Fall 12-1-2012

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

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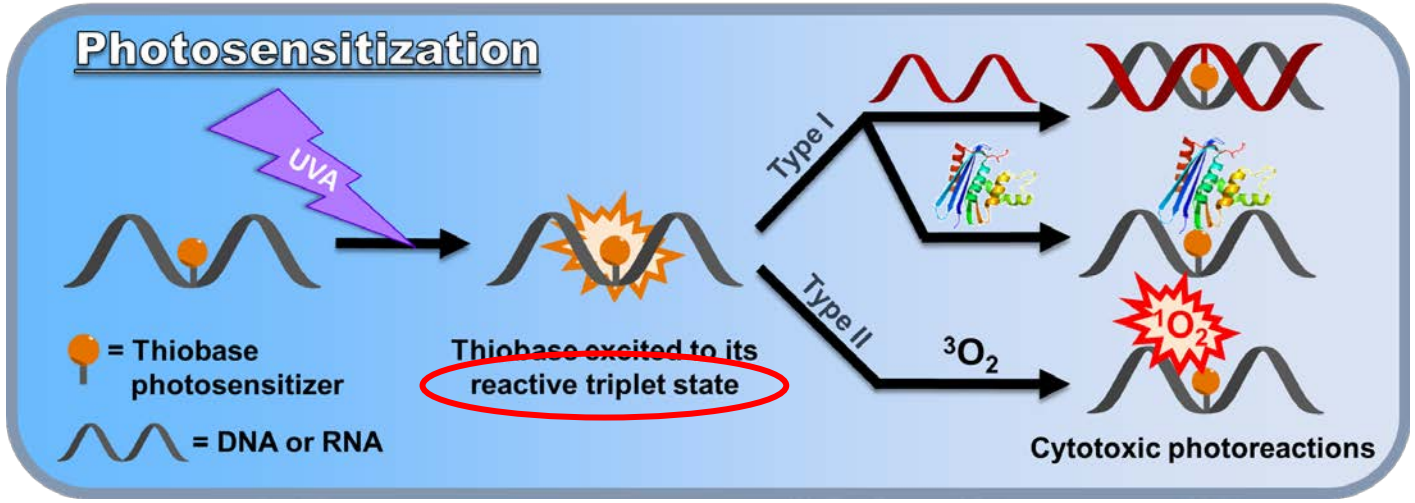
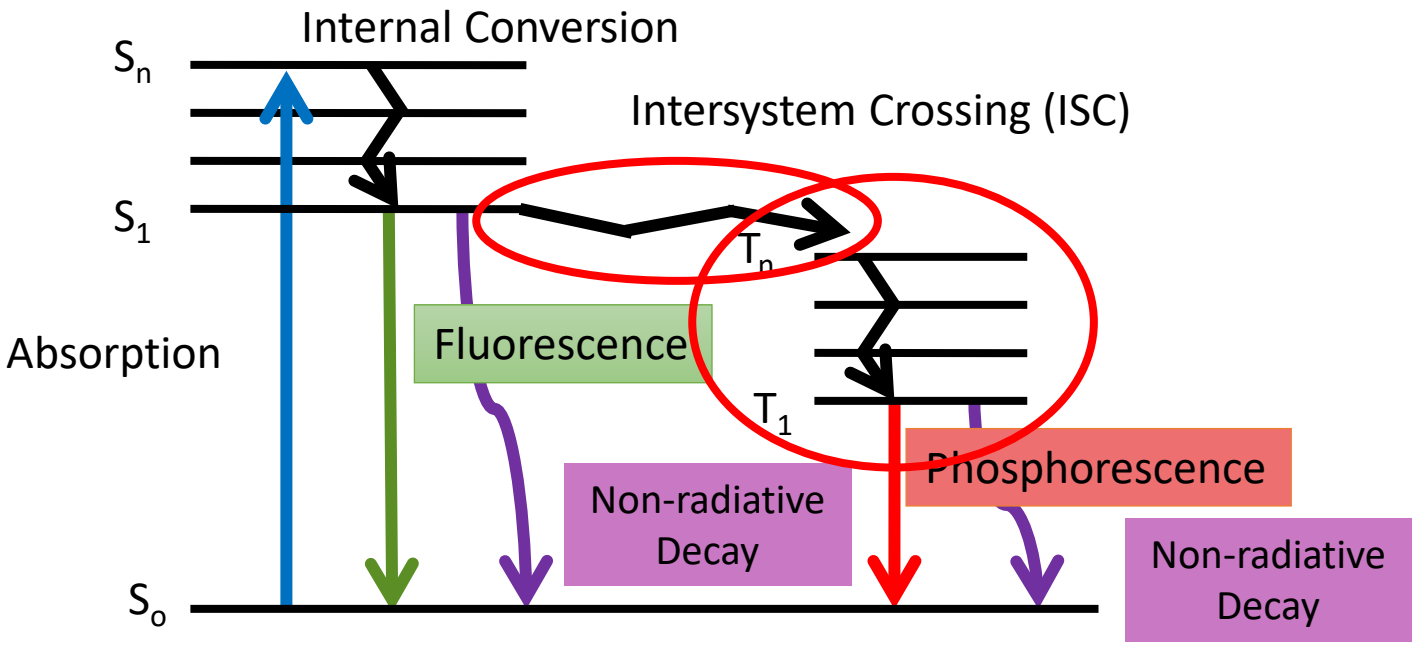
Photodynamic Therapy

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



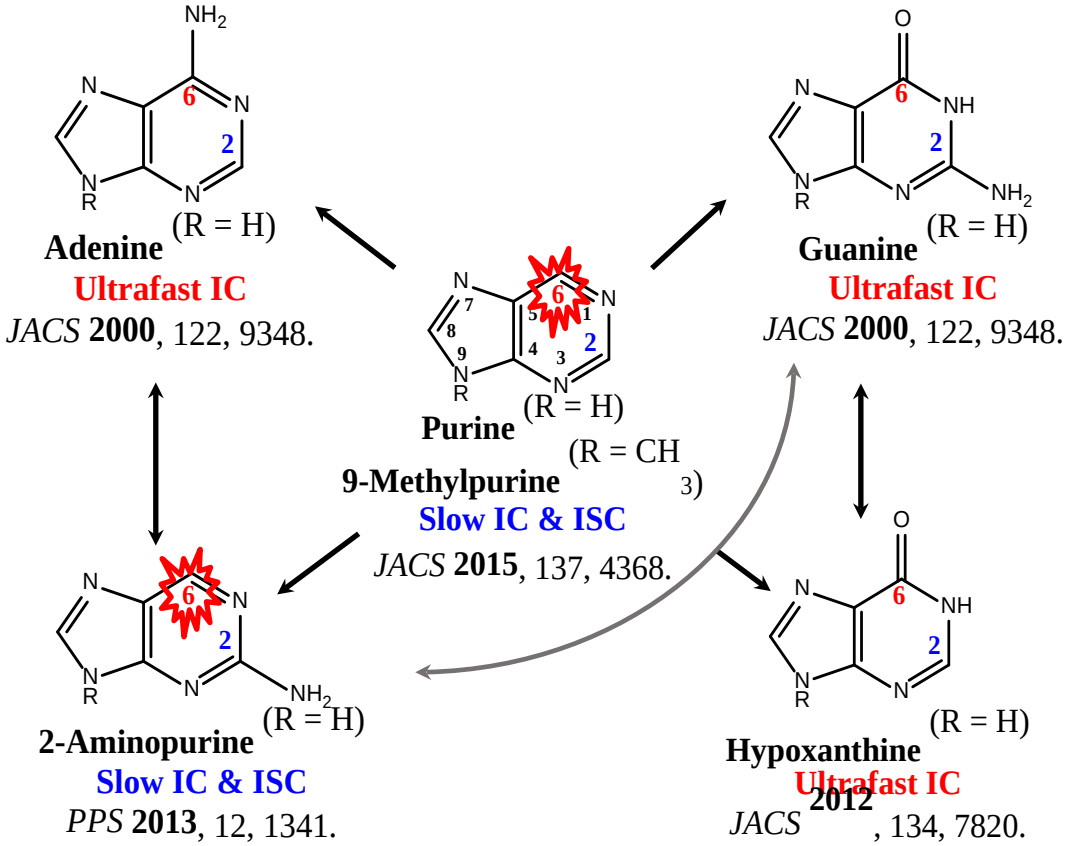
Ashwood, B.; Pollum, M.; Crespo-Hernández, C. E. Photochemical and Photodynamical Properties of Sulfur-Substituted Nucleic Acid Bases,. *Photochem. Photobiol.* **2019**, *95* (1), 33–58.

Excitation and Relaxation



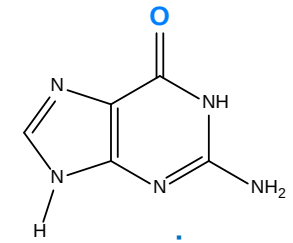
Functionalization Controls Relaxation Mechanisms

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

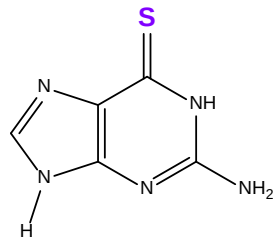


Crespo-Hernández, C. E.; Martínez-Fernández, L.; Rauer, C.; Reichardt, C.; Mai, S.; Pollum, M.; Marquetand, P.; González, L.; Corral, I. Electronic and Structural Elements That Regulate the Excited-State Dynamics in Purine Nucleobase Derivatives. *J. Am. Chem. Soc.* **2015**, *137* (13), 4368–4381.

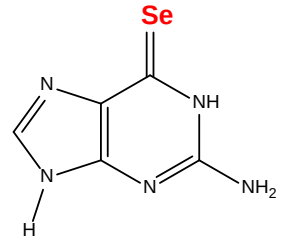
Heavy Atom Substitution



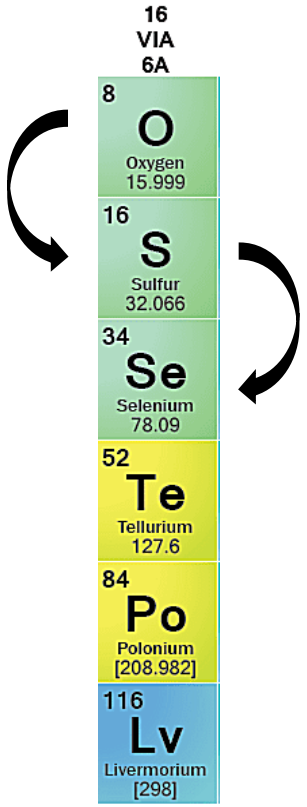
guanine

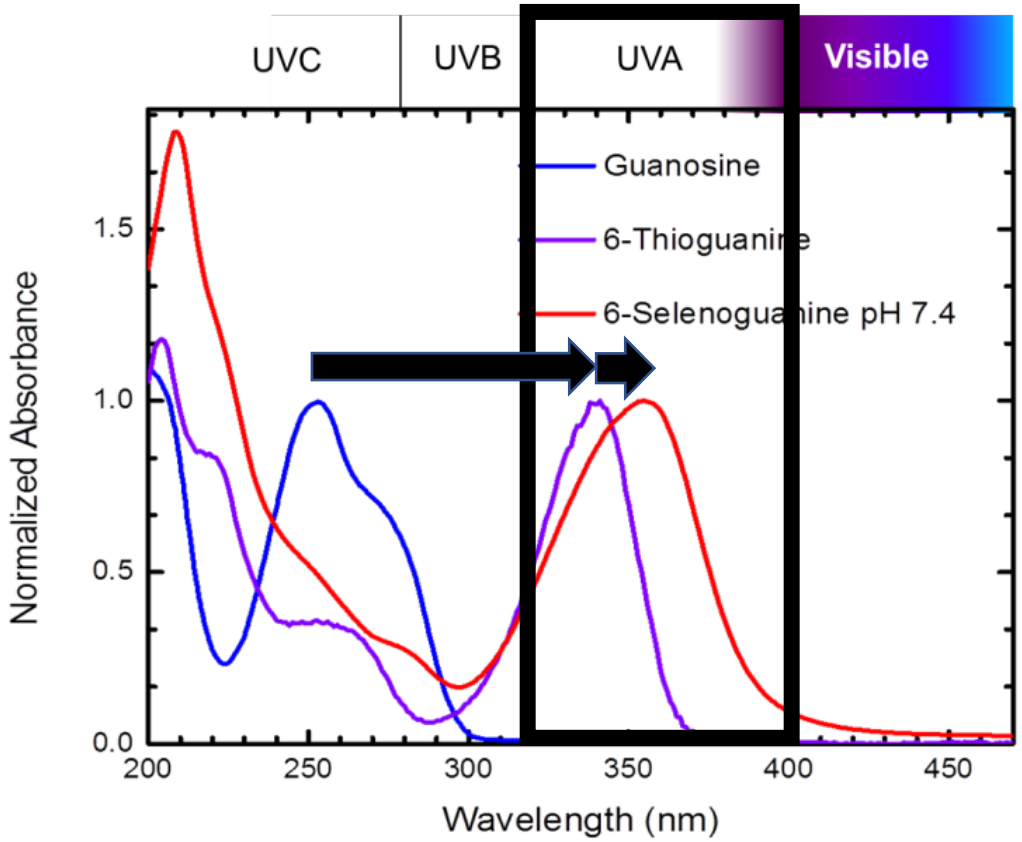


6-thioguanine



6-selenoguanine





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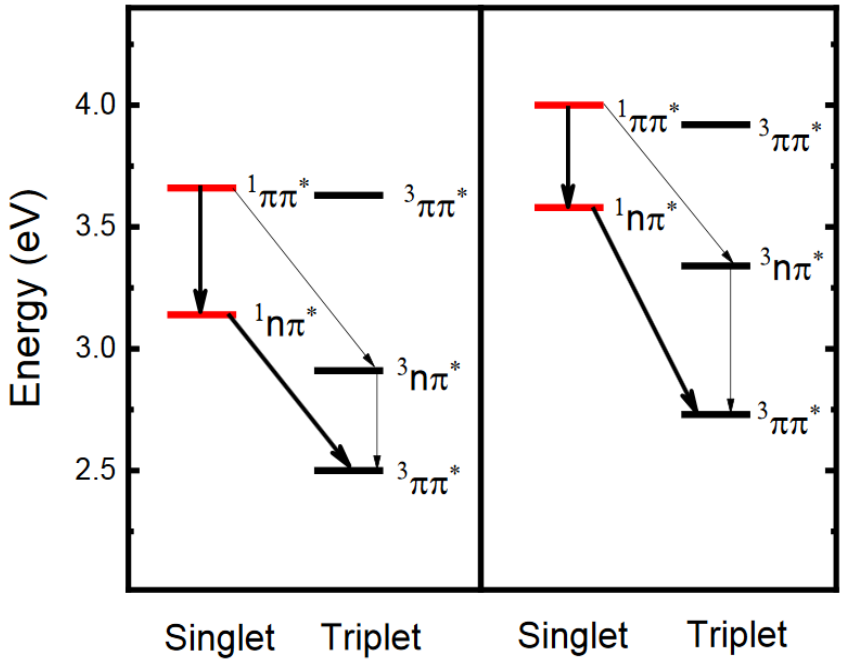


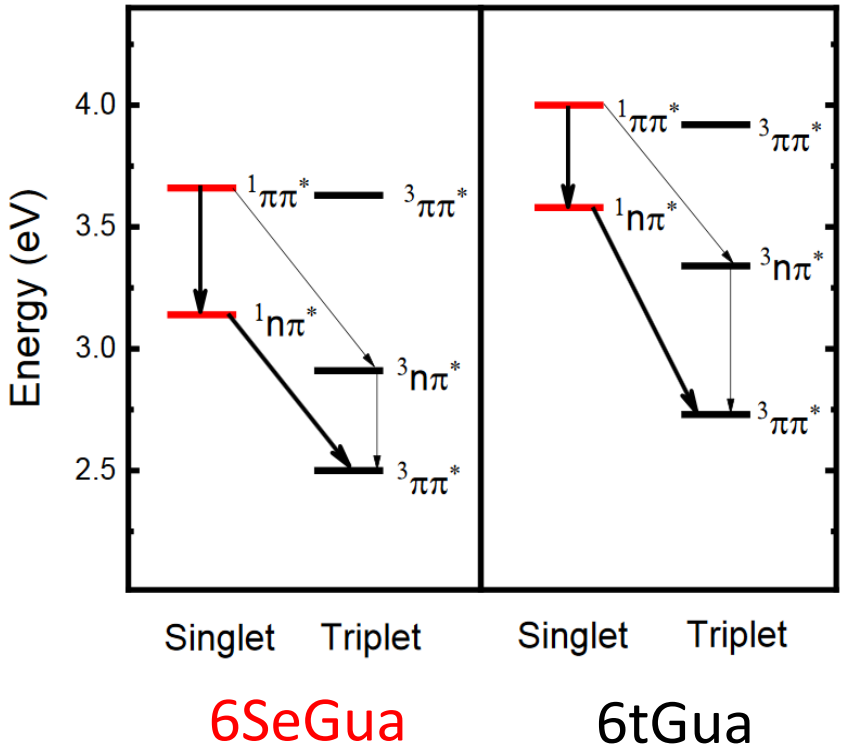
Table 1. Global lifetimes for 6SeGua and 6tGua following excitation at 352 nm under N_2-saturated conditions

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]

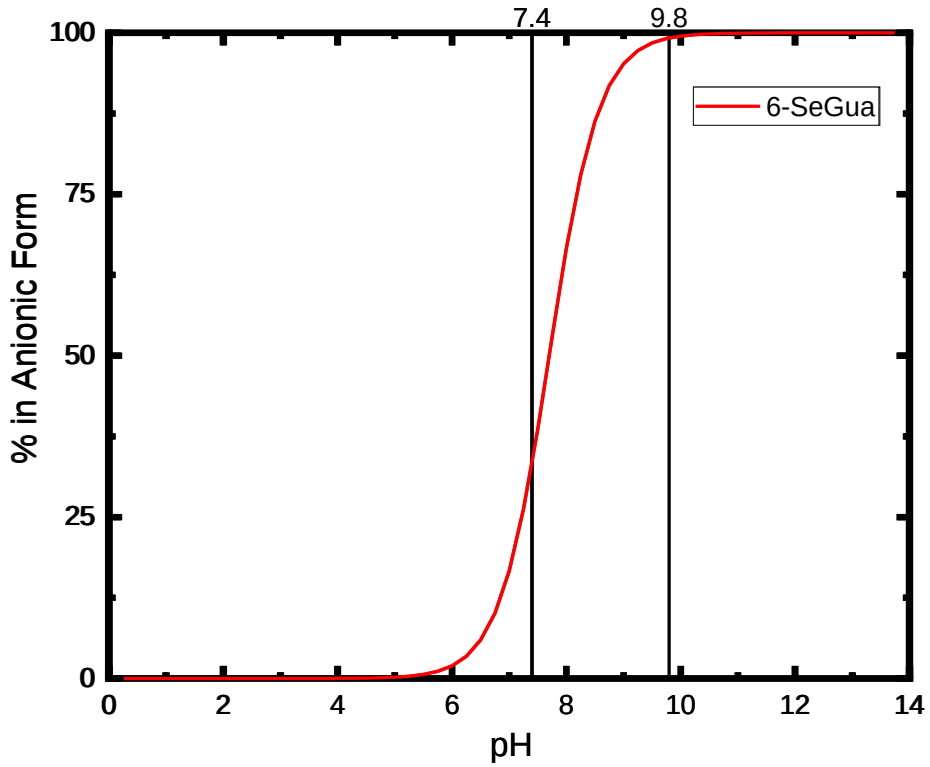
[a] Same lifetime value was obtained within experimental uncertainties exciting at 342 nm; [b] Reproduced from ref. 22, where an excitation wavelength of 345 nm was used; [c] Estimated by extrapolating fit past 1 ns.

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



6SeGua 6tGua



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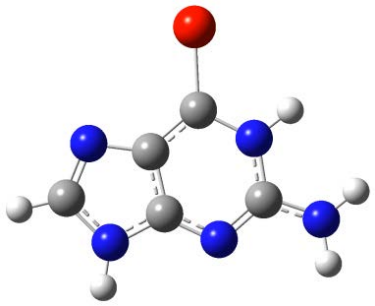
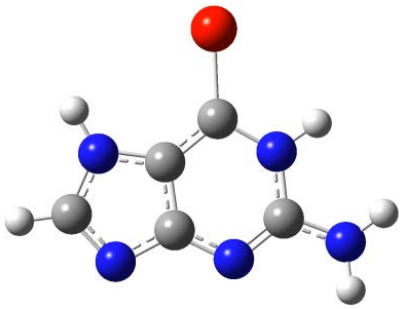
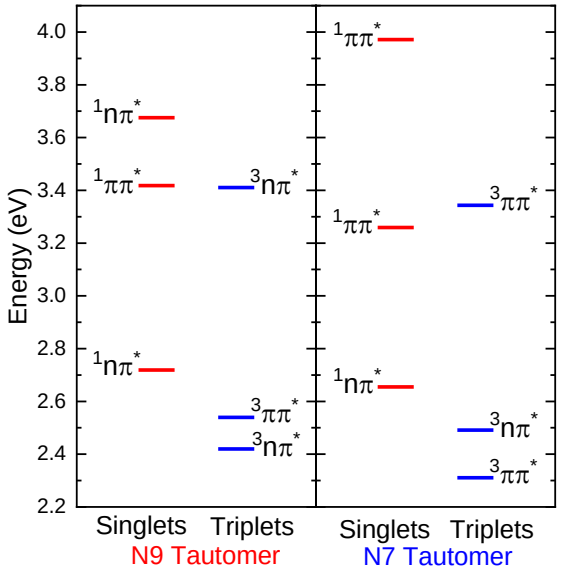
6-Selenoguanine (6SeGua)

At pH 7.4

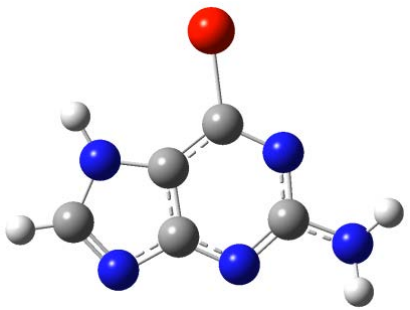
~70%
Neutral Tautomers

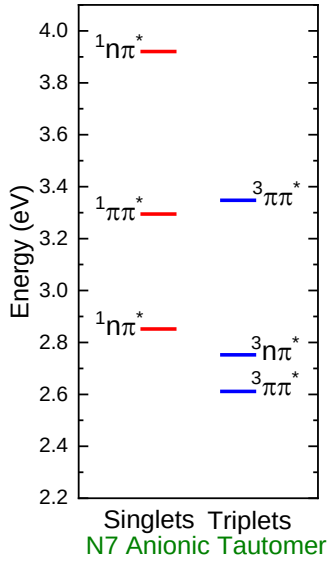






~30%
Anionic Tautomer





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

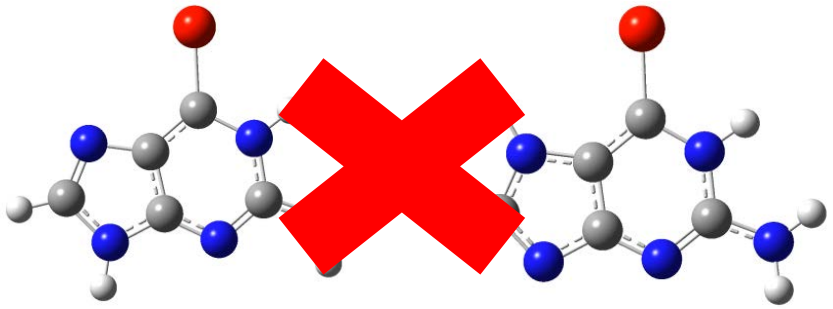
Vertical excitation energies calculated at the TD-PBE0/IEFPCM/6-311++G(d,p) level of theory

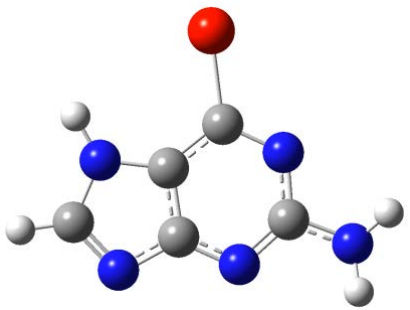
6-Selenoguanine (6SeGua)

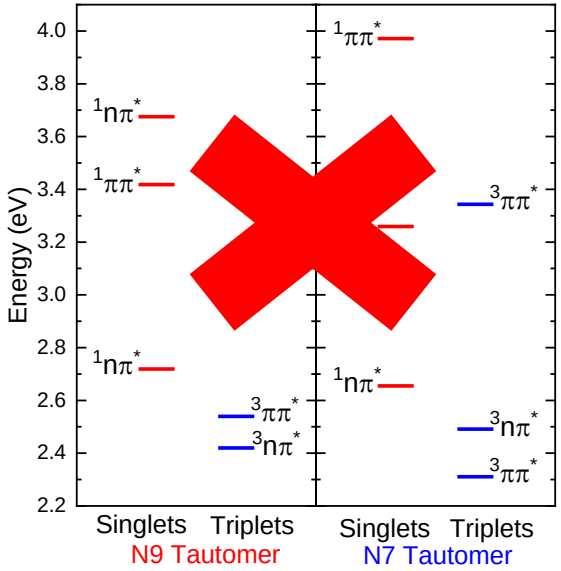
At pH 9.8

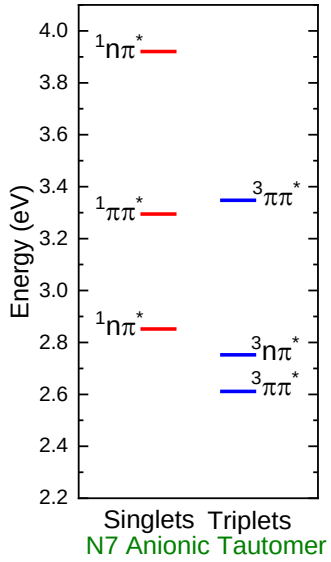
~100%
Anionic Tautomer

Neutral Tautomers









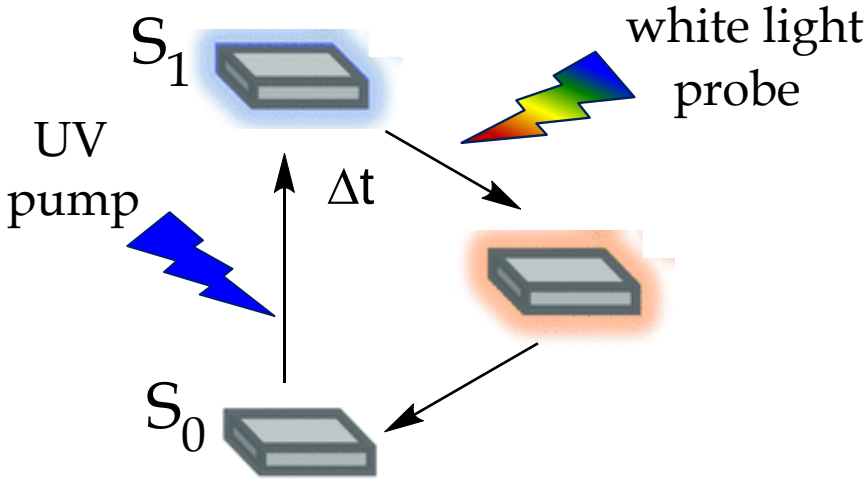
Ground state optimized structures calculated at the B3LYP/IEFPCM/6-311++G(d,p) level of theory

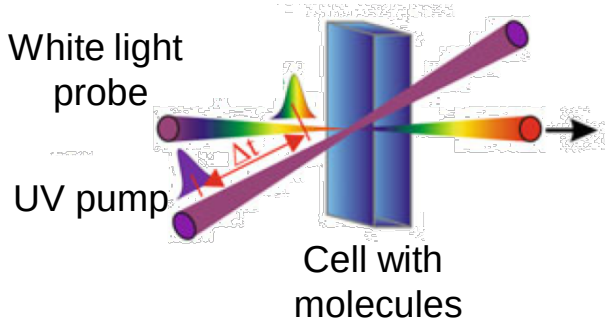
Vertical excitation energies calculated at the TD-PBE0/IEFPCM/6-311++G(d,p) level of theory

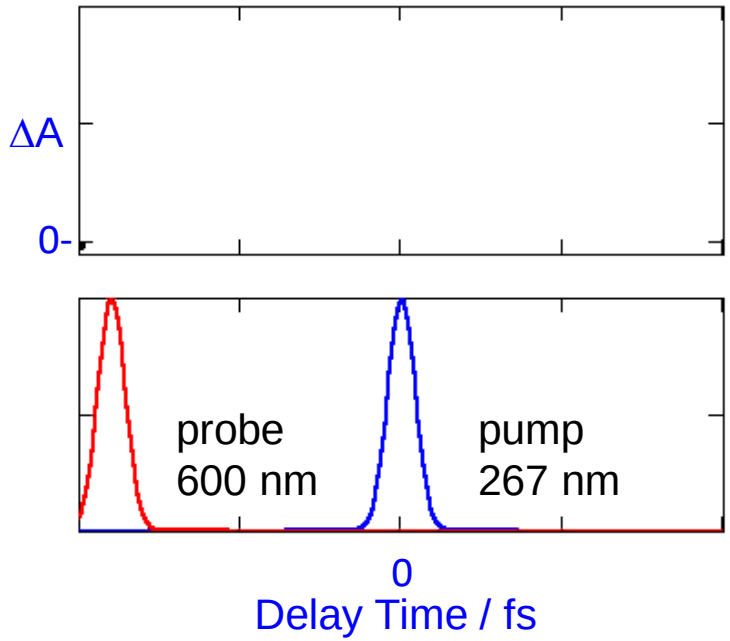
Transient Absorption Spectroscopy

- 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



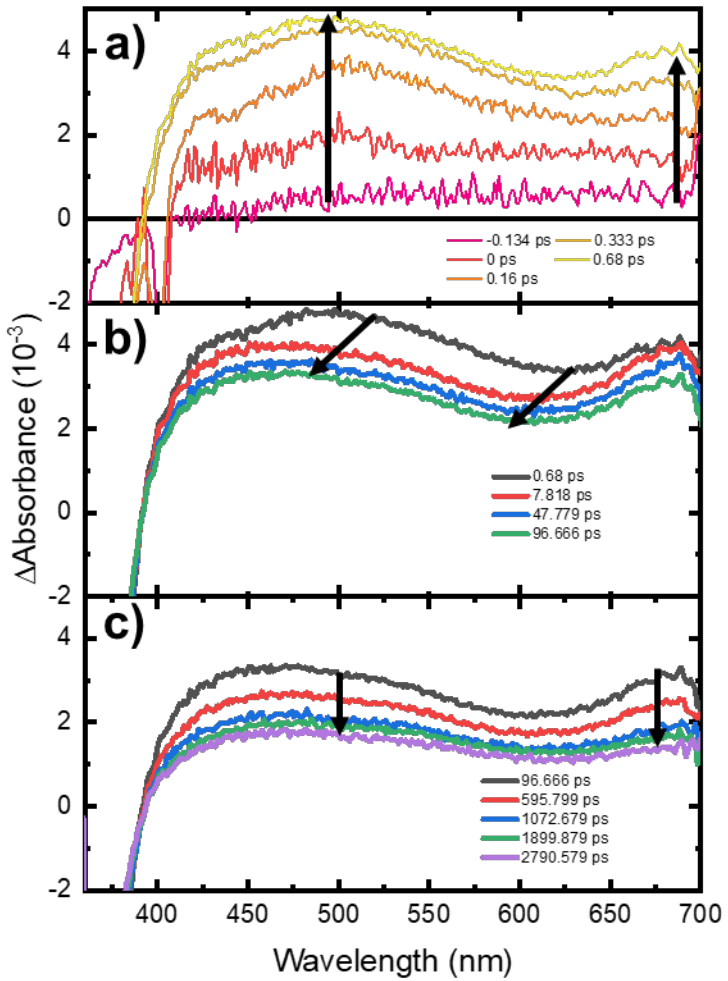




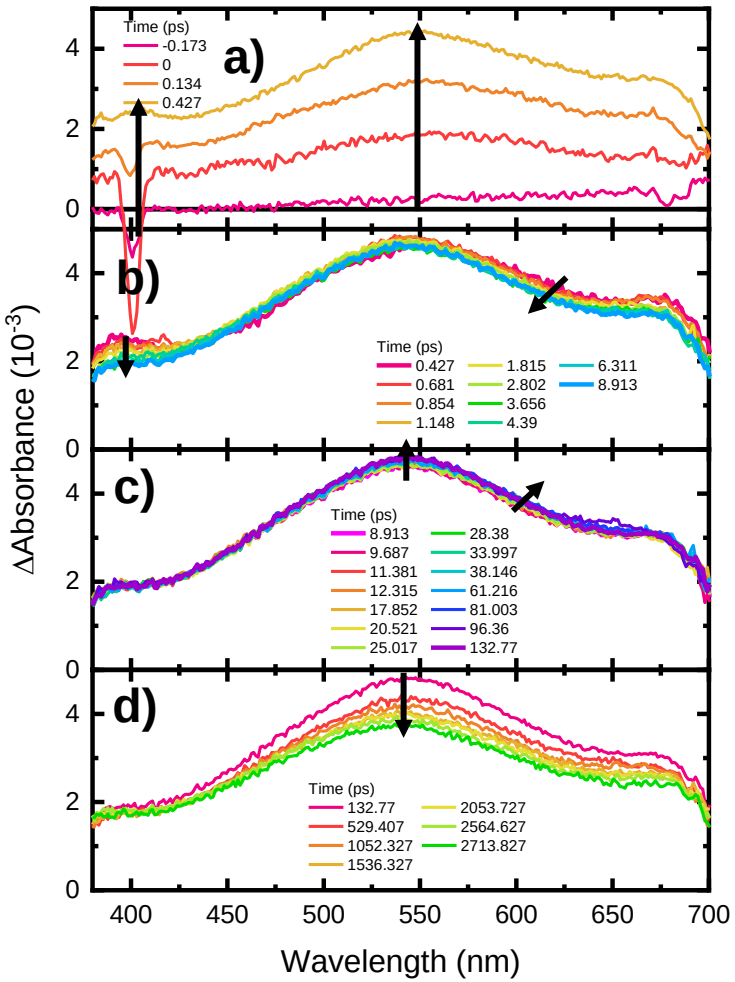
1 femtosecond = 1×10^{-15} seconds

Reichardt, C.; Vogt, R. A.; Crespo-Hernández, C. E. *J. Chem. Phys.* 2009, 131, 224518.

Evolution Associated Spectra (EAS)

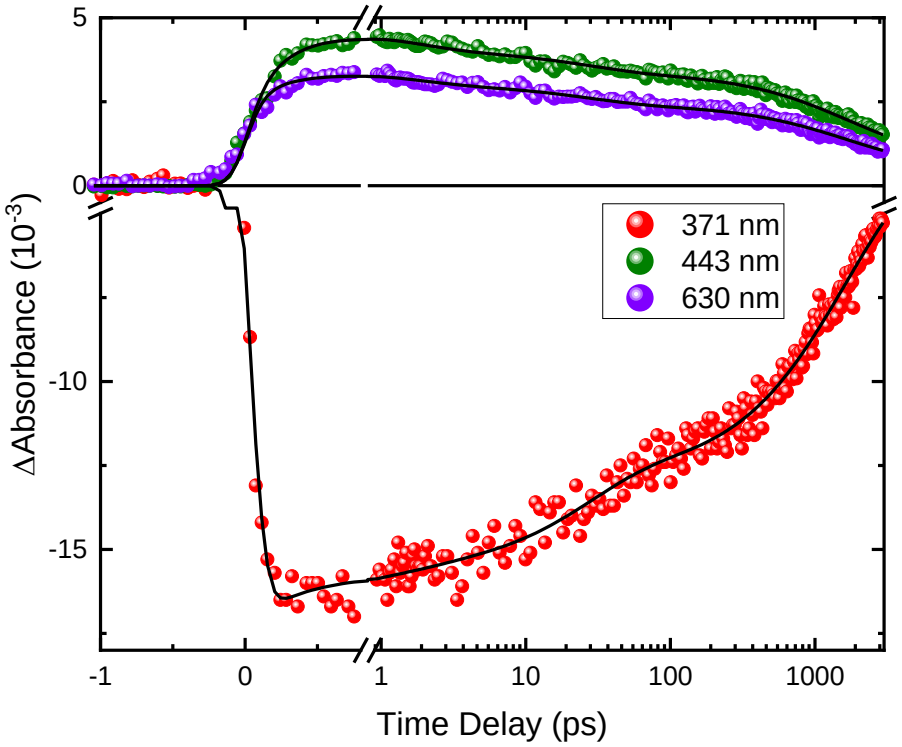


pH 7.4

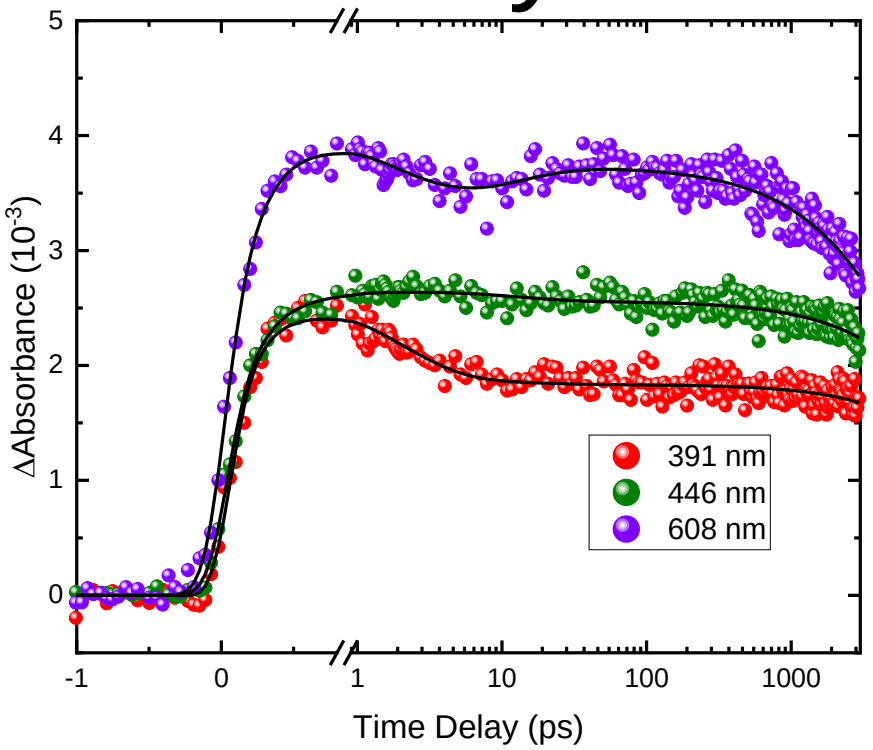


pH 9.8

Kinetic Traces with Global Analysis



pH 7.4



pH 9.8

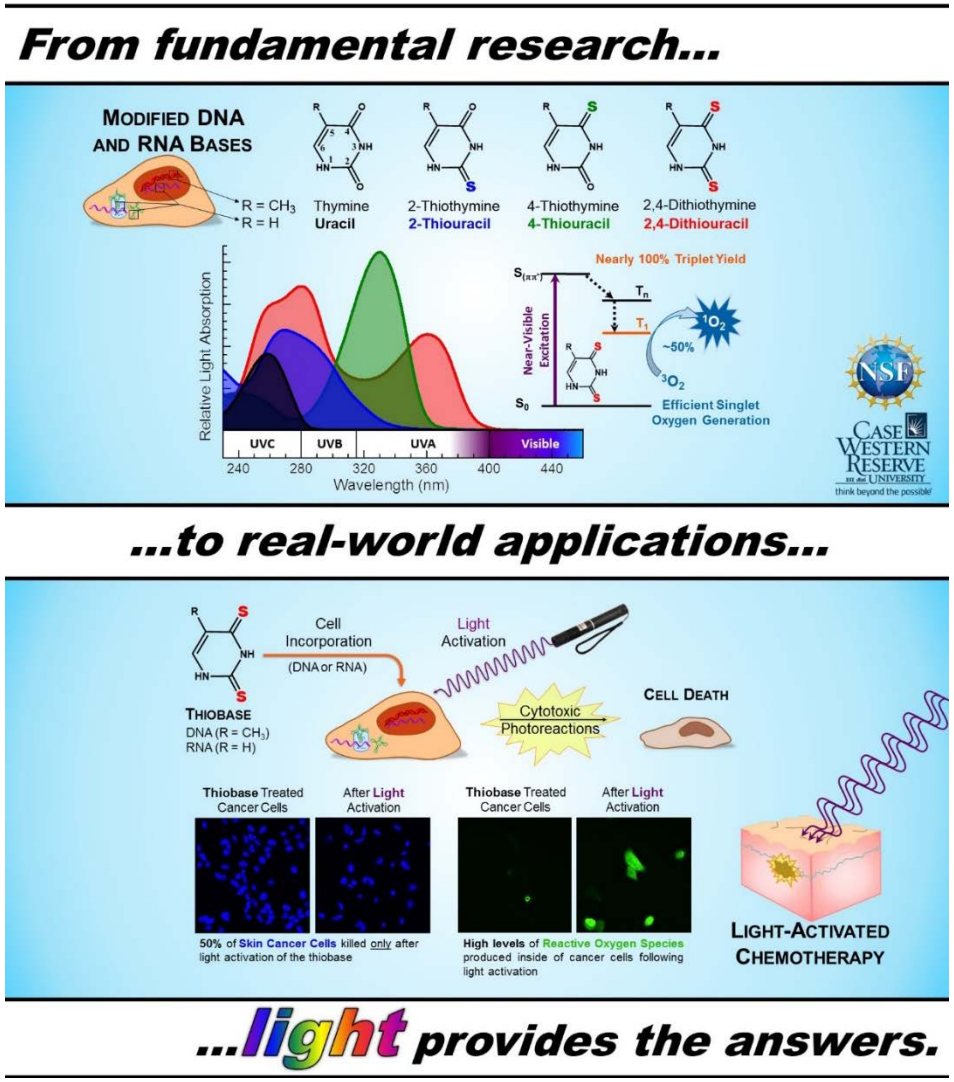
Lifetimes	τ_1 / ps	τ_2 / ps	τ_3 / ps	τ_4 / ns	τ_5 / ns
$6SeGua_{7.4}$	0.243 ± 0.006	1.47 ± 0.05	25.5 ± 0.5	*13.2	Offset
$6SeGua_{9.8}$	0.208 ± 0.006	2.0 ± 0.1	12 ± 1	*4.9	Offset

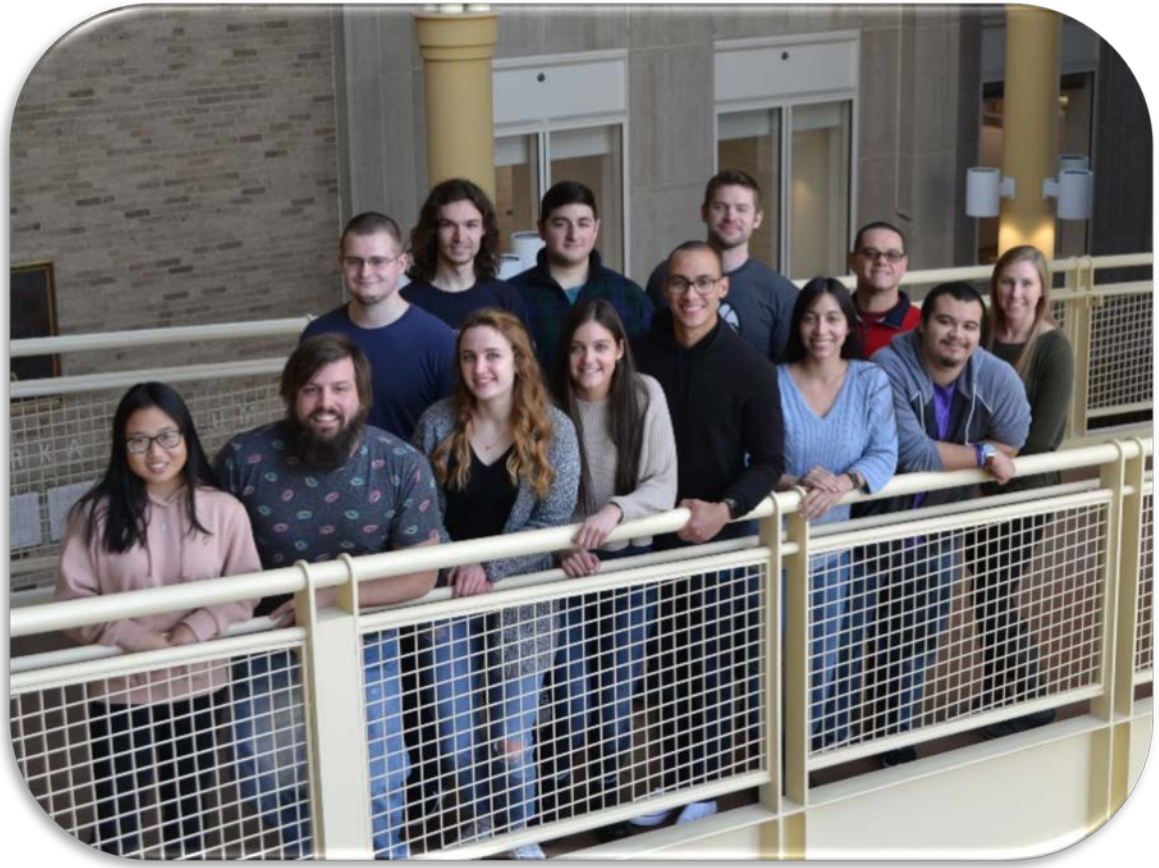
*Estimates based on mathematical fitting beyond the time window of the experiment

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!





NSF Grant (CHE-1800052)