

CONFORMATIONAL ANALYSIS ON THE C₄-PHOTO- CYCLODIMERS OF 4,5',8-TRIMETHYLPSORALEN

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Abstract — A semiempirical methods (PM3-CI-UHF, MM2) for the evaluation of ground and excited state electronic structures of electron-donating substituents are applied to 4,5',8-trimethylpsoralen (TMP) with TMP dimer. Three types of product have been proposed; (1) pyrone < > pyrone, (2) pyrone < > furan, (3) hetero dimer resulting from the C₄-cycloaddition between the furan end of one TMP moiety and the pyrone end of the other, with *cis-syn* configuration.

INTRODUCTION

Natural occurrence of 4,5',8-trimethylpsoralen (TMP) has been reported in celery diseased with the fungus sterotina¹, but no other natural source has been reported. TMP is known to be highly photoreactive bifunctional furocoumarin to the nucleic acid.

Kanne et al. investigated the photoreaction of TMP with DNA, in which *cis-syn* furan side monoadduct was isolated as a major product.² It is interesting that TMP showed a preference of furan side addition over pyrone side addition. TMP has also been reported to give C₄-photodimers on UV irradiation in dioxane solution and in the solid state.³ The dimerization reaction monitored by UV spectroscopy and melting point measurements proved the formation of more than one photoproduct both in the solid phase and in solution.⁴

In this paper, we have calculated the electronic structure of excited states by PM3-UHF-CI and molecular structure and conformational analysis of the C₄-photocyclodimers of TMP by the Molecular Mechanics (MM) calculations.

Electron-donating substituents, such as methyl as in 4,5',8-trimethylpsoralen (TMP) raise the ¹(n, π*) and thus enhance the photoreaction by way of the singlet state due to a weakening the vibronic interaction between ¹(n, π*) and ¹(π, π*) states.

CALCULATIONS

In molecular mechanics, a molecule is considered to be a collection of atoms held together by elastic and harmonic forces. These forces can be described by potential energy functions of structural features like bond lengths, bond angles, nonbonded interaction, and so on. The combination of these potential energy function is the force field.^{5,6} Molecular mechanics calculations were performed by using MM2 force field and BDNR method as a minimum algorithm.^{7,8} The optimized structures of each excited states of TMP were calculated by using PM3 an unrestricted Hartree-Fock wave function (UHF) and the energies and coefficients were estimated by the CI method.

RESULTS AND DISCUSSION

The results of photocyclodimers of TMP are summarized in Table 1. In the excited state, the estimated energy and coefficients of higher singly occupied molecular orbital (HSOMO) and lower singly occupied molecular orbital (LSOMO) by means of the PM3-UHF-CI method and in the ground state by PM3 method the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are shown in Table 1. As the photocyclodimers were sensitized by some excited states, they were inferred to go through photocycloaddition path, and that this steps were mainly influenced by coefficients and energies of the frontier orbitals, respectively. The electronic factors consist of the degree of local excitation and the electron density at the 3,4 and 4',5' double bond in the excited state. They exhibited the significant differences. The 3,4

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double bond of pyrone is locally excited in the triplet state, not observed in the 4',5' double bond. The calculation results of the electron density in these excited states of TMP show that the 3,4-double bond has more charge transfer character than the 4',5'-double bond.

Table 1. The estimated energy and coefficients of the lowest triplet HSOMO and LSOMO, and ground LUMO and HOMO by PM3-UHF-CI calculation

ATOM	LUMO	HSOMO	LSOMO	HOMO
C3	-0.4748	-0.2581	0.0137	0.1020
C4	0.4588	0.2471	-0.0534	-0.0099
C5	-0.4577	-0.5657	0.4270	-0.3217
C4'	0.1358	0.1967	-0.2868	0.3490
C5'	-	-0.3071	-0.3586	-
Energy (eV)	-0.9235	-3.6775	-6.7122	-9.0458

Relative conformational energies and geometries for TMP appear to be affected by the position of the pyrone and furan moieties. All of the TMP dimers we have studied to date showed a considerable preference for the pyrone or furan to be pseudo-equatorial in the energy minimized conformations. The geometries of TMP was optimized starting from the probable bond angles, bond length and dihedral angles by the PM-3 UHF² calculation.

In order to provide some insight into the geometry of the photocyclodimers, MM2 calculations were carried out on the possible photocyclodimers with proper arrangement for geometry optimization and results are summarized in Table 2 and Figure 1.

Based on the Figure 1, it has been suggested that the triplet state photoreactivity resides with the pyrone moiety rather than with the furyl group. Namely, spin density accumulates at position C3 and C4 and the C3-C4 bond order decreases, thus lengthening the C-C double bond in the triplet state.

Table 2 shows all the possible stereoisomers of TMP C₂-photocyclodimers. The photocyclodimerization between pyrone and furan can produce three different types of stereoisomers; pyrone< >pyrone and furan< >furan homodimer, pyrone< >furan-pyrone< >furan and pyrone< >pyrone-furan< >furan bicyclomer, and furan< >pyrone heterodimer. The proposed structure is further supported by the NOE experiments⁹. 3-H, 4'-H and 5-H show a NOE enhancement when 4-CH₃ and 5'-CH₃ are irradiated. The 4-CH₃ and 5'-CH₃ also show a weak NOE enhancement when each of 3-H or 4'-H is irradiated.

Table 2. The interaction energy and heats of formation for TMP photocyclodimers (in kcal/mol)

Formation	E _{total}	E _{isom}	E _{stabil}	ΔH _f
Pyrone<>Pyrone				
cis-anti	72.166	24.177	62.666	-178.653
cis-syn	76.545	30.570	67.045	-173.563
trans-anti	73.089	24.633	63.589	-178.122
trans-syn	73.961	21.670	64.461	-177.211
Pyrone<>furan				
cis-anti	74.177	29.398	62.207	-178.743
cis-syn	77.567	35.690	65.656	-174.505
trans-anti	78.144	30.763	66.174	-172.926
trans-syn	75.583	29.563	63.613	-177.012
Furan<>Furan				
cis-anti	76.786	35.593	62.346	-176.670
cis-syn	81.618	41.152	66.178	-168.605
trans-anti	78.359	35.124	63.919	-175.952
trans-syn	79.560	34.977	64.119	-173.253
Py<>Py-Fu<>Fu	126.082	60.563	97.482	-164.502
Py<>Fu-Py<>Fu	114.339	54.344	96.739	-176.647

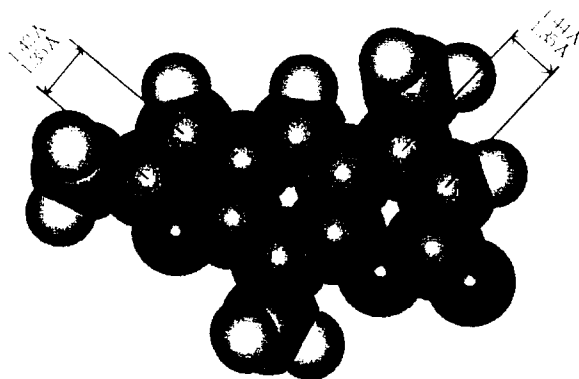


Figure 1. The optimized geometry for the excited states by the PM3-UHF calculation. upper value is triplet state and below is singlet state.

It is general that the number and approximate location of energy minima are less sensitive to the force field than their energies. The possible stereoisomers of photodimerization are shown in Figure 2. In the TMP C₂-cyclodimerization, the heats of formation are observed in the range -164kcal/mol ~ -178kcal/mol for homo and hetero dimers.

On the basis of the structure of TMP dimers

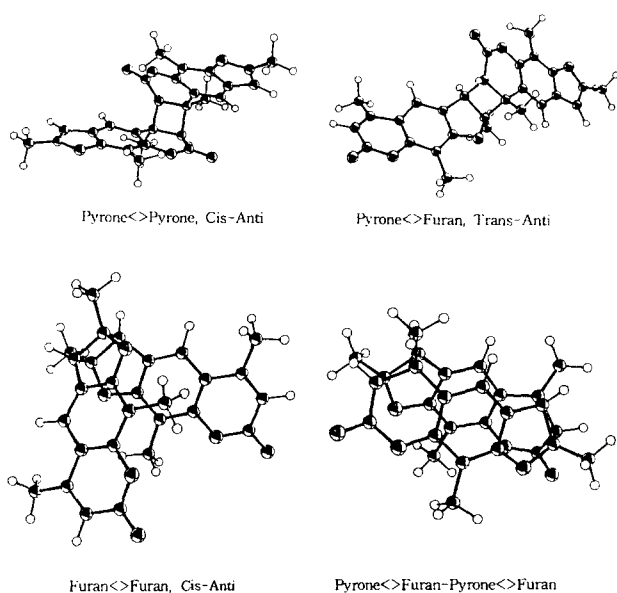


Figure 2. Stereo ORTEP drawing for possible molecular conformation of TMP Photocyclodimers.

quantum mechanical studies have allowed us to get a better understanding of the photochemistry of psoralen dimers.

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