

## Theoretical Studies on the Photochemical Reaction of Psoralen with Purine and Pyrimidine Base

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The spectroscopic studies of the 5,7-dimethoxycoumarin(5,7-DMC) and 4,5',8-trimethylpsoralen(TMP) and the conformational stability of 5,7-DMC-thymidine, 4,5',8-TMP-thymine were carried out by the CNDO/S and molecular mechanics calculation. Theoretical transition energies and direction of polarizations calculated by the CNDO/S method have been used for the interpretation of the observed results. The calculated absorption spectra of 5,7-DMC are qualitatively similar to experimental ones with their characteristic visible bands. MM2 force field calculation on the possible C<sub>4</sub>-cyclophotoadducts formed between 5,7-DMC and thymidine through a cycloaddition of C<sub>3</sub>, C<sub>4</sub> bond of 5,6-DMC to C<sub>5</sub>, C<sub>6</sub> bond of thymidine showed the most stable photocycloadduct to have the *anti*-head to tail configuration. The major photoadduct of 4,5',8-TMP-thymine has the *cis-anti* configuration.

### Introduction

Psoralens are known to photoreact with pyrimidine bases in DNA upon irradiation with near UV light producing skin erythema, and lethal and mutagenic effects in bacteria.<sup>1-3</sup>

The biological activity of psoralen is primarily due to the result of the covalent bonding they undergo with nucleic acids. This process is believed to involve three major steps: (1) noncovalent intercalative binding to the DNA helix, (2) formation of monoaddition product between the psoralen and DNA base upon long-wavelength ultraviolet irradiation and (3) absorption of a second photon by some monoadducts to form diadducts, which result in interstrand cross-links.<sup>4</sup>

The molecular orbital calculations predict that the triplet excited state is the better condition for the cycloaddition reaction than the singlet excited state. The photoreaction of 5,7-DMC with only one photochemically reactive functional group(pyrone double bond) with thymidine has been reported as a model reaction in order to elucidate the stereochemistry of photoadducts.<sup>5</sup>

4,5',8-TMP is known to be highly photoreactive bifunctional furocoumarin to the nucleic acid. The relative rates of the photoaddition of 4,5',8-TMP to DNA is about eight times higher than that of psoralen in aqueous system, higher due in part to the high quantum yield and to higher absorbance quantum yield and to higher absorbance at the exciting wavelength.<sup>6</sup> The skin sensitizing potency of psoralens has been correlated with their photoreactivity toward pyrimidine bases of DNA *via* cycloaddition.<sup>7-9</sup>

In this paper, we describe the spectroscopic studies of the 5,7-DMC, 4,5',8-TMP and the conformational stability of 5,7-DMC-thymidine, 4,5',8-TMP-thymine photocycloadducts.

### Calculation

The electronic transition energies were calculated by the CNDO/S calculation.<sup>10</sup> In the hypothetical molecular complexes, the chemical reactivity index can be used as a measure of the relative reactivity index of the various position of the photocycloaddition.

Molecular mechanics calculations were performed by using

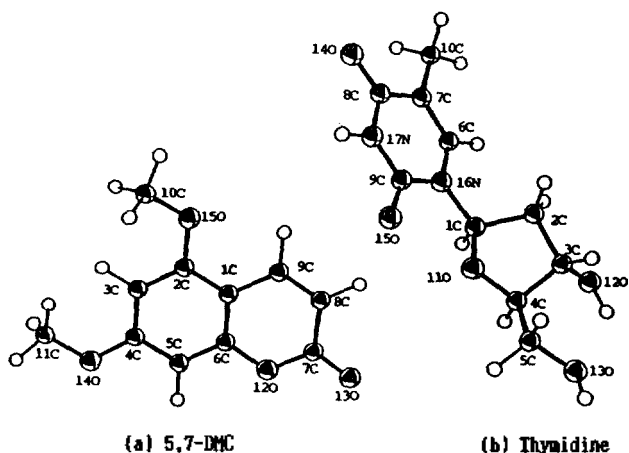


Figure 1. The numbering scheme of 5,7-DMC and thymidine for calculation.

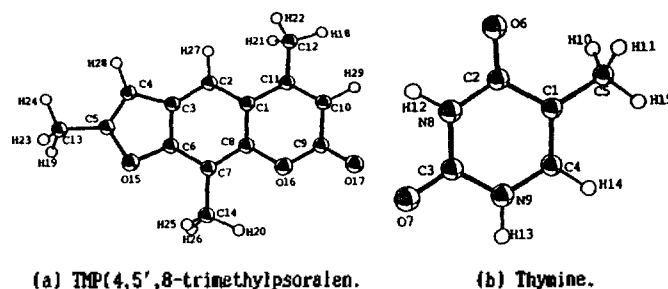


Figure 2. The numbering scheme of TMP and thymine.

MM2 force field and BDNR method as a minimum algorithm.<sup>11,12</sup> The numbering scheme for heavy atoms for 5,7-DMC, thymidine and 4,5',8-TMP, thymine photocycloadducts are shown in Figure 1, 2.

### Results and Discussion

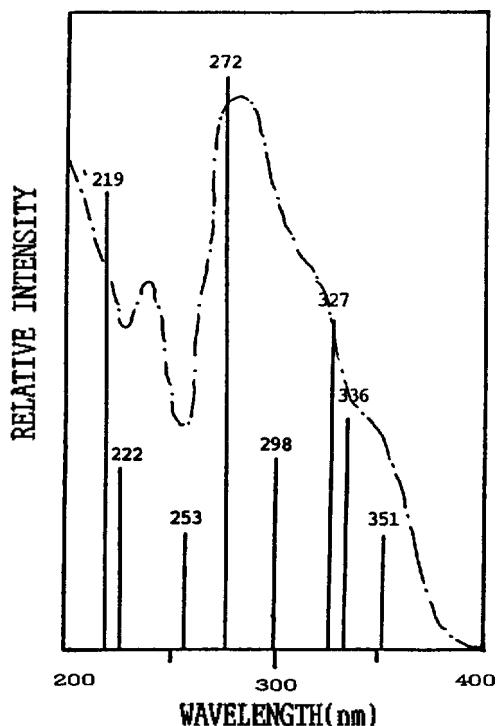
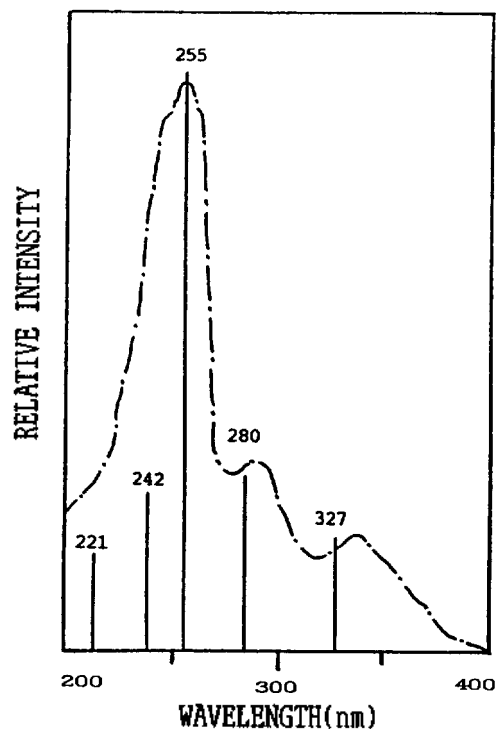
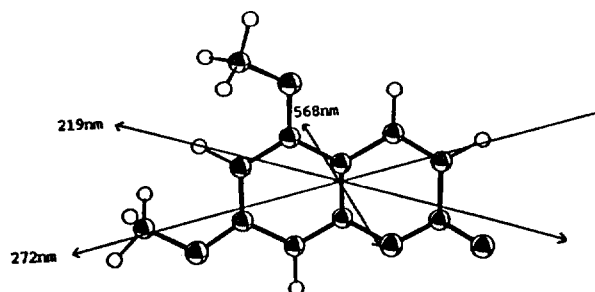
The spectral data of the 5,7-DMC are compared with the results obtained from the oscillator calculation. Oscillator st-

**Table 1.** The CNDO/S Calculation of Excite State Arising from Low Energy Configuration for 5,7-DMC

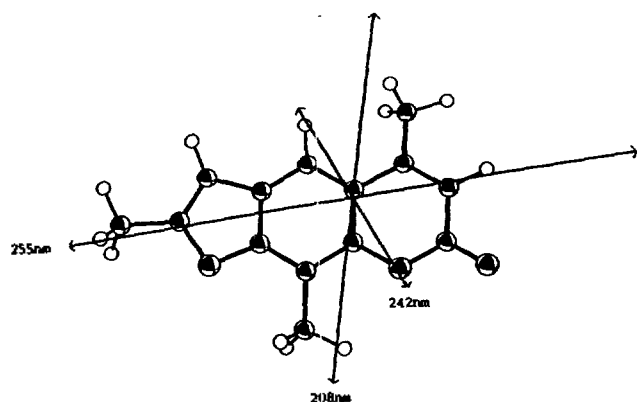
Configuration	Energy(nm)	Transition moment	Oscillator strength
29-40	568	1.569	0.132
30-40	425	1.228	0.108
32-40	351	1.483	0.190
33-40	336	2.138	0.413
34-40	327	2.648	0.650
34-41	298	1.908	0.372
35-42	272	3.379	1.277
36-40	253	1.510	0.274
37-40	222	1.898	0.492

**Table 2.** The CNDO/S Calculation of Excite State Arising from Low Energy Configuration for 4,5',8-TMP

Configuration	Energy(nm)	Transition moment	Oscillator strength
37-44	327	0.957	0.085
38-44	280	0.427	0.020
38-45	255	3.548	1.497
40-44	247	0.363	0.016
40-46	242	1.567	0.308
41-44	221	0.885	0.108
41-45	212	0.435	0.027
42-45	208	1.951	0.555
42-46	202	0.600	0.054
42-47	201	0.653	0.064

**Figure 3.** Calculated UV transition energy with correction energy for 5,7-DMC by CNDO/S calculation (---: experiment, —: calculation).**Figure 4.** Calculated UV transition energy with correction energy for TMP by CNDO/S calculation (---: experiment, —: calculation).**Figure 5.** Polarization of transitions predicted by CNDO/S calculation for 5,7-DMC (the transition lengths mean relative intensity of transition moment).

length,  $f$ , is used quantitatively to indicate the relative intensity of various transitions, primarily in the visible UV and vacuum UV region. Table 1, 2 and Figure 3, 4 show theoretical predictions of the transition energies and absorption spectrum of 5,7-DMC, 4,5',8-TMP respectively. The oscillator strength is directly proportional to the integrated area corresponding to an absorption band. Absorption spectra were resolved by Gaussian curve analysis. Peak areas in the near UV region were determined by multiplying the area under the curve from max of UV region to the longer wavelength region by two. A good agreement between the predicted and observed transition energies can be seen. The lowest  $\pi \rightarrow \pi^*$  transition is polarized nearly along the long molecular axis in Figure 5, 6 but it is mainly localized in the pyrone ring. 5,7-DMC exhibits  $\lambda_{max}$  at 272 nm<sup>13</sup> where as 4,5',8-TMP shows blue shifts of this band to 255 nm. This behavior



**Figure 6.** Polarization of transitions predicted by CNDO/S calculation for 4,5',8-TMP (the transition lengths mean relative intensity of transition moment).

**Table 3.** The Results of Molecular Mechanics Calculation for Possible Photocycloadducts of 5,7-DMC < > Thymidine (in Kcal/mol)

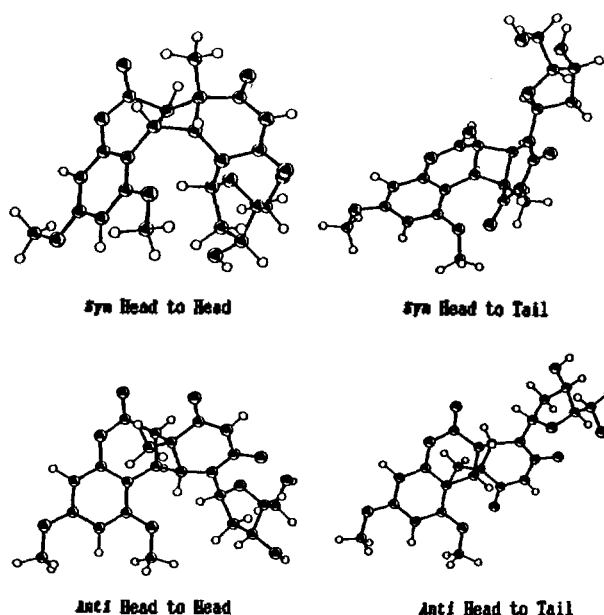
Conformation	$E_{total}$	$E_{torsion}$	$E_{strain}$	$\Delta H_f$
<i>Syn</i> -H,H	112.972	46.133	91.202	-314.151
<i>Syn</i> -H,T	60.494	37.853	38.924	-365.831
<i>Anti</i> -H,H	56.204	34.496	34.434	-371.043
<i>Anti</i> -H,T	54.602	34.886	32.832	-372.660

is reconcilable in terms of CNDO/S results, which include the highering of the  $f$  value for the first band and the alternation of the polarization direction from near long axis in 5,7-DMC to near short axis in 4,5',8-TMP. These differences are due to a significant gap between the low lying ( $\pi$ ,  $\pi^*$ ) and ( $n$ ,  $\pi^*$ ) singlet states in 5,7-DMC. Configuration analysis of the  $S_1(\pi$ ,  $\pi^*)$  state of 5,7-DMC suggests that this state possesses significant charge transfer character in the  $C_3$ ,  $C_4$  bond of the pyrone ring. Thus the singlet excited state becomes electron-rich at the  $C_3$ ,  $C_4$  bond, relative to the ground state, as the  $C_3$ ,  $C_4$  bond becomes photochemically reactive and the most reactive position of thymidine is predicted at  $C_5$ ,  $C_6$ .

Relative conformational energies and geometries for 5,7-DMC with thymidine appear to be affected by the reactive position. The photocycloaddition of a thymidine to a 5,7-DMC generates a cyclobutane ring with four asymmetric centers. This photocycloaddition can occur in either a *syn* or *anti* configuration, where *syn* refers to a configuration where the  $C_5$ ,  $C_6$  position of the thymidine and the  $C_3$  or  $C_4$  position of the 5,7-DMC are at diagonally opposed corners of the cyclobutane ring. *Anti*, then refers to a configuration where the  $C_5$ ,  $C_6$  position of the thymidine is adjacent to either the  $C_3$  or  $C_4$  position of the 5,7-DMC.

The results of molecular mechanics calculation for possible photocycloadducts of 5,7-DMC with thymidine are shown in Table 3 and Figure 7. In all cases, rotations about the 5,7-DMC with thymidine bond were investigated in order to locate the lowest energy conformation.

The calculated heats of formation and the energies given in Table 3 refer to the stable conformer for possible photocy-



**Figure 7.** Stereo ORTEP drawing of molecular configuration of the possible photocycloadducts of 5,7-DMC < > Thymidine.

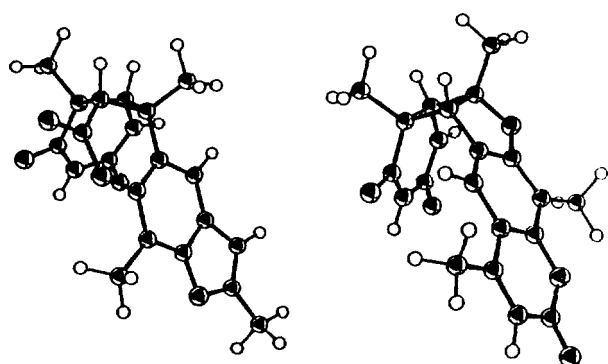
**Table 4.** The Results of Molecular Mechanics Calculation for Possible Photocycloadducts of TMP < > Thymine (in Kcal/mol)

Conformation	$E_{total}$	$E_{torsion}$	$E_{strain}$	$\Delta H_f$
$C_3$ , $C_4$ <i>trans-anti</i>	27.438	19.339	19.968	-220.218
of <i>trans-syn</i>	28.443	20.169	20.973	-219.277
TMP <i>cis-anti</i>	28.050	19.488	20.580	-220.415
<i>cis-syn</i>	26.958	17.813	19.488	-221.429
$C_4'$ , $C_5'$ <i>trans-anti</i>	26.691	25.418	19.751	-220.311
of <i>trans-syn</i>	30.923	25.546	20.983	-219.157
TMP <i>cis-anti</i>	28.402	25.377	18.461	-221.419
<i>cis-syn</i>	30.502	25.447	20.562	-219.501

cloadducts. The heats of formation are calculated in the range -314 Kcal/mol ~ -372 Kcal/mol. For the *anti* configuration, the *anti*-head to tail was found to have the lowest energy and the *anti*-head to head form has 1 Kcal/mol higher energy. The *anti*-head to tail form was calculated to be most stable structure for the photocycloaddition of 5,7-DMC with thymidine.

Kanne *et al.* investigated the photoreaction of 4,5',8-TMP with DNA, in which *cis-syn* furan side monoadducts was isolated as a major product.<sup>14</sup> It is interesting that 4,5',8-TMP showed a preference of furan side addition over pyrone side addition. 4,5',8-TMP has also been reported to give  $C_4$ -photodimers on UV irradiation in dioxane solution and in the solid state.<sup>15</sup>

Table 4 and Figure 8 show the results of molecular mechanics calculation for the possible monofunctional cycloaddition for 4,5',8-TMP with thymine. Dihedral drive calculations were indicative of the torsion angle allowing minima at  $60^\circ$  and  $270^\circ$ . This torsional preference is also borne out experimentally.<sup>16</sup> It is general that the number and approximate location of energy minima are less sensitive to the force



(a)  $\text{TMP}(3,4)\langle \text{Thy. } \underline{\text{cis-syn}} \rangle$  (b)  $\text{TMP}(4',5')\langle \text{Thy. } \underline{\text{cis-anti}} \rangle$

**Figure 8.** Stereo ORTEP drawing of molecular conformation of photocyclo adducts of  $\text{TMP}\langle \text{Thymine} \rangle$ .

field than their energies.

In Table 4 compare eight photocycloadducts, *cis-syn* conformation for 4,5',8-TMP's pyrone ring and *cis-anti* conformation for 4,5',8-TMP's furan ring with thymine are most profitable to formation, stereo ORTEP drawing for these two conformers are given in Figure 6. The *cis* conformation found for the model adduct is that which might be expected from the position of intercalation of 4,5',8-TMP with thymine which is often assumed.<sup>1</sup>

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## Transformation of Bicyclic Ketal Compound to 1,2-Cyclopentanediol via 1,5-Diketone

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New method for preparing cyclopentanediol from bicyclic ketal is described. Bicyclic ketal is cleaved to give 1,5-diketone, which is then reductively coupled intramolecularly to yield 1,2-cyclopentanediol. A solution of bicyclic ketal (**1a**) in methylene chloride was treated with aluminum chloride(2 eq.)-sodium iodide(1.5 eq.) at ambient temperature for 3 h to give the 1,5-diketone (**2a**) in 71% yield after basic work-up followed by short path column chromatography. A solution of the 1,5-diketone (**2a**) in THF was reacted with titanium tetrachloride(6 eq.)-Mg(Hg)(0.3 eq.) at 0°C for 4 h to give the 1,2-cyclopentanediol (**3a**) in 75% yield after basic work-up followed by short path column chromatography.

## Introduction

There has been an increased interest in methods for form-

ing cyclopentane ring systems, reflecting the increasing number of natural products known to incorporate such ring systems as a major structural entity.<sup>1</sup>