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A NEW ILLUSTRATIVE MODEL TO SHOW THE PREFERENCE OF THE EXO [6+4] DIELS-ALDER CYCLOADDITION REACTION VERSUS THE CORRESPONDING ENDO MANNER

Abstract: *By the help of the Molecular Orbital theory (MO) and the calculations of the molecular orbital coefficients of each carbon atoms in the (Ψ3) HOMO and HOMO-16 for 1,3,5-hexatriene at M06/def2-TZVP level of theory, a new model is illustrated to show the preference of the exo-product of the [6+4] Diels-Alder cycloaddition reaction versus the corresponding endo-sense.*

Key words: *[6+4] Diels-Alder cycloaddition reaction, exo-product, endo-product, HUMO-LUMO, M06/def2-TZVP level of theory.*

Language: *English*

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Introduction

The Diels–Alder cycloaddition reaction was explained in 1928 by the two German chemists, Otto Paul Hermann Diels (who was born in Hamburg in 23rd of January 1876, and died at the age of 78 in Kiel in 7th of March 1954. He went to the University of Berlin in 1895 and studied chemistry under the supervision of Professor Emil Fischer. Then he went to the university of Kiel until his retirement in 1945) and Kurt Alder (who was born in Königshütte in 10th of July 1902, and died at the age of 55 in 20th of June 1958 in Cologne. He got his PhD in 1926 at the University of Kiel under the supervision of Professor

Otto Diels). They were awarded the Nobel Prize in Chemistry in 1950 for the discovery of this reaction. The Diels–Alder reaction is a chemical reaction between a conjugated diene (as a diene) and a substituted alkene (as a dienophile), to form the unsaturated cyclic compounds.

Apparently, the first proposed reaction was the reaction between butadiene and ethylene, leading to the formation of a 6-membered ring which is classified as a thermally-allowed [4+2] cycloaddition reaction follows the Woodward-Hoffmann law.

Later, the basic concept was improved as a reliable procedure by various chemists all over the

worlds and several new reactions suggested and applied, i.e. formation of other ring sizes and the hetero-Diels–Alder reaction which involves the use of the π-system containing compounds, such as carbonyls and imines to form the corresponding heterocycles with the relevant stereochemical control.

Among the various cycloaddition reactions, the [6+4] Diels-Alder reaction is a reliable procedure for the preparation of new materials, e. i., the [6+4] reaction of tropones with dienes [1] which is potentially a good method for the synthesis of natural product [2-4]. Despite this potential, few synthetic efforts have relatively used the tropone strategy [5] due to the low yields and poor selectivity observed with more functionalized tropones and dienes [2-4]. Cookson and coworkers claimed that they reported the first example of the [6+4] cycloaddition reaction between tropone and cyclopentadiene[1]. Also, Ito and coworkers claimed that they reported the first example of the [6+4] cycloaddition reaction between tropone and cyclopentadiene [6]. Woodward and Hoffmann predicted the reaction to be exo-selective [7], a prediction amply demonstrated in thermal [6+4] cycloadditions [8]. A number of [6+4]-cycloadditions of trienes and dienes were discovered by Houk in the Woodward laboratory [9-10]. Houk proposed the reaction mechanism which involves a regio-, and stereo-selective $[6_F+4_T]$ cycloaddition of dimethylfulvene [6π] with tropone [4π], followed by a [1,5]-hydrogen shift, with a second [6+4] cycloaddition of tropone [6π] to the cyclopentadiene moiety [4π] [11]. Paddon-Row and Warrener proposed an alternative mechanism which the initial cycloaddition involves a different $[6_T+4_F]$ cycloaddition in which fulvene acts as the 4π molecule with a subsequent Cope rearrangement to produce the $[6_F+4_T]$ adduct [12]. About 50 years later, Houk and coworkers investigated the mechanisms and selectivities of the cycloadditions of tropone with dimethylfulvene by the use of M06-2X and B3LYP-D3 density functional theory (DFT) calculations and quasi-classical direct molecular dynamics simulations [13] and demonstrated that the initial cycloaddition proceeds via an ambimodal transition state that can lead to both of the proposed [6+4] adducts. These adducts can interconvert through a [3,3]-sigmatropic shift (Cope rearrangement).

Garst and coworkers examined the thermal [6+4] cycloaddition reactions of cyclohepta- trienone and ten dienes to find the diene substituent effects. The [6+4] adducts from the electron-rich dienes were formed faster with the less thermodynamic stability compared with the formed adducts from the more electron-poor dienes [14]. Rigby and his coworker reported a [6+4] cycloaddition-pinacol rearrangement method to obtain the nine-membered carbocycles by Cr(0) with complete control of stereochemistry [15]. Rigby and his coworker synthesized bicyclo[4.4.1]-undecatriene from the [6+4] cycloaddition reaction of tropones with butadiene derivatives by Cr(0) as an starting material to be used for preparation of the ansa bridge species which is the main part of the structure of streptovaricin D, streptovaricin C and damavaricin D [16]. On the basis of a [6+4] Diels-Alder cycloaddition reaction, a ten-membered carbocycle containing an oxygen bridge (11-oxabicyclo[6.2.1]undec-9-ene) was obtained from the reaction of a dicobalt hexacarbonyl acetylene complex having the benzoyloxy and an allylsilane with furans and $EtAlCl_2$ in CH_2Cl_2 via the stepwise pathway by Tanino and coworkers [17]. Gleason and coworkers performed the [6+4] cycloaddition reaction of several mono-, di-, and tri-substituted tropones with 2-silyloxycyclo- pentadienes by the use of $ZnCl_2$ to obtain the carbocyclic core of Phomoidride A (CP-225,917) and Phomoidride B (CP-263,114) [18].

More recently, the [6+4] cycloadditions byorgano-catalytic have been reported, providing rapid access to the biologically relevant pyrrolo-azepine core [19]. Highly enantioselective [6+4] cycloadditions proceed for a series of compounds such as pyrroles, imidazoles and pyrazoles.

Several other processes compete with the [6+4] cycloaddition reactions. Many of the reported (6+4] cycloaddition reactions were rearranged through the sigmatropic/cyclo-reversion-re-addition to [4+2] products [2]. Further investigation of the reaction pathway of the [6+4] cyclo-addition was performed through combined computational and experimental study [20].

Despite all the talk and arguments about the [6+4] or the [4+2] reaction mechanisms, definite judgment is still controversial [21], but chemists now believe that the Diels-Alder reaction can be used as a reliable procedure and powerful scientific tool for the synthesis of new compounds.

Results and Discussion

In the old schemes, the preference of the endo-product of the [4+2] Diels-Alder cycloaddition reaction versus the corresponding exo-product has been shown as below (Scheme 1) [22].
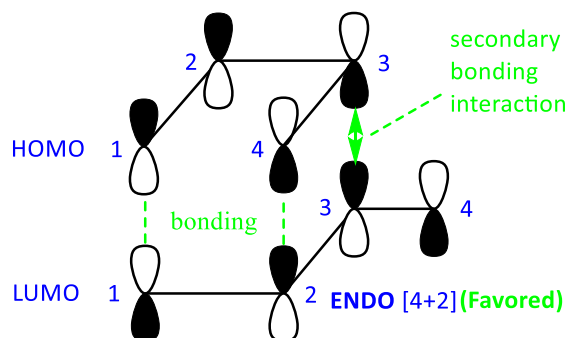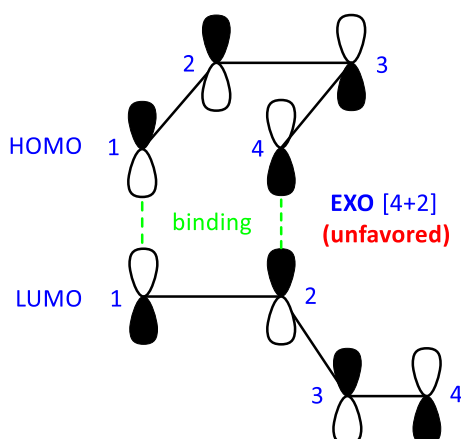
Scheme 1. The stereochemistry of the endo [4+2] Diels-Alder cycloaddition reaction of two molecules of 1,3-butadiene (favored stereochemistry).

According to the Scheme 1, the overlap between the lobes on C_1 and C_4 of the diene (HOMO) and the lobes on C_1 and C_2 of the ene (LUMO, dienophile) are seen. Also, a lobe of C_3 of diene is brought close to a lobe of C_3 of the ene to produce a secondary bonding interaction, and the arm of the ene will go inside rather than outside. In the other hand, any other unsaturated group in the dienophile tends to lie near the developing double bond in the diene moiety. This kind of weak bonding between these atoms helps to stabilize the transition state to produce the more favorable endo-product.

In the corresponding exo-product (Scheme 2), this kind of interaction does not exist.

Scheme 2. The stereochemistry of the exo [4+2] Diels-Alder cycloaddition reaction of two molecules of 1,3-butadiene (unfavored stereochemistry).

A closer look shows that, in contrast to the [4+2] cycloaddition reaction, the [6+4] reaction will take place with the preference of the exo manner.

In the old schemes, the preference of the exo [6+4] Diels-Alder cycloaddition reaction versus the corresponding endo sense has been shown as below (Schemes 3 & 4) [23].
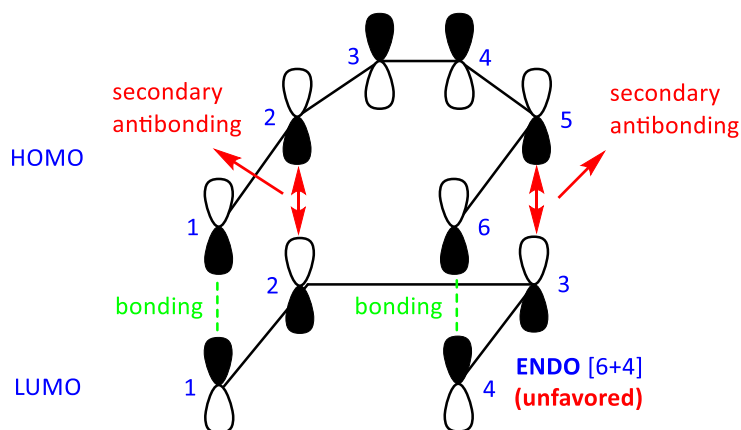
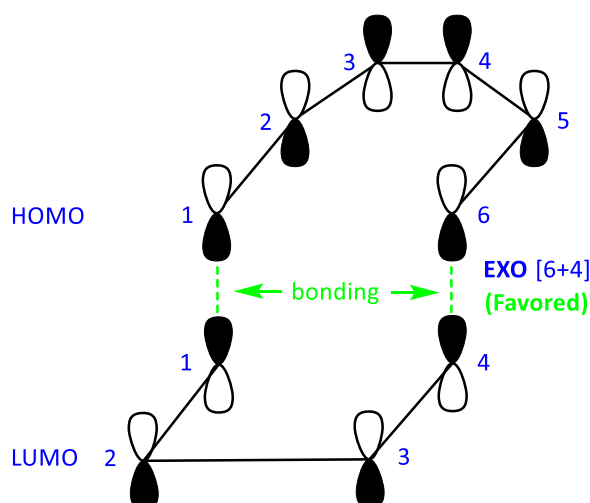**Scheme 3.** The old stereochemistry of the endo [6+4] Diels-Alder cycloaddition reaction of 1,3,5-hexa- triene with 1,3-butadiene (**unfavored stereochemistry**).

As the Scheme 3 shows, due to the secondary anti-bonding interactions between the C_2 and the C_5 lobes of triene (HOMO) with the C_2 and the C_3 lobes of diene (LUMO), the endo manner is not favored, so the exo product is more favorable (Scheme 4).

Scheme 4. The old stereochemistry of the exo [6+4] Diels-Alder cycloaddition reaction of 1,3,5-hexa- triene with 1,3-butadiene (**favored stereochemistry**).

Now and regardless of the fact that the stereochemistry of 6+4 cycloaddition reaction is exo and which molecule plays the role of diene and which molecule plays the role of dienophile, we would like to illustrate a new model to show the preference of the exo [6+4] Diels-Alder cycloaddition reaction versus the corresponding endo manner.

Both **A** or **B** can be used as a HOMO ($\Psi3$) orbital of the 1,3,5-hexatrienecompound (Scheme 5) since both has two nodes with the approximate similar symmetries, and we are allowed to choose any one that suits our idea as a $\Psi3$ HOMO orbital.

Scheme 5. The HOMO orbital ($\Psi3$) of the 1,3,5-hexatriene compound.

So, to prove our claim, the molecular structure of the 1,3,5-hexatriene has been optimized at M06/def2-TZVP level of theory. The harmonic vibrational frequency measurements are conducted at the same theoretical level to ensure that there are no imaginary frequencies in 1,3,5-hexatriene. The natural bond orbital (NBO) analysis was used for calculating molecular orbital coefficients of each carbon atoms in

the 1,3,5-hexatriene at M06/def2-TZVP level of theory. Result indicated that the Ψ3 is a bonding molecular orbital which was shown mainly in HOMO and also very weakly in HOMO-16. The molecular

orbital coefficients of carbon atoms of 1,3,5-hexatriene in HOMO and HOMO-16 are represented in Scheme 6.
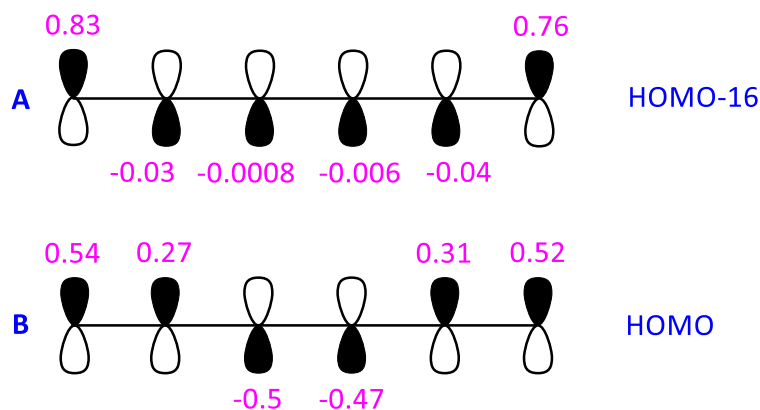
Scheme 6. Calculations of the molecular orbital coefficients of each carbon atoms in the Ψ3 HOMO and HOMO-16 for 1,3,5-hexatriene at M06/def2-TZVP level of theory.

Hence and despite the low share of **A** in the above M06/def2-TZVP level of theory calculations, **A** can be chosen as a HOMO orbital (Ψ3) of 1,3,5-hexatriene.So, inspired from the Schemes 1 & 2 and the corresponding explanations, by choosing **A** in place of **B** as a HOMO orbital (Ψ3) of 1,3,5-

hexatriene, and a LUMO orbital (Ψ4) of another molecule of 1,3,5-hexatriene, the Scheme 7 illustrates the new proposed stereochemistry model to show the preference of the exo [6+4] Diels-Alder cycloaddition reaction versus the endo manner.
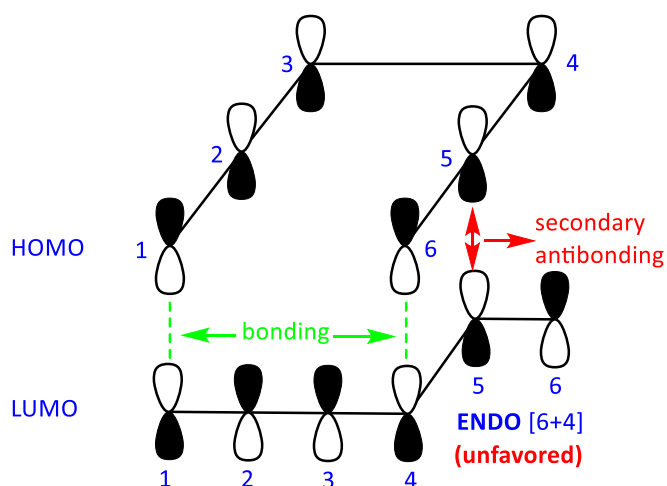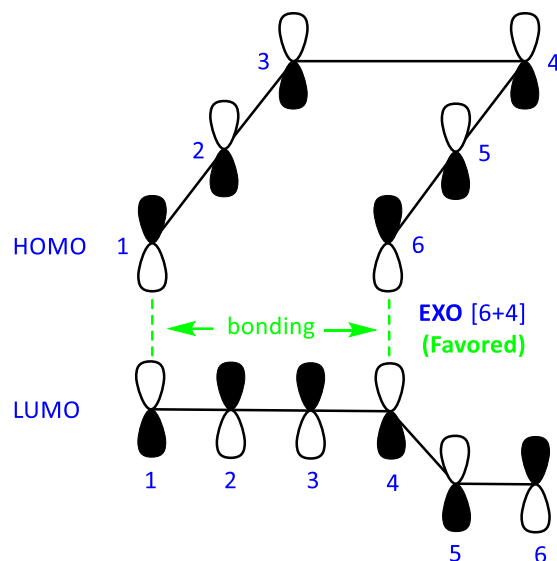

Scheme 7. The new stereochemistry of the endo [6+4] Diels-Alder cycloaddition reaction of two molecules of 1,3,5-hexatriene (**unfavored stereochemistry**).

As the Scheme 7 shows, due to the secondary anti-bonding interactions between the C_5 lobe of triene (HOMO, Ψ3) with the C_5 lobe of another triene

molecule (LUMO, Ψ4), the endo manner is not favored, so the exo product is more favorable (Scheme 8).

Scheme 8. The new stereochemistry model of the exo [6+4] Diels-Alder cycloaddition reaction of two molecules of 1,3,5-hexatriene (favored stereochemistry).

Conclusion

In conclusion, by the help of the Molecular Orbital Theory (MO) as well as the calculations of the molecular orbital coefficients of each carbon atoms in the ($\Psi 3$) HOMO and HOMO-16 for 1,3,5-hexatriene at M06/def2-TZVP level of theory, a new model was illustrated to show the preference of the exo-product of the [6+4] Diels-Alder cycloaddition reaction versus the corresponding endo-sense.

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