

# Theoretical Study of Light-Induced Crosslinking Reaction Between Pyrimidine DNA Bases and Aromatic Amino Acids

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# Content

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- 1 The general problem of the DNA – protein crosslinking (Pro and Contra)
- 2 Short presentation of the DNA – protein crosslinking reaction
- 3 Model system for describing the UV-induced DNA – protein crosslinking reaction at quantum mechanics level
- 4 Conclusions

# The general problem of the DNA – protein crosslinking

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## **Contra:**

- Damage of the DNA code;
- DNA replication error;
- Strong covalent bond, is hard to be broken (repaired);

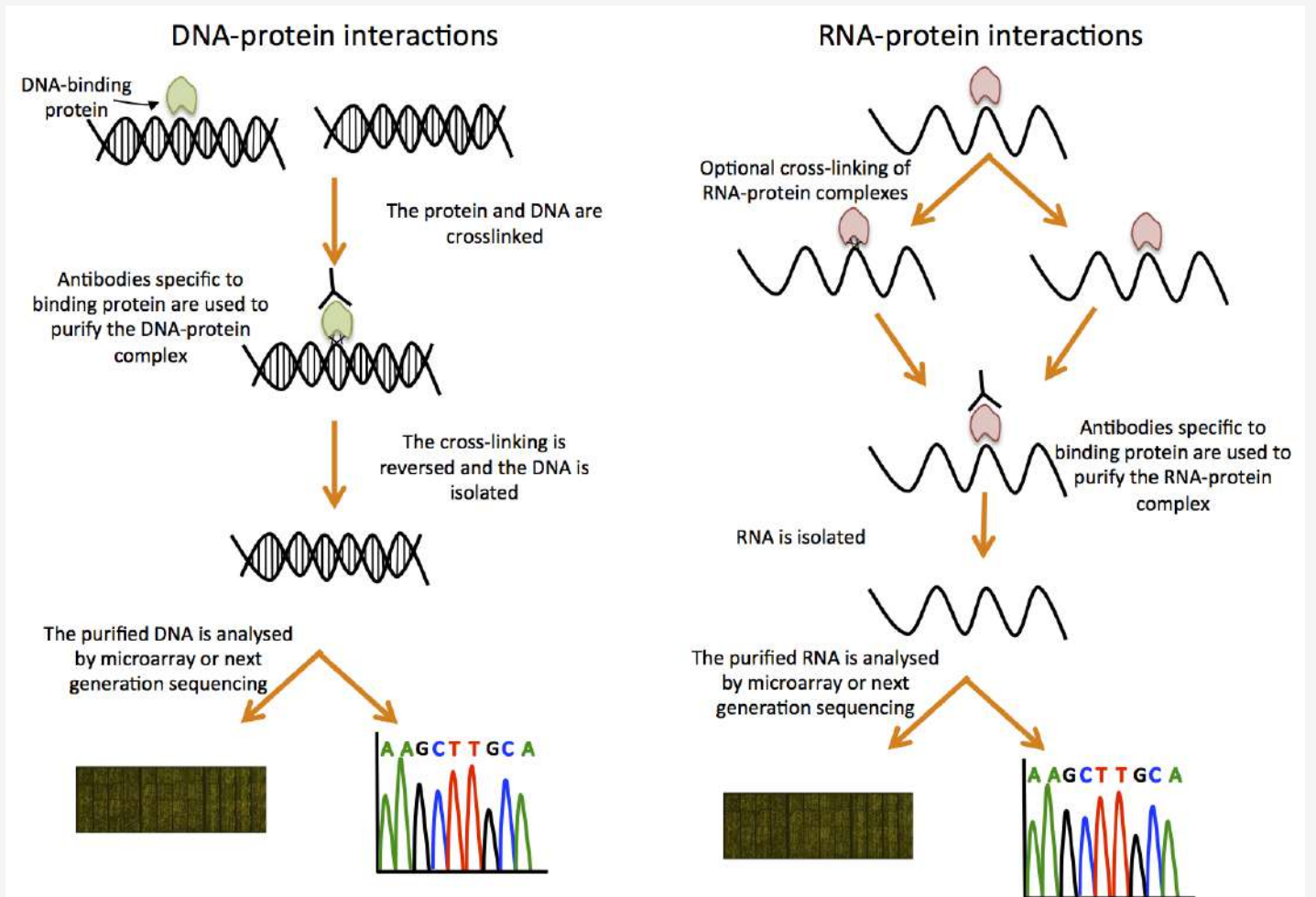
I will talk a little bit later about this problem

## **Pro:**

- Targeted analysis of the DNA code;
- Monitoring the transcription regulation through histone modification (ChIP technique);
- ChIP-qPCR – quantifying DNA concentrations from multiple samples in real time;

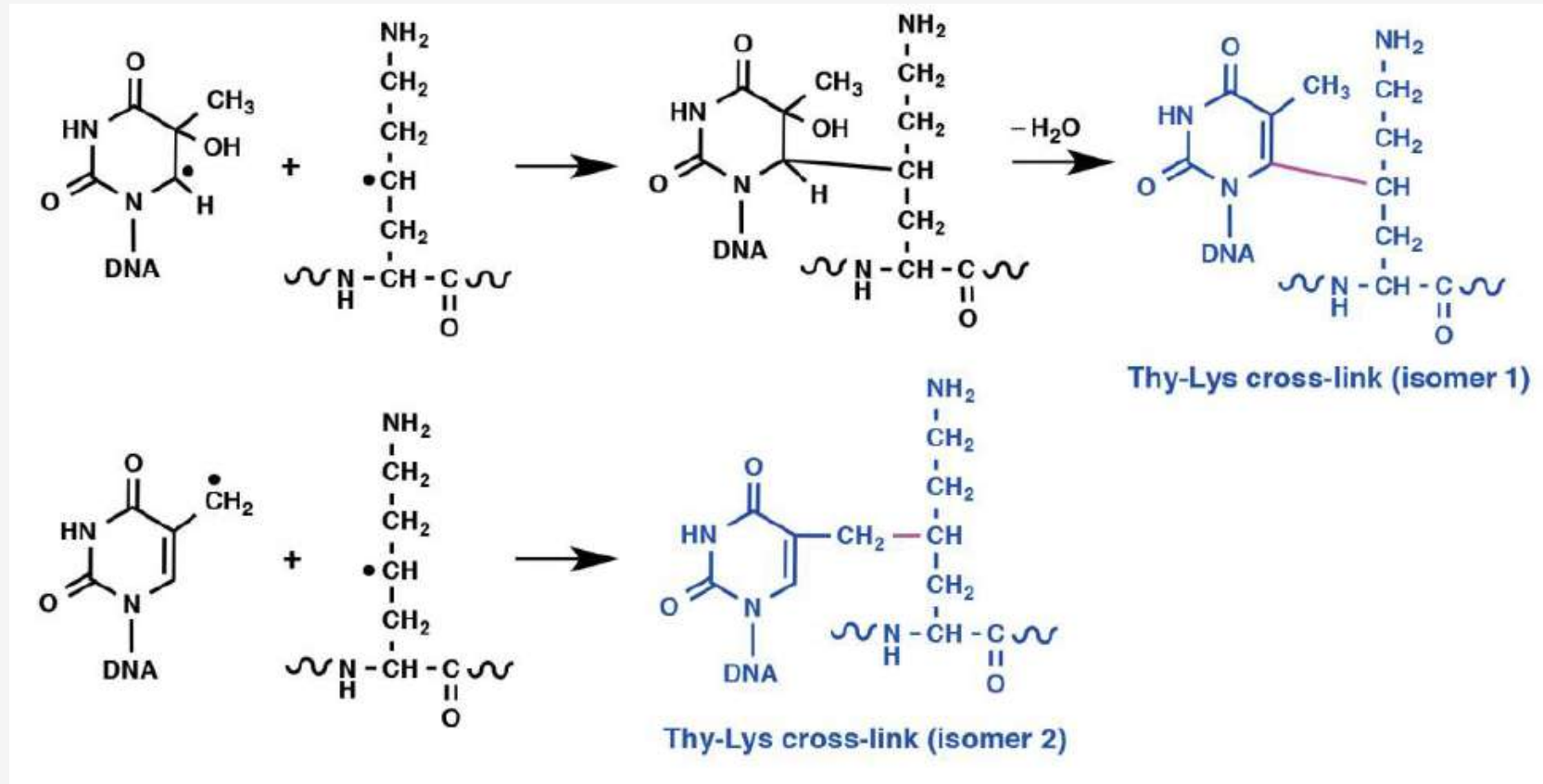
# DNA-Protein crosslinking:

## Cross-linking Chromatin immunoprecipitation (ChIP) Protocol



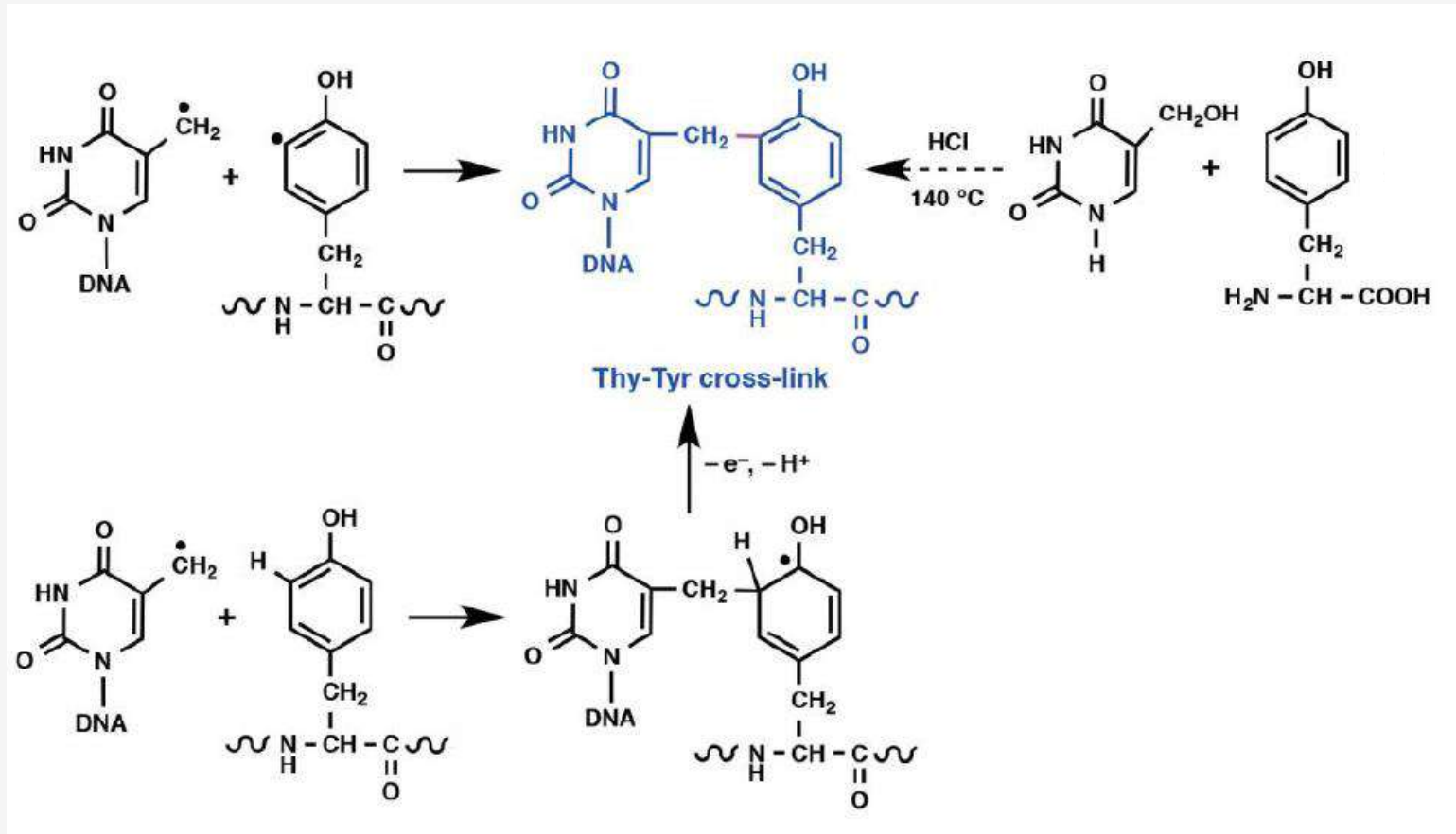
# Crosslinking reactions:

Thymine – Lysine:



# Crosslinking reactions:

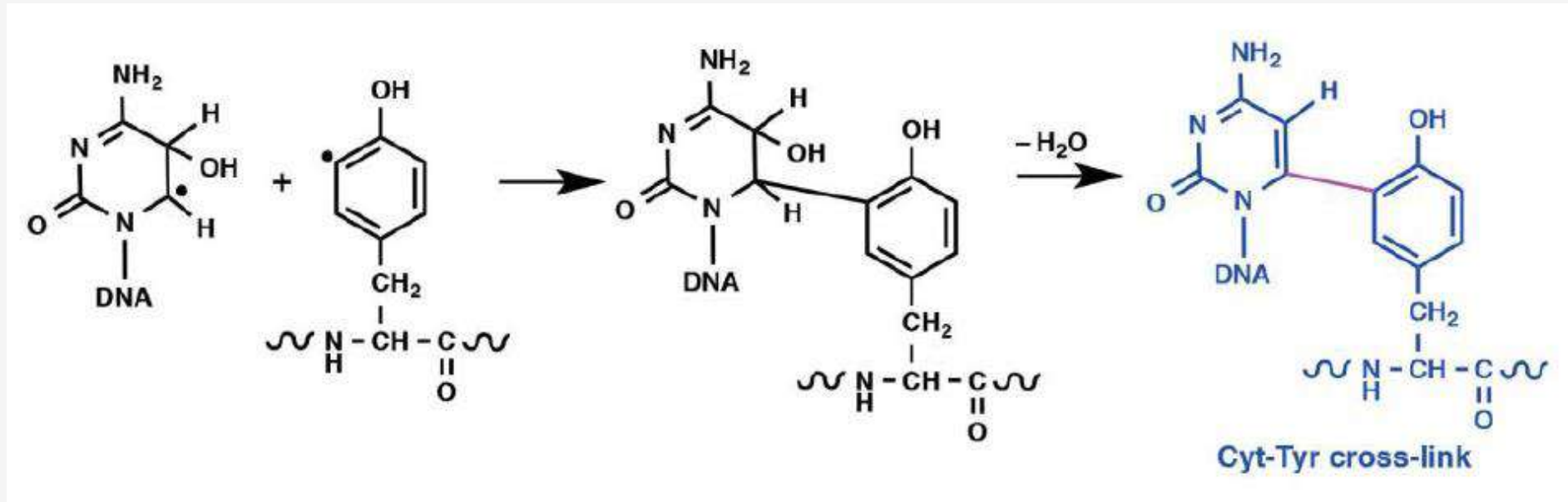
## Thymine – Tyrosine:



# Crosslinking reactions:

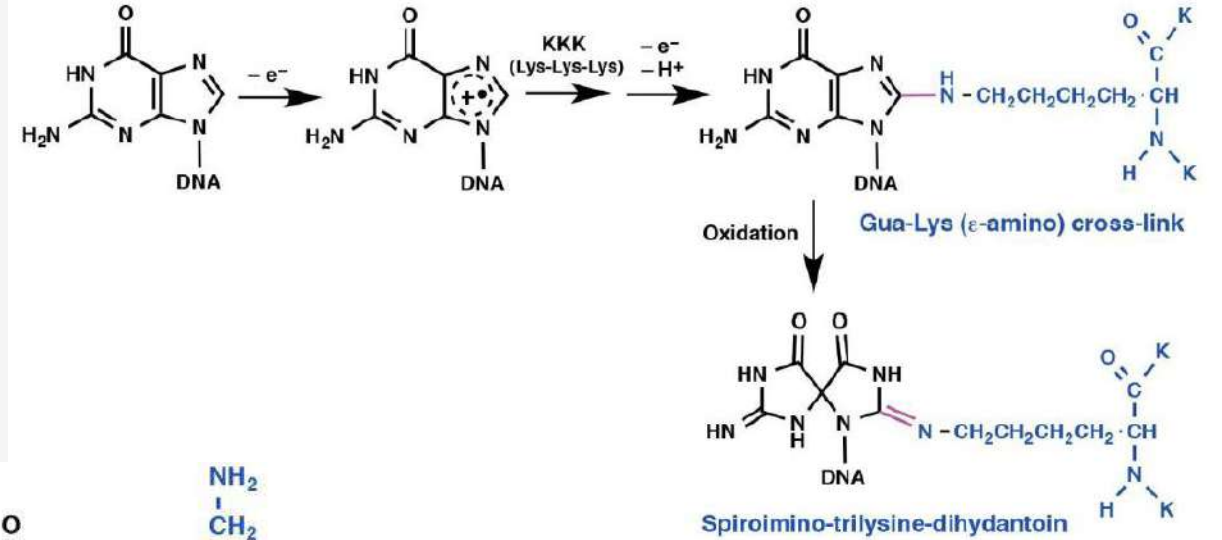
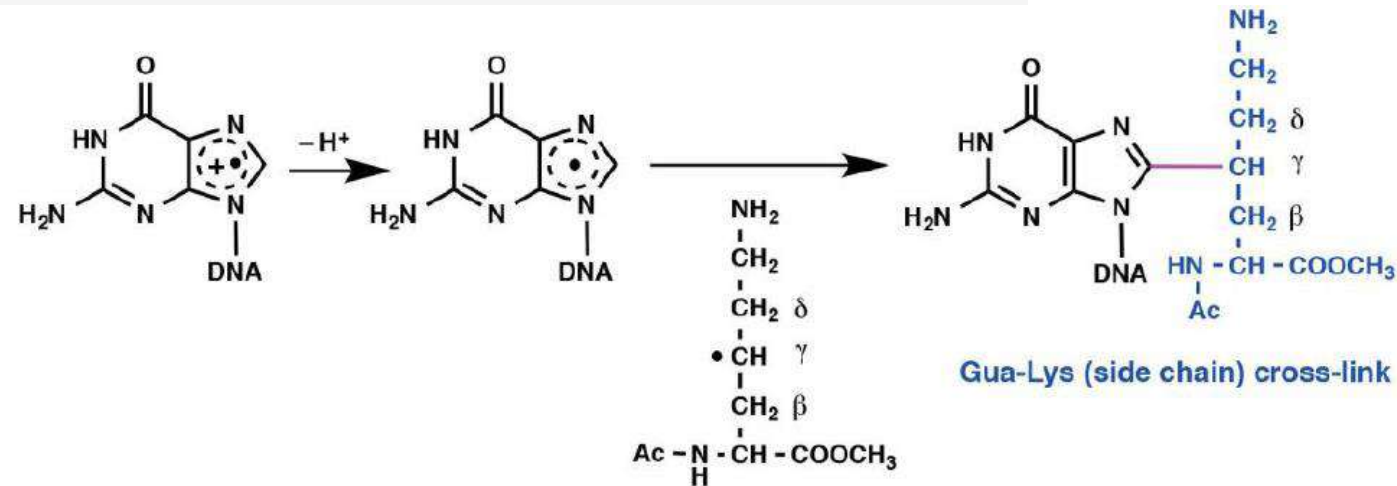
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Cytosine – Tyrosine:



# Crosslinking reactions:

Guanine – Lysine:



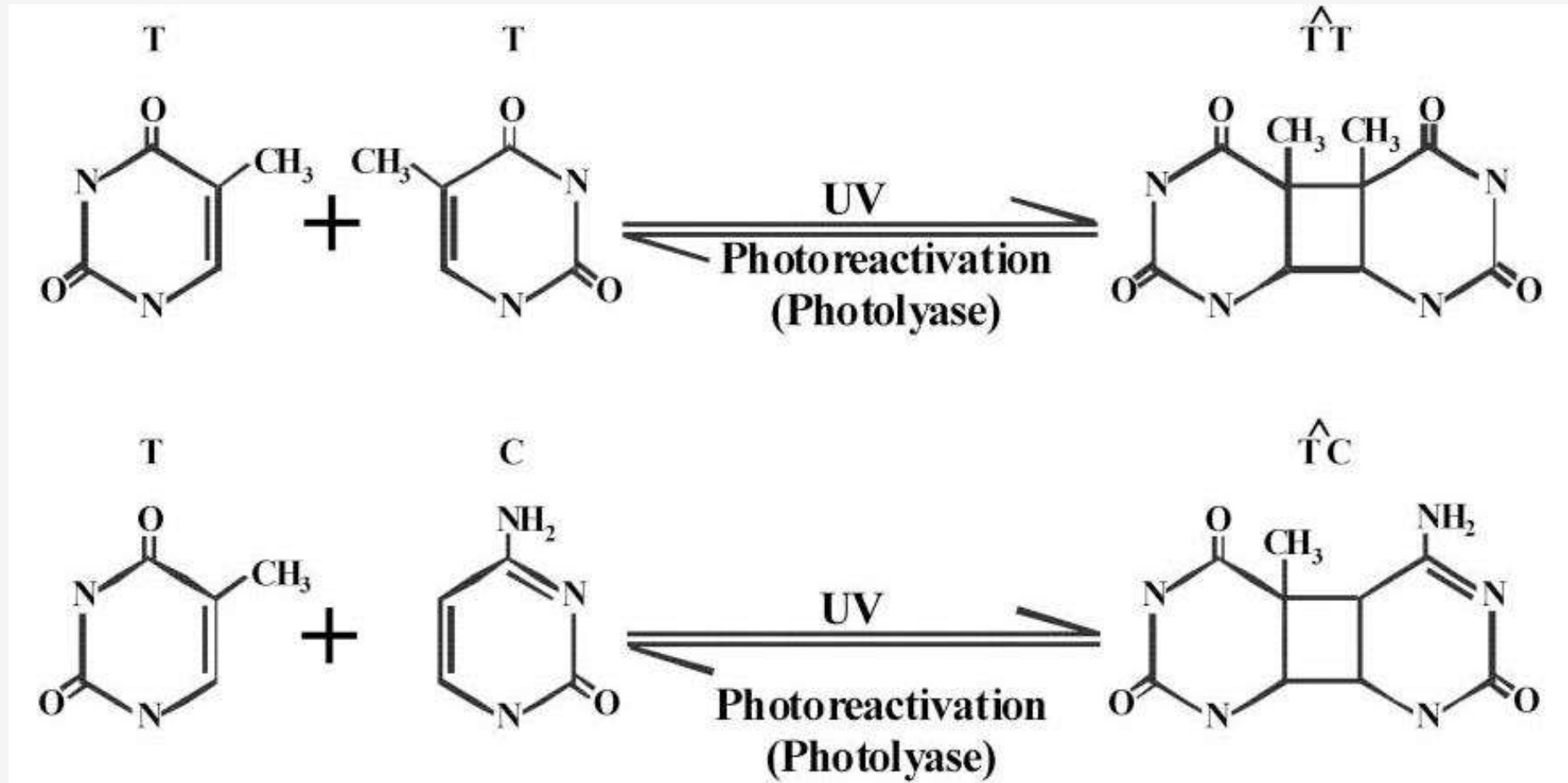


# Crosslinking reactions:

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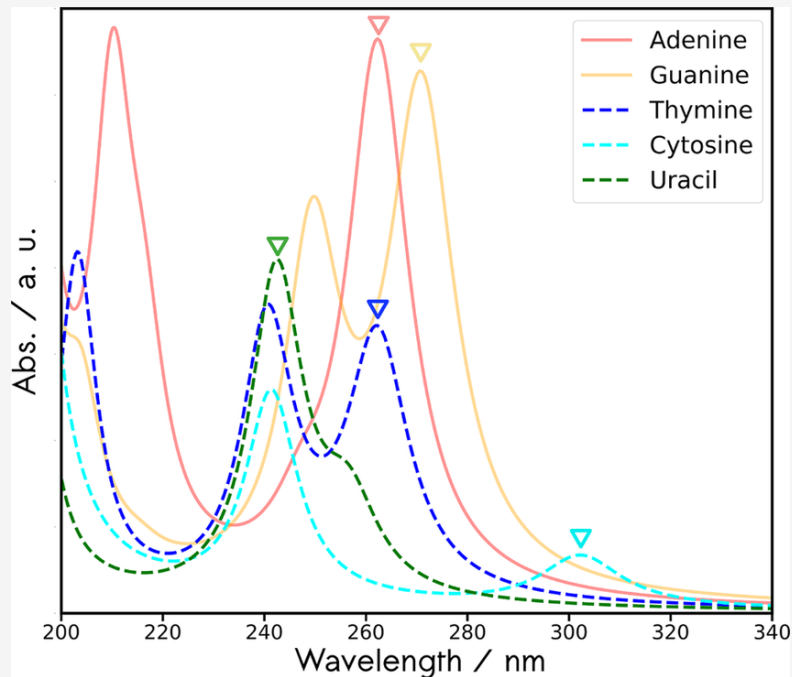
Thymine – Thymine or Thymine – Cytosine:

Photodamage !!!



# Photoreaction induced by UV source:

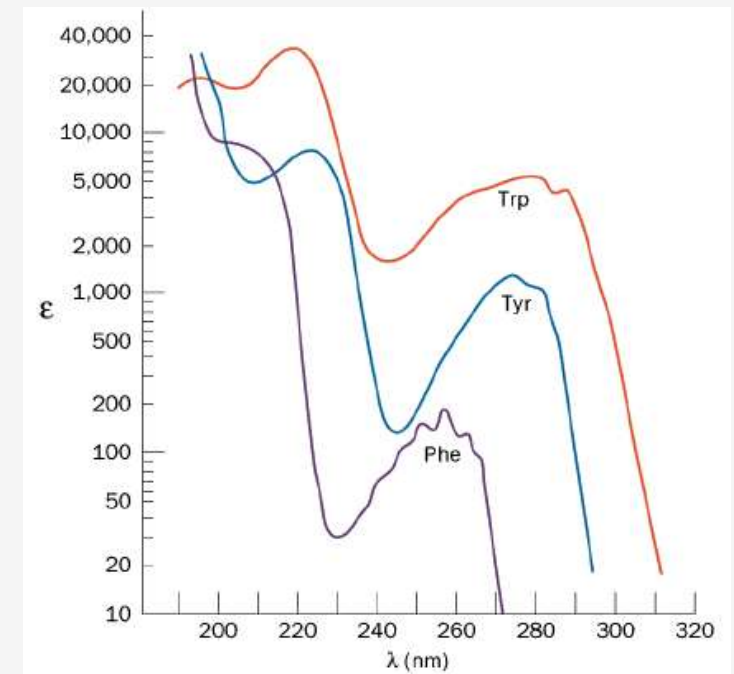
- Either DNA bases or amino acids (mainly the aromatic forms) are electronically excited by the UV light



*J. Phys. Chem. A* 2019, 123, 10, 2065

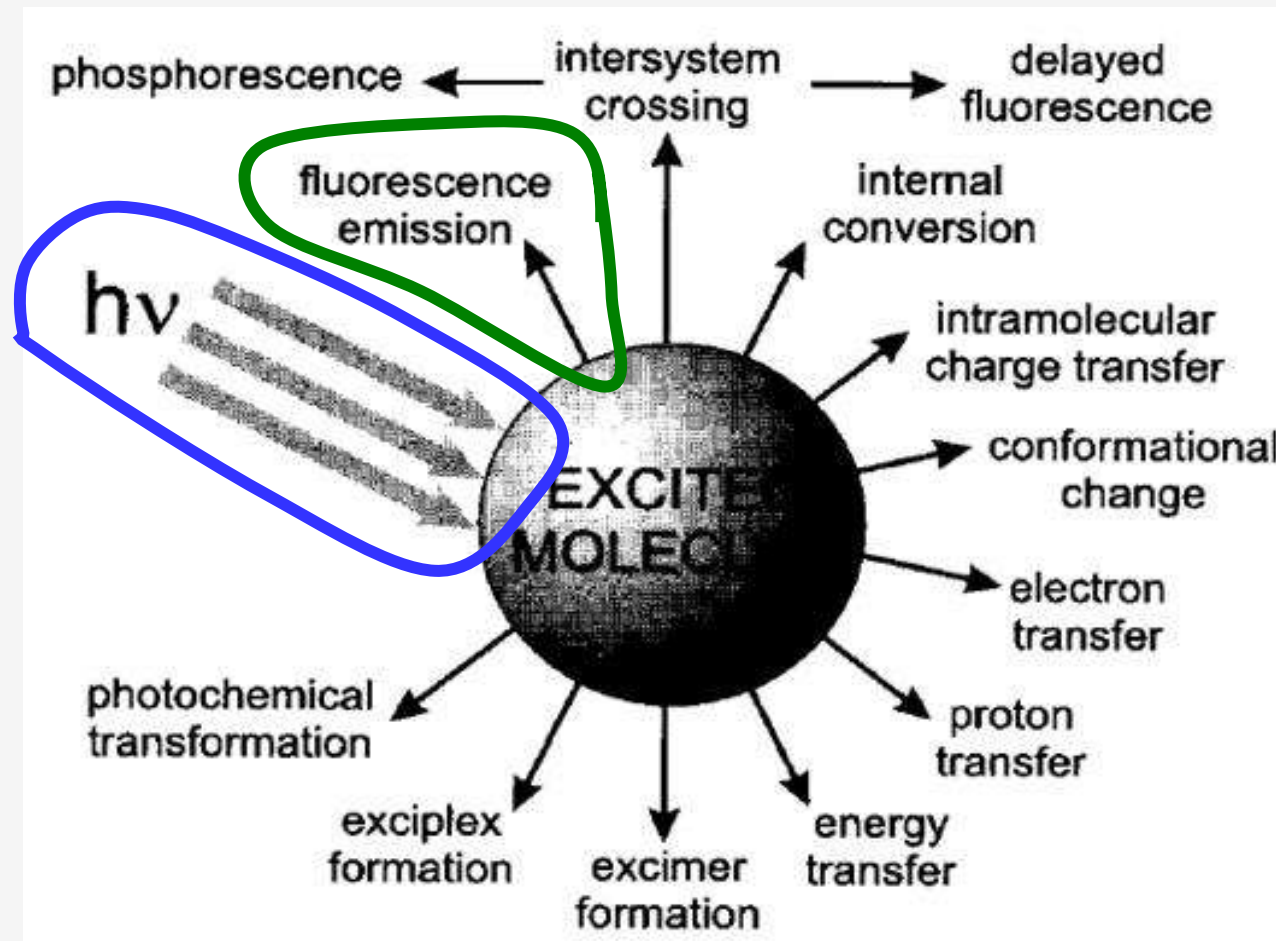
$\lambda$ :  
260 - 320 nm

UV-B  
and partially  
UV-C



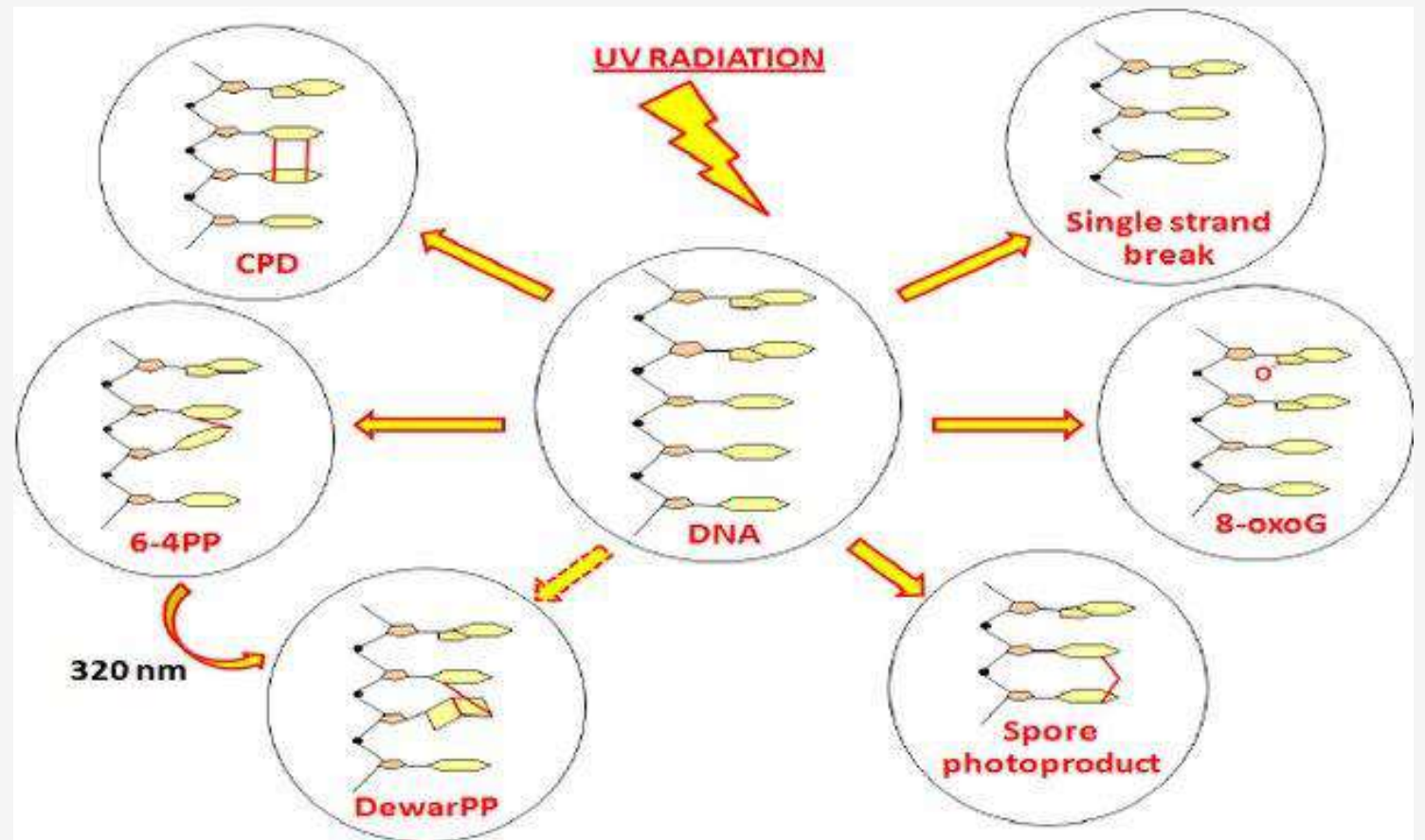
# Photochemical processes:

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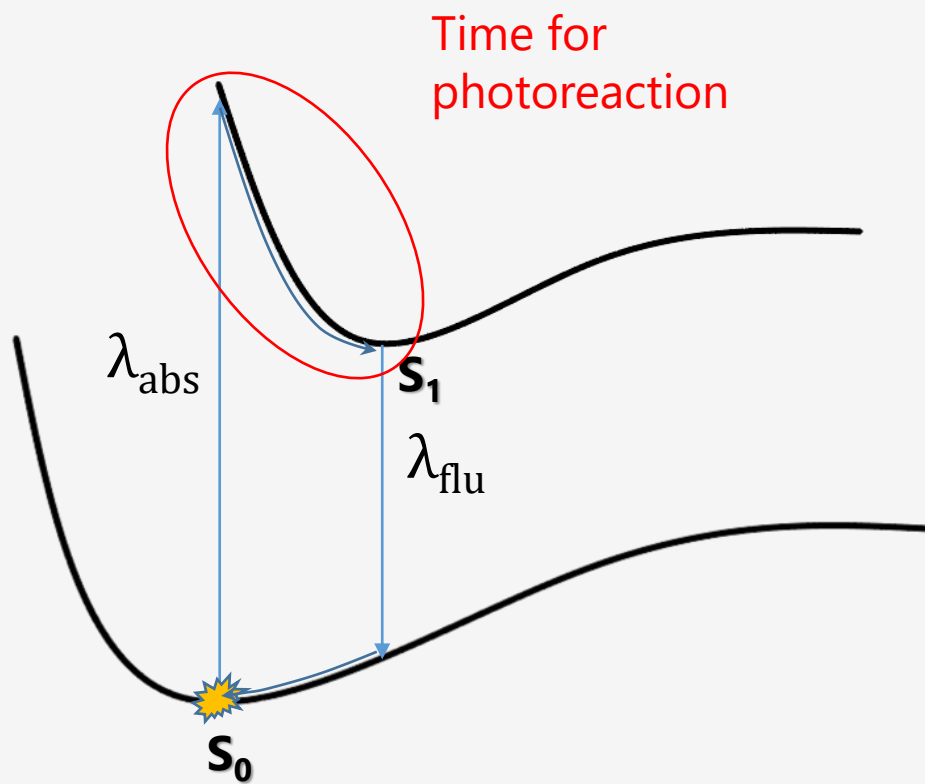
# DNA Photodamage:

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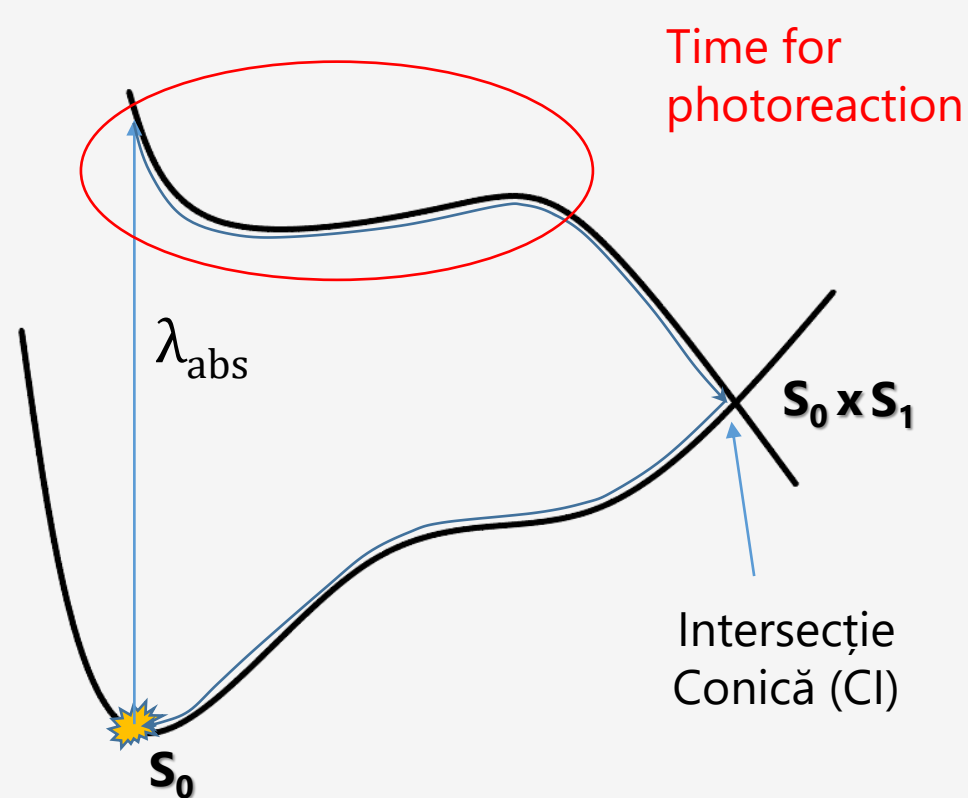
# Photochemistry reaction and relaxation

**Radiative:**



**Time scale:**  $\approx 100$  ps – 100 ns

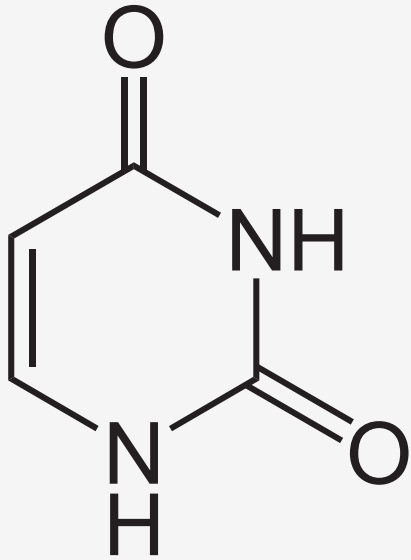
**Nonradiative**



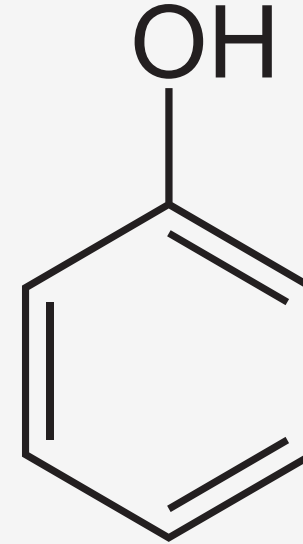
**Time scale:**  $\approx 100$  fs – 100 ps

## Model system for DNA-Protein crosslinking:

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Uracil as RNA (DNA) base



Benzene (Phe) and phenol (Tyr) as aromatic amino acids

Bende A, Farçaş A-A and Toşa V (2022) Theoretical Study of Light-Induced Crosslinking Reaction Between Pyrimidine DNA Bases and Aromatic Amino Acids. *Front. Bioeng. Biotechnol.* 9:806415.

# Model system for DNA-Protein crosslinking:

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## Theoretical method:

- Quantum level considering the **Density Functional Theory (DFT)** and **Coupled Cluster (CC)** methods;
- Basis set: **ma-def2-TZVPP** triple- $\zeta$  basis set of the Karlsruhe group;
- Exchange-Correlation functionals:  **$\omega$ B97X-D3**; **SCS-PBE-QIDH**;
- Solvent model: conductor-like polarizable continuum (**CPCM**) model for **Water**;
- Electronic excited state: Time-dependent DFT (**TDDFT**) with Tamm–Dancoff approximation (**TDA**);
- Conical intersection localization: Spin-flipped TDDFT (**SF-TDDFT**);
- Quantum Chemistry program: **Orca 5.0.1**;

# Model system for DNA-Protein crosslinking:

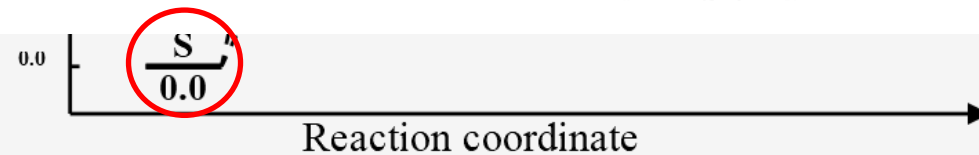
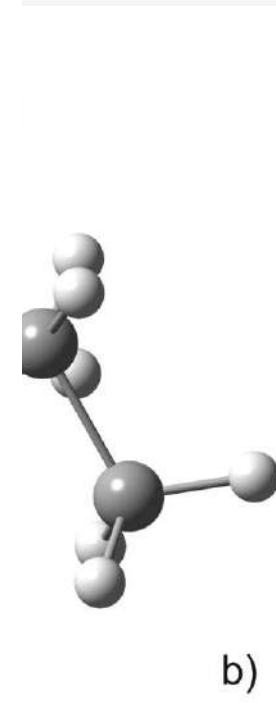
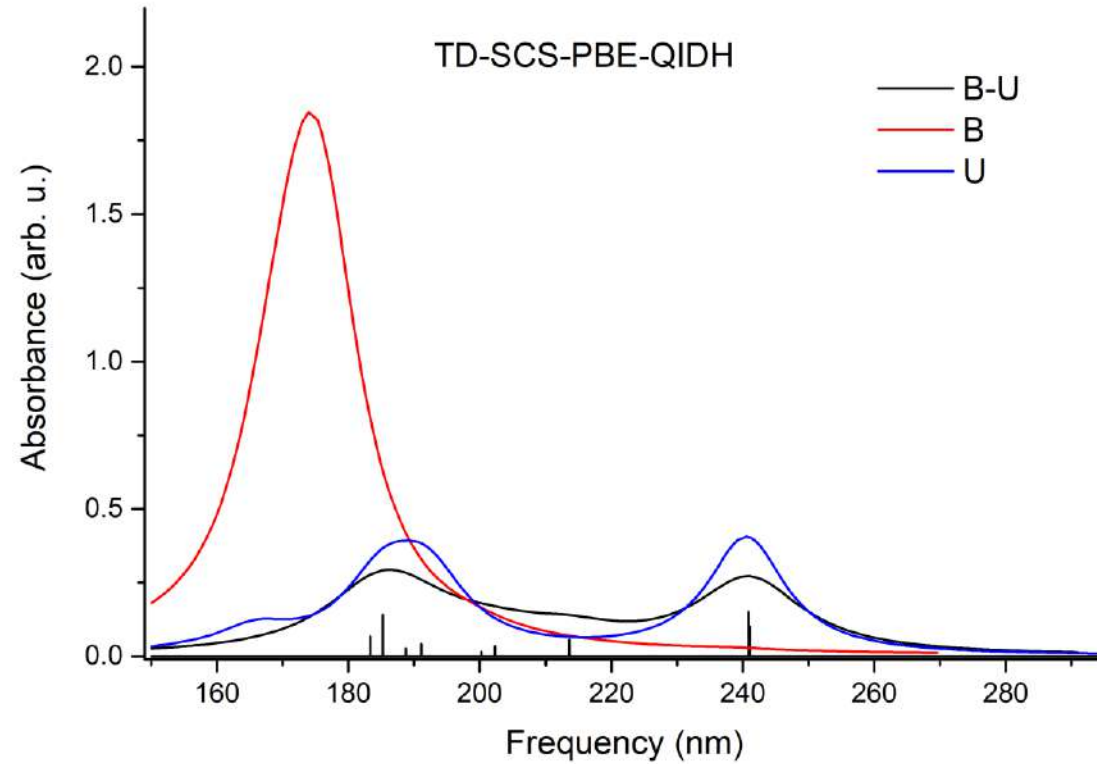
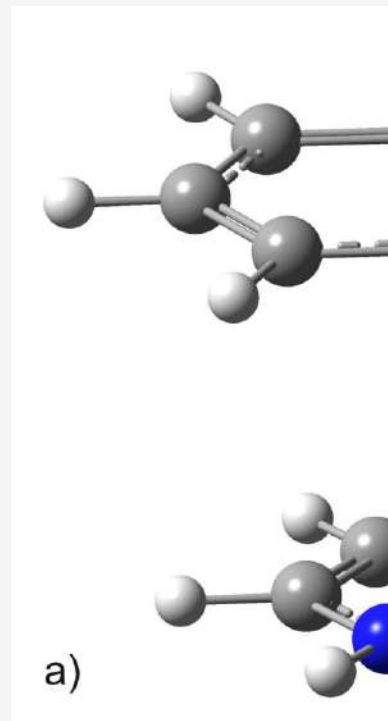
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## Protocol:

- Computing the uracil-benzene and uracil-phenol stacking and cyclic adduct dimer equilibrium geometries in ground state ( $S_0$ ) electronic level;
  - Computing the vertical electronic excited states for the stacking dimers  $\rightarrow$  UV absorption spectra;
  - Computing the uracil-benzene and uracil-phenol stacking and cyclic adduct dimer equilibrium geometries for the first excited state ( $S_1$ ) electronic level;
  - Computing the transition state geometry between the stacking and cyclic adduct configuration;
  - Locating the conical intersection geometries for the crossing between the ground and the first excited electronic state
- $\rightarrow$  Building the excitation-relaxation scheme along the potential energy hyper-surface**



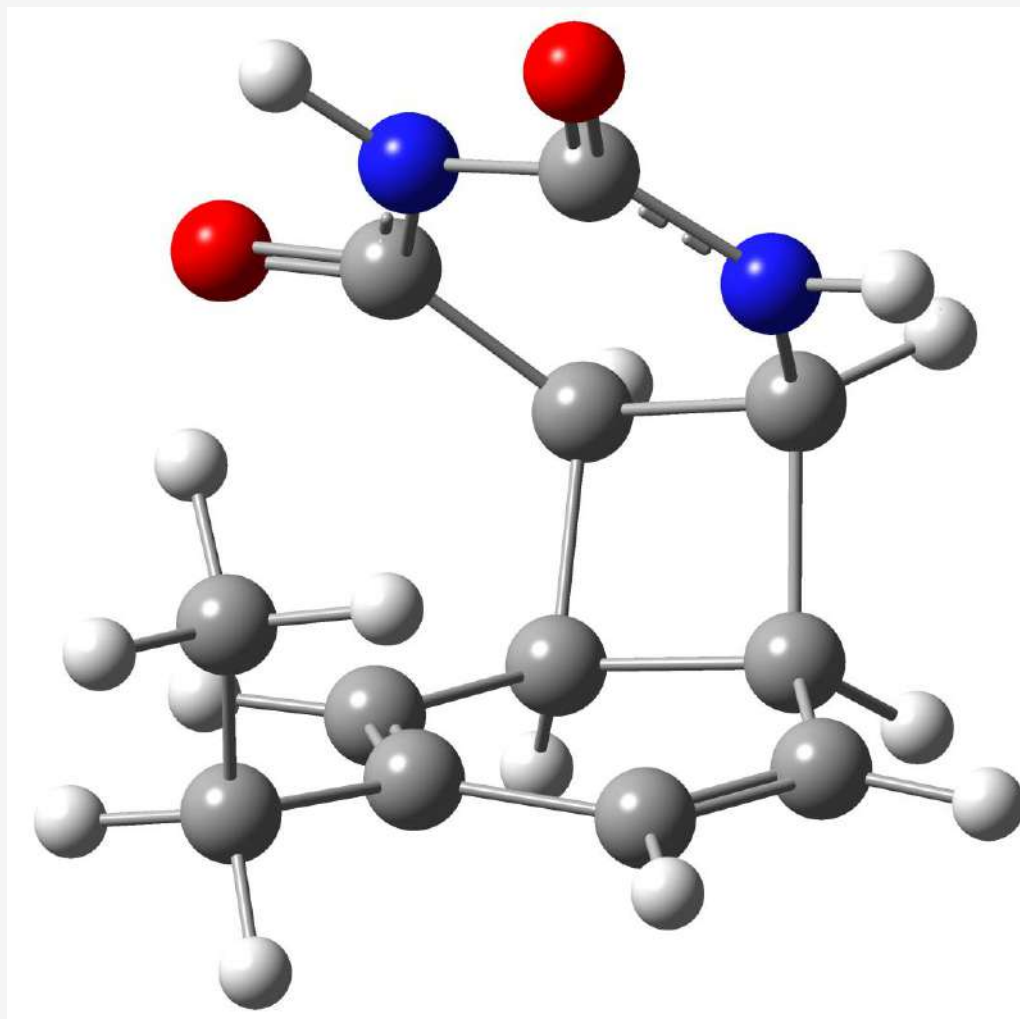
# Model system for DNA-Protein crosslinking:



# Model system for DNA-Protein crosslinking:

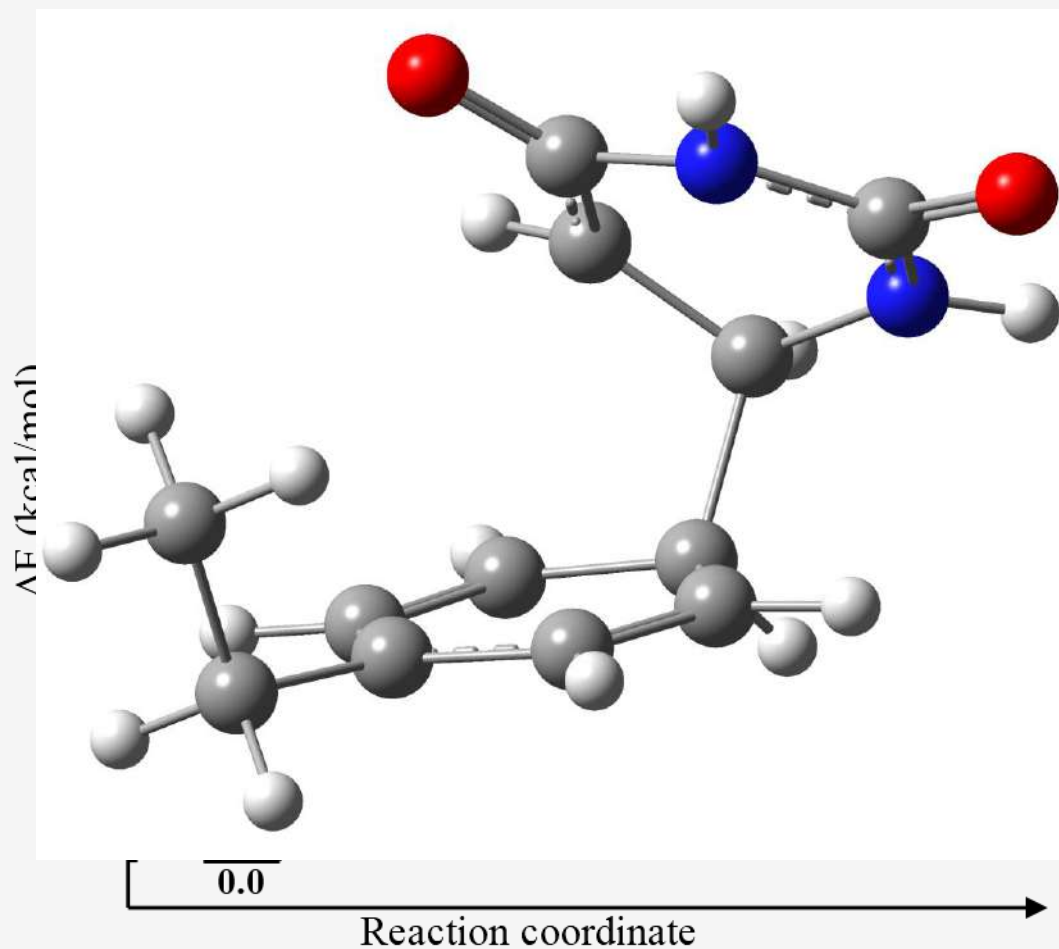
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$\Delta E$  (kcal/mol)

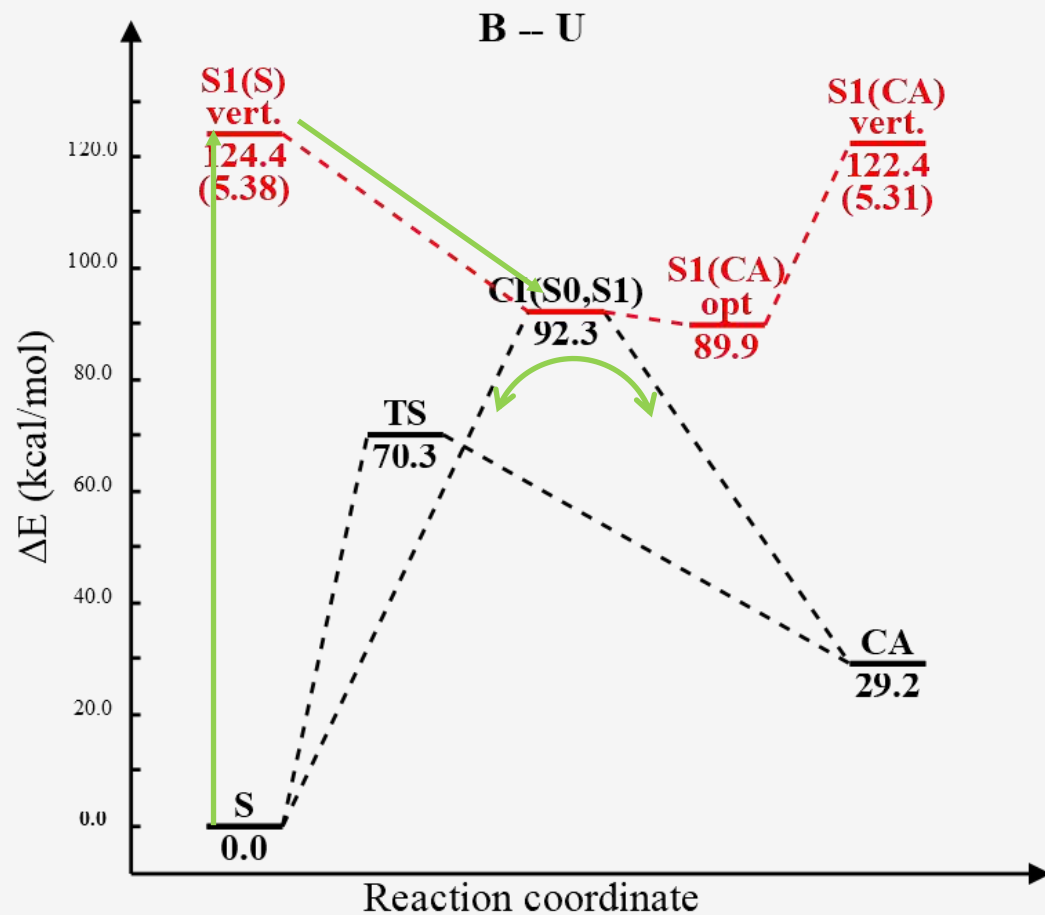


# Model system for DNA-Protein crosslinking:

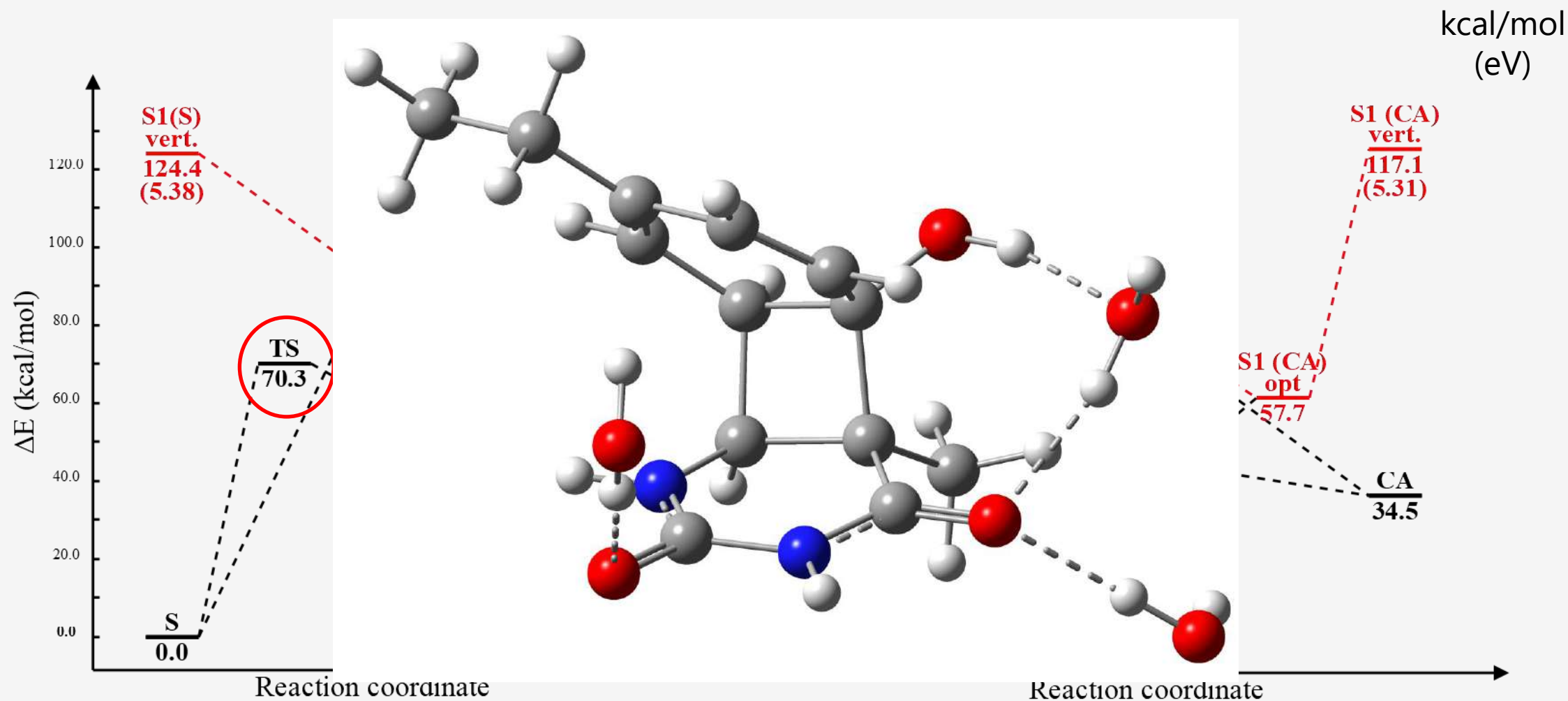
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# Model system for DNA-Protein crosslinking:



# Model system for DNA-Protein crosslinking:



# Conclusions:

- The DNA – protein crosslinking reaction can be a useful technique for reading DNA sequences;
- Using specific UV radiation sources, selective binding between DNA bases and amino acids can be induced;
- Crosslinking based on Uracil – Benzene binding is more stable than that of Uracil – Phenol;

Thank You for Your Attention