Indian Journal of Chemistry
Vol. 54A, July 2015, pp. 877-882

DFT investigation of Diels-Alder reaction of 1,3-cyclohexadiene with tetracyclo[6.2.2.1^{3,6}.0^{2,7}]trideca-4,9,11-triene-9, 10-dicarboxylic anhydride dienophile

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Received 28 January 2015; revised and accepted 29 June 2015

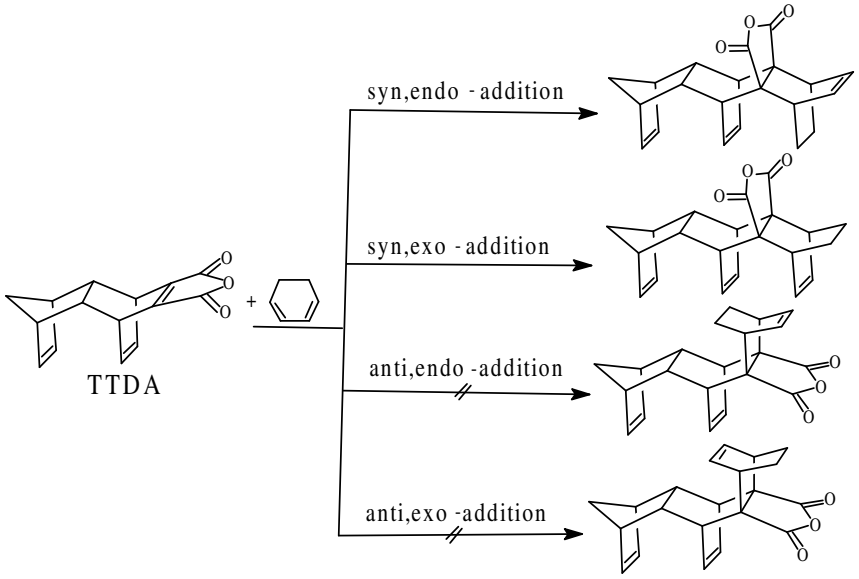
The geometry and the electronic structure of the tetracyclo-[6. 2.2.1^{3,6}.0^{2,7}]trideca-4,9,11-triene-9,10-dicarboxylic anhydride (TTDA) have been investigated by DFT/B3LYP and /B3PW91 methods using the 6-311G(d,p) and 6-31+G(d,p) basis sets. Anhydride double bond of TTDA molecule is *anti*-pyramidalized. Potential energy surface of addition reaction of 1,3-cyclohexdiene to TTDA molecule (*syn,endo-, syn,exo-, anti,endo- and anti,exo*-addition) is calculated by B3LYP/6-31+G(d,p) method and configurations (transition states and products) corresponding to stationary points (saddle points and minima) is determined. Kinetic and thermodynamic parameters of cycloaddition reactions have also been calculated. *Syn* addition reactions have lower activation energies, enthalpies, entropies and free energies than *anti* addition reactions. According to the results of theoretical calculations, *syn* addition reactions are expected to occur. The most stable reaction product is of the *syn,endo*-addition reaction. There is a correlation between the *syn*-π-face selectivity of the cycloaddition reaction and the pyramidalization of anhydride double bond of the TTDA molecule.

Keywords: Theoretical chemistry, Density functional calculations, Diels-Alder reaction, *Syn*-π-face selectivity, Pyramidalization, Steric hindrance

Diels-Alder reactions are among the most important pericyclic reactions. These reactions are a very attractive tool in organic synthesis. The analogous cycloaddition reactions between dienes and dienophiles have also been demonstrated for the regio- and stereoselective synthesis of a wide range of organic compounds. Diels-Alder reactions are widely used in the synthesis of many polycyclic compounds with two, three and four parallel double bonds (parallel face-to-face (juxtaposed) double bonds)[1-7]. Experimental results show that *syn,endo* and *syn,exo* stereoisomers of hexacyclo[6.6.2.2^{3,6}.1^{10,13}.0 ^{2,7}.0 ^{9,14}]-nonadeca-4,11,15-triene-2,7-dicarboxylic anhydride (HNDA) are obtained as a result of Diels-Alder reaction between tetracyclo[6.2.2.1^{3,6}.0^{2,7}]-trideca-4,9,11-triene-9,10-dicarboxylic anhydride (TTDA) and 1,3-cyclohexadiene (Scheme 1)[4]. In cycloaddition reactions, *anti,endo* and *anti,exo* stereoisomers are not formed (Scheme 1)[4]. Formation of only *syn* stereoisomers of HNDA molecule shows that cycloaddition reaction only takes place on only *syn* face of anhydride double bond of TTDA molecule. In other words, *syn*-π-face selectivity is observed in cycloaddition reaction. In order to interpret *syn*-π-face selectivity of cycloaddition reaction, geometric and electronic structure of TTDA molecule and structural deformation of its anhydride double bond should be investigated. π-Facial selectivity of cycloaddition reaction depends on the geometry and electronic structure of the anhydride double bond of TTDA molecule to a large extent. The investigation of the pyramidalization of the anhydride double bond of TTDA molecule is important. The calculation of the pyramidalization parameters of the double bond of TTDA molecule helps to determine the π-facial selectivity. In general, stereochemical aspects of Diels-Alder reactions have been the subject of many theoretical studies[8-14].

Calculation of potential energy surface (PES) of Diels-Alder reaction of TTDA molecule with 1,3-cyclohexadiene is vital to understand better the causes of formation of *syn* products and other aspects of the reaction. In order to study the structure and energy changes that are realized during the course of cycloaddition reactions in question, it is crucial to evaluate the PES of the reaction. This shall allow the inner mechanism and dynamic stereochemistry of the cycloaddition reaction to be understood in detail. Also, the determination of the structures and energies of the configurations (transition states and products) corresponding to the stationary points (saddle points or minima) by studying the PES of the cycloaddition reaction is important in order to understand the inner mechanism and dynamic stereochemistry of the cycloaddition reaction. The study of the stability and stereochemistry of the different configurations of the reaction products is vital so as to interpret the many features of the cycloaddition reactions.

In this work, the potential energy surface (PES) of the TTDA-1,3-cyclohexadiene system has been



Scheme 1

investigated by DFT method. The structure and energies of the configurations transition states [TS(*syn,endo*), TS(*syn,exo*), TS(*anti,endo*) and TS(*anti,exo*)] and products [P(*syn,endo*), P(*syn,exo*), P(*anti,endo*) and P(*anti,exo*)] corresponding to the (saddle points and minima) are determined and the stereochemistry of the cycloaddition reaction is discussed. Activation (kinetic) (ΔE^*, ΔH^*, $\Delta S^*$and ΔG^*) and thermodynamic (ΔE, ΔH, ΔS and ΔG) parameters of cycloaddition reactions have been calculated. The *syn*-π-face selectivity in cycloaddition reactions have been studied. The electronic and geometric structures of TTDA molecule have been investigated by DFT methods.

Computational methods

The geometry and the electronic structure of the TTDA molecule have been investigated by using the DFT method at the B3LYP[15,16] and B3PW91[17] levels with the 6-311G(d,p) and 6-31+G(d,p)[18] basis sets. The configurations (transition states and products] corresponding to the stationary points (saddle points and minima) of potential energy surface of the cycloaddition reaction have been investigated using the B3LYP/6-31+G(d,p) method. Solvent effects were calculated at the same theory level as the optimizations were performed by single-point calculations on the optimized structures using the CPCM (conducting polarized continuum model)[19,20] method (with UAKS cavities[21]) in $C_6H_5CH_3$ (ε = 2.379). All stationary points were characterized by calculating the vibrational frequencies and zero point vibrational energies were added for all species. The reactants and products were characterized by all the real frequencies. The transition state had only one imaginary frequency. Connections of the transition states between two local minima have been confirmed by intrinsic reaction coordinate (IRC)[22-24] calculations at the B3LYP/6-31+G(d,p) level. The intrinsic reaction coordinates were followed to verify the energy profiles connecting each transition state to the correct local minima. The calculations were performed with Gaussian 03[25] program with an IBM PC Pentium IV computer.

Results and discussion

Full geometric optimization of the TTDA molecule was performed at the DFT/B3LYP and /B3PW91 levels with the 6-311G(d,p) and 6-31+G(d,p) basis sets, and the structure of the molecule was also investigated in detail. In the light of the results of each method, pyramidalization parameters[26-29] of the molecule were determined in order to establish the structural deformation of the anhydride double bond. The values of pyramidalization angle (ϕ)[26] and of out-of-plane bending angle (χ)[27] were calculated and are given in Table 1. The results show that the anhydride double bond (anhydride olefinic bond) of TTDA molecule is *anti*-pyramidalized, and the two faces of double bond are no longer equivalent.

The electron density in the *syn* face of *anti*-pyramidalized double bond of molecule must be larger than that in *anti* face. On the other hand, in

Table 1—Calculated energies of frontier molecular orbitals (eV), anhydride double bond lengths (nm) and pyramidalization parameters (deg.) of TTDA molecule

Method	ε_{HOMO}	ε_{LUMO}	$r_{C=C}$	ϕ	χ
B3LYP/6-311G(d,p)	-0.242	0.105	0.1337	2.600	2.118
B3LYP/6-31+G(d,p)	-0.243	0.113	0.1343	2.891	2.346
B3PW91/6-311G(d,p)	-0.242	0.106	0.1336	2.578	2.104
B3PW91/6-31+G(d,p)	-0.243	0.113	0.1341	2.843	2.508

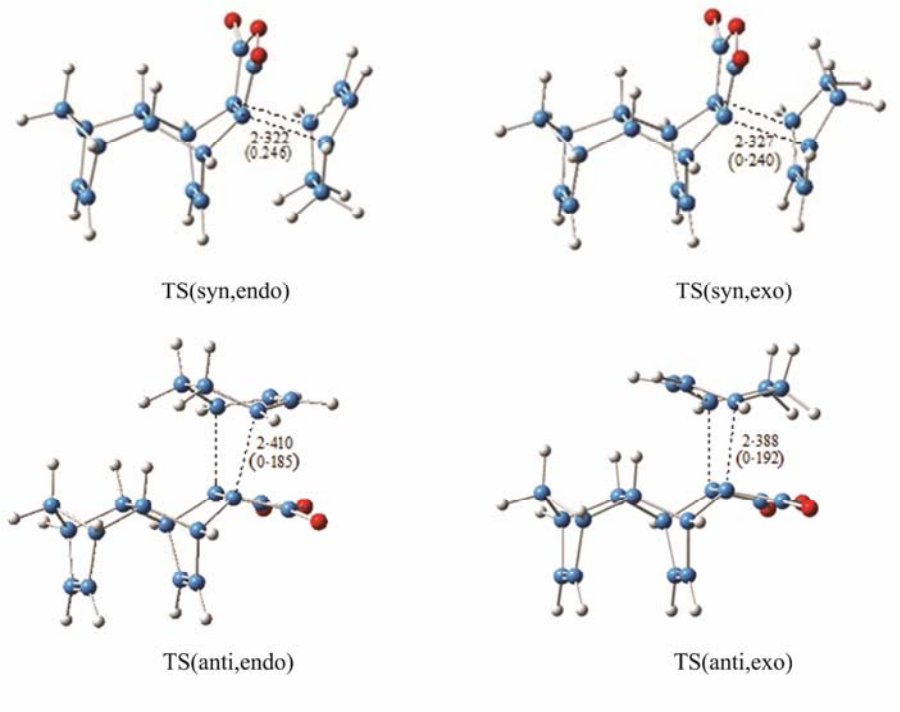


Fig. 1 – The optimized geometries of transition states [B3LYP/6-31+G(d,p)]. [Bond distances in Å, bond order (in parenthesis)].

TTDA molecule, etheno bridge *syn* face addition was almost not hindered, while addition from *anti* face was hindered due to the steric hindrance caused by ethano bridge. This feature causes a very noticeable *syn*-π-face selectivity in cycloaddition reaction. Thus, cycloaddition reaction of 1,3-cyclohexadiene with TTDA molecule in which the anhydride double bond is *anti*-pyramidalized, is expected to show the *syn*-π-face selectivity. Therefore, the cycloaddition should be realized from *syn* face. These results are in agreement with the experimental results.[4]

In order to better understand and interpret the *syn*-π-face selectivity observed in Diels-Alder reaction of TTDA molecule with 1,3-cyclohexadiene, PES of the reaction was calculated by B3LYP/6-31+G(d,p) method. Intrinsic reaction coordinate (IRC) calculations were performed to characterize the transition states on the PES. Full geometric optimization of transition state of each addition reaction (*syn,endo*-, *syn,exo*-, *anti,endo*-, and *anti,exo*-addition) corresponding to saddle point (critical point) in PES [accordingly TS(*syn,endo*), TS(*syn,exo*), TS(*anti,endo*) and TS(*anti,exo*)] was performed by B3LYP/6-31+G(d,p) method and its stability and structure were determined (Fig. 1). By using the optimized geometries of transition states at the B3LYP/6-31+G(d,p) level, their single point energies have been computed using B3LYP/6-311++G(d,p) and CPCM-B3LYP/6-311++G(d,p) methods. The calculated relative energies are given in Table 2.

According to the results of both method TS(*syn,endo*) transition state is more stable than TS(*syn,exo*) transition state and there is little difference between them (Table 2). Most probably, secondary orbital interaction (Alder's *endo* rule) carry importance in higher stability of TS(*syn,endo*) transition state than that of TS(*syn,exo*). TS(*syn,endo*)

Table 2—Calculated relative energies of transition states

Transition states	Rel. energy (kJ mol^{-1})		
	B3LYP/ 6-31+ G(d,p)	B3LYP/6-311++G(d, p)// B3LYP/6-31+G(d,p)	CPCM-B3LYP/6-311++G(d, p)// B3LYP/6-31+G(d,p)
TS(*syn,endo*)	0.0	0.0	0.0
TS(*syn,exo*)	2.820	2.054	6.226
TS(*anti,endo*)	43.505	42.418	42.443
TS(*anti,exo*)	22.426	21.355	23.882

Table 3—Kinetic parameters (activation energies, enthalpies, entropies, free energies in vacuum, and activation energies in toluene) of the Diels-Alder reaction of 1,3- cyclohexadiene with TTDA molecule. [(B3LYP/6-31+G(d,p) and (CPCM-B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p)]

Addition	ΔE^* (kJ mol^{-1})	ΔH^* (kJ mol^{-1})	ΔS^* (J mol^{-1} K^{-1})	ΔG^* (kJ mol^{-1})	$\Delta E^*_{solv.}$ (kJ mol^{-1})
Syn,endo	116.110	119.755	210.861	183.364	105.838
Syn,exo	118.930	122.445	208.832	184.703	112.052
Anti,endo	159.615	166.063	211.694	225.551	147.799
Anti,exo	138.536	142.089	210.974	204.983	129.708

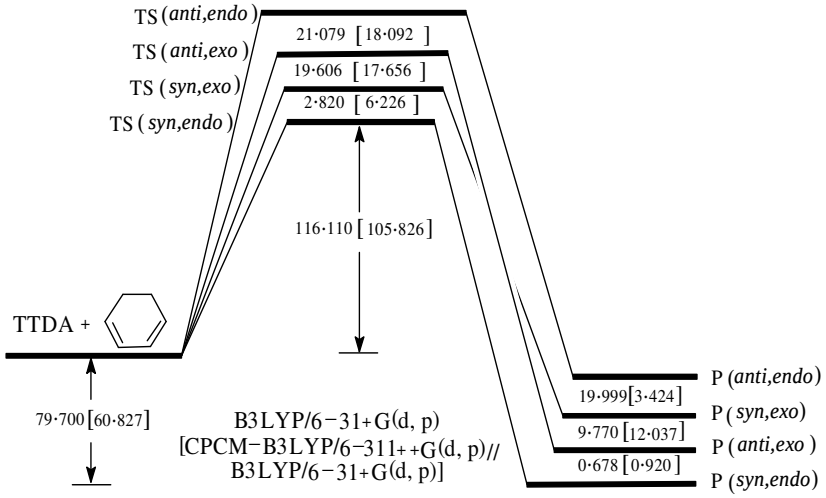


Fig. 2 – The potential energy profile of the Diels-Alder reaction of 1,3-cyclohexadiene with TTDA molecule (kJ mol^{-1}) [B3LYP/6-31+G(d,p)].

and TS(*syn,exo*) transition states are more stable than TS(*anti,endo*) and TS(*anti,exo*) transition states (Table 2). In other words, transition states of *syn* addition reactions are more stable than transition states of *anti* addition reactions. Transition state of *anti,endo*-addition reaction TS(*anti,endo*) is the most unstable transition state. Mutual interaction (steric hindrance) between hydrogen atoms of ethano bridges is effective in unstable nature of TS(*anti,endo*) transition state (Fig. 1). Kinetic parameters of (ΔE^*, ΔH^*, ΔS^*, ΔG^* and ΔE^*_{solv}) each cycloaddition reaction were calculated. The results are given in Table 3.

The lowest activation energy (ΔE^*=116.110 kJ mol^{-1}) is for the *syn,endo*-addition reaction and the second lowest (ΔE^*=118.930 kJ mol^{-1}) for the *syn, exo*-addition reaction. The highest activation energy (ΔE^*=159.615 kJ mol^{-1}) belongs to *anti,endo*-addition reaction. In other words, *syn* cycloaddition reactions have lower activation energies (activation energy barrier) than *anti* cycloaddition reactions (Table 3, Fig. 2). *Syn* cycloaddition reactions also have lower activation energies (activation energy barrier) than *anti* cycloaddition reactions in liquid medium. At the same time, *syn* addition reactions have lower enthalpies (ΔH^*) and free energies (ΔG^*) of activation than *anti*

addition reactions (Table 3). Thus, theoretical calculations confirm experimental results, in other words, *syn* addition reactions should take place.

Reaction product of each cycloaddition reaction corresponding to a minimum in PES was identified. By fully optimizing the geometrics of the products [P(*syn,endo*), P(*syn,exo*), P(*anti,endo*) and P(*anti,exo*)] (Fig. 3) of the reaction of 1,3-cyclohexadiene with TTDA molecule calculated by using B3LYP/ 6-31+G(d,p) method, their total energies were calculated and their stereochemistry were investigated. The single point energies of products were calculated by using B3LYP/ 6-311++G(d,p)//B3LYP/6-31+G(d,p) and CPCM-B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p) methods. The calculated relative energies are given in Table 4.

According to the results obtained, the most stable product is P(*syn,endo*) product formed by *syn, endo*-addition reaction. The P(*syn,endo*) product is thermodynamically 10.443 kJ mol^{-1} [B3LYP/ 6-31+G(d,p)] more stable than the P(*syn,exo*) product. According to the calculated thermodynamic parameters (ΔE, ΔH, ΔS and ΔG) of cycloaddition reactions, the most stable product is the P(*syn,endo*) product (Table 5), while the least stable product is the P(*anti,endo*) product (Table 4).

Mutual interaction between hydrogen atoms of ethano bridges causes P(*anti,endo*) product to be unstable (Fig. 3), although TS(*syn,exo*) transition state is more stable than TS(*anti,exo*) transition state and the P(*anti,exo*) product (which is not formed in cycloaddition) (Scheme 1) is more stable than P(*syn,exo*) product (Table 4, Fig. 2). Therefore, there is no similarity between the stability of transition state [TS(*syn,exo*)] of *syn,exo*-addition and the stability of [P(*syn,exo*)] product. Thus, *syn,exo*-addition takes place under kinetic control and P(*syn,exo*) product is a kinetic product. *Syn,endo*-addition reaction has the least activation energy and P(*syn,endo*) product is the most stable product. *Syn,endo*-addition takes place under kinetic and thermodynamic control and P(*syn,endo*) product is formed (Fig. 2).

The present study shows that the anhydride double bond of TTDA molecule is *anti*-pyramidalized. The electron density in the *syn* face of *anti*-pyramidalized double bond of molecule must be larger than in *anti* face. The pyramidalized anhydride double bond (dienophilic double bond) appears to correlate well with the observed *syn*-facial selectivity. Transition states [TS(*syn,endo*) and TS(*syn,exo*)] of *syn* cycloaddition reactions are more stable than transition states [TS(*anti,endo*) and TS(*anti,exo*)] of *anti*

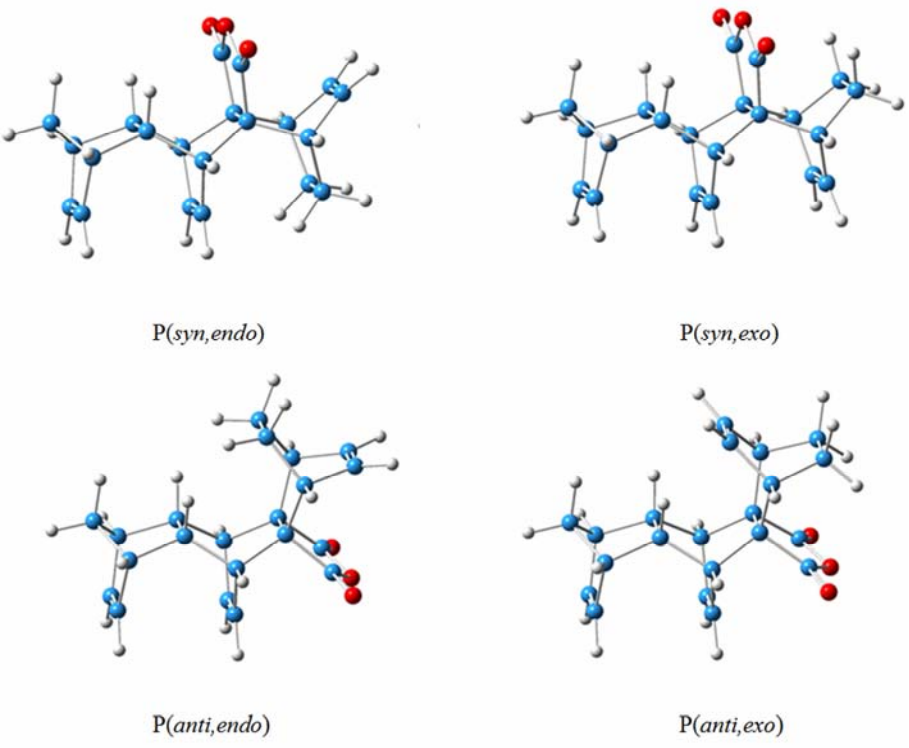


Fig. 3 – The optimized geometries of products [B3LYP/6-31+G(d,p)].

Table 4—Calculated relative energies of products

Products	Rel. energy (kJ mol^{-1})		
	B3LYP/ 6-31+G(d,p)	B3LYP/6-311++G(d, p)// B3LYP/6-31+G(d,p)	CPCM-B3LYP/6-311++G(d, p)// B3LYP/6-31+G(d,p)
P(*syn,endo*)	0.0	0.0	0.0
P(*syn,exo*)	10.443	10.167	12.749
P(*anti,endo*)	30.242	30.418	27.075
P(*anti,exo*)	2.560	4.063	0.921

Table 5—Thermodynamic parameters (reaction energies, enthalpies, entropies, free energies in vacuum and reaction energies in toluene) of the Diels-Alder reaction of 1,3- cyclohexadiene with TTDA molecule [(B3LYP/6-31+G(d,p) and (CPCM-B3LYP/6-311++G(d,p)// B3LYP/6-31+G(d,p)]

Addition	ΔE^* (kJ mol^{-1})	ΔH^* (kJ mol^{-1})	ΔS^* (J mol^{-1} K^{-1})	ΔG^* (kJ mol^{-1})	$\Delta E^*_{solv.}$ (kJ mol^{-1})
Syn,endo	–79.700	–66.798	–242.660	4.770	–60.748
Syn,exo	–69.254	–55.500	–234.597	12.778	–47.999
Anti,endo	–46.647	–40.543	–221.283	29.514	–33.648
Anti,exo	–79.023	–66.316	–239.588	5.113	–59.823

cycloaddition reactions. There is little difference between the stability of TS(*syn,endo*) and TS(*syn,exo*) transition states. In gas and liquid media, *syn* addition reactions have smaller activation energies, enthalpies and free energies than *anti* addition reactions. *Syn,endo*-addition reaction has the least activation energy (ΔE^* = 116.110 kJ mol^{-1}), followed by (ΔE^* = 118.930 kJ mol^{-1}) *syn,exo*-addition reaction. *Anti,endo*-addition reaction has the largest activation energy (ΔE^* = 159.615 kJ mol^{-1}). *Syn, endo*-addition reaction has the least activation energy and the most stable product [P(*syn,endo*)]. Therefore, formation of P(*syn,endo*) product is kinetically and thermodynamically controlled. P(*anti,endo*) product which is not formed in cycloaddition is more stable than P(*syn,exo*) product and P(*syn,exo*) product is a kinetic product.

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