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## Semiempirical calculations in the prediction of regioselectivity of cyclopentenone [2+2] photocycloaddition

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### ABSTRACT

The [2+2] photocycloaddition of enone such as cyclopentenone to substituted chiral ethylene as alkene has been studied using semiempirical methods (AM1, PM3 and MNDO) were applied. The results showed that, the reaction occurs in the triplet state of enone and the ground state of alkene, also, we have deduced that the regioselectivity can be explained assuming that the [2+2] photocycloaddition reaction is frontier orbital controlled. © 2012 Trade Science Inc. - INDIA

### KEYWORDS

[2+2] Photocycloaddition;  
Regio- and stereoselectivity;  
Biradical intermediate;  
FMO theory;  
Semiempirical;  
*Ab initio* methods.

### INTRODUCTION

The [2+2] photocycloaddition has been a source of considerable interest for almost a century and it has been extensively investigated<sup>[1]</sup>. In addition, the general reaction pathway has often been used in the total synthesis of natural products<sup>[2-4]</sup>.

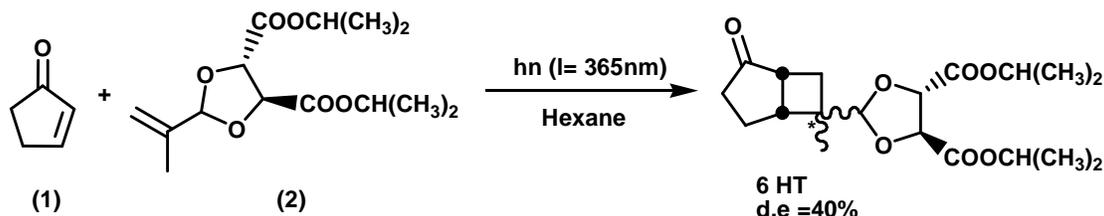
Beginning in the early 1960's with the work of De Mayo<sup>[5]</sup>, Eaton<sup>[6]</sup> and Corey<sup>[7]</sup> and continuing up to the present day<sup>[8,9]</sup>, numerous groups have explored synthetic applications and conducted mechanistic investigation of the photochemical cycloaddition reaction between alkenes and cyclopentenones and cyclohexenones to yield cyclobutane adducts.

Since the enone addition to alkenes to yield cyclobutanes is synthetically very useful, studies have been carried out in an attempt to direct the reaction towards regio- and stereoselective products. The general approach is to introduce a chiral center either on the enone, or on the incoming alkene frame

work<sup>[9]</sup>. Mechanistic studies have revealed much about the intermediates of the [2+2] photocycloaddition, but their high reactivity has made it difficult to control regio- and stereoselectivity<sup>[10,11]</sup>. Broecker<sup>[12]</sup> and al. have reported a UHF study of the regioselectivity of photocycloadditions of triplet acrolein to a variety of substituted alkenes and showed that in cases where cyclisation is fast relative to reversion of the biradical intermediate to reactants, the rates of initial bond formation determine the product regioselectivity of [2+2] photocycloaddition of acrolein to alkene using *ab initio* CASSCF calculations and the 6-31G\* basis set. Recently, Wilsey<sup>[13]</sup> and al have carried out detailed computational studies on the [2+2] photocycloaddition of acyclic enones (acrolein) to ethylene. The results indicate that transition states on both the triplet and ground state surfaces play a part in controlling product selectivity, are in accord with the experimental results of Weedon and co-workers.

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This paper presents a theoretical study of the [2+2] photocycloaddition reaction of cyclopentenone (**1**) to diisopropyl – D- (-) - tartrate modified ethylene methanoite (**2**). This theoretical approach based on the combination of the FMO theory with semiempirical [AM1, PM3 and MNDO] methods will be applicable for determining the regioselectivity observed.



The cyclopentenone (**1**) irradiation with the diisopropyl D-(-)-tartrate modified ethylene methanoite (**2**) using monochromatic lamp HPW 125W (365 nm) in the hexane conduct to addition product with 50% yield. Spectroscopy analysis of reaction product indicates that only regioisomer was obtained with diastereomeric excess (e.d) = 40% (see experimental part).

## METHODS AND COMPUTATIONS

Our calculations are carried out by using Pentium 133 MHz using Hyperchem 6.03 professional package<sup>[14]</sup>. We used the algorithm Polack- Ribiere (energy gradient = 0.01 kcal/mol.Å<sup>o</sup>). The geometric optimization of the structures was obtained by the semiempirical methods (AM1, MNDO and PM3). The electronic structure and the reactivity of reactants (**1**) and (**2**) have been calculated using AM1, PM3 and MNDO at restricted Hartree Fock (RHF) for ground states, and at unrestricted Hartree Fock (UHF) for triplet states.

## RESULTS AND DISCUSSION

According to authors<sup>[15,16]</sup>, in the photochemical reaction of cyclopentenone and alkyl- substituted alkenes, biradical intermediates, head-to-head (HH) and head-to-tail (HT) are formed by bonding of both the  $\alpha$  and  $\beta$  positions of the enone to the less substituted of the alkene

## EXPERIMENTAL RESULTS

Before describing our computational work, a summary of the experimental results of the enantioselective photocycloaddition of cyclopentenone to diisopropyl D-(-)-tartrate modified ethylene methanoite will be presented:

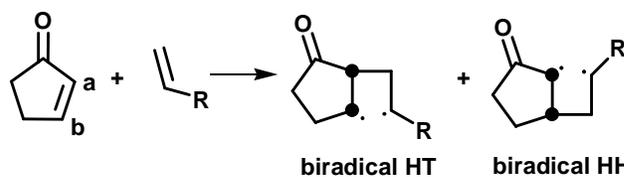


Figure 1 : The two possible biradical intermediates in the photoaddition of cyclopentenone to substituted alkene.

It has been concluded also, that the regiochemistry and stereochemistry of reaction products are determined by the rates of initial bond formation<sup>[12]</sup> or by the outcome of the competition between reversion to starting material and closure to product for each of the various intermediate biradicals which lead to each of the reaction products<sup>[13,17]</sup>.

In order to explain the observed selectivity during the formation of cyclobutane adduct, in a preliminary step, we have examined the regioselectivity by using frontier molecular orbital (FMO) theory. According to the FMO theory applied to the [2+2] photocycloaddition, the regioselectivity can be predicted from the interactions between the highest occupied molecular orbital (HOMO) of the alkene (**2**) in the ground state (GS) and the lowest singlet occupied molecular orbital (LSOMO) of the cyclopentenone (**1**) in the excited triplet state (T.S)<sup>[18,19]</sup>.

The favorite site in cyclopentenone for the photocycloaddition to the alkene (**2**) was analyzed by comparison the HOMO, the lowest unoccupied molecular orbital (LUMO), the highest singlet occupied molecular orbital (HSOMO) and LSOMO energies and orbital interactions (orbital coefficients). The electronic

structures have been calculated on the ground state for both reactants and on the triplet state for cyclopentenone and are presented in TABLE 1.

**TABLE 1 : HOMO, LUMO, HSOMO and LSOMO energies (e V) for cyclopentenone 1 and alkene 2.**

	Cyclopentenone		Alkene Ground state
	Ground state	Triplet State	
AM1			
HOMO	-10.41	-	-10.10
LUMO	-0.03	-	0.76
HSOMO	-	-8.64	-
LSOMO	-	-10.79	-
PM3			
HOMO	-10.44	-	-10.24
LUMO	-0.125	-	0.63
HSOMO	-	-8.68	-
LSOMO	-	-10.88	-
MNDO			
HOMO	-10.40	-	-10.21
LUMO	-0.12	-	-0.57
HSOMO	-	-8.93	-
LSOMO	-	-10.83	-

The information contained therein results performed at the UHF/ RHF level of theory by using (AM1, PM3 and MNDO) semiempirical methods.

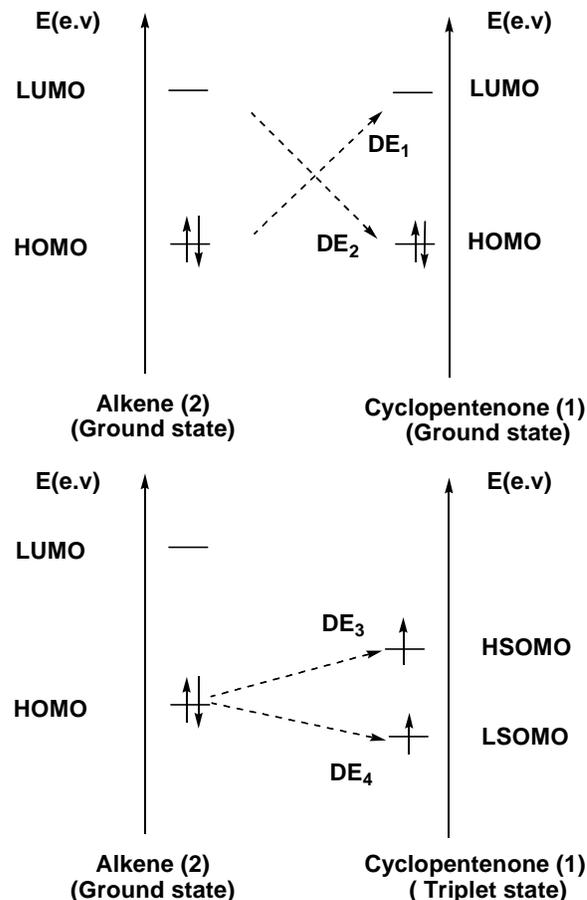
From these results, we found that the three semiempirical methods give approximately the same values and in each energetic state. From these values, we calculated the energetic differences between the orbital frontiers of the two molecules, in order to know the favorable state in the photoaddition to the cyclopentenone. The found energetic differences are illustrated in TABLE 2 as follows:

**TABLE 2 : Relative orbital energies (e.V) of cyclopentenone 1 and alkene 2 calculated using the semiempirical and *ab initio* methods<sup>(a)</sup>**

	Interaction A		Interaction B	
	$\Delta E_1$	$\Delta E_2$	$\Delta E_3$	$\Delta E_4$
AM1	10.06	11.17	1.46	0.69
PM3	10.11	11.07	1.56	0.63
MNDO	10.09	10.97	1.28	0.62

<sup>a</sup> Interaction A (ground state 1- ground state 2):  $\Delta E_1 = \text{LUMO}(1) - \text{HOMO}(2)$  //  $\Delta E_2 = \text{LUMO}(2) - \text{HOMO}(1)$   
Interaction B (triplet state 1- ground state 2):  $\Delta E_3 = \text{HSOMO}(1) - \text{HOMO}(2)$  //  $\Delta E_4 = \text{LSOMO}(1) - \text{HOMO}(2)$

$\Delta E_1$  and  $\Delta E_2$  present the frontier orbital interactions at the ground states between reactants;  $\Delta E_3$  and  $\Delta E_4$  are the frontier orbital interactions between cyclopentenone at the triplet state and the alkene (2) at the ground state (Figure 2).



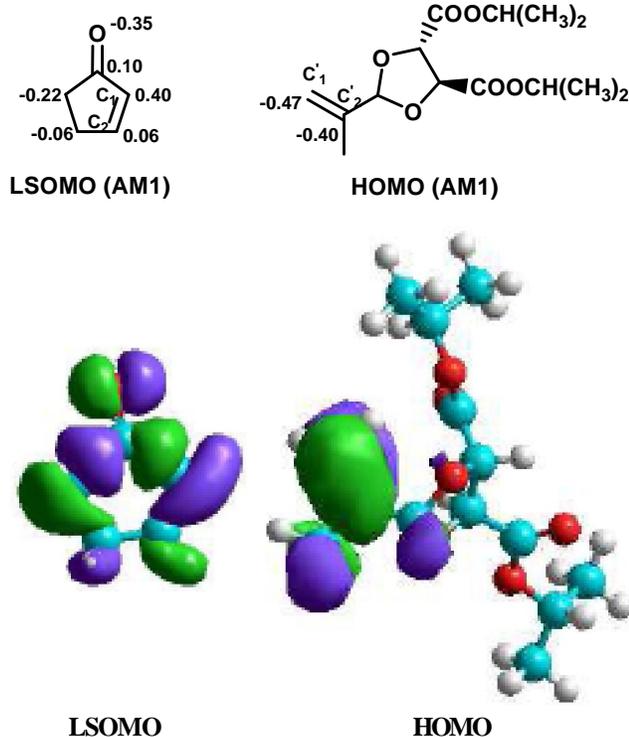
**Figure 2 : Molecular orbital of the [2+2] photocycloaddition of 1 to 2.**

As shown in TABLE 2, the energetic gap changes according to the cyclopentenone states:  $\Delta E_{\text{HOMO-LUMO}}(\text{GS}) > \Delta E_{\text{HOMO-LSOMO}}(\text{Triplet})$ . From these results and according to the frontier-orbital theory applied to the 2+2 photocycloaddition, the main contributor to the rate determining step is the transfer of electrons from the alkene (2) to the enone (1). Where the best interaction occurs between the LSOMO of the excited triplet state of cyclopentenone and the HOMO of the fundamental singlet state of alkene ( $0.68 < \Delta E < 1.46$  e.V)

The regioselectivity of the reaction can be predicted from the LSOMO and HOMO polarization of cyclopentenone and alkene (2) (match up the larger coefficient on one component with the larger on the

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other). The HOMO is distributed at the  $C'_1 - C'_2$  double bond of alkene with -0.47 and -0.40 orbital coefficients values, and the LSOMO is located at the  $C_1 - C_2$  double bond of cyclopentenone and the orbital coefficients are 0.06 and 0.40 respectively (Figure 3).



**Figure 3 :** Orbital coefficients of HOMO and LSOMO for the two reactants 1 and 2 respectively (calculated by AM1).

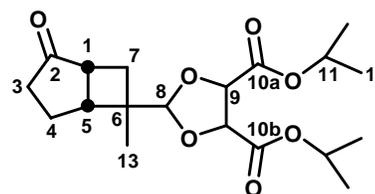
We can see clearly that, in this case, we have the total superposition between the molecules of the reagents, and the first bond formed is  $C_1 - C'_1$ . Interestingly, the observed regioselectivity is in accordance with the orbital coefficients. These results can explain the formation of only head-to-tail regioisomers by interaction of the lobes according to the maximum overlapping principle.

### EXPERIMENTAL SECTION

To a photochemical immersion well (250 ml) equipped with a reflux condenser and a water cooled Pyrex well was added a 100 mg (3.4 mmol) of alkene (2) and 100 mg (1.2 mmol) of cyclopentenone in 100 ml of hexane.

Solution irradiation was started using monochromatic lamp HPW 125 W (365 nm) for 144

h. Solution concentration and purification with flash chromatography on 250 g of silica gel with 10 % ethyl acetate/hexane provided 50% of regioisomers as 40% diastereomeric excess (e.d). 250MHz  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ,  $\delta$ ) : 1.09 (1s, 3H); 1.24 (m, 12H); 4.65 (d,  $J=5\text{Hz}$ , 1H); 4.73 (d,  $J=5\text{Hz}$ , 1H); 5.12 (1m, 3H). IR ( $\text{cm}^{-1}$ ): 2990.2945; 1740- 1755; 965.  $\text{M}^+$ : 312. 250MHz  $\text{RMN}^{13}\text{C}$  ( $\text{CDCl}_3$ ,  $\delta$ ): 222.62 ( $\text{C}_2$ ); 169.51 ( $\text{C}_{10a}$ ); 169.52 ( $\text{C}_{10b}$ ); 111.43 ( $\text{C}_6$ ); 77 ( $\text{C}_9$ ); 69.85 ( $\text{C}_{11}$ ); 43.65 ( $\text{C}_1$ ); 40.65 ( $\text{C}_3$ ); 37.64 ( $\text{C}_5$ ); 31.40 ( $\text{C}_6$ ); 22.62 ( $\text{C}_7$ ); 21.77 ( $\text{C}_4$ ); 17.99 ( $\text{C}_{13}$ ); 15.59 ( $\text{C}_{12}$ )(Figure 4).



**Figure 4**

### CONCLUDING REMARKS

It is shown that the regioselectivity of the photocycloaddition reaction between cyclopentenone (1) and diisopropyl – D- (-)- tartrate modified ethylene methanoite (2) can be explained with frontier molecular orbital theory by means semiempirical methods. Thus, the favored initial bond formation allows us to predict the major product by means the orbital coefficients.

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