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On the Endo/Exo Stereoselectivity of Intramolecular Diels–Alder Reactions of Hexadienylacrylates: An Interesting Failure of Density Functional Theory

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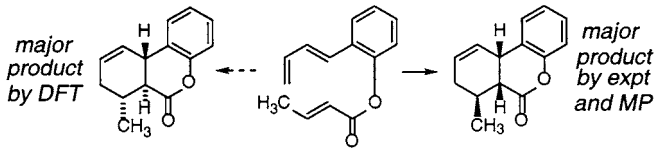
ABSTRACT



A combined experimental and computational study of endo/exo stereoselectivity in a series of IMDA reactions of hexadienylacrylates has found that DFT makes erroneous predictions when the endo and exo transition states possess differing degrees of conjugation. These problems are overcome by carrying out calculations at the MP2 level of theory, which gives remarkably accurate Boltzmann distributions of products. These findings are used to predict ways to obtain either endo- or exo-cycloadducts exclusively.

In recent times, significant advances have been made in our understanding of both intermolecular Diels−Alder and intramolecular Diels−Alder (IMDA) reactions, using both experiment and computational quantum chemical calculations.[1] With regard to the latter, it has been found that density functional theory (DFT) is an excellent theoretical model for predicting both structures and energetics for pericyclic reactions in general and Diels−Alder reactions in particular, and it serves as a viable alternative, in terms of quantitative accuracy, to the computationally more expensive MP2 theoretical model.[2−9] The B3LYP functional, used in conjunction with either the 6-31G(d) or 6-31+G(d) basis sets, has been particularly effective in predicting a wide range of outcomes from IMDA reactions, including endo:exo selectivity[5−9] and π-facial selectivity.[6−9] However, unlike ab initio methods such as MP2, the majority of currently used nonlocal density functionals are essentially empirically derived entities; consequently, they are occasionally prone to unexpected serious failure. Such an occurrence has now manifested itself in an IMDA reaction, specifically, that of **3** (Figure 1), and this forms the basis of this communication.

IMDA reactions of hexadienylacrylates, such as **1**, are well-known to favor an endo stereochemical outcome.[9,10] The motivation behind investigating the IMDA reaction of **3**, which incorporates an *ortho*-disubstituted benzene ring into

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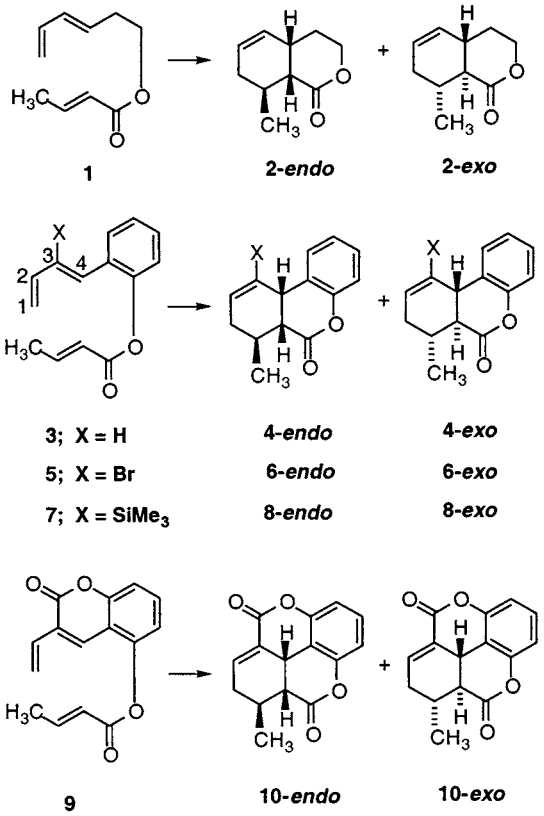

Figure 1. Hexadienyl acrylate IMDA reactions under scrutiny.

the tether, was to examine the feasibility of hexadienylacrylate IMDA reactions for the preparation of cannabinoids.[11]

1,3,9-Decatrienone IMDA precursors **1** and **3** were prepared in high yields by esterification of known dienols.[12] Heating the unsubstituted tethered system **1** in 1,2-dichlorobenzene at 180 °C for 113 h led to the clean formation of the two stereoisomeric cis- and trans-fused IMDA products, **2**-*endo* and **2**-*exo*, respectively, with an endo:exo ratio of 92:8 (Table 1, entry 1). The IMDA reaction of benzannulated system **3** was considerably faster (presumably due to the restricted conformation freedom) but less stereoselective than that of **1**: once again, the endo product predominated, but the endo:exo product ratio was 73:27 (Table 1, entry 5). Despite the high temperatures used to promote the IMDA reactions of **1** and **3**, these product ratios do reflect kinetically controlled processes, since samples of each of the four stereoisomers were found to be stable in 1,2-dichlorobenzene at 180 °C.

Table 1. Experimental and Computed Endo:Exo Product Ratios for IMDA Reactions of **1**, **3**, **5**, **7**, and **9**[14]

entry	method	reactant	endo:exo
1	experiment[a]	**1**	92:8
2	BP//BP[b]	**1**	80:20
3	MP//BP[c]	**1**	89:11
4	MP//MP[d]	**1**	92:8
5	experiment[a]	**3**	73:27
6	BP//BP[b]	**3**	23:77
7	MP//BP[c]	**3**	62:38
8	MP//MP[d]	**3**	71:29
9	MP//BP[c]	**5**	98:2
10[d]	MP//BP[c]	**7**	100:0
11	MP//BP[c]	**9**	0:100

[a] Conditions: $[\text{substrate}]_{\text{initial}} = 5$ mM in 1,2-$Cl_2C_6H_4$, BHT (0.1 equiv), reflux 113 h, 76% for **1** and 2.2 h, 100% for **3**. [b] B3LYP/6-31+G(d)//B3LYP/6-31+G(d). [c] MP2/6-31+G(d)//B3LYP/6-31+G(d). [d] MP2/6-31+G(d)//MP2/6-31+G(d).

The calculated endo:exo product ratios given in Table 1 were obtained from the Boltzmann populations (at 180 °C) which, in turn, were calculated from the relative energies (including ZPE corrections) of the fully optimized endo and exo transition structures (TSs) using both the B3LYP/6-31+G(d) and MP2/6-31+G(d) levels of theory.[13,14] Three different theoretical models were used, namely, B3LYP/6-31+G(d) using the B3LYP/6-31+G(d)-optimized TSs (denoted by BP//BP), MP2/6-31+G(d) using B3LYP/6-31+G(d)-optimized TSs (MP//BP)), and MP2/6-31+G(d) using the MP2/6-31+G(d)-optimized TSs (MP//MP).[15]

The BP//BP endo:exo ratio of 80:20 for the IMDA reaction of **1** is in fairly good agreement with the experimental ratio of 92:8.[16] Both MP//BP and MP//MP calculations gave product ratios that are in even better agreement with the experimental result, i.e., 89:11 (MP//BP).

The BP//BP product ratio for the IMDA reaction of **3** is catastrophically incorrect, erroneously predicting (high) exo stereoselectivity with an endo:exo product ratio of only 23:

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(14) See Supporting Information for full details.

(15) B3LYP TSs were characterized by carrying out harmonic frequency calculations, from which ZPEs were calculated. Frequency calculations were not carried out on the MP2-optimized TSs due to prohibitive computational overheads. Consequently, the ZPE corrections that were applied to the MP2 energies were those that were calculated at the B3LYP level.

(16) Note that for system **1**, there are boatlike and half-chairlike transition structures for both the **2**-*endo* and **2**-*exo* products. All four TSs were considered when calculating the endo:exo ratios.

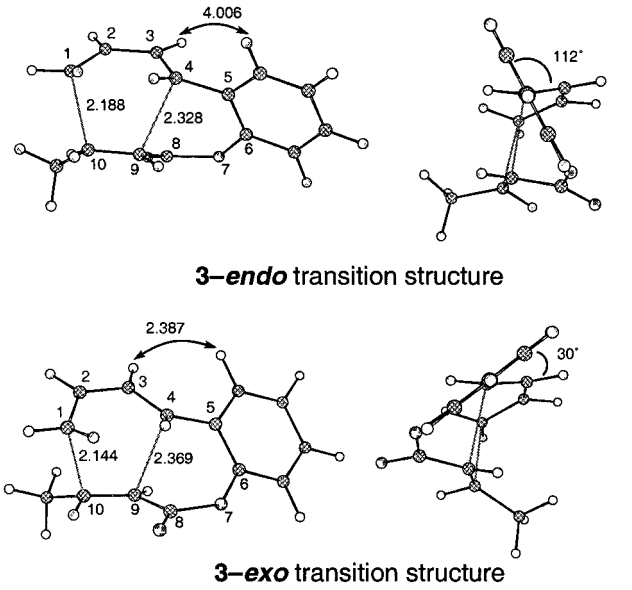

Figure 2. Perspectives of the B3LYP/6-31+G(d)-optimized endo and exo transition structures for the IMDA reaction of **3**. Distances shown are in Å.

77 (Table 1, entry 6). In contrast, the MP2 results correctly predict the observed weak endo selectivity for this reaction, and this is true even for the single-point MP//BP calculation. Thus, the MP//BP product ratio of 62:38 is quite close to the experimental value of 73:27, and this good agreement means that the cause of the poor BP//BP result lies in the computed BP energies rather than in erroneous geometry optimizations. In fact, optimized BP and MP TS geometries are quite similar.

Inspection of the optimized endo and exo TSs for the IMDA reaction of **3** (Figure 2) reveals the origin of the poor performance of the BP method. The BP (MP)-optimized dihedral angles between the planes of the benzene ring and the C3−C4 double bond of the diene unit in the endo and exo TSs are 112° (118°) and 30° (31°), respectively. Consequently, there is substantially more conjugation between the benzene and diene groups in the exo TS than in the endo TS in which the two groups are nearly perpendicular to each other. It has been established that DFT methods overestimate the stability of conjugated systems.[17,18] For example, the B3LYP/6-31G(d) rotational barrier for styrene (18.4 kJ/mol) is about 7 kJ/mol higher than the MP2/6-31G(d) value, which was attributed to B3LYP overestimating the stability of the planar conformation of styrene relative to the perpendicular conformation.[17]

That this problem is the cause of the present difficulty with the B3LYP method was confirmed by calculating the relative energies of the two conformations of 1-phenyl-1,3-butadiene, which resemble those existing in this substructure within the endo and exo TSs for the IMDA reaction of **3**; that is, the dihedral angle between the phenyl and diene groups were set at 30° in one conformation (quasi-exo) and 112° in the other (quasi-endo). Both B3LYP/6-31+G(d) and MP2/6-31+G(d) methods favor the quasi-exo conformation of 1-phenyl-1,3-butadiene over the quasi-endo conformation by 11.7 and 5.8 kJ/mol, respectively. Thus, the B3LYP method overestimates the stability of the quasi-exo conformation of 1-phenyl-1,3-butadiene by 6 kJ/mol compared to the MP2 method. This overestimation largely accounts for the energy required (6.5 kJ/mol) to change the endo:exo ratio from 23:77 (BP) to 62:38 (MP) in the IMDA reaction of **3**.

Clearly, these results warrant caution in using the DFT method to compare the energies of two structures having different degrees of conjugation. In such cases, it is advisable to use the single-point MP//BP energies.[19]

The markedly different dihedral angles between the aromatic ring and the C3−C4 double bond in the TSs for the IMDA reaction of **3** suggest ways of tuning the endo:exo ratio in this system. Thus, placement of a sterically large group at C3 in **3** should disfavor the exo TS even more relative to the endo TS. Indeed. the MP//BP endo:exo ratio increases from 62:38 for the parent benzo system, **3**, to 98:2 for the 3-bromo system **5** (with an endo/exo energy difference between the TSs of −13.9 kJ/mol). Essentially 100% endo preference is predicted at the MP//BP level for the 3-trimethylsilyl molecule **7** (with an endo/exo energy difference between the TSs of −22.5 kJ/mol).

In contrast, linking the phenyl ring to C3 by a two atom tether, as in **9**, should disfavor the endo TS while having only a minor effect on the exo TS energy. The MP//BP calculations confirm this reasoning: the tether induces severe structural distortions in the endo TS, namely, loss of resonance within the acrylate ester group (the C6−O7−C8═O dihedral angle is 62° in **9** compared to 153° in **3**) and a marked increase in the internal forming bond length (2.658 Å in **9** compared to 2.048 Å in **3**). The endo/exo selectivity is strongly reversed for **9**, with an endo:exo ratio of ∼0:100 (with an endo/exo energy difference between the TSs of 54.9 kJ/mol).

In summary, DFT should not be used to calculate the relative energies of stereoisomeric TSs that possess differing degrees of conjugation. Instead, we recommend the MP2//B3LYP method in conjunction with the 6-31+G(d) basis set, which appears to be free of this problem. The MP2//B3LYP method has been used to predict ways to obtain either endo products or exo products exclusively through the judicious substitution of the benzo system **3**. These predictions will be verified experimentally.

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(19) Note that our results suggest that BP-optimized TS geometries are adequate for single-point MP2 calculations and that it is not necessary to carry out full MP2 TS geometry optimizations.

Supporting Information Available: Cartesian coordinates, energies of optimized structures, energies of single-point calculations, zero-point energy corrections, and magnitudes of imaginary frequencies. This material is available free of charge via the Internet at http://pubs.acs.org.

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