atomic number, symbol, name, and atomic mass.

16	VIA 6A	
8	O	Oxygen 15.999
16	S	Sulfur 32.066
34	Se	Selenium 78.09
52	Te	Tellurium 127.6
84	Po	Polonium [208.982]
116	Lv	Livermorium [298]



Heavy Atom Substitution

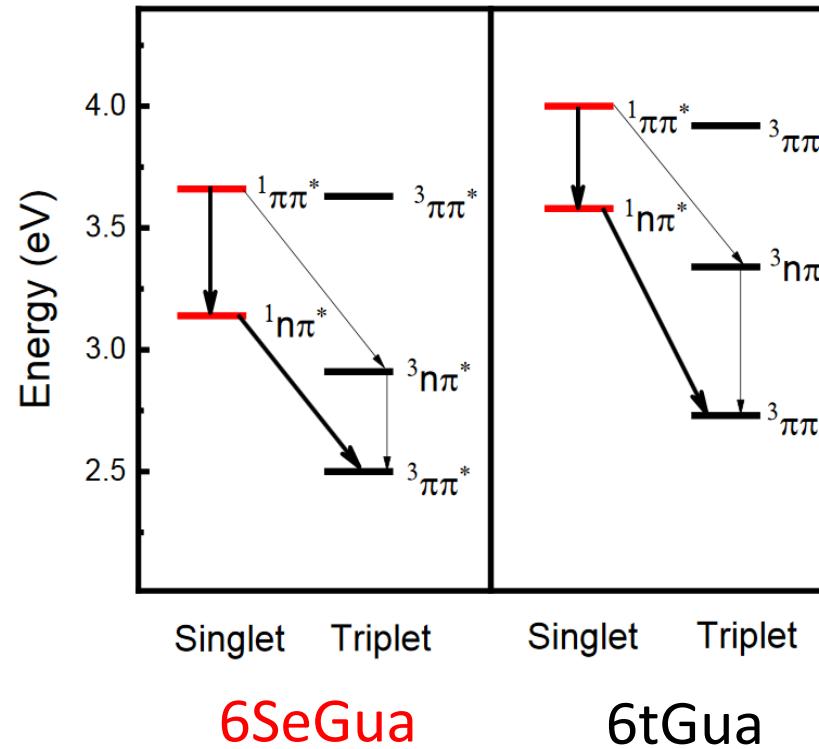


Table 1. Global lifetimes for 6SeGua and 6tGua following excitation at 352 nm under N₂-saturated conditions

Lifetimes	τ_1 / ps	τ_2 / ps	τ_3 / ns
6tGua	0.35 ± 0.04^a	18 ± 1	1420 ± 180^b
6SeGua	0.13 ± 0.05	31 ± 2	1.7 ± 0.1^c

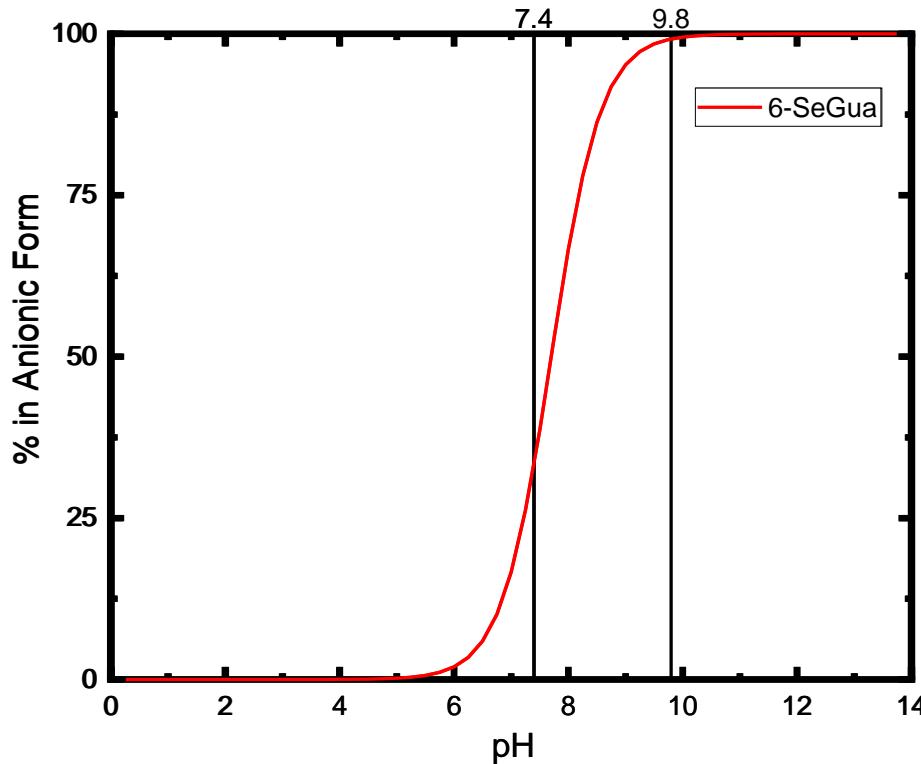
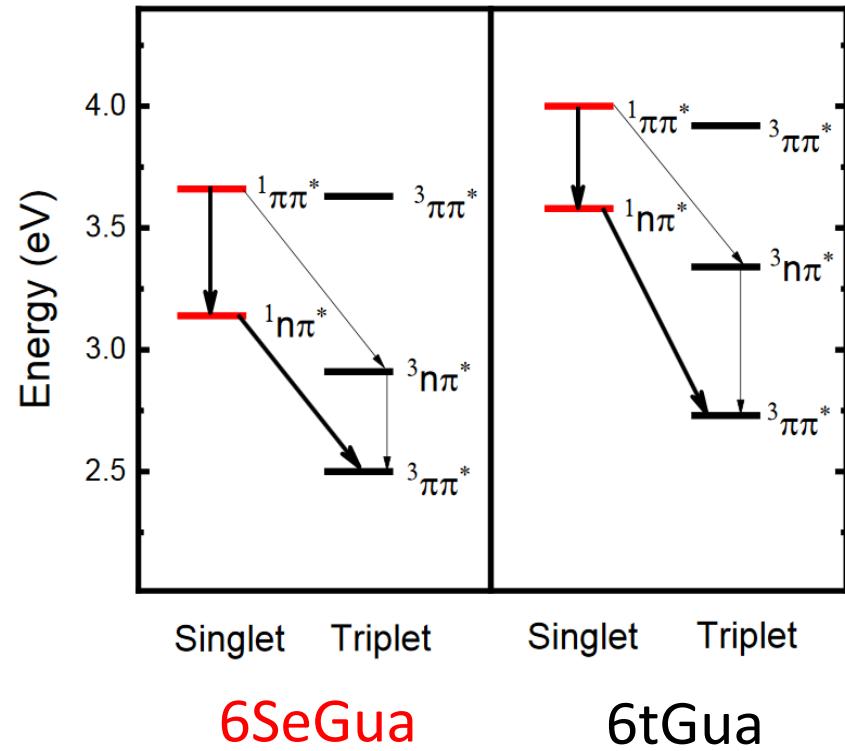
^a Same lifetime value was obtained within experimental uncertainties exciting at 342 nm;

^b Reproduced from ref. 22, where an excitation wavelength of 345 nm was used;

^c Estimated by extrapolating fit past 1 ns.

Farrell, K. M.; Brister, M. M.; Pittelkow, M.; Sølling, T. I.; Crespo-Hernández, C. E.
Heavy-Atom-Substituted Nucleobases in Photodynamic Applications: Substitution of
Sulfur with Selenium in 6-Thioguanine Induces a Remarkable Increase in the Rate of
Triplet Decay in 6-Selenoguanine. *J. Am. Chem. Soc.* **2018**, *140* (36), 11214–11218.

Heavy Atom Substitution

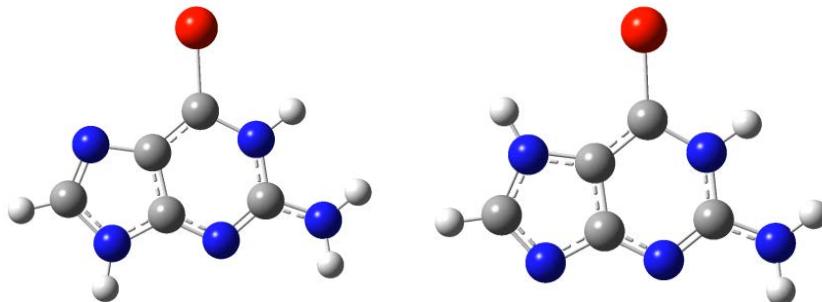


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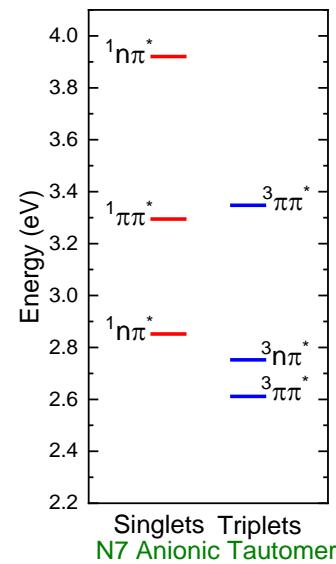
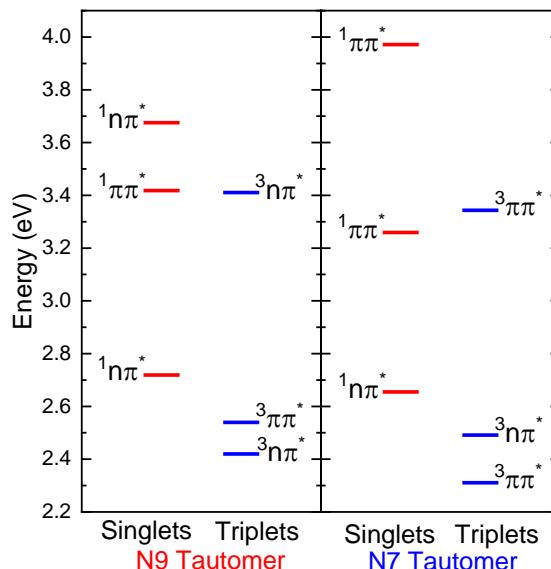
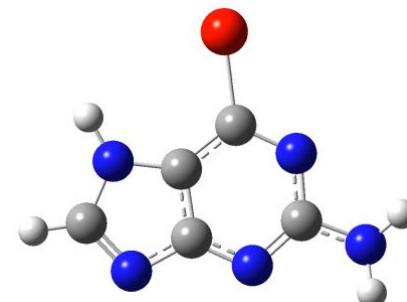
6-Selenoguanine (6SeGua)

At pH 7.4

~70%
Neutral Tautomers



~30%
Anionic Tautomer



Ground state optimized structures calculated at the B3LYP/IEFPCM/6-311++G(d,p) level of theory

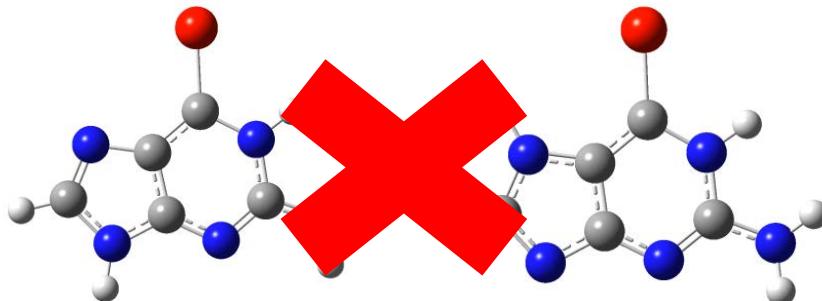
Vertical excitation energies calculated at the TD-PBE0/IEFPCM/6-311++G(d,p) level of theory

6-Selenoguanine (6SeGua)

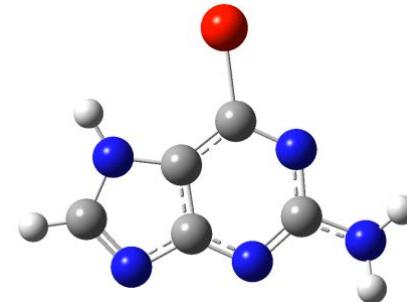
At pH 9.8

~100%

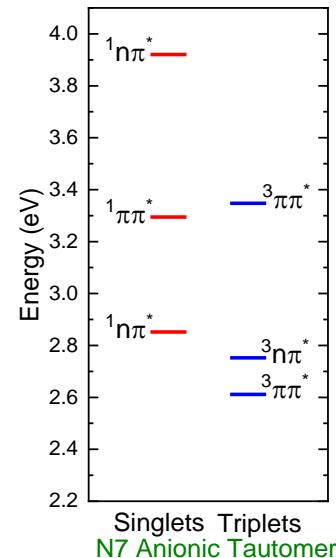
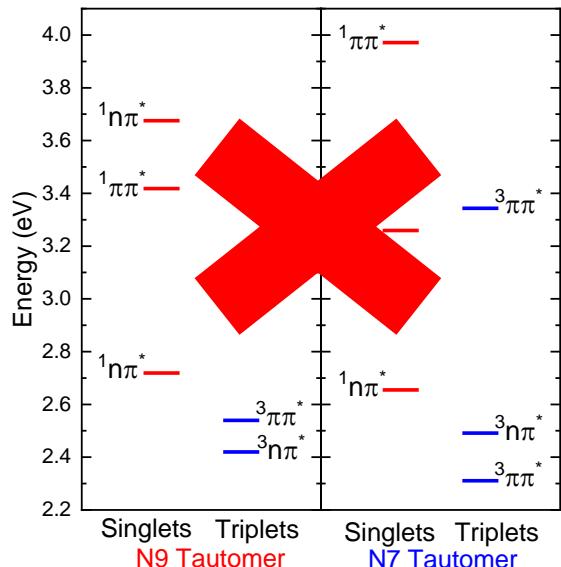
Neutral Tautomers



Anionic Tautomer



Ground state optimized structures calculated at the B3LYP/IEFPCM/6-311++G(d,p) level of theory

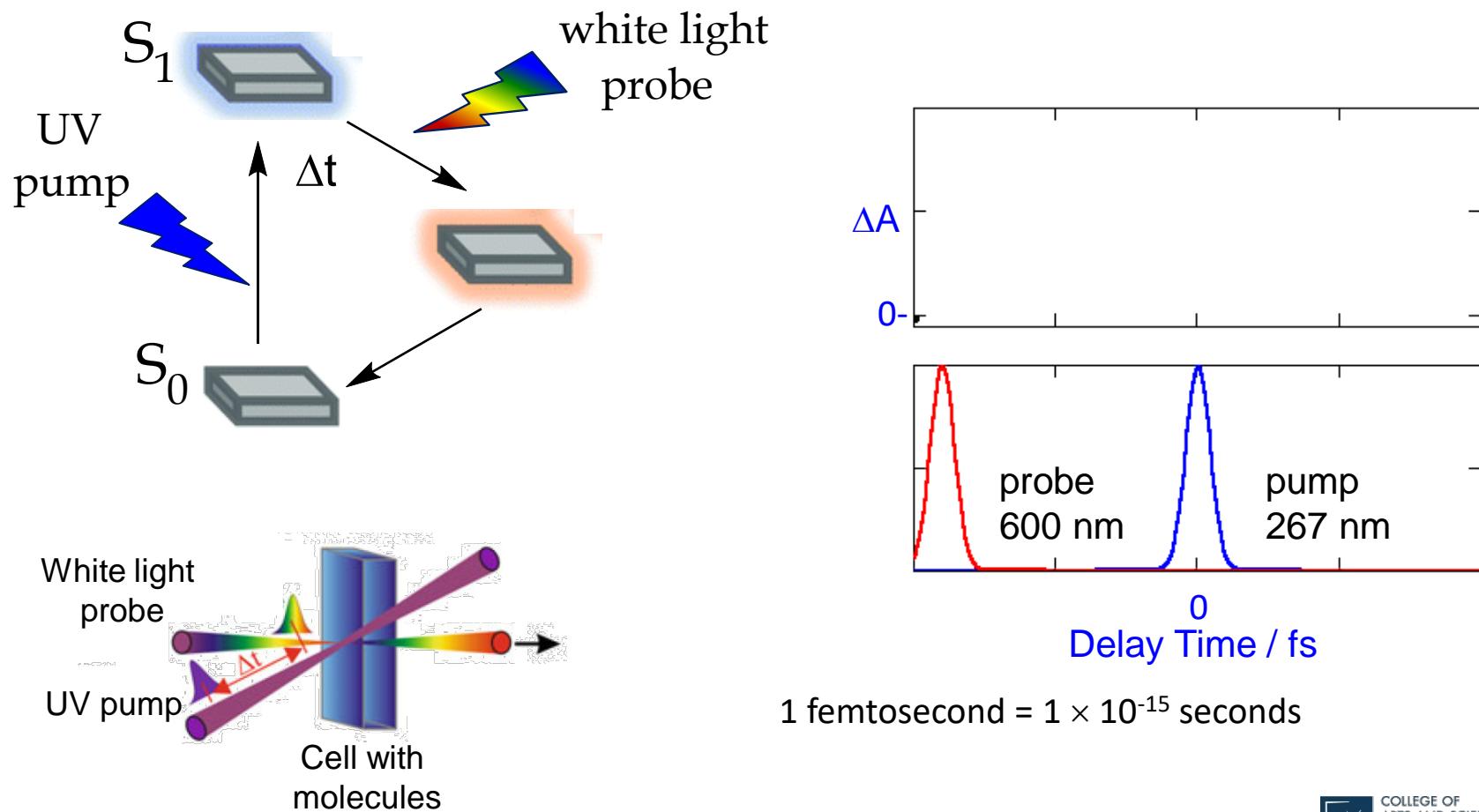


Vertical excitation energies calculated at the TD-PBE0/IEFPCM/6-311++G(d,p) level of theory

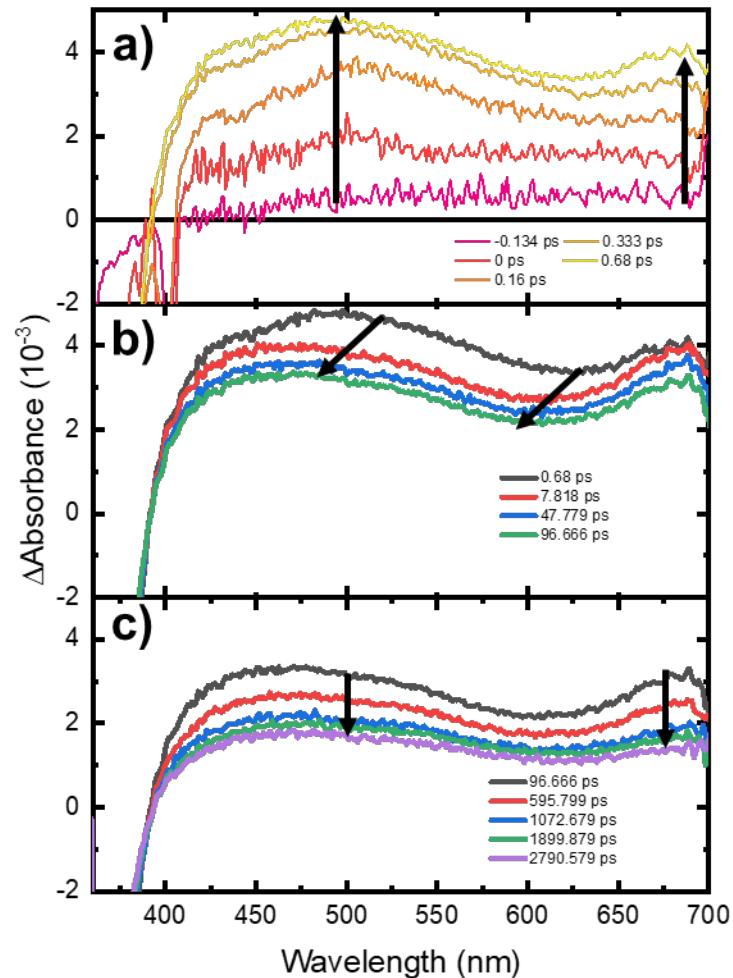
Transient Absorption Spectroscopy

- Measures changes in absorbance (ΔA)
- Produces 2 plots
 - Spectra: ΔA vs wavelength
 - Comparing spectra at different time delays provides evidence for relaxation processes
 - Kinetics: ΔA vs time
 - Fit mathematically to obtain lifetimes
 - Challenge of not over-fitting data

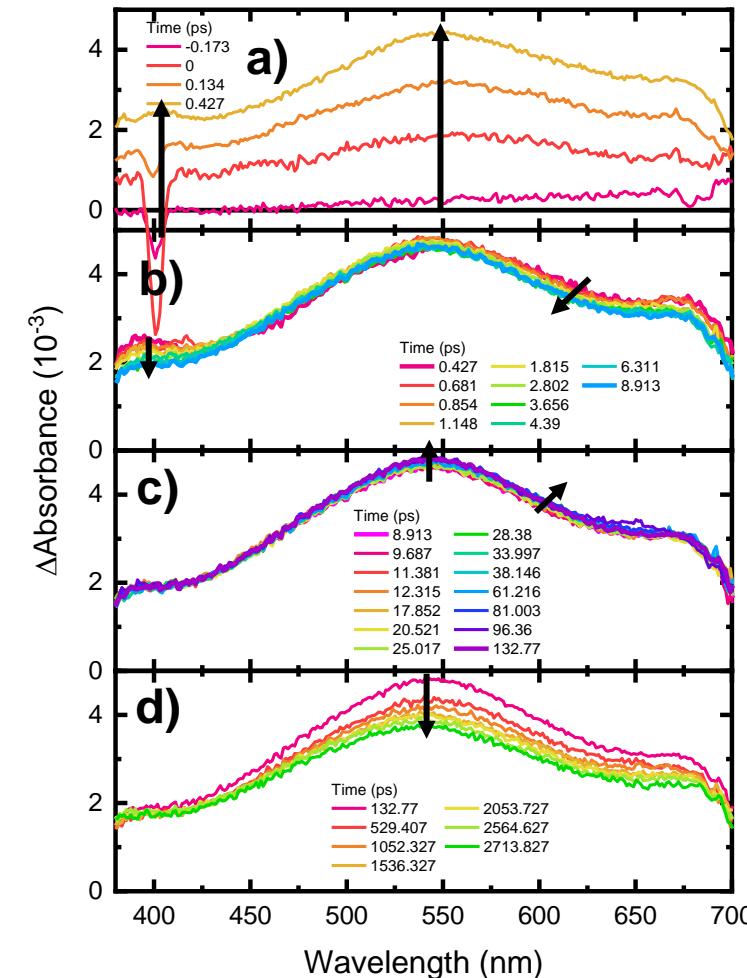
Transient Absorption Spectroscopy



Evolution Associated Spectra (EAS)

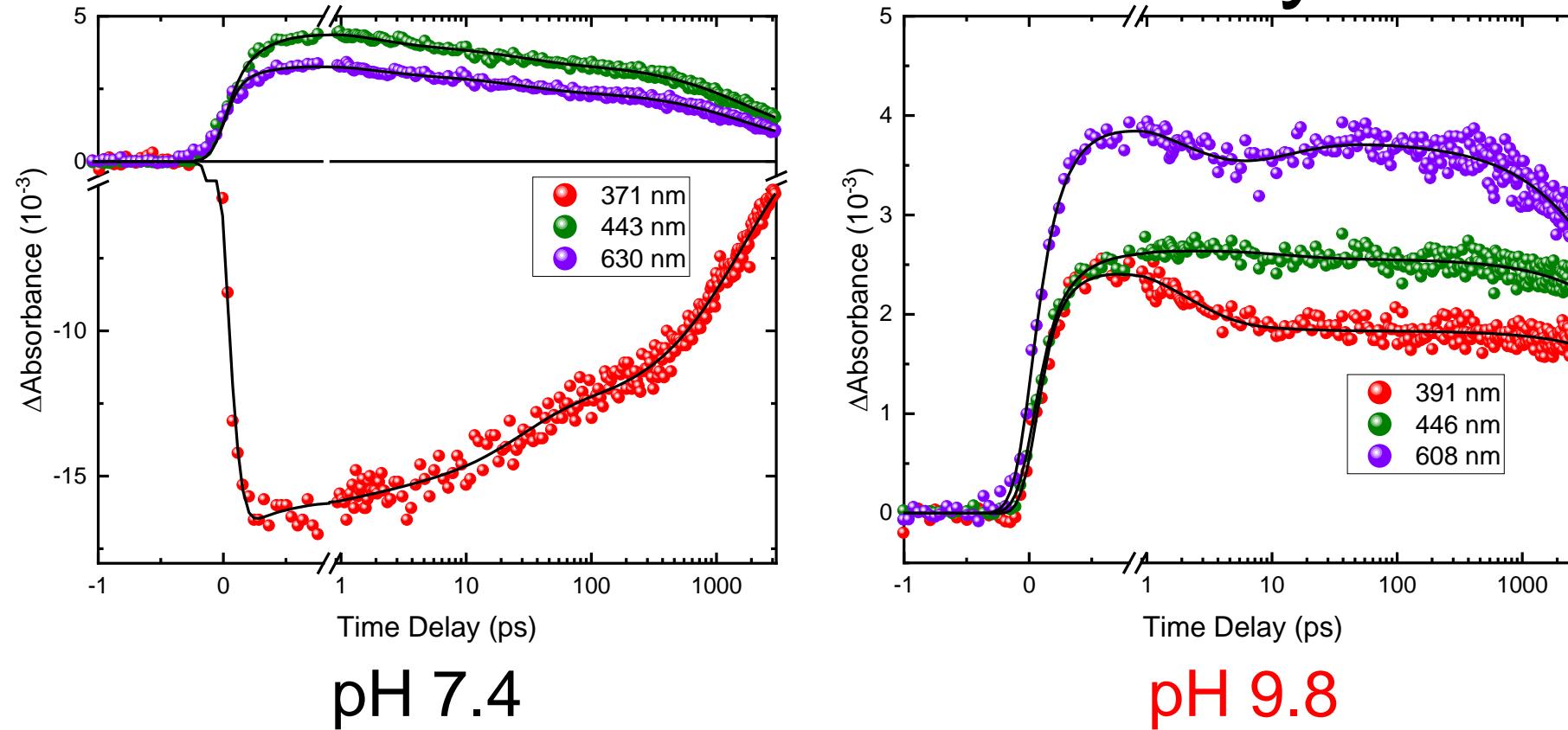


pH 7.4



pH 9.8

Kinetic Traces with Global Analysis



Lifetimes	τ_1 / ps	τ_2 / ps	τ_3 / ps	τ_4 / ns	τ_5 / ns
$6\text{SeGua}_{7.4}$	0.243 ± 0.006	1.47 ± 0.05	25.5 ± 0.5	*13.2	Offset
$6\text{SeGua}_{9.8}$	0.208 ± 0.006	2.0 ± 0.1	12 ± 1	*4.9	Offset

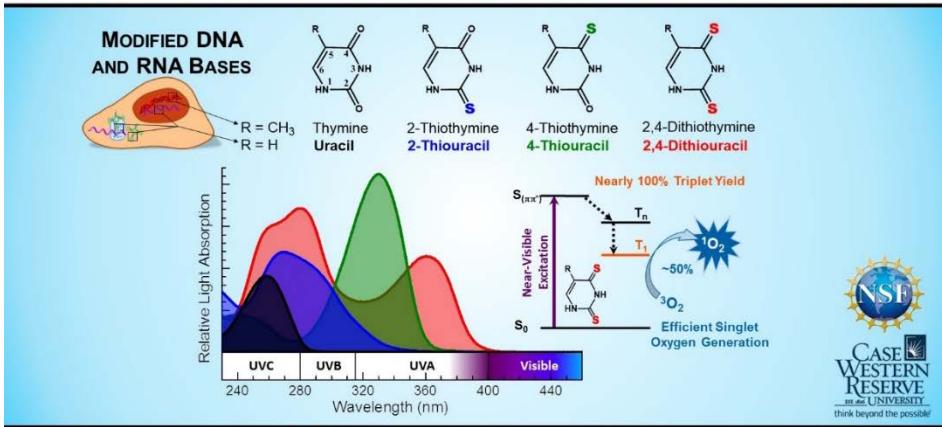
*Estimates based on mathematical fitting beyond the time window of the experiment

Conclusions

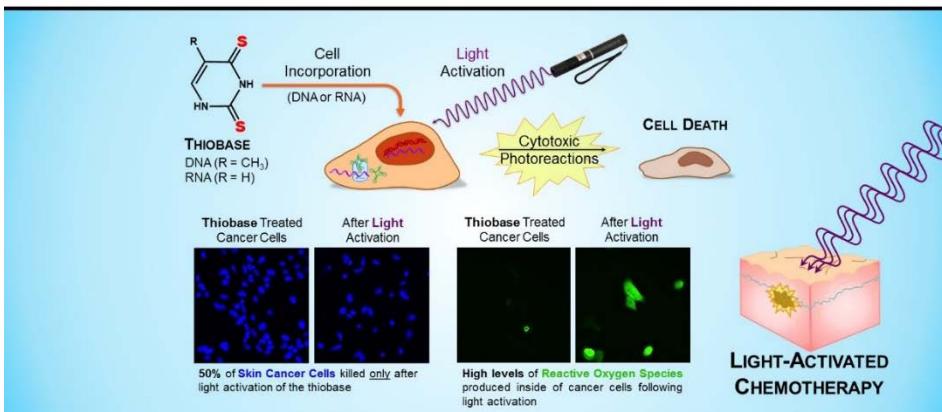
- The relaxation pathway of 6SeGua at pH 9.8 is different than at pH 7.4
 - EAS and global analysis vary greatly
 - Need quantum chemical calculations to identify exact mechanism
- The photophysics of the neutral and anionic mixture at pH 7.4 do not primarily reflect that of the anionic species
- Further investigation of the isolated neutral species is required

Thank You!

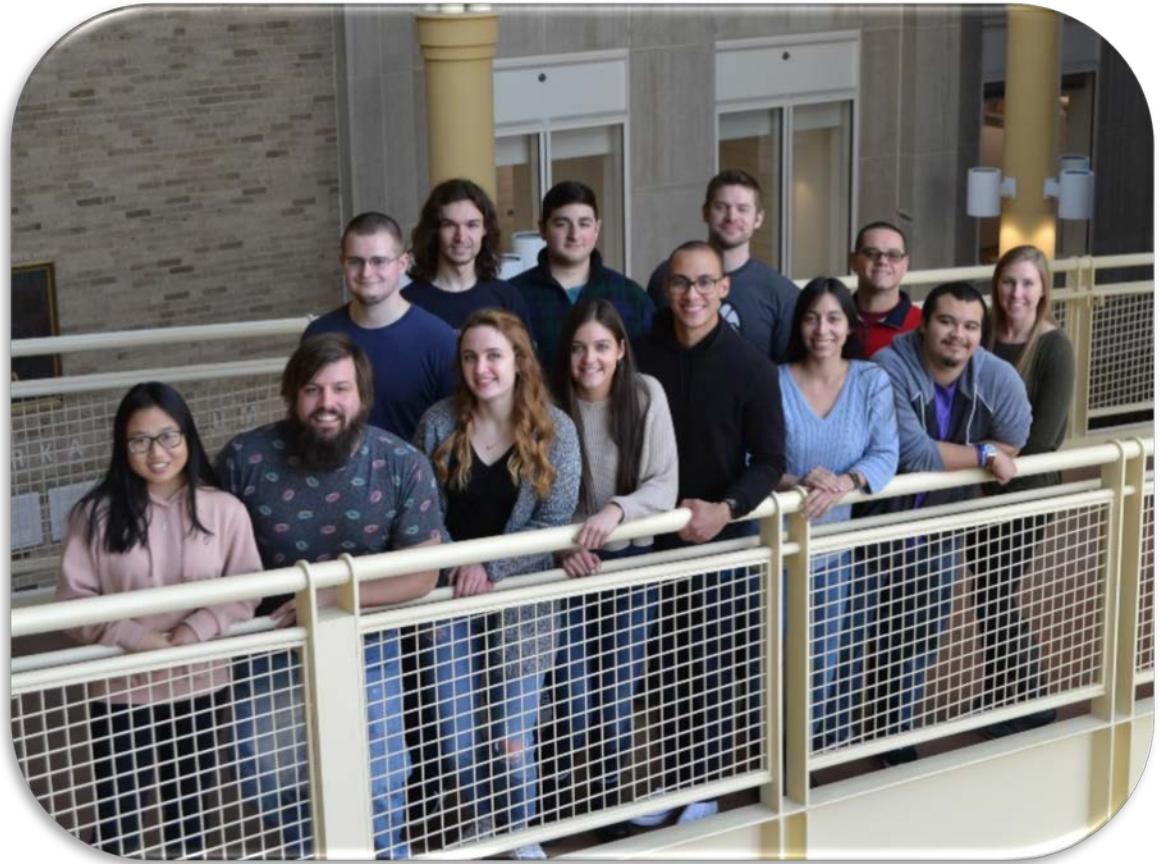
From fundamental research...



...to real-world applications...



...light provides the answers.



NSF Grant (CHE-1800052)