

Origin of *Exo/Endo* Selectivity in the Intramolecular Diels-Alder Reaction

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The stereoselectivity of the intramolecular Diels-Alder reactions of **1** and its derivatives were investigated by *ab initio* calculations. The stereoselectivity mainly originates from the steric repulsion and the orbital interactions. The additional *s-cis* and *s-trans* conformations by introducing the carbonyl group at the neighbor of diene or dienophile may change the stereoselectivity, hence this kind of substitution can be utilized for stereoselective asymmetric synthesis.

Key Words: Intramolecular Diels-Alder reaction, DFT, Selectivity, Orbital interaction, Steric repulsion

Introduction

The Diels-Alder (DA) reaction¹ is one of the most efficient and widely used approaches to carbon-carbon bond formation. Its mechanism has been a subject of importance, and sometimes gives controversies. For asymmetrically substituted dienes and dienophiles, DA reaction results in product selectivity due to the asymmetric transition state. It is well established that most DA cycloaddition reactions proceed through the concerted pathways. In this connection, the product selectivity of various DA reactions have been investigated by both the experimental and theoretical studies.² Once we understand the origin of the product selectivity, we could design efficient reactants that could generate what we wanted through the enantioselective or diastereoselective DA reactions. Basically, the relative energy of the transition states (TSs) is responsible for the product selectivity because the reactants are the same.

Recently, a natural product, Tubelactomicin A, was synthesized stereoselectively by a Intramolecular Diels-Alder (IMDA) reaction.³ However, origin of the stereoselectivity was not explained. Thus, it should be very interesting to understand the

origin of the stereoselectivity. In this letter, we investigated origin of the stereoselectivity of the IMDA reactions of (2*E*,6*S*,7*S*,8*E*,10*E*)-ethyl-12-hydroxy-7-methoxymethoxy)-2,6,10-trimethyldodeca-2,8,10-trienoate (**1**) and its derivatives, **2** and **3** (Figure 1). **2** has a different chirality from **1** at C7 with *R* configuration, and **3** has a different substituent from **1** at C7 with a ketone instead of a methoxymethoxy group.

Calculation Methods

The designed *exo* and *endo* products of **1**, **2**, and **3** were shown in Figure 2. All the 24 TS structures were confirmed to be the correct TSs from the one negative frequency and the normal modes are consistent with the IMDA reactions coordinates. The density functional theory (DFT) calculations have been successful in explaining the product selectivity for the intramolecular DA reactions.⁴ In particular, the B3LYP exchange functional⁵ with 6-31G* basis set has been very effective in predicting the structures and relative energies of the TSs for various intramolecular DA reactions, hence giving the *exo/endo* ratio consistent with experimental results. In recent studies, the energies obtained at the DFT calculations were failed to explain the experimental observation in several DA reactions because the DFT inherently is lack of dispersive interactions.⁶ Thus, we carried out MP2/6-31+G(d) calculations at the B3LYP/6-31G* geometries as suggested in the earlier study.⁶ All the calculations were performed using a suite of Gaussian 03 programs.⁷

Results and Discussion

The TSs of the IMDA reactions of **1**, **2**, and **3** were obtained at the B3LYP/6-31G* and the structures were shown in Figure 3. It has been indicated that the IMDA reactions proceeded predominantly through a boat-like TS.^{4c,8} Here, for **1** and **2**, both the boat-like and the chair-like TSs have been explored for the *exo* and the *endo* cyclization. The TS structures and the relative energies were given in Figure 4, and only the lowest energy structures for the *exo* and *endo* cyclization were shown in Figure 3 in all the IMDA reactions investigated. For **1** and **2**, there is a striking difference between the *exo* and the *endo* TS

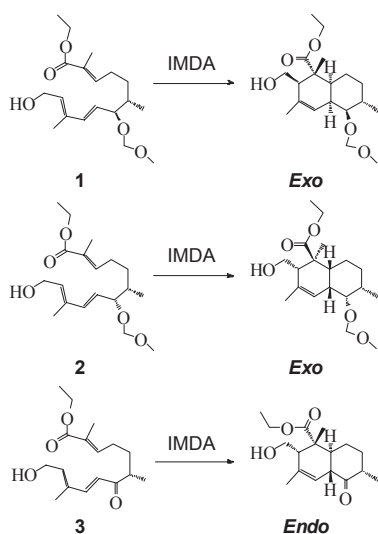


Figure 1. *Exo/Endo*-selective IMDA reactions of **1**, **2**, and **3**.

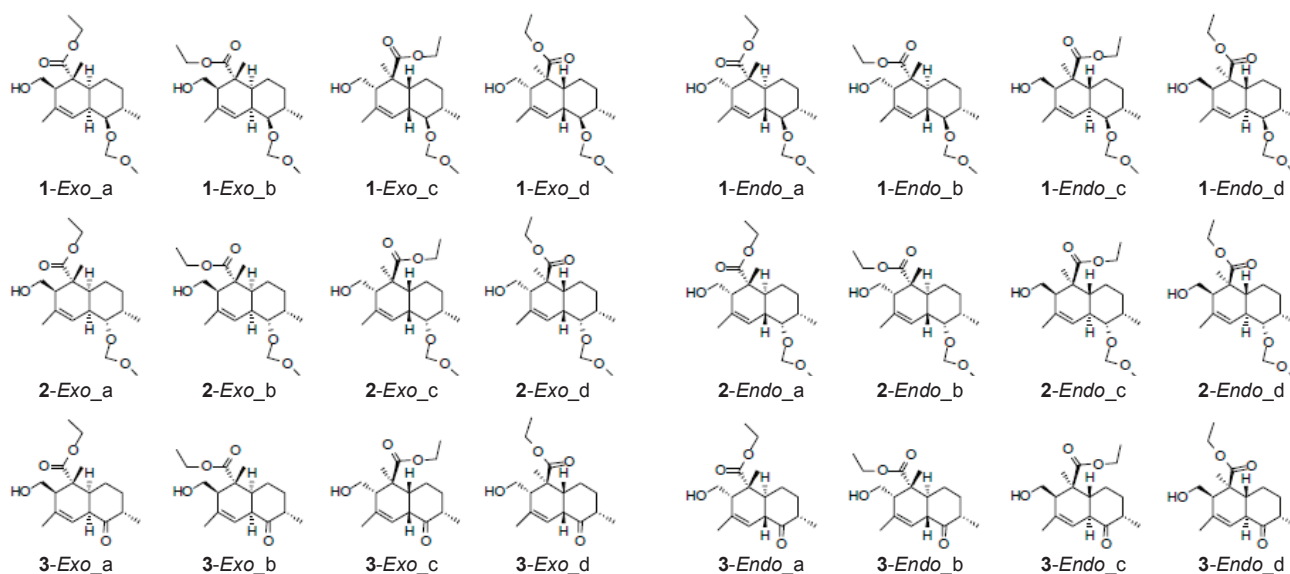


Figure 2. The designed *exo* and *endo* products of **1**, **2**, and **3**.

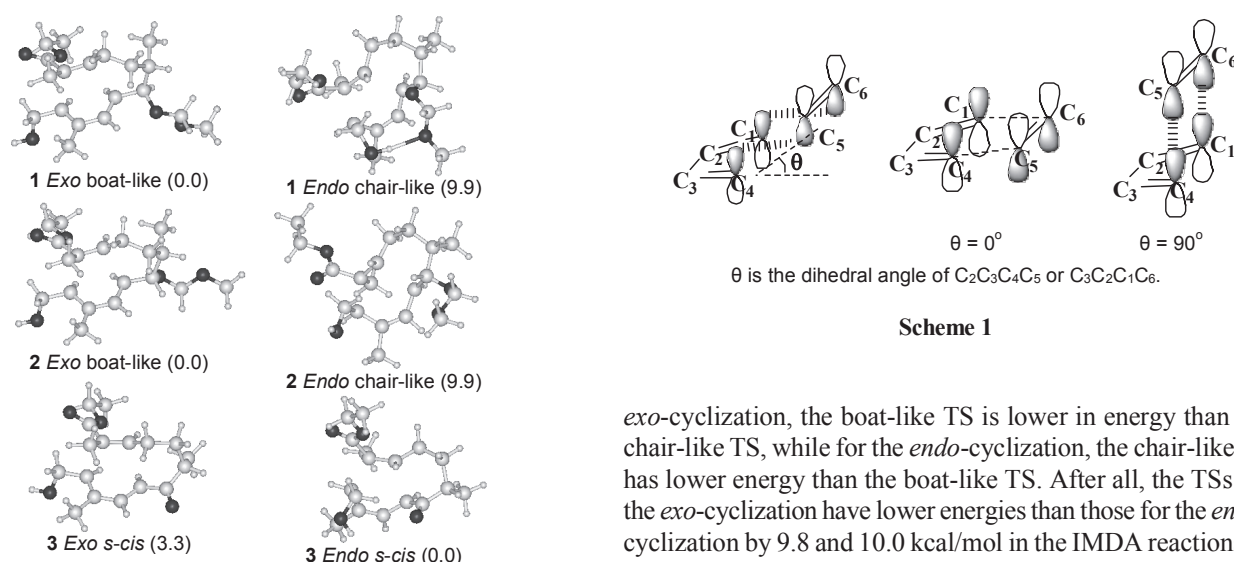


Figure 3. B3LYP/6-31G* optimized transition state structures of **1**, **2**, and **3**. Relative energies represented in the parenthesis are in kcal/mol. Oxygens are shown in black, Carbon and hydrogen atoms are in grey.

structures. The C₁-C₆ bond lengths in the *exo* TS are 2.202 and 2.164 Å for **1** and **2**, respectively, while those are 1.953 and 1.953 Å in the *endo* TS. In addition, the dihedral angles of C₂C₃C₄C₅ in the *exo* TS are 56.2° and 55.6° for **1** and **2**, respectively, while those are -7.5° and 7.0° in the *endo* TS. On the other hand, the *exo* and *endo* TS structures are quite similar for **3**. The DFT calculations resulted that the *exo* TSs for **1** and **2** are lower than the *endo* TSs by 11.1 and 9.9 kcal/mol, respectively, which is consistent with the experimental results. However, the DFT results sometimes give wrong predictions due to the lack of dispersive interactions.⁶ Thus, we need to discuss the stereoselectivity based on the MP2 energies.

Hereafter, all the discussion is based on the MP2 energies, otherwise specified. In the IMDA reactions of **1** and **2**, for the

exo-cyclization, the boat-like TS is lower in energy than the chair-like TS, while for the *endo*-cyclization, the chair-like TS has lower energy than the boat-like TS. After all, the TSs for the *exo*-cyclization have lower energies than those for the *endo*-cyclization by 9.8 and 10.0 kcal/mol in the IMDA reactions of **1** and **2**, respectively. This is consistent with the previous experimental observation⁵ that the treatment of **1** and **2** under thermal IMDA conditions resulted the undesired *exo*-cyclization contrary to the Tadano group's result.⁹

For **1** and **2**, the origin of the energy difference between the TSs for the *exo* and the *endo* cyclization mainly originates from the steric effect and the orbital interactions. The steric repulsion between -CH₂OH at C11 of the diene and -CO₂C₂H₅ at C2 of the dienophile should be larger for the *endo*-cyclization than the *exo*-cyclization as can be noted in Figure 3. The TS structures for the *exo* and the *endo*-cyclization of **1** and **2** show the remarkable difference in the arrangement of the diene and the dienophile.

In addition, in the TS for the *exo*-cyclization, the dienophile (ene) was found to be located above the diene resulting in the strong orbital interactions, while for the *endo*-cyclization, the ene and the diene were almost in the same plane resulting in the weak orbital interactions as sketched in Scheme 1. This is clearly shown from the molecular orbital interactions based on

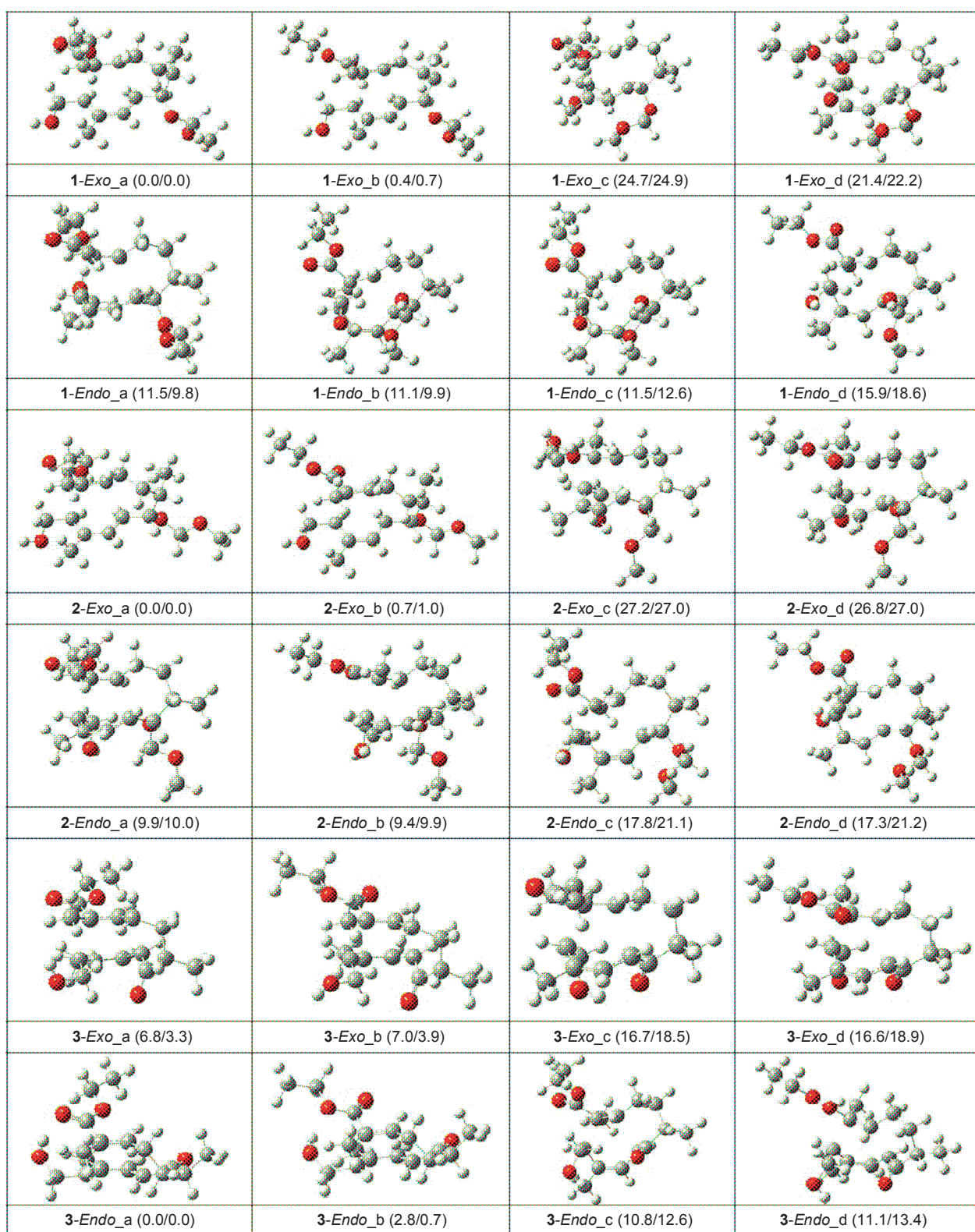


Figure 4. TS Structures for all *exo* and *endo* geometries. The relative energies represented in parentheses are in kcal/mol (B3LYP/6-31G(d)/MP2/6-31+G(d)).

the MO coefficients for the HOMO orbitals listed in Table 1. The orbital interactions ($A \times B$) (in arbitrary unit) in *exo* TSs are much larger than those in *endo* TSs for **1** and **2**, while for **3**, the orbital interactions in *endo* TS are larger than *exo* TS.

However, this approach can be applicable for one reactant with the same basis functions, and cannot be applicable for general purpose in different molecular systems or with different basis functions. Both the steric effect and the orbital interactions in

Table 1. Orbital interactions between the π -orbitals of C₁ and C₆ and between those of C₄ and C₅.

	1		2		3	
	<i>Exo</i>	<i>Endo</i>	<i>Exo</i>	<i>Endo</i>	<i>Exo</i>	<i>Endo</i>
A	0.0117	0.0003	0.0159	0.0003	0.0080	0.0230
B	0.0176	0.0015	0.0270	0.0026	0.0379	0.0417
C	0.0211	0.0015	0.0313	0.0027	0.0387	0.0476

A and B are the absolute values of the product of the MO coefficients of the π -orbitals of C₁ and C₆ and C₄ and C₅ respectively. For example, $A = C_{C1,pz} \times C_{C6,pz}$ where $C_{\mu,pz}$ is the MO coefficient of the p_z orbital (z -axis is perpendicular to the bonding plane formed by C₁, C₄, C₅, and C₆) of the atom μ . $C = (A^2 + B^2)^{1/2}$

the TSs favor the *exo*-cyclization over the *endo*-cyclization of **1** and **2**, which is consistent with the experimental results. It should be noted that the difference in configuration (*R* or *S*) at C₇ does not change the preference of the *exo* cyclization of both **1** and **2**.

In the experiment, when the methoxymethoxy group at C₇ was replaced by a carbonyl group to give **3**, the IMDA reaction resulted the *endo*-cyclized product. At first, it was quite surprise because the steric effect for **3** appears to be similar to those for **1** and **2**. How the carbonyl group at C₇ makes the difference? For **3**, there exist additional *s-cis* and *s-trans* conformations in the arrangement of the diene and the carbonyl group along the C₇-C₈ bond. Previously, the *exo/endo* selectivity involving *s-cis* and *s-trans* conformations has been extensively explored.⁷ In our system of **3**, the carbonyl group is involved in the diene. The calculated relative energies of the eight TSs for the 3-*exo_a*, 3-*exo_b*, 3-*exo_c*, 3-*exo_d*, 3-*endo_a*, 3-*endo_b*, 3-*endo_c*, and 3-*endo_d* cyclizations are 3.3, 3.9, 18.5, 18.9, 0.0, 0.7, 12.6, and 13.4 kcal/mol, respectively, which supports the *endo* preference in the IMDA reaction. It was found that the *s-cis* TSs are preferred to the corresponding *s-trans* TSs for both the *exo* and *endo* cyclization, where these two *s-cis* TSs are boat-like.

It has been pointed out that the concerted Diels-Alder reaction prefers the *endo* product while the stepwise reaction results in the *exo* structure.¹⁰ Generally, the extent of the synchronicity (concertedness) is measured by the difference between the distances of two bonds to be formed in the reactions. The calculated bond differences are 0.158 and 0.174 Å for *exo s-cis* and *endo s-cis* transition states, respectively, and these are quite small. Therefore, it is reasonable that the energy of *endo s-cis* transition state is lower than the *exo s-cis* transition state. The contact distance of the H(C3) and H(C8) atoms in *exo s-cis* transition state is 2.280 Å. The electrostatic repulsion between these two H atoms also contributes to the higher energy for the *exo* cyclization than the *endo* cyclization. Oppositely, the steric effects between -CH₂OH and -CO₂C₂H₅ groups favors the *exo* cyclization than the *endo* one, which makes the energy difference between the *exo* and the *endo* cyclization smaller.

Conclusion

In summary, we investigated the stereoselectivity in the IMDA reactions of **1**, **2**, and **3** based on the MP2/6-31+G(d)//B3LYP/6-31G* calculations. All the possible TS structures were investigated and the relative energies are in excellent

agreement with the experimental observations. The origin of the stereoselectivity mainly originates from the steric repulsion and the orbital interactions. It was also confirmed that the additional *s-cis* and *s-trans* conformations by introducing the carbonyl group at the neighbor of diene or dienophile may change the stereoselectivity, hence this kind of substitution can be utilized for stereoselective asymmetric synthesis.

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