**DFT investigation of Diels-Alder reaction of ethyl propiolate to cage-annulated hexacyclo[7.5.2.01,6.06,13.08,12.010,14]hexadeca-2,4-diene-7,16-dione**

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Abstract:The Diels-Alder (DA) reaction between cage-annulated diene hexacyclo[7.5.2.01,6.06,13.08,12.010,14]hexadeca-2,4-diene-7,16-dione (HHDD) with cyclohexa-1,3-diene moiety and ethyl propiolate (EP) dienophile were investigated by DFT method at B3LYP/6-31+G(d,p) level to elucidate mechanism and regioselectivity features of the reaction. The geometrical and electronic structures of caged diene HHDD and EP were studied at B3LYP/6-31+G(d,p) level. In order to identify facial- and regio-selectivity of the DA reaction of HHDD and EP, frontier molecular orbital (FMO) interactions of reactants according to FMO theory, and molecular electrostatic potential map of HHDD were examined. Potential energy surface (PES) of the related DA reaction was calculated, and optimizations of transition states and of products corresponding to critical points on PES were performed at B3LYP/6-31+G(d,p), and their configurations were determined. In addition, thermodynamic and kinetic parameters of each possible cycloaddition reaction were calculated using B3LYP/6-31+G(d,p) method to find out that the reaction takes place under thermodynamic or kinetic control. The thermochemical results showed that the related DA cycloaddition proceed under kinetic kontrol, and activation energies of *syn* cycloadditions are clearly lower than that of *anti* cycloadditions. The theoretical calculations are in good agreement with experimental results.

*Keywords*:DFT calculations; Diels-Alder cycloadditions; cage-fused dienes; π-facial selectivity

INTRODUCTION

The Diels-Alder (DA) reactions of cage compounds with facially differentiated 1,3-diene moieties have been subjects of extensive studies in recent years.1-8 Cage-fused cyclohexa-1,3-dienes are widely used for this type DA reactions as very useful substrates due to the absence of conformational uncertainties in its structures. Isolated cases of such reactions of some dienophiles with π-facially differentiated cyclohexa-1,3-diene, e.g., hexacyclo[7.5.2.01,6.06,13.08,12.010,14]hexadeca-2,4-diene-7,16-dione (HHDD)9 has been studied. We now report a related study of the DA cycloaddition reaction of ethyl propiolate (EP) to caged diene HHDD. Experimental results showed that only P3 and P4 (product ratio 40:60, respectively)9 stereoisomers of four possible cycloadducts as a result of this reaction were obtained (Fig. 1). These cycloadducts were formed with the attack of EP to syn-π-face of HHDD. In order to scrutinize the facial- and regio-selectivity of the related reaction, we theoretically investigated the geometrical and electronic structures of reactants. The presence of *syn*-π-facial selectivity in the reaction arise from the steric interactions between hydrogens of cyclobutane ring on *anti* face of HHDD and EP dienophile. Namely, the steric interactions in the attack of EP to anti-π-face of HHDD cause unstable cycloadducts. Mutual orbital overlaps between diene and dienophile according to frontier molecular orbital (FMO10-15)theory were calculated by B3LYP/6-31+G(d,p) method to explore reaction mechanism. Molecular electrostatic potential (MEP)16,17 map of cage diene HHDD were investigated at the B3LYP18,19 level with 6-31+G(d,p)20 basis set to explain the selectivities of reaction. Potential energy surface (PES) of this cycloaddition was computed by B3LYP/6-31+G(d,p), and transition states and products corresponding to stationary points (saddle points and minima) were determined. Furthermore, kinetic parameters (ΔE\*, ΔH\*, ΔS\*, ΔG\*) and thermodynamic parameters (ΔE, ΔH, ΔS, ΔG) of each cycloaddition were also calculated at B3LYP/6-31+G(d,p) level to determine reaction pathway.

COMPUTATIONAL METHODS

The DA reaction between HHDD and ethyl propiolate was investigated by DFT/B3LYP method with 6-31+G(d,p) basis set. The electronic structures of HHDD and EP were investigated by same method. The PES of the DA cycloaddition reaction were calculated at B3LYP/6-31+G(d,p) level. All transition states with only one imaginary frequency and all reactants and products with all real frequencies were characterized. Intrinsic reaction coordinate (IRC)21,22 calculations were carried out to verify the association between reactants, transition states and products of each reaction pathway. Solvent effects were performed at same theory level with 6-311++G(d,p) basis set with a conductor-like polarizable continuum solvation model (CPCM)23,24 (with UAKS cavities25) in toluene (ε=2.38). Frequency calculations were performed by B3LYP/6-31+G(d,p) method to obtain thermochemistry parameters of each cycloaddition. The all calculations were performed with Gaussian 03.26



**Fig. 1.** Diels-Alder reaction between HHDD and EP

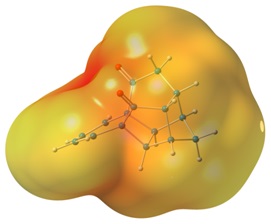
RESULTS AND DISCUSSION

The mutual interaction between FMO orbitals of diene and dienohile in intermolecular DA reactions, which is either between the HOMO of diene and the LUMO of dienophile or the LUMO of diene and HOMO of dienophile, can help to explain reaction mechanism. According to Klopman-Salem equation,27,28 the smaller the HOMO-LUMO energy gap between FMO orbitals of reactants, the mutual overlap energy of the molecules is higher, and overlapping of the orbitals is stronger.29 In our study, frontier molecular orbital interactions of the reactants were investigated by B3LYP/6-31+G(d,p) method in order to explain mechanism of DA reaction between HHDD and EP. According to theoretical results, favorable orbital overlapping was found to be between HOMO orbital of HHDD diene and LUMO of EP dienophile (Fig. 2). Namely, the related DA cycloaddition is controlled by HOMOHHDD-LUMOEP interaction and classified as normal Diels-Alder reaction.



**Fig. 2.** FMO interaction diagrams, HOMO-LUMO gap energies of reactants calculated with B3LYP/6-31+G(d,p) method

Molecular electrostatic potential (MEP) map is widely used to identify the most probable site of molecules for cycloaddition in the intermolecular DA reactions.30,31 The red on the map indicates the negative region pertaining to electrostatic potential, representing the region with high electron density on the entire molecule, which is hence prone to cycloaddition. The blue indicates the region with partially positive charges, and this site is unfavorable for cycloaddition. In order to identify the reaction-prone site of caged diene HHDD , the MEP map of the molecule was obtained from its geometry optimized by B3LYP/6-31+G(d,p) method. As can be seen from computed MEP map, the reaction-prone site of HHDD (more red) is on its *syn*-π face for cycloaddition (Fig. 3). The reason for more red on the *syn*-face of the molecule is due to both the precence of carbonyl substituents on syn-face of HHDD and being more electron density on the syn-face compared to that of on anti-face of HHDD.



**Fig. 3.** MEP map of HHDD

In order to better explain mechanism of the related DA reaction, the geometries of transition states of the reaction corresponding to stationary points on PES were optimized at HF/3-21G, HF/6-31\*, B3LYP/6-31G(d) and B3LYP/6-31+G(d,p) methods in gas phase and their structures and stabilities were compared with each other (Fig. 4) (Table I). According to calculated the relative energies of transition states, TS4 and TS3 transition states are clearly more stable than TS1 and TS2. Additionally, the most stable transition states, TS4, is energetically 0.589 kcal mol-1 (at B3LYP/6-31+G(d,p) level) and 0.788 kcal mol-1 (at HF/6-31G\*) less than TS3 (Table I).

TABLE I.Relative energies of transition states

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Transition States | Relative Energy / kcal mol-1 | | | |
|  | HF/3-21G | HF/6-31G\* | B3LYP/6-31G(d) | B3LYP/6-31+G(d,p) |
| TS1 | 10.217 | 8.523 | 6.271 | 5.886 |
| TS2 | 8.407 | 5.474 | 2.990 | 2.548 |
| TS3 | 1.204 | 0.788 | 0.363 | 0.589 |
| TS4 | 0 | 0 | 0 | 0 |



TS 1 TS2



TS3 TS4

**Fig. 4.** Optimized geometries of transition states (at B3LYP/6-31+G(d,p) level). Bond formation lengths in Å, bond orders in paranthesis

The bond formation length and bond order are used to gain an insight into bond formation or bond breaking in a chemical reaction. The bond formation lengths and bond orders (in parenthesis) in the transition states of the DA reaction between HHDD and EP are shown in Fig. 4 and Table II. In TS3 and TS4 transition states, the C(14)-C(29) and C(15)-C(30) bond formation lengths were calculated at B3LYP/6-31+G(d,p) level as 2.193-2.418 Å and 2.297-2.292 Å, respectively, and the bond orders were calculated as 0.192-0.133 and 0.157-0.168, respectively. This information also indicates that the C(14)-C(29) and C(15)-C(30) in TS4 is more advanced than that in TS3 transition state for bond formation. We can also say that when all the transition states are compared in terms of bond formation length and bond order, this DA cycloaddition will proceeds on the *syn*-π face of HHDD.

TABLE II.Bond formation lengths (Å) and bond orders of transition states (at B3LYP/6-31+G(d,p))

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Transition States | | | |
|  |  | TS1 | TS2 | TS3 | TS4 |
| Bond length | rC(14)-C(27) | 2.103 | 2.807 | - | - |
|  | rC(15)- C(28) | 2.615 | 2.027 | - | - |
|  | rC(14)- C(29) | - | - | 2.193 | 2.297 |
|  | rC(15)- C(30) | - | - | 2.418 | 2.292 |
| Bond order | C(14)-C(27) | 0.219 | 0.076 | - | - |
|  | C(15)-C(28) | 0.097 | 0.247 | - | - |
|  | C(14)-C(29) | - | - | 0.192 | 0.157 |
|  | C(15)-C(30) | - | - | 0.133 | 0.168 |

Kinetic parameters of each DA cycloaddition were calculated using B3LYP/6-31+G(d,p) method. According to theoretical results, *syn*-cycloadditions (TS3 and TS4) have the lowest activation energies. The lowest activation free Gibbs energy (ΔG\*) and activation enthalpy (ΔH\*) are also in the *syn*-cycloadditions (see Table III), so this DA reaction proceeds on TS4 transition states.

TABLE III.Kinetic parameters of DA cycloaddition between HHDD and EP (B3LYP/6-31+G(d,p))

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Transition States | ΔE\* /  kcal mol-1 | ΔH\* /  kcal mol-1 | ΔS\* /  cal mol-1.K-1 | ΔG\* /  kcal mol-1 |
| TS1 | 29.711 | 29.119 | 43.475 | 42.081 |
| TS2 | 26.499 | 25.902 | 44.724 | 39.209 |
| TS3 | 24.474 | 23.877 | 46.501 | 37.715 |
| TS4 | 23.885 | 23.293 | 46.260 | 37.086 |

The geometries of cycloadducts of each DA reaction between HHDD and EP corresponding to minima on PES were also optimized at HF/3-21G, HF/6-31\*, B3LYP/6-31G(d) and B3LYP/6-31+G(d,p) methods in gas phase (Fig. 5) (Table IV). According to calculated the relative energies of cycloadducts, the relative energies of cycloadducts (P1 and P2) of *anti*-cycloadditions are less than that of cycloadducts (P3 and P4) of *syn*-cycloadditions.



P1 P2



P3 P4

**Fig. 5.** Optimized geometries of products (at B3LYP/6-31+G(d,p) level)

TABLE IV.Relative energies of products

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Products | Relative Energy / kcal mol-1 | | | |
|  | HF/3-21G | HF/6-31G\* | B3LYP/6-31G\* | B3LYP/6-31+G(d,p) |
| P1 | 0.041 | 0.038 | 0.058 | 0.124 |
| P2 | 0 | 0 | 0 | 0 |
| P3 | 1.589 | 1.480 | 1.532 | 1.819 |
| P4 | 0.418 | 0.403 | 0.499 | 0.774 |

Thermodynamic parameters of each DA cycloaddition were calculated by B3LYP/6-31+G(d,p) method (Table V). According to the results of theoretical calculations, the *anti*-cycloadditions (P1 and P2) have the lowest reaction energies and enthalpies. Namely, *anti*-cycloadditions have favorable thermodynamic values for cycloaddition but the reactions with the lowest activation energies are in *syn*-cycloadditions (Fig. 6). Therefore, this DA cycloaddition takes place from *syn-*face of HHDD under kinetic control. In addition, these theoretical results are consistent with experimental results.

TABLE V. Thermodynamic parameters of DA cycloaddition between HHDD and EP (B3LYP/6-31+G(d,p))

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Products | ΔE / kcal mol-1 | ΔH / kcal mol-1 | ΔS / cal mol-1.K-1 | ΔG / kcal mol-1 |
| P1 | -40.824 | -41.416 | -51.856 | -25.956 |
| P2 | -40.917 | -41.509 | -51.900 | -26.035 |
| P3 | -39.199 | -39.792 | -53.196 | -23.932 |
| P4 | -40.204 | -40.796 | -52.536 | -25.132 |



**Fig. 6.** The potential energy diagram for DA reaction of EP to HHDD

CONCLUSIONS

The DA cycloaddition reaction between HHDD diene and EP dienophile was theoretically investigated by using DFT method at B3LYP level. The mutual overlapping of frontier orbitals was found to occur between HOMO of HHDD diene and LUMO of EP dienophile according to FMO theory as well as on the basis of Klopmann-Salem equation. The MEP surface of HHDD diene was also examined, and chemically favorable reactive region of the molecule for cycloaddition was found to be its *syn*-π face. The DA cycloaddition is *syn*-face selective. The PES of cycloaddition reactions was calculated, and configurations of transition states corresponding to stationary points on PES were identified. The most stable transition state is energetically TS4. The calculated kinetic and thermodynamic parameters of each reaction pathway showed that activation energies of *syn* cycloaddition reactions, TS4 (23.885 kcal mol-1) and TS3 (24.474 kcal mol-1), were lower than that of *anti* cycloadditions, and reaction energies of *anti* cycloadditions, P1 (-40.824 kcal mol-1 ) and P2 (-40.917 kcal mol-1), were the lowest values. Therefore, the DA cycloaddition reaction of HHDD and EP theoretically proceeds on TS4 pathway under kinetic control, and *syn* cycloadducts are favorable products. The results of all theoretical calculations were in good agreement with experimental results.

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