

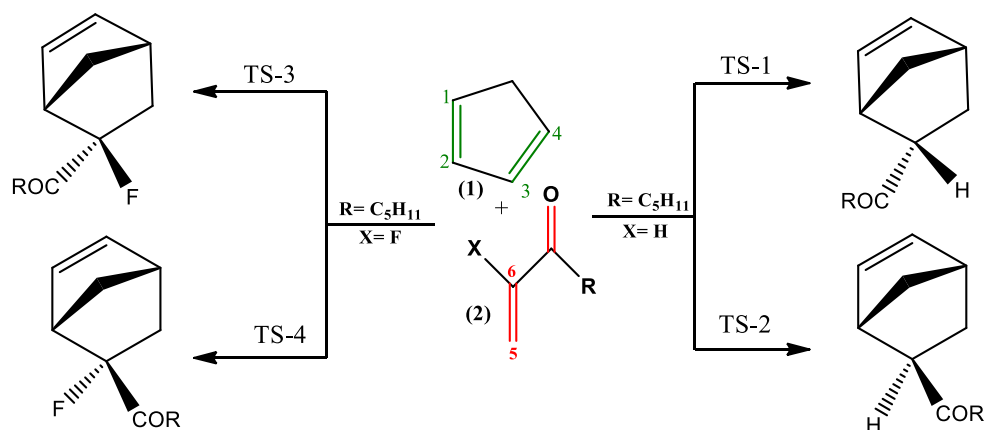
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## A Mechanism Study and an Investigation of the Reason for the Stereoselectivity in the [4+2] Cycloaddition Reaction between Cyclopentadiene and Gem-substituted Ethylene Electrophiles

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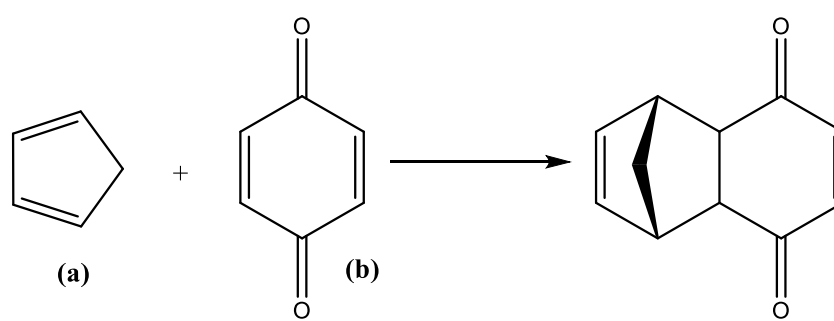
**Abstract:** The Molecular Electron Density Theory is applied to the [4+2] cycloaddition reaction between cyclopentadiene and gem-substituted ethylene electrophiles. Calculations are made for reactions, activation energies, and reactivity indices. The results of the experiment are perfectly consistent with activation energies, which unequivocally show that this cyclization's are is highly stereoselective, in addition, based on ELF examination, the mechanism of these [4+2] cycloadditions occurs in two phases, The mechanisms of these reactions demonstrate that the term "pericyclic reaction" is no more relevant in the 21st century and has been replaced by the term "pseudocyclic".

**Keywords:** Pericyclic reaction, Pseudocyclic, MEDT, Cyclopentadiene, Gem-substituted ethylene electrophiles

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## Introduction

A reaction in which two molecules arrange to create a cyclic adduct is called a cycloaddition. The [4+2] cycloaddition, also commonly known as the Diels-Alder reaction, is among the best known and most essential reactions, and is used widely in chemistry. The biography of the [4+2] cycloaddition reaction began in 1928, when Otto Diels and his student Kurt Alder published the work in which they described the cycloaddition of cyclopentadiene (a) to quinone (b) (Scheme 1) [1].



Scheme 1. The historically first Diels-Alder reaction between cyclopentadiene (a) and quinone (b)

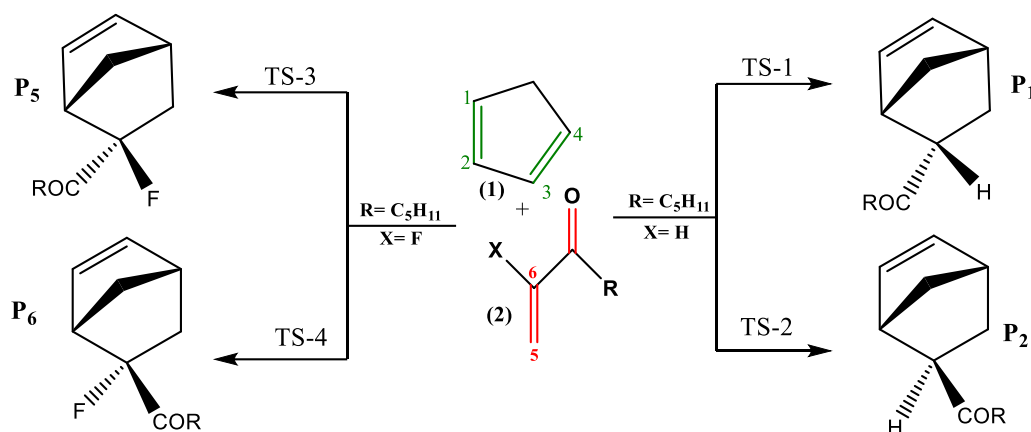
Currently, this reaction, named after the discoverers of the Diels and Alder reaction, is the most general method of obtaining six-membered carbon and heterocyclic structures [2-4]. Today, in addition to conjugated 1,3-dienes, conjugated nitroalkenes [5-7] are tried quite often as hetero-analogues of dienes. The use of ethene heteroanalogues as components of the cycloaddition reaction includes molecular segments containing nitrogen [8,9], oxygen [10,11], sulphur [12,13], selenium [14].

In the transition state corresponding to the Diels-Alder reaction, the diene and dienophile approach each other in approximately parallel planes. For the majority of systems, experimental and theoretical studies are in agreement with a concerted mechanism [2]. It has been observed that in a reaction containing asymmetric dienes and dienophiles, the degree of bond formation progress may be different at one pair of ends than at the other. This is typical of an asynchronous stepwise mechanism with the formation of a zwitterionic intermediate [3].

Following the classical institution of organic chemistry, the evolution of the [4+2] cycloaddition reaction was usually explained on the basis of the FMO theory and the rules of orbital symmetry conservation [15,16]. Now, this practice based on molecular orbital analysis

seems rather outdated as it does not always provide consistent information [17], instead, today, the new MEDT theory is widely used to study cycloaddition reactions.

In this study we want to examine the stereoselectivity of the studied reactions, as well as the reaction mechanism of these reactions and to show that the word "pericyclic reaction" is outdated in the 21st century and the new word is pseudocyclic.



Scheme 2. Possible routes of the [4+2] cycloaddition reaction between cyclopentadiene and gem-substituted ethylene electrophiles

## Computations methods

The optimization of the geometry of reactants, products and transition states was performed by DFT computations applying the B3LYP functional [18] set plus 6-311G(d,p) basis [19]. Frequency calculations were used to characterize optimized stationary positions to make sure that none of the reactants or products had any imaginary frequencies, and that the transition states have just one imaginary frequency. An intrinsic reaction coordinates (IRC) [20] paths were plotted in both directions, with the aim of verifying the energy profiles linking each transition stage to its two corresponding minimum. By employing the Tomasi group polarizable continuum model (PCM) to re-optimize the stationary points obtained in the gas phase, the solvent impact of dichloromethane was implicitly taken into account [21]. The global electrophilicity index was calculated using the equation shown below [22]:

$\omega = \frac{\mu^2}{2\eta}$ ; wherein the electronic chemical potential and chemical hardness are represented by  $\mu$  and  $\eta$ , respectively, the two quantities  $\mu$  and  $\eta$  according to the aforementioned formulas, they were calculated utilizing the HOMO and LUMO values [23-25]:

$$\mu = \frac{E_{HOMO} + E_{LUMO}}{2} \text{ and } \eta = \frac{E_{LUMO} - E_{HOMO}}{2}.$$

The overall nucleophilicity index  $N$  was calculated according to the following formula:  $N = E_{HO}(Nu) - E_{HO}(TCE)$ , with  $E_{HO}(Nu)$  corresponds to the HOMO energy of the reagent and Tetracyanoethylene's HOMO energy is known as  $E_{HO}(TCE)$  [25].

All reactivity indices were evaluated utilizing B3LYP/6-31G(d) level in accordance with Domingo's suggestions [25].

The total of the naturally found atomic charges ( $q$ ), as determined by a natural population analysis (NPA) [27], was used to calculate the overall GEDT [26] electron density transfer of the atoms belonging to each reactant ( $f$ ) at the transition state  $GEDT = \sum q_f$ . The Topmod program has been employed to undertake a topological inquiry of the ELF electronic localization function. The VMD program was applied to illustrate the ELF pool isosurfaces with an isovalue of 0.80.

## Results and discussion:

### Prediction of the reactivity of the reactants

To determine the donor (nucleophile) or acceptor (electrophile) character of the reactants, we calculated the electronic chemical potential  $\mu$ , the electrophilicity indices  $\omega$ , and the nucleophilicity indices  $N$  of the reactants (Table 1).

Table 1. Chemical hardness  $\eta$ , electronic chemical potential  $\mu$ , global electrophilicity  $\omega$ , and global nucleophilicity  $N$  in eV

Reactants	$\eta$	$\mu$	$\omega$	$N$
Cyclopentadiene (1)	5.42	-3.31	1.01	2.98
(2) X=F ; R=C <sub>5</sub> H <sub>11</sub>	5.41	-4.63	1.98	1.70
X= H ; R= C <sub>5</sub> H <sub>11</sub>	3.64	-4.35	1.82	2.08

From Table 1 we deduce that:

- The electronic chemical potential of **(1)** (-3.31) is greater than that of **(2)** for all four cases (-4.63; -4.35), implying that electron transfer will take place from **(1)** to **(2)**.
- The electrophilicity index of **(2)** (1.98; 1.82) is higher than that of **(1)** (1.01), so in this cycloaddition, **2** are a strong electrophile within the electrophilicity scale,  $\omega = 1.98, 1.82$  eV, while Cyclopentadiene **(1)**, is a moderate electrophile,  $\omega = 1.01$  eV. On the other hand, both **1** and **2** are moderate nucleophiles [28]. Dienophyl **(2)** will behave as an electrophile while Cyclopentadiene **(1)** will behave as a nucleophile.

## Evaluating the energy of the cycloaddition reaction between cyclopentadiene and gem-substituted ethylene electrophiles

With the objective of determining the majority product, the different possibilities of transition states corresponding to the [4+2] cycloaddition Reaction between cyclopentadiene and gem-substituted ethylene electrophiles (Scheme 2) have been determined and optimized, the formation of four possibilities P1, P2, P3 and P4 have been obtained. The relative energies in the gas phase are assigned in table 2.

Table 2. Energies (in a.u) and relative energies (in kcal/mol) of products and different transition states of the [4+2] cycloaddition reaction between cyclopentadiene and gem-substituted ethylene electrophiles.

System	In gas		In toluene (T=383.15°K)	
	E	$\Delta E$	E	$\Delta E$
(1)	-194.15372029	-----	-194.15654018	-----
(2) X=F; R=C <sub>5</sub> H <sub>11</sub>	-487.86021003	-----	-487.86349100	-----
X=H; R=C <sub>5</sub> H <sub>11</sub>	-388.59921178	-----	-388.60193950	-----
TS-1	-582.72643378	16.6	-582.72987282	17.9
P <sub>1</sub>	-582.77620044	-14.5	-582.77870578	-12.6
TS-2	-582.72687097	16.1	-582.72995775	17.8
P <sub>2</sub>	-582.77898625	-16.3	-582.78134411	-14.3
TS-3	-681.98895445	15.4	-681.99242233	17.3
P <sub>3</sub>	-682.04335797	-18.4	-682.04587539	-16.2
TS-4	-681.99025400	14.7	-681.99377336	16.4
P <sub>4</sub>	-682.04575340	-19.9	-682.04830236	-17.7

The activation barriers in gas for paths 1, 2, 3, and 4 associated with the [4+2] cycloaddition reaction between cyclopentadiene and gem-substituted ethylene electrophiles are **TS-1** (16.6 kcal/mol), **TS-2** (16.1 kcal/mol), **TS-3** (15.4 kcal/mol), and **TS-4** (15.4 kcal/mol), as indicate in Table 2. These values enable us to draw the conclusion that these reactions are stereoselective and the products **P2** and **P4** are kinetically preferred. Products **P1**, **P2**, **P3** and **P4** are exothermic respectively by: (14.5 kcal/mol), (16.3 kcal/mol), (18.4 kcal/mol) and (19.9 kcal/mol), these values indicates that the products **P2** and **P4** are also thermodynamically preferred.

Introducing the effect of toluene on the [4+2] cycloaddition reaction between cyclopentadiene and gem-substituted ethylene electrophiles increases the activation energy by: **TS-1** (1.3 kcal/mol), **TS-2** (1.7 kcal/mol), **TS-3** (1.8 kcal/mol) and **TS-4** (1.7 kcal/mol), which shows that toluene destabilises these two reactions.

Figure 1, demonstrate the geometries of the transition states attributed to the chemical channels of the [4+2] cycloaddition process between cyclopentadiene and gem-substituted ethylene electrophiles. The distances are presented in Angstroms (Å).

The geometric properties of the transition states shown in Figure 1, can be used to draw some important conclusions, including the fact that bond lengths strongly imply that new single bonds are generated asynchronously.

Global electron density transfer (GEDT) values were analyzed for all optimized TS structures using a natural population analysis in terms of residual charge on reagent 1. The positive global electron density transfer (GEDT) values reported in the figure reveal that electron density flux occurs from the cyclopentadiene acting as a nucleophile to the dipole

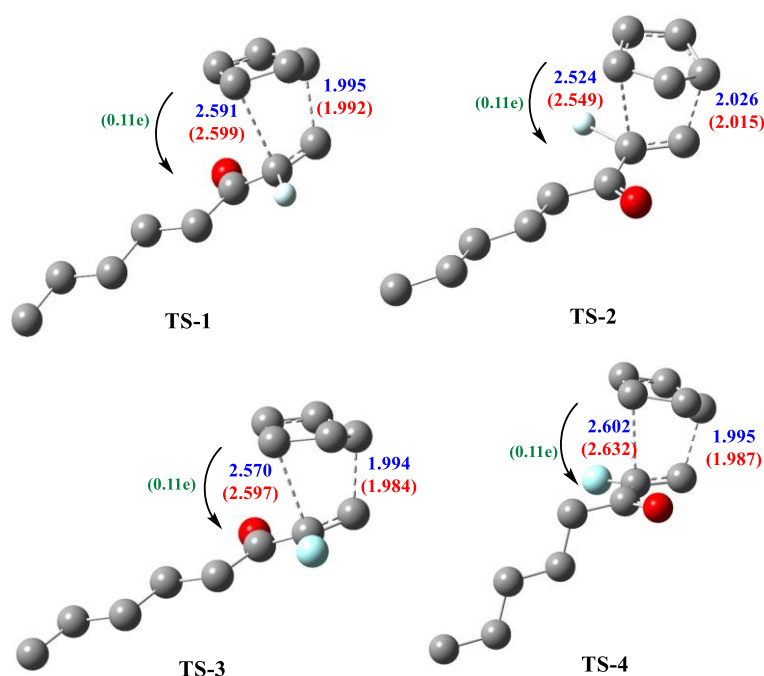


Fig. 1. The transition state geometries distinct cycloaddition paths of [4+2] cycloaddition process between cyclopentadiene and gem-substituted ethylene electrophiles

acting as an electrophile, which is in good agreement with the electron chemical potential values covered in the CDFT section. The fact that the results are higher implies that the DA reactions studied have a high degree of polarity [30].

### ELF topological analysis of the formation of C2-C6 and C3-C5 bonds along the [4+2] Cycloaddition reaction between Cyclopentadiene and gem-substituted ethylene electrophiles

To describe the formation of C2-C6 and C3-C5 bonds along the [4+2] cycloaddition reaction between cyclopentadiene and gem-substituted ethylene electrophiles, a topological study of the ELF [31, 32] along the IRC related to the most favorable reaction path was performed. The IRC structures involved in the formation of the new C2-C6 and C3-C5 single

bonds were chosen by performing a topological examination of the ELF for all the IRC structures. The complete examination of the ELF is presented in Tables 3 and 4, while the positions of the attractors of the ELF basins are illustrated in Figure 2 and Figure 3. Some appealing conclusions can be drawn from this topological study of the ELF:

Table 3. ELF valence basin populations, distances of the forming single bonds along the in the [4+2] cycloaddition reaction between cyclopentadiene and  $\text{FC}(\text{CH}_2)\text{COC}_2\text{H}_{11}$

Structure	V(C1,C2)	V(C2,C3)	V(C3,C4)	V(C5,C6)	V(C4)	V(C5)	V(C4,C5)	V(C1)	V(C6)	V(C1,C6)
F1	3.96	2.26	3.25	3.50	----	----	----	----	----	----
F2	3.19	2.38	3.11	3.40	----	----	----	----	----	----
F3	3.09	2.52	3.02	3.31	----	----	----	----	----	----
F4	2.97	2.71	2.57	2.78	0.40	0.39	----	----	----	----
F5	2.89	2.87	2.32	2.58	----	----	1.08	----	----	----
F6	2.83	2.96	2.29	2.46	----	----	1.33	----	----	----
F7	2.54	3.07	2.19	2.33	----	----	1.42	0.23	0.50	----
F8	2.44	3.13	2.14	2.28	----	----	1.51	0.30	0.59	----
F9	2.36	3.20	2.10	2.21	----	----	1.59	0.37	0.69	----
F10	2.35	3.21	2.09	2.20	----	----	1.60	0.38	0.71	----
F11	2.31	3.23	2.08	2.18	----	----	1.62	0.40	0.75	----
F12	2.18	3.32	2.08	2.12	----	----	1.68	----	----	1.42
F13	2.10	3.34	2.02	2.06	----	----	1.72	----	----	1.58
F14	2.01	3.37	1.99	2.00	----	----	1.77	----	----	1.80

Table 3 shows that in the three structures F1, F2 and F3, the two fragments are separated as if there were two distinct reactants, because the values of the pools are almost identical to the values of the basins of the reactants. In structure F4 we see the appearance of two monosynaptic pools carried by carbon atoms C4 and C5 with values respectively  $V(\text{C4})=0.40e$  and  $V(\text{C5})=0.39e$ . In this next structure F5 the two monosynaptic pools carried by carbon atoms C4 and C5 will unite to form the first C4-C5 bond with a population of  $1.08e$ , in structure F7 we see the appearance of two monosynaptic basins carried by carbon atoms C1 and C6 their values become in structure F11:  $V(\text{C1})=0.40e$  and  $V(\text{C6})=0.75e$ . In structure F12 the basins  $V(\text{C1})=0.40e$  and  $V(\text{C6})=0.75e$  will form the second bond.

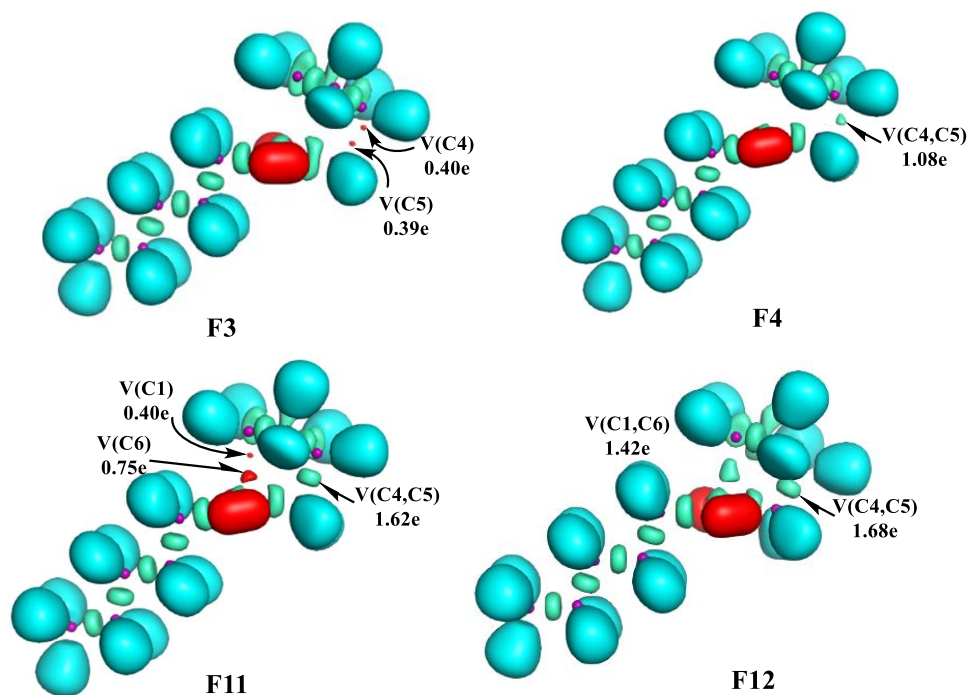


Fig. 2. The structures **F4**, **F5**, **F11** and **F12** that are involved in the production of the two C-C single bonds of the cycloadduct and their ELF localization domains.

Table 4. ELF valence basin populations, distances of the forming single bonds along the in the [4+2] cycloaddition reaction between cyclopentadiene and HC(CH<sub>2</sub>)COC<sub>2</sub>H<sub>11</sub>

Structure	V(C1,C2)	V(C2,C3)	V(C3,C4)	V(C5,C6)	V(C4)	V(C5)	V(C4,C5)	V(C1)	V(C6)	V(C1,C6)
H1	3.27	2.26	3.26	3.15	----	----	----	----	----	----
H2	3.05	2.54	3.03	3.08	----	----	----	----	----	----
H3	2.98	2.63	2.74	3.03	0.26	----	----	----	----	----
H4	2.85	2.74	2.58	2.67	0.41	0.31	----	----	----	----
H5	2.79	2.87	2.43	2.50	----	----	0.97	----	----	----
H6	2.50	3.00	2.30	2.35	----	----	1.18	----	----	----
H7	2.40	3.09	2.22	2.23	----	----	1.35	0.25	0.37	----
H8	2.33	3.14	2.15	2.16	----	----	1.49	0.33	0.45	----
H9	2.28	3.22	2.11	2.13	----	----	1.55	0.37	0.50	----
H10	2.26	3.25	2.09	2.09	----	----	1.60	0.41	0.57	----
H11	2.18	3.28	2.07	2.06	----	----	1.63	----	----	1.04
H12	2.00	2.44	1.99	1.88	----	----	1.78	----	----	1.68



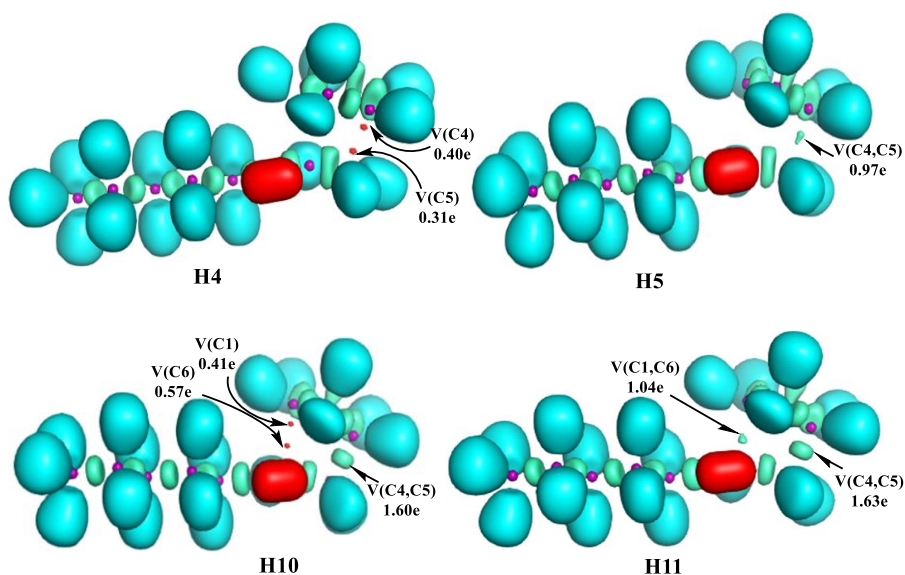


Fig. 3. The structures **H4**, **H5**, **H10**, and **H11** that are involved in the production of the two C-O single bonds of the cycloadduct and their ELF localization domains.

As the values of the basins are almost comparable with the values of the reactant basins, Table 3 shows that in the two structures H1 and H2, the two fragments are separated as if there were two independent reactants. Two monosynaptic basins are observed in structure H4, carried by carbon atoms C4 and C5, with values of  $V(C4)=0.40e$  and  $V(C5)=0.31e$ . The following structure H5 will see the first C4-C5 bond with a population of  $0.97e$  and the union of the two monosynaptic pools carried by carbon atoms C4 and C5. Two monosynaptic basins carried by carbon atoms C1 and C6 appear in structure F7; their values in structure F11 are  $V(C1)=0.25e$  and  $V(C6)=0.37e$ , the values of these two basins become in structure H10:  $V(C1)=0.41e$  and  $V(C6)=0.57e$ , these last two will form the second bond without structure F11 with a density  $1.04e$ . A study of the mechanism of cycloaddition reactions between cyclopentadiene and  $XC(CH_2)COC_2H_{11}$  shows that these reactions follow a two-step mechanism in which the formation of the second bond takes place once the first has been formed.

## Conclusion

The Diels-Alder [4+2] cycloaddition reaction between cyclopentadiene and gem-substituted ethylene electrophiles has been analysed within the framework of the MEDT at the DFT level B3LYP/6-311G(d,p). Analysis of the CDFT reactivity indices leads to the conclusion that cyclopentadiene acts as a nucleophile and gem-substituted ethylene electrophiles as an electrophile. A study of the activation energies indicates that these reactions are stereoselective, in complete agreement with the experimental results.

However, a topological ELF study of the electron density assignment of the stationary points along the IRC predicted that this Diels-Alder [4 + 2] reaction follows a two-step mechanism in which the formation of the second bond takes place once the first is almost completely formed.

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