Theoretical Studies on the Photo-Skinsensitizing Psoralens (I)

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The electronic structure of photo-skinsensitizing psoralens has been investigated by the FMO method. On the basis of theoretical calculations, optimum value of indices (Ft=0.33) has been proposed which corresponds to the sum of frontier electron density. The results indicate that this index is closely correlated with photo-skinsensitizing carcinogenic activity. The formations of molecular complexes between DNA and photo-skinsensitizing carcinogens is discussed in terms of charge transfer interactions.

Introduction

The molecular basis of cutaneous photosensitivity due to psoralens are not definitively established even though the relationship between the chemical structure of furocoumarins and their photosensitizing and carcinogenic activity has been extensively studied.[1~3] The photosensitivity of psoralens is generally correlated with their photoreactivity toward pyrimidine bases in DNA.[4~6] The formation of interstrand crosslinking through the C_4-photocycloaddition of 3,4- and 4',5'- double bond of psoralen with the 5,6-double bond of the pyrimidine bases, especially thymine, in DNA is suggested for the cause of photosensitization.[7~10]

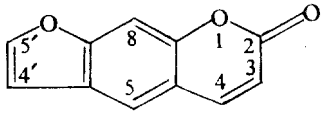
Attempts have been made to describe the phototoxicity of furocoumarins in terms of spectroscopic and theoretical calculations. Song *et al.*, have investigated the excited states of coumarins and psoralen derivatives.[11~14] Theoretical molecular orbital calculations have predicted that the triplet excited state is more likely candidate for the cycloaddition reaction than the singlet excited state. This prediction is consistent with the finding[15] that oxygen and paramagnetic ions quench the photoreaction between psoralen and thymine.

From the theoretical and experimental results,[16~18] a mechanistic model for the carcinogenic reaction in which carcinogenophore contributes to the stabilization of the psoralens is postulated in our work. According to this model, a theoretical index which corresponds to the sum of frontier electron density of the psoralens is adopted for explaining the carcinogenic activity and charge transfer interactions.

Calculations

The chemical reactivity indices, frontier electron density, and superdelocalizability as described in the previous papers[19,20] were applied to photo-skinsensitizing psoralens. The calculation is to show how the carcinogenic activity can be explained theoretically in the framework of a frontier orbital method[21] which has provided a basis for explaining several aspects of charge transfer interactions.

The parameters[22] in this calculations were obtained from Pullman's value and frontier molecular orbitals and charge transfer quantity were calculated for both the psoralens and DNA bases and for their pair complexed forms with HEWLETT PACKARD-3000 computer. The numbering scheme for non-hydrogen atoms is given below for the psoralen.



Results and Discussion

Results of calculations are summarized in Table 1, where frontier electron density, $F_p^{(N)}$ is the principal carcinogenophore, $F_s^{(N)}$ is the subsidiary carcinogenophore, and $F_t^{(N)}$ is the total carcinogenophore $(F_t^{(N)}=F_p^{(N)}+F_s^{(N)})$ of psoralens.

In Table 1, the chemical reactivity index, frontier electron density, can be used as a measure of the relative reactivity of the various positions of the psoralens. A theoretical index which corresponds to the sum of frontier electron density of the principal and subsidiary carcinogenophore is adopted to explain the photo-skinsensitizing carcinogenic activity.

It was found that this index has a good correlation with photo-skinsensitizing carcinogenic activity. The optimum value of theoretical indices was found to be approximately 0.33. The indices of many kinds of organic compounds such as polycondensed aromatic compounds and hetero-aromatic compounds such as azaaromatic compounds and 4-dimethylaminoazobenzene and related compounds were reported and compared with theoretical index (0.5).[23]

The theoretical indices indicate that psoralen, 8-methoxypsoralen, 5-methoxypsoralen, 4,5,8-trimethylpsoralen are active carcinogens, while pseudopsoralen, isopsoralen,

TABLE 1. The Frontier Electron Densities of Photo-Skinsensitizing Psoralens

Psoralens	$F_p^{(N)}$	$F_t^{(N)}$	Carcinogenic activity
Pseudopsoralen	0.2194	0.2881	Inactive
Isopsoralen	0.2549	0.3236	Inactive
Psoralen	0.3274	0.3961	Active
8-Methoxypsoralen	0.2978	0.3413	Active
5-Methoxypsoralen	0.3194	0.3629	Active
4, 5, 8-Trimethylpsoralen	0.8024	0.9934	Active
Furanochromone	0.0767	0.1998	Inactive

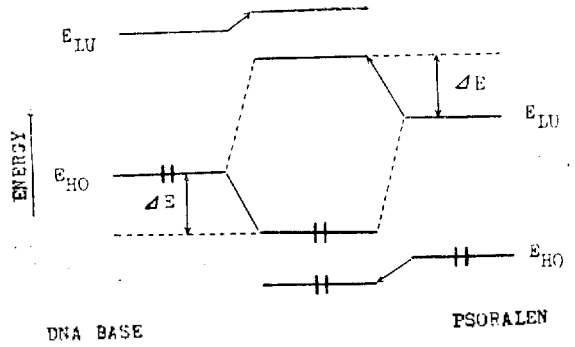


Figure 1. The interaction of a donor DNA base with an acceptor, psoralen.

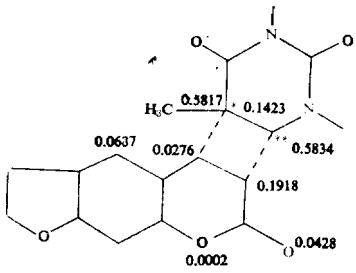


Figure 2. Charge transfer interaction in the hypothetic molecular complex, between DNA and psoralen. *structure of I, **structure of II. *The numbers refer to the frontier electron densities for electrophilic reaction.*

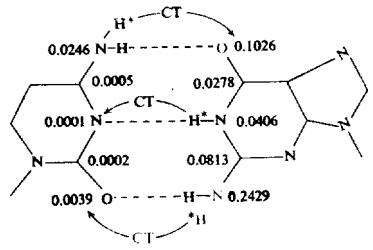


Figure 3. Charge transfer interactions between hypothetic base pairs in DNA. CT: charge transfer. *The numbers refer to the frontier electron densities for electron densities for electrophilic reaction.*

furanochromone are inactive carcinogens. From these prediction the calculated optimum value for psoralens are in good agreement with the experimental results.[24]

In the FMO approximation, only the nucleophile HOMO ($F_r^{(N)}$) and electrophile LUMO ($F_r^{(E)}$) which are closest in energy are taken into account. The difference in the stabilization energy ΔE may be considered to reflect the difference in the activation energies, as illustrated in Figure 1.

Charge transfer interactions in hypothetic molecular complex are shown in Figures 2, 3. The chemical evidence for C_4-photocycloaddition product between psoralens and pyrimidine bases is scarce. Musajo *et al.*[24] have isolated non-fluorescent photo-addition products of psoralen and pyrimidine bases from aqueous or frozen aqueous solutions after irradiation with 365 nm uv light.

They proposed these products to be C_4-cycloaddition products of both the pyrone and the furan double bonds

TABLE 2: The Charge Transfer Quantity From DNA Bases to Psoralens

Psoralens	Adenine	Guanine	Thymine	Cytosine
Pseudopsoralen	0.0440	0.1699	0.0793	0.1011
Isopsoralen	0.0646	0.1416	0.0753	0.1466
Psoralen	0.0703	0.1547	0.0914	0.1540
8-Methoxypsoralen	0.0461	0.1004	0.0818	0.1138
5-Methoxypsoralen	0.0611	0.1368	0.0777	0.1466
4,5,8-Trimethylpsoralen	0.1442	0.3044	0.2593	0.3398
Furanochromone	0.0460	0.0877	0.0768	0.0890

TABLE 3: The Charge Transfer Quantity from Base Pairs in DNA to Psoralens

Psoralens	A/A=T	T/A T	G/G≡C	C/G≡C
Pseudopsoralen	0.0006	0.0906	0.0752	0.0033
Isopsoralen	0.0004	0.1396	0.0734	0.0051
Psoralen	0.0006	0.1527	0.0877	0.0056
8-Methoxypsoralen	0.0007	0.0993	0.0761	0.0037
5-Methoxypsdralen	0.0006	0.1349	0.0738	0.0050
4,5,8-Trimethylpsoralen	0.0020	0.3010	0.2442	0.0111
Furanochromone	0.0001	0.0867	0.0762	0.0028

of furocoumarins to the 5,6-double bond of the pyrimidine bases. By irradiation of an aqueous solution of psoralen and thymine, only photoproducts corresponding to the structures of I and II are formed.[25]

The increase in the frontier electron densities in the intermolecular region originates from the overlapping of the occupied molecular orbitals of psoralen and the unoccupied molecular orbitals of DNA base. The approximate stabilization energy, superdelocalizability is therefore greater when charged nucleophile are involved.

In Table 2 and 3, charge transfer quantities from DNA bases or base pairs in DNA to psoralens are shown. Table 2 gives the charge transfer quantities in hypothetic molecular complex of DNA and psoralens and they are in the order of guanine, cytosine>thymine>adenine.

Table 3 shows that the frontier electron densities in the carcinogenic region between psoralens and adenine-thymine pair increase by the charge transfer interaction. The thymine of adenine-thymine pair is more strongly bound than the adenine in hypothetic molecular complex. While the guanine of guanine-cytosine pair is more strongly bound than the cytosine.

If the charge transfer interaction in hypothetic molecular complexes between the psoralens and the tissue components is the first step of the photo-skinsensitizing carcinogenesis, the most probable orientation between the psoralens and adenine-thymine pair (A=T) or guanine-cytosine pair (G≡C) can be derived from the above calculations.

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