Titolo: Modelling photochemistry and spctroscopy of sulfur-substituted DNA bases

Research project

Thiobases are non-canonical nucleobases obtained by replacing oxygen with sulphur atoms. This substitution dramatically changes the photophysics, with a red shift of the absorption spectrum and a loss of photostability. Differently from nucleobases, which relax to the ground state mainly via harmless ultrafast internal conversion mediated by conical intersections, in thiobases a long-lived triplet state is populated with high quantum yield via an ultrafast intersystem crossing. Due to the high transfer efficiency to the triplet states and the high rate of singlet oxygen formation, thiobases are used as photosensitizers in photodynamic therapy. On the other hand, thiobases are widely employed as prodrugs for the treatment of a variety of diseases, such as leukemia and gliomas, and the long-lived triplet states may in this case lead to DNA damage. Understanding the ultrafast photochemistry of thiobases is thus crucial both for their use as phototherapeutic agents and for the design of prodrugs with reduced photochemical side effects.

Deciphering the excited state relaxation pathways in thiobases has been so far difficult because: i) the speed of the involved processes, on the 100-fs timescale, challenges the temporal resolution of conventional UV-visible transient absorption (TA) spectroscopy setups; ii) excited state dynamics in thiobases often involves dark excited states of $n\pi^*$ character, which do not have an oscillator strength and therefore cannot be readily observed by UV-visible TA spectroscopy; iii) theoretical simulations of excited states dynamics have been mostly carried out in a semi-classical fashion, sacrificing accuracy by neglecting environmental effects and/or electronic correlations.

We will employ advanced numerical simulations based on mixed quantum-classical dynamics within a hybrid quantum mechanics/molecular mechanics (QM/MM) framework explicitly including correlation energy and environmental effects, to quantitatively reproduce experiments and assign the observed spectral signals and the corresponding time constants to the specific pathways responsible for the decay. Computational data will finally expose the early stages of excited state relaxation in thiobases, with groundbreaking impact both on fundamental knowledge and on the medical applications of these biomolecules.

Activity plan

Months 1-6: We will employ advanced numerical simulations to run mixed quantum-classical non-adiabatic surface hopping dynamics within a hybrid quantum mechanics/molecular mechanics (QM/MM) framework explicitly including correlation energy and environmental effects.

Months 7-12: We will model non-linear transient absorption signals spanning the NIR-VUS-UV-XUV spectral window and assign the observed spectral signals and the corresponding time constants to the specific pathways responsible for the decay. Comparison between computational nd experimental data collected in PoliMi and CNR (Prof. Giulio Cerullo and Dr. Cristina Vozzi) will finally disclose the molecular movie of the early stages of excited state relaxation in thiobases.