Abstract

In this thesis, the use of biomimetic media such as serum albumins (SAs), α_1-acid glycloproteins (AAGs), cyclodextrins (CDs) and sodium dodecyl sulfate (SDS) micelles is combined with photophysical techniques (fluorescence (F) and laser flash photolysis (LFP)) to investigate the issue of photosensitization by drugs or drug derivatives containing a triciclyc heteroaromatic chromophore, namely carbazole (**CBZ**) or phenothiazine (**FTZ**).

The photobehavior of the methyl ester of carprofen (**CPFMe**) in the presence of bovine serum albumin (BSA) has been addressed first. The decay of triplet excited state of **CPFMe** in the presence of BSA at 1:2 molar ratio, monitored at 430 nm, needed two monoexponential terms and thus two triplet lifetimes (τ_T) for a satisfactory fitting, which revealed binding to two different sites within the protein. The shorter value of τ_T was ascribed to **CPFMe** present in site I, based on the quenching of ^{3}**CPFMe*** by the tryptophan (Trp) residue located in this pocket, through an electron transfer mechanism. No significant differences were found between (*S*)- and (*R*)-**CPFMe**. Within bovine α-acid glycloprotein (BAAG), only one binding site was observed for both **CPFMe** enantiomers. In this case, stereodifferentiation was observed in the triplet lifetimes in **CPFMe**@BAAG complexes, with the shorter τ_T values for the (*S*)-enantiomer. Moreover, **CPFMe** photobinding to BAAG was detected by following the changes in the fluorescence spectra of **CPFMe**@BAAG mixtures before and after irradiation. The process was more efficient for (*S*)-**CPFMe**. The proposed mechanism involves a reductive photodehalogenation from the triplet excited state of (*S*)-**CPFMe**, giving rise to covalent adduct (*S*)-**CBZMe**-BAAG.

In chloroaromatic derivatives, dehalogenation is assumed to proceed from the triplet excited state, although its energy is often insufficient to promote a clean homolytic C-Cl cleavage leading to aryl radicals and chlorine atoms. As a way to circumvent the unfavorable thermodynamics of this step, it has been proposed that the actual operating mechanism involves formation of triplet excimers. In this context, to deepen into the mechanism of **CPFMe** dehalogenation, two

diastereomeric dyads based on **CPF** (**CPF-CPF** and **CPF-CBZ**) have been synthesized and irradiated. The self-quenching of the triplet excited states in both dyads is much faster than in **CPFMe**, and is related to formation of charge transfer species, clearly disfavored in non-polar solvents (THF). The trends observed in the triplet lifetimes, as well as the solvent effects on photoreactivity, are in full agreement with the mechanistic picture of a photoreductive dechlorination as operating mechanism in **CPF**-based systems.

The photochemistry of the neuroleptic drug cyamemazine (**CMZ**) has been investigated in biomimetic media. The encapsulation process has been followed by fluorescence spectroscopy, as a hypsochromic shift of the band, concomitant with enhanced quantum yields and lifetimes. Laser flash photolysis revealed important changes associated with encapsulation, specifically more selective generation of the triplet excited state, which turns to be longer-lived. Light-induced oxidation of **CMZ** afforded the corresponding radical cation, which was trapped by oxygen to afford the *N,S*-dioxide. The reaction has been monitored by fluorescence spectroscopy, by the progressive appearance of a characteristic emission band at shorter wavelengths. The process resulted to be disfavored in the employed microenvironments, due to their lipophilic nature. The slowest photooxidation rate corresponds to **CMZ** in SDS micelles and in AAGs, where the drug is located in a more hydrophobic domain, hardly accessible from the aqueous medium, and photoionization is nearly negligible.

Laser flash photolysis of the anti-psychotic chlorpromazine (**CPZ**) and two phase I metabolites, **CPZ-MD** and **CPZ-DD** (mono and didemethylated, respectively) in the presence of increasing amounts of HSA, has allowed monitoring binding to the protein, from the enhancement of the ΔA_{max} value of ^{3}**CPZ*** (monitored at 470 nm). As expected, the binding degree was higher for the parent drug, in agreement with its more hydrophobic character. The use of warfarin as site I displacement probe indicated that the three compounds only bind to this site. Marginal photobinding to HSA was observed in all cases, which was monitored by following subtle changes in the fluorescence spectra.