

Ab initio Calculation for Photochemistry of Psoralen Derivatives

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Received April 26, 2011, Accepted June 9, 2011**Key Words** : *Ab initio*, C₄-cycloaddition, Thy<>5-MOP<>Thy

Psoralens (Ps)* are a class of heterocyclic aromatic compounds that have been extensively utilized in the photochemotherapy of skin disorders such as psoriasis and vitiligo,^{1,2} cutaneous T-cell lymphoma.³ On exposure to ultraviolet light, especially in the range of 320-400 nm, psoralens form chemical crosslinks to the DNA bases in the three steps.⁴⁻⁸ The first step is intercalation of psoralen between to adjacent base-pairs. The second step is formation of monoadduct; that is one psoralen molecule photo-react with one strand of DNA. The third step is the cross-linking of the same psoralen molecule to the other strand of DNA, thus covalently linking the two strand of a double stranded DNA.

Psoralens have two photochemical reaction sites, 3,4-pyrone double bond and 12,13-furan double bond, both of which are engaged in cross-linking of DNA bases. The formation of interstrand cross-linking through C₄-cycloaddition of 3,4- and 12,13-double bonds to the 5,6-double bond of the pyrimidine bases, especially thymine, in DNA has been correlated with the biological effects of photo-excited psoralens.

Binding of Ps to DNA⁹ is generally the consequence of two successive events¹⁰ (1) intercalation into DNA between the base pairs; and (2) photocycloaddition reaction of 3,4-Pyrone double bond and/or 12,13-furan double bond with 5,6-double bond of thymine.

Although several photoproducts of purine bases from direct and photosensitized irradiation of purines are known,¹¹ the photoaddition reaction between the excited psoralens and purine bases are not well understood.

In the present paper, we report that the formation of interstrand cross-linking through C₄-cycloaddition of 3,4- and 12,13-double bonds to the 5,6-double bond of the pyrimidine bases, especially thymine, in DNA is calculated by the *ab initio* method.

The molecular geometries are optimized at HF levels of theory with the 6-31G* basis set by using the Gaussian 03 program.¹²

The 6-31G* optimizations of the final structures are done to include the effect of electron correlation and the basis set with polarization function.

The photosensitization activity of psoralens is generally correlated to their photoreactivity with pyrimidine bases in

DNA.

The cross-linkage is caused by the formation of cyclobutane adducts, which are produced by photoreactions of the psoralen 3,4-pyrone and 12,13-furan double bonds to two pyrimidine bases.

The association energies for photocycloadduct (ΔE) are obtained by subtracting the sum of the energies of the 5-MOP and two thymine from the energy of the full optimized photocycloadduct.

$$\Delta E = \{E(\text{Thy} \langle \rangle (3,4)5\text{-MOP}(12,13) \langle \rangle \text{Thy})\} - \{E(5\text{-MOP}) + E(\text{Thy}) \times 2\}$$

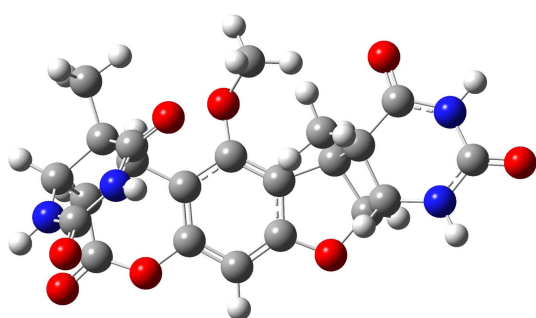
Gibbs free energies (ΔG°) for structures involved in 5-MOP, thymine and photocycloaddition paths are calculated by following equation.

$$\Delta G^\circ = \{\Delta G^\circ_f(\text{Thy} \langle \rangle (3,4)5\text{-MOP}(12,13) \langle \rangle \text{Thy})\} - \{\Delta G^\circ_f(5\text{-MOP}) + \Delta G^\circ_f(\text{Thy}) \times 2\}$$

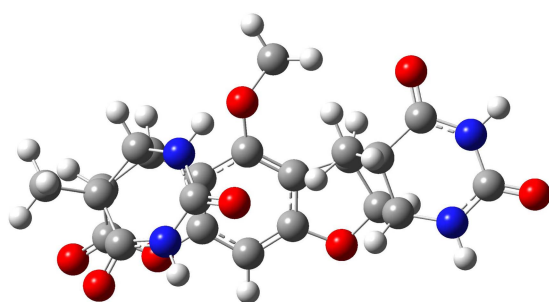
The association energies for photocycloadducts of Thy<>(3,4)5-MOP(12,13)<>Thy are summarized in Table 1.

Table 1. Energy and Gibbs free energy of Thy<>(3,4)5-MOP(12,13)<>Thy at HF/6-31G* level
(1 Hartree = 4.3597482 × 10⁻¹⁸ J/mol = 627.5095 kcal/mol)

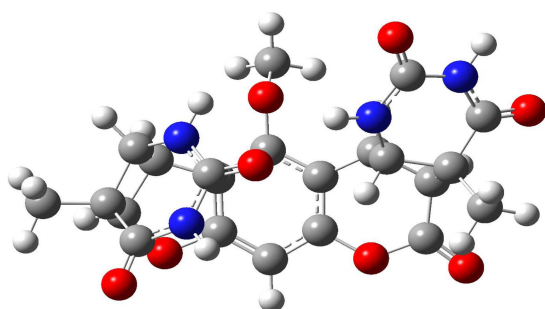
Photocycloadducts	E (Hartree)	ΔG°_f (Hartree)	ΔE (kcal/mol)	ΔG° (kcal/mol)
(<i>cis anti</i>)(<i>cis anti</i>)	-1660.736581	-1660.343760	28.053	61.247
(<i>cis anti</i>)(<i>cis syn</i>)	-1660.744099	-1660.349372	23.336	57.726
(<i>cis anti</i>)(<i>trans anti</i>)	-1660.748974	-1660.353979	20.277	54.835
(<i>cis anti</i>)(<i>trans syn</i>)	-1660.750743	-1660.355176	19.167	54.084
(<i>cis syn</i>)(<i>cis anti</i>)	-1660.745445	-1660.351619	22.491	56.316
(<i>cis syn</i>)(<i>cis syn</i>)	-1660.739044	-1660.346261	26.508	59.678
(<i>cis syn</i>)(<i>trans anti</i>)	-1660.742952	-1660.351247	24.056	56.549
(<i>cis syn</i>)(<i>trans syn</i>)	-1660.747089	-1660.352682	21.460	55.649
(<i>trans anti</i>)(<i>cis anti</i>)	-1660.750950	-1660.355593	19.037	53.822
(<i>trans anti</i>)(<i>cis syn</i>)	-1660.745803	-1660.351867	22.267	56.160
(<i>trans anti</i>)(<i>trans anti</i>)	-1660.743010	-1660.350093	24.019	57.273
(<i>trans anti</i>)(<i>trans syn</i>)	-1660.746736	-1660.354303	21.681	54.632
(<i>trans syn</i>)(<i>cis anti</i>)	-1660.748735	-1660.354303	20.427	54.632
(<i>trans syn</i>)(<i>cis syn</i>)	-1660.746427	-1660.351802	21.875	56.201
(<i>trans syn</i>)(<i>trans anti</i>)	-1660.745146	-1660.352907	22.679	55.508
(<i>trans syn</i>)(<i>trans syn</i>)	-1660.751893	-1660.357472	18.445	52.643



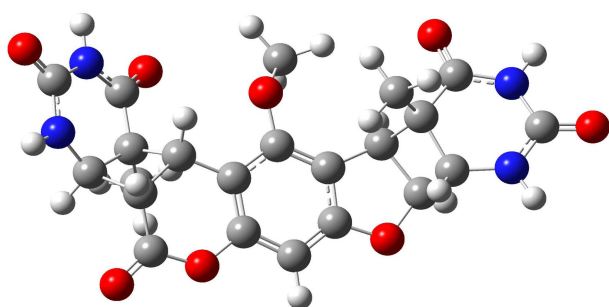
(*cis anti*)Thy<->(3,4)5-MOP(12,13)<->Thy(*trans syn*)



(*cis syn*)Thy<->(3,4)5-MOP(12,13)<->Thy(*trans syn*)



(*trans anti*)Thy<->(3,4)5-MOP(12,13)<->Thy(*cis anti*)



(*trans syn*)Thy<->(3,4)5-MOP(12,13)<->Thy(*trans syn*)

Figure 1. The four possible photocycloadducts photocycloadducts of Thy<->(3,4)5-MOP(12,13)<->Thy by HF/6-31G*.

of Thy<->(3,4)5-MOP(12,13)<->Thy are shown in Figure 1.

As shown in Table 1, there are four types of photoisomer, (*cis anti*)Thy<->(3,4)5-MOP(12,13)<->Thy, (*cis syn*)Thy<->(3,4)5-MOP(12,13)<->Thy, (*trans anti*)Thy<->(3,4)5-MOP(12,13)<->Thy, (*trans syn*)Thy<->(3,4)5-MOP(12,13)Thy cycloadducts.

The association energy (E) of these photocycloadducts in (*cis anti*)Thy<->(3,4)5-MOP(12,13)<->(trans *syn*)Thy structure is 19.167 kcal/mol. The Gibbs free energies (ΔG°) is 54.084 kcal/mol. This result indicate that the most probable photocycloadduct is (*trans syn*)Thy<->(3,4)5-MOP(12,13)<->Thy.

The ΔE and ΔG° for (*cis syn*)(*trans syn*) structures are 21.460 kcal/mol, 55.649 kcal/mol respectively. This tendency is similar to that obtained for the photocycloadducts for (*trans anti*)(*trans syn*) are 21.681 kcal/mol (ΔE), 54.632 kcal/mol (ΔG°) and (*trans syn*)(*trans syn*) are 18.445 kcal/mol(ΔE), 52.643 kcal/mol (ΔG°) respectively.

The optimized geometrical structures for possible photocycloadducts are shown in Figure 1. The most stable photocycloadduct is (*trans syn*), (*trans syn*), in Thy<->(3,4)5-MOP(12,13)<->Thy by HF/6-31G*.

Comparison of these energy values with available experiment shows that the photocycloaddition can explain the photocrosslink Thy<->Ps<->Thy completely. Therefore, this study will give a better understanding of the photocycloaddition reaction of psoralens derivatives with detailed molecular model.¹³

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