Psoralen Photochemistry: The Role Of Electron Transfer

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Psoralens are photoactivatable furocoumarin drugs that are used in conjunction with UVA irradiation (PUVA therapy) to treat a variety of dermatological diseases and for *ex vivo* blood purification. The generally accepted mode of action involves intercalation of the psoralen between the base pairs in the DNA duplex followed by two photocycloaddition reactions that cross-link adjacent DNA strands. However, there is increasing evidence that other reactions may also be important. Recent work has shown that 8-methoxypsoralen undergoes monophotonic photoionization (Φ = 0.015) upon UVA irradiation in aqueous buffer. The generality of these results has been demonstrated by generating the radical cations of a number of psoralens and related coumarins by both photoinduced electron transfer and photoionization. The reactivity of psoralen and coumarin radical cations with biological substrates such as DNA bases and amino acids is dominated by electron transfer reactions that regenerate the substrate psoralen or coumarin.

The photoionization of psoralens and coumarins has also been studied in heterogeneous media (micelles, DNA, vesicles) that provide a better model for cellular photochemistry. In anionic micelles (eg, sodium dodecyl sulfate) the photoionization yield is significantly increased since electrostatic repulsion between the ejected electron and the negatively charged micellar interface favors efficient charge separation of the initial geminate radical cation/electron pair. Quenching studies using anions that are localized in the aqueous phase demonstrate that exit of the radical cations from anionic sodium dodecyl micelles occurs with rate constants $< 10^5$ s^{-1}. The quenching rate constant for reaction of micelle-localized radical cations with anions is approximately two orders of magnitude slower than that for the same quencher in aqueous solution, clearly demonstrating the importance of electrostatic effects. The behavior of the same radical cations is significantly different in neutral Triton X-100 micelles, with faster exit rate constants (10^6 s^{-1}) and higher reactivity toward anionic quenchers. Preliminary data indicate that electron transfer reactions play a key role in the photochemistry of psoralens complexed to proteins. For example, irradiation of complexes of several psoralens and coumarins with HAS (human serum albumin, a protein responsible for transport of small molecules) provides evidence for generation of a tryptophan-derived radical. This is consistent with initial electron transfer quenching of the excited substrate by an adjacent tryptophan in the drug binding site.