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Ja Hong Kim and Sang Chul Shim

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Theoretical Studies on the Photo-Skinsensitizing Psoralens (II)

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The photocycloaddition reaction of 8-methoxypsoralen with purine and/or pyrimidine bases is studied as a model for the charge transfer interactions of psoralens with DNA bases by the FMO method. The results indicate that, in the case of the molecular complex formation between psoralens and purine and/or pyrimidine bases, the most probable photocycloaddition should occur in the following order: Thy (5,6)◇(3,4) 8-MOP, Cyt(5,6)◇(3,4)8-MOP, Ade (7,8)◇(3,4)8-MOP, Gua(7,8) ◇(3,4)8-MOP. The theoretical results for the photocycloaddition reaction are also correlated with the experimental results. The photoadducts between 8-methoxypsoralen and adenine are likely to be C_4-cycloadducts through the cycloaddition of 3,4-pyrone double bond of 8-methoxypsoralen to 7,8-double bond of adenine.

Introduction

The photobiological reactivities of psoralens as skin-sensitizers can be described in terms of the localized $(\pi, \pi^*)^3$ state, which is supposed to be the reactive state for the cycloaddition reaction of psoralens with pyrimidine bases in DNA.[1-4]

In our previous reports,[5-6] it has been shown that the optimum value of indices is closely correlated with photo-skinsensitizing carcinogenic activity and the formation of molecular complexes between DNA and photo-skinsensitizing carcinogens is discussed in terms of charge transfer interactions.

Although several photo-products of purine bases from direct and photosensitized irradiation of purines are known,[7] the photoaddition reactions between the excited psoralens and purine bases are not well understood. In view of the fact that the photoaddition of psoralens to poly A is quite efficient and one adenine base in *E. coli* tRNA is involved in photoaddition of 8-methoxypsoralen,[8] it is important to elucidate the nature of photobinding reactions between psoralens and adenine base.

In the present paper, we report that the charge trnasfer interaction in the hypothetic molecular complexes between the psoralens and the base components of nucleic acids are the first step of the photo-skinensitizing carcinogenesis and the most probable photocycloaddition reaction between psoralens

and purine and/or pyrimidine bases is derived from FMO methods.

Calculations

In the hypothetic molecular complexes, the chemical reactivity index and frontier electron density[9,10] can be used as a measure of the relative reactivity index of the various positions of the photocycloaddition. The increase in the frontier electron densities in the intermolecular region originates from the overlapping of the occupied molecular orbitals of purine and pyrimidine bases.

The parameters[11] as descibed in the previous papers were obtained from Pullman's value and frontier molecular orbitals and charge transfer quantity were calculated for both the psoralens and purine and/or pyrimidine bases for their complexed forms with HEWLETT PACKARD-3000 computer.

It is postulated that the photocycloaddition of adenine to the excited psoralens may yield the following adducts. The numbering scheme for nonhydrogen atoms is given below for the psoralens and purine bases.
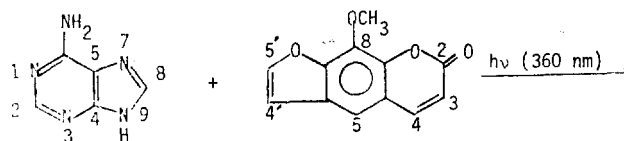
Ade (4, 5) <>(4′, 5′) 8–MOP (I), Ade (7, 8) <> (4′, 5′) 8–MOP (II), Ade (4, 5)<> (3, 4) 8–MOP (III), Ade (7, 8) <> (3, 4) 8–MOP (IV).

Of these cycloadducts, II and IV are very unlikely to be formed as the photocycloaddition of olefins to C=N group is very rare. For guanine base, in addition to the similar photocycloaddition reactions, pyrone double bond can add to the carbonyl group of guanine base to give oxetanes.
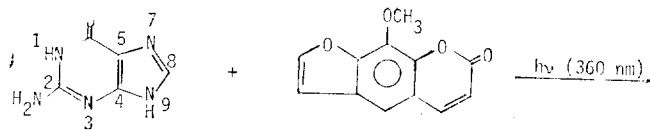
Gua (4, 5)<>(4′, 5′)8–MOP (V), Gua(4, 5)<>(3, 4)8–MOP (VI), Gua [C₆=O] (4′, 5′)8–MOP (VII), Gua [C₆=O]<> (3,4) 8–MOP (VIII).

Results and Discussion

In the hypothetical molecular complexes formed by the intermolecular interactions between psoralens and purine and/or pyrimidine bases, the charge transfer quantity is approximated as frontier orbital energies.

Results of calculations are summarized in Table 1. In Table 1, LUMO(lowest unoccupied molecular orbital) electron density of psoralens is the electron acceptor and HOMO (highest occupied molecular orbital) electron density of purine and pyrimidine bases is the electron donor, and frontier orbital electron density is the charge transfer quantity of possible photoadducts. The stereochemistry of thymine–psoralen–thymine cross–cycloadducts in DNA(producing crosslinked DNA) is likely to be dictated by the photoreactivity of psoralens toward adenine, which forms base pairs with thymine. It was found that Thy<>Ps<>Thy cycloadducts are favored if the excited psoralen does not add to adenine by the FMO calculations. On the other hand, Ade –Ps<>Thy adducts (cycloadducts and/or noncyclic adducts) result if the photoaddition of psoralen to adenine occurs. The charge transfer interactions in the photocycloaddition reaction are shown in Figures 1 and 2. No direct chemical or structural proof for either of these cross–adducts has been reported in the literature. However, on the basis of these calculations, we can predict that photo-cross–linking of poly(dA), poly(dT) with psoralen is very probable. Before planning experiment, it is pertinent to investigate the possible complexities of the photoreactions of psoralen and 8–methoxypsoralen with purine bases, especially adenine. One of the most probable reactions is the cross–

cycloaddition between psoralens and adenine (and/or guanine)

In Tables 2 and 3, charge transfer quantities from purine bases to 8–methoxypsoralen are shown. Table 2 shows that FMO interpretation of charge transfer interactions, the photocycloaddition reaction order can be explained in terms of Ade(7, 8)<>(3, 4)8–MOP and Gua(7, 8)<> (3, 4)8–MOP repectively. In Table 3, the theoretically possible cycloaddition products, Thy(5, 6)<>(3, 4)8–MOP, Cyt (5, 6)<>(3, 4)8–MOP are considered. On irradiation of aqueous solution of psoralen and thymine, only 3,4–photocycloadduct was formed. By contrast, irradiation of a frozen aqueous solution in which the molecules are immobilized in an ice matrix, yielded both 3,4 and 4′,5′–photocycloproducts.[12-14] According to the theoretical calculations, 3,4–pyrone double bond is more reactive than 4,5–furyl double bond for C₄-photocycloaddition reaction from the excited triplets state. The reverse case are explained for
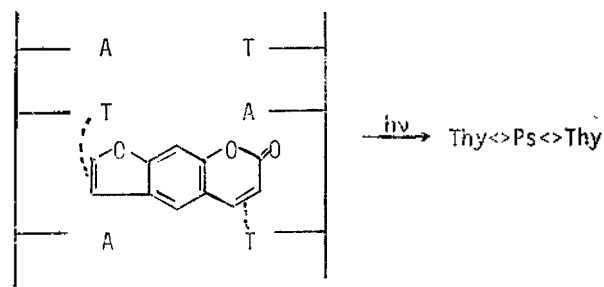

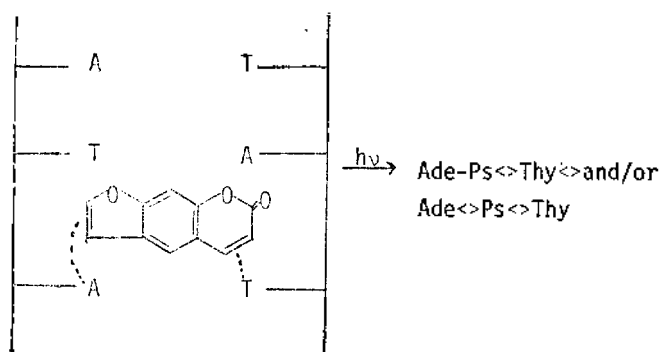**Figure 1.** Charge transfer interactions in the thymine–psoralen–thymine cross–cycloadducts in DNA.

Figure 2. Charge transfer interactions in the adenine–psoralen–thymine cross–cycloadducts in DNA

TABLE 1: The Charge Transfer Quantity from Purine and/or Pyrimidie Bases to Psoralens.

Possible photoadduct	Charge transfer quantity
Thy<>Ps<>Thy	0.1346
Ade<>Ps<>Thy	0.0213
Ade–Ps<>Ade	0.0483
Gua<>Ps<>Gua	0.0579
Cyt<>Ps<>Cyt	0.1124

TABLE 2: The Charge Transfer Quantity from Purine Bases to 8–Methoxypsoralen

Possible Photoadduct	8–MOP–3	8–MOP–4	8–MOP–4′	8–MOP–5′
Ade(4, 5)<>(3, 4)Ps Ade(4, 5)<>(4′, 5′)Ps	0.260	0.0034	0.0046	0.0007
Ade(7, 8)<>(3, 4)Ps Ade(7, 8)<>(4′, 5′)Ps	0.0805	0.0040	0.0142	0.0008
Gue(4, 5)<>(3, 4)Ps Gua(4, 5)<>(4′, 5′)Ps	0.0444	0.0138	0.0078	0.0028
Gua(7, 8)<>(3, 4)Ps Gua(7, 8)<>(4′, 5′)Ps	0.0551	0.0055	0.0097	0.0011
Gua(C₆=O)<>(3, 4)Ps Gua(C₆=O)<>(4′, 5′)Ps	0.0293	0.0013	0.0052	0.003

TABLE 3: The Charge Transfer Quantity from Pyrimidine Bases to 8-Methoxypsoralen

Possible photoadduct	8-MOP-4	8-MOP-4	8-MOP-4'	8-MOP-5'
Thy(5, 6)◇(3, 4)Ps Thy(5, 6)◇(4', 5')Ps	0.1456	0.0077	0.0256	0.0016
Thy(6, 1)◇(3, 4)Ps Thy(6, 1)◇(4', 5')Ps	0.0374	0.03000	0.0066	0.0062
Cyt(5, 6)◇(3, 4)Ps Cyt(5, 6)◇(4', 5')Ps	0.1396	0.0010	0.0246	0.0002
Cyt(6, 1)◇(3, 4)Ps Cyt(6, 1)◇(4', 5')Ps	0.0048	0.0299	0.0008	0.0061

photosubstitution reaction.[2] In attempt to obtain the more precise information for the photoreactions between furocoumarins and DNA, a solution of a labelled furocoumarin and a native DNA was irradiated under long wavelength uv light.[15] The photoadducts isolated were identical with the photoadducts formed between psoralen and pyrimidine bases[16].

In conclusion, the results of FMO method are in good agreement with the experimental observations in interpreting the regioselectivity of photocycloaddition reactions between psoralens and DNA and can be utilized in predicting the photoreactivities of psoralens to purine and/or pyrimidine bases of DNA.

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Reactions of Thioxanthylium Ion with Organomercurials

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Reactions of thioxanthylium ion with dimethyl-, dibenzyl-, diisopropyl-, and diphenylmercury in the air gave 9,9'–methylenedithioxanthene, 9-benzylthioxanthene, 9-acetonylthioxanthene, and 9-phenylthioxanthene, respectively, as a 9-substituted thioxanthene. In contrast with reactions with aromatics with an electron-donating group, large amount of thioxanthene and thioxanthone were obtained. However, only trace amounts of thioxanthene and thioxanthone were obtained from the reaction with dibenzylmercury under nitrogen atmosphere. In order to explain these reactions, one electron transfer between thioxanthylium ion and organomercurials was proposed.

Indroduction

Thioxanthylium ion has been prepared by adding either thioxanthene or thioxanthene 10-oxide in 96% sulfuric acid and identified clearly by the spectroscopic methods.[1] The products obtained from the sulfuric acid solution