

Summary

The 1,3-dicarbonyl functional groups are present in a wide range of compounds. Their photochemistry displays interesting features due to the presence of various isomers that exhibit particular spectroscopic properties or photoreactivity. In this context, the large UVA absorption of the chelated enol isomer of dibenzoylmethanes has been widely used in cosmetic industry for photoprotection purposes. The β -dicarbonyl compounds are also found in the structure of photoreactive thymidine or uridine derivatives bearing a pivaloyl or formyl group at C5 position.

The main objective of this thesis is to contrast the role of these 1,3-dicarbonyl compounds as DNA damaging agents to their photoprotective potential. Thus, on the one hand the properties of β -dicarbonyl compounds as part of the DNA structure have been addressed through the study of C5-pivaloyl substituted dihydropyrimidines as photolabile precursors of carbon centered radicals, but also through the assessment of the DNA oxidatively generated damage, 5-formyl uracil, as a potential intrinsic DNA photosensitizing agent. On the other hand, the diketo isomer of the most representative UVA filter *ie.* 4-*tert*-butyl-4'-methoxydibenzoylmethane, the so-called avobenzene filter, contains two photoremovable phenacyl groups. This has led to the development of a new strategy for photoprotection based on the photorelease of a photosensitizing topical drug together with its protecting UVA filter.

Firstly, 5,6-dihydropyrimidines have been derivatized using a *tert*-butyl ketone photolabile group in order to study the generation of C5-centered radicals in non aqueous media. This is of particular importance as the microenvironment provided by the DNA structure and its complexes with proteins such as histones may not be fully reproduced by aqueous media, and the pyrimidine-derived radical would be embedded into the complex DNA/RNA system, which constitutes a heterogeneous environment. Thus, laser flash photolysis study in acetonitrile of the designed 1,3-dicarbonyl derivatives gives rise to the formation of the purported 5,6-dihydropyrimidin-5-yl radicals. Their characterization shows long lived transient species, which do not decay in the μ s range and are centered at 400-420 nm or 350-400 nm for the 5,6-dihydrouridine or 5,6-dihydrothymidine derivatives, respectively. Moreover, radical generation has also been evidenced by steady state fluorescence experiments by using a profluorescent radical trap (AAA-TEMPO). This probe has been especially designed to fulfill principally two requirements: (*i*) be excited at wavelengths higher than 350 nm, where DNA does not absorb and (*ii*) show little if any absorption in the 260-330 nm range in order to not interfere with the absorbance of the *tert*-butyl ketone moiety. Thus, irradiation of the photolabile nucleic acid derivatives in the presence of AAA-TEMPO results in an increased emission, in agreement with the trapping of C5 radical by the paramagnetic probe. Formation of the resulting adduct has been confirmed by UPLC-HRMS. Experimental data have been corroborated with *ab initio* CASPT2//CASSCF theoretical calculations.

In a second chapter, another 1,3-dicarbonyl derivative of pyrimidine has been investigated. Indeed, the oxidatively generated damage 5-formyluracil (ForU) presents interesting features as a potential intrinsic DNA photosensitizing agent. Thus, spectroscopic studies reveal that ForU has not only an absorption in the UVA/UVB range, where canonical

bases barely absorb, but also a triplet excited state ($^3\text{ForU}^*$) with a lifetime of some μs and with an energy high enough to photosensitize the well-known cyclobutane pyrimidine dimers (CPDs) through triplet-triplet energy transfer. This process has been confirmed by means of the synthesis of model Thy-Thy and Cyt-Cyt dyads, which after irradiation in the presence of ForU have been demonstrated to produce CPDs. Finally, the study extended to plasmid DNA allows establishing the ability of ForU to produce single strand breaks and CPDs.

Next, the attention has been focused on the development of a new strategy for photoprotection of bioactive molecules taking advantage of the photochemical reactivity of the 1,3-diketo tautomer of the UVA filter avobenzone (AB). The selected bioactive compounds are two photosensitive topical non steroidal anti-inflammatory drugs, namely (S)-ketoprofen (KP) and diclofenac (DF). In this context, the diketo tautomer of avobenzone contains two phenacyl moieties, which are well-known photoremovable protecting groups. Thus, a judicious design of a pro-drug/pro-filter dyad allows the photorelease of the drug and its protecting shield, avobenzone. The viability of this controlled release of the active ingredients was checked in different solvents of different H donating properties and viscosity to simulate topical formulation. In addition, laser flash photolysis studies in ethanol allow characterization of a transient absorption band at 400-420 nm assigned to the triplet excited state of the dyad by comparison with that of the diketo form of AB.

Finally, the photosafety of the photoactivatable dyad formed between ketoprofen and avobenzone has been assessed. An interesting result is obtained from the transient absorption spectra of the KP-AB dyad in cyclohexane where, by contrast with ethanol, the observed species is the triplet excited state of KP and not that of the AB in its diketo form. This is of paramount importance in terms of phototoxicity and photogenotoxicity in connection with the widely studied photosensitizing properties of KP. The impact on the cellular membrane has been addressed by UVA irradiation of linoleic acid solutions in the presence of the dyad. Phototoxic potential of the dyad has been evidenced by UV-Vis spectrophotometry through the formation of the conjugated dienic hydroperoxides derived from linoleic acid. However, AB-KP does not exhibit a photogenotoxic potential as demonstrated by comet assay experiments, where by contrast with KP, the non damaged round shape of the cell is still observed after UVA irradiation.