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Stereoselectivities of Diels-Alder Cycloadditions of π-Facially Nonequivalent Dienes to MTAD, PTAD, and *N*-Methylmaleimide: A Theoretical Study

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Abstract. 1,2,3,4,9,9-hexachloro-1α,4α,4aα,8aβ-tetrahydro-1,4-methanonaphthalene (**1**) and 1,2,3,4,9,9-hexachloro-1α,4α,6,7-tetrahydro-1,4-methanonaphthalene (**2**) undergo π-facially diastereoselective Diels-Alder reactions with 4-methyl- and 4-phenyl-1,2,4-triazoline-3,5-dione [MTAD and PTAD, respectively] and with *N*-methylmaleimide (NMM). In contrast with the results of AM1 calculations, those obtained via ab initio calculations performed at the HF/3-21G* level of theory predict that the computed Diels-Alder transition states are synchronous in all cases studied. Furthermore, these computational results account quantitatively for: (i) the observed π-facial selectivities of the various Diels-Alder reactions studied, (ii) the observed relative lack of dienophilic reactivity of NMM *vis-à-vis* MTAD and PTAD, and (ii) the observed enhanced diene reactivity of **1** *vs.* **2** in the reactions studied.

Introduction. Recently, we reported the results of an experimental study of thermal [4 + 2] cycloadditions between two isomeric tricyclic compounds, i.e., **1** and **2** (see Schemes 1 and 2, respectively), each of which contains a facially dissymmetric conjugated diene system, and such highly reactive dienophiles as 4-methyl- and 4-phenyl-1,2,4-triazoline-3,5-dione (MTAD and PTAD, respectively) and *N*-methylmaleimide (NMM).[1] Not surprisingly, the differing steric and electronic enviroments presented by the diene systems in **1** and **2** toward an approaching dienophile were found to exert a dramatic influence on the stereoselectivity of their respective Diels-Alder reactions. We now report the results of our attempts to provide a theoretical basis for our experimental results via application of molecular orbital computational methods.

Experimental Results. The syntheses of dienes **1** and **2** have been reported previously.[1] In each case, either (or both) of two [4 + 2] cycloadducts can possibly result via Diels-Alder cycloadditions of diene **1** to MTAD, PTAD, and/or NMM (Scheme 1). In our hands, cycloaddition of **1** to all three reactive dienophiles occurred with exclusive attack of the dienophile upon the *exo* face of the diene, thereby producing a single cycloadduct in each case (i. e., **3b**, **4b**, and **5b**, respectively, Scheme 1). The regiochemistry of each of these Diels-Alder cycloadditions was established unequivocally via subsequent facile intramolecular [2 + 2] photocyclization of **3b**, **4b**, and **5b** to the corresponding polycarbocyclic "cage" structure.[1]

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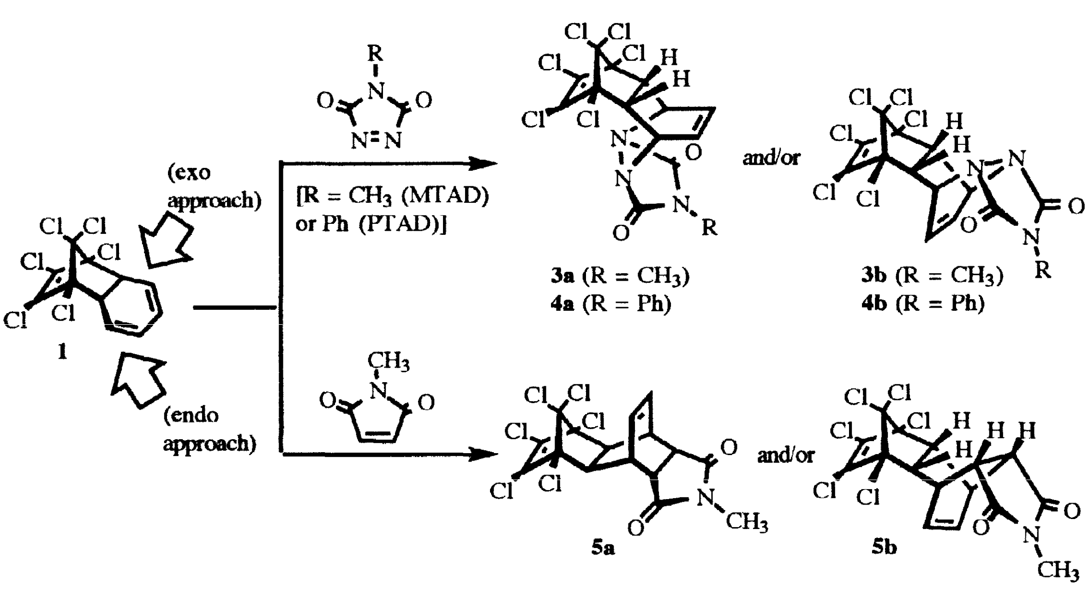
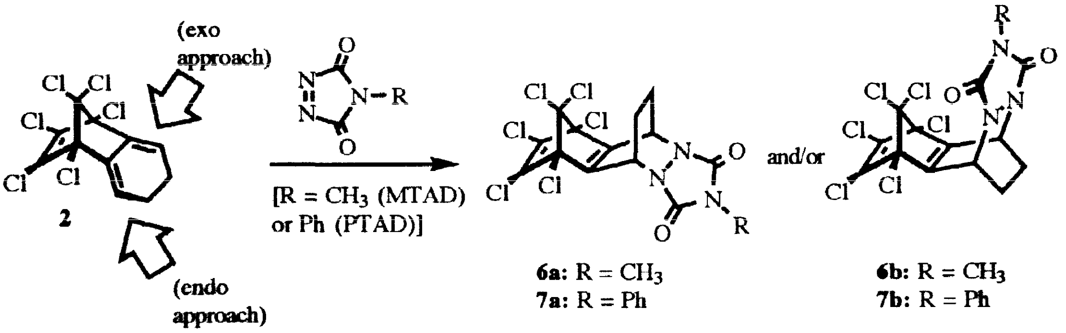
Scheme 1



Thermal Diels-Alder cycloadditions of **2** to MTAD and to PTAD both occurred significantly more slowly than the corresponding reactions of diene **1** with these same two dienophiles. Thus, [4 + 2] cycloaddition of **2** to MTAD afforded two isomeric cycloadducts, **6a** and **6b** (product ratio: 4.3 : 1, Scheme 2). Similarly, [4 + 2] cycloaddition of **2** to PTAD again afforded two isomeric cycloadducts, **7a** and **7b** (product ratio: 4.8 : 1).[1]

Scheme 2



Diels-Alder cycloaddition of **1** to NMM occured much more slowly than did the corresponding [4 + 2] cycloadditions of **1** to MTAD and/or PTAD. Interestingly, **2** could not be induced to undergo Diels-Alder cycloaddition to NMM, even when a solution of the two reactants was refluxed for 60 h.[1]

The experimental results indicate that diene **1** leads exclusively to the formation of *exo* cycloadducts with all dienophiles studied. By way of contrast, diene **2** affords primarily the *endo* cycloadduct via Diels-Alder reaction with MTAD and with PTAD. However, the Diels-Alder reactions involving **2** were found generally to be considerably slower than the corresponding reactions involving diene **1**. In addition, our results suggest that NMM is a considerably less reactive dienophile toward **1** and **2** when compared with MTAD and PTAD. In order to account for these observations, semi-empirical (AM1)[2a] and ab initio calculations[2b] were undertaken.

Computational Methodology. Spartan, version 5.0 was used for semi-empirical AM1 calculations,[3a] while Gaussian 94 was used for the ab initio calculations.[3b] The transition state geometries were optimized at the HF/3-21G* level of theory. In addition, the Becke3LYP hybrid HF-DFT method with 6-31G* basis set was used to calculate the activation barriers by using 3-21G*-optimized geometries.[4] Complete vibrational analyses were performed at the same level of theory to characterize the transitions states.

Results of Semi-empirical and Ab Initio Molecular Orbital (MO) Calculations. The results of semi-empirical AM1 calculations[2a] for Diels-Alder cycloadditions of dienes **1** and **2** with MTAD, PTAD, and NMM are shown in Table 1. The activation barriers have been calculated by determining the transition states for all three reactions. The computational results indicate that approach of MTAD, PTAD and NMM should be favored toward the *exo* face for diene **1** but toward the *endo* face for diene **2**.

Alhough the calculated activation barriers appear to be somewhat high, the computational (AM1) results generally are in accord with experiment for Diels-Alder reactions of **1** and **2** with MTAD and with PTAD. However, the results obtained for the corresponding reactions of **1** and **2** with NMM do not provide a basis for understanding the experimentally observed sluggishness of both of these Diels-Alder reactions (see data in Table 1). The activation barriers to both reactions are either comparable to or less than the energy barriers associated with the corresponding reactions of **1** and **2** with MTAD and PTAD.

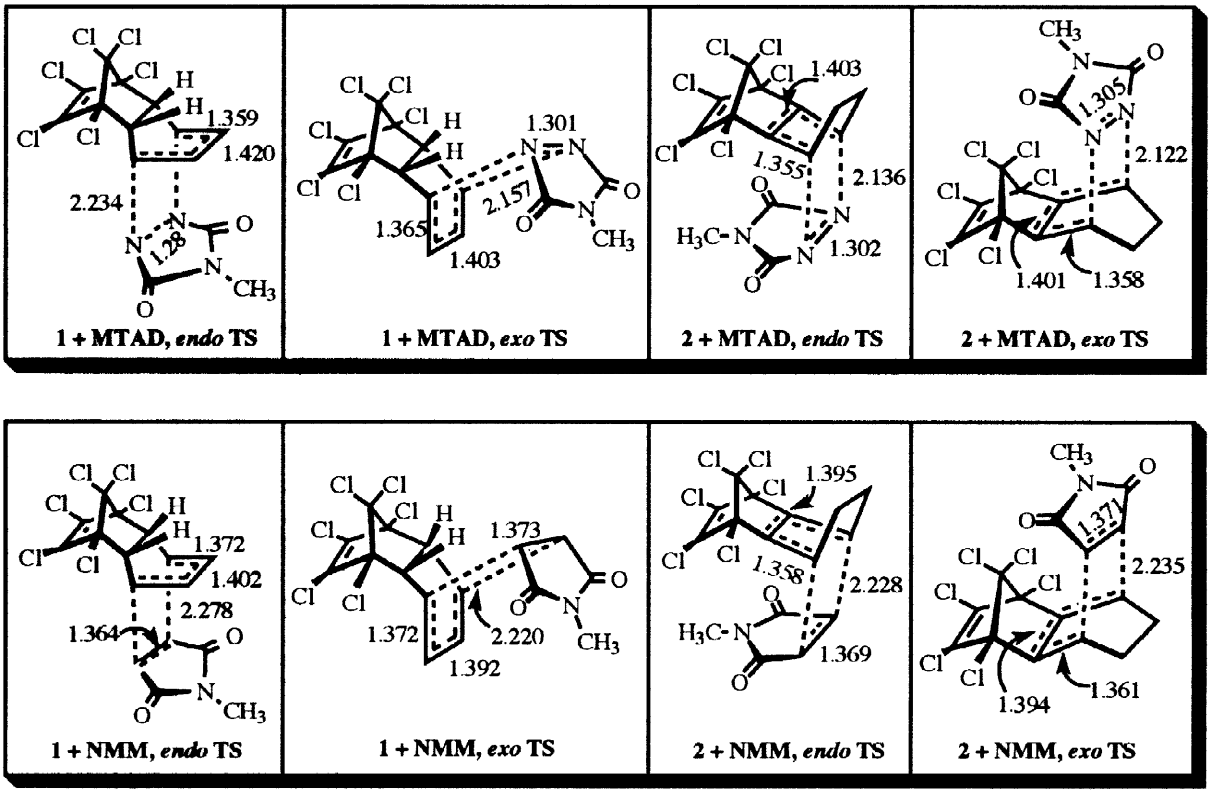
An analysis of the AM1 transition state geometries suggests that the computed transition structures obtained for MTAD and PTAD with diene **1** and **2** differ from those obtained for the corresponding reactions of these dienes with NMM. Importantly, we find that [4 + 2] cycloaddition of **1** with NMM proceeds via a concerted, synchronous transition state, while the corresponding reactions of **1** with MTAD and PTAD both proceed via highly asynchronous transition states. It appears that one of the newly-forming C···N bonds is nearly completely formed at a C-N distance of *ca.* 1.53 Å. However, the remaining C-N bond distance in this calculated (AM1) transition state is *ca.* 2.63 Å!

Others[5] have reported that, in transition states for hetero-Diels-Alder reactions, interactions of nitrogen and oxygen lone-electron pairs with π-systems could lead to the development of concerted, asynchronous transition states. However, the controversy that surrounds synchronous *vs.* asynchronous concerted transition states has not yet been settled.[6] Nevertheless, it should be noted that synchronous transition structures are predicted for [4 + 2] cycloadditions between symmetrically substituted dienes and dienophiles.[7] Experimentally observed kinetic isotope effects (KIEs) provide the strongest evidence for synchronicity in such symmetrical Diels-Alder reactions.[8,9]

As a next step toward understanding these cycloaddition reactions, a series of ab initio calculations was performed. For purposes of initial comparison, we have modeled Diels-Alder cycloaddition of 1,3-butadiene to MTAD at both semi-empirical (AM1 Hamiltonian) and ab initio 3-21G* levels of theory. The results of these calculations indicate that the AM1 transition state is asynchronous, as was computed previously for the corresponding Diels-Alder reactions with dienes **1** and **2**. However, at the HF/3-21G* level of theory, a highly synchronous transition state is obtained for each of these Diels-Alder reactions that possesses an activation barrier of 11 kcal-mol^{-1}. The corresponding AM1-calculated activation barrier is 20 kcal/mol higher than calculated at the HF/3-21G* level of theory. These highly disparate computational results, together with available reports of concerted, synchronous transition states for Diels-Alder reactions between sysmmetrical dienes and symmetrical dienophiles, prompted us to examine our systems at ab initio levels of theory.

The computed activation barriers obtained for diene **1** and **2** with MTAD and NMM by using an HF/3-21G* basis set are summarized in Table 2. It can be seen (Figure 1) that the transition states thus formed are synchronous in nature.

The computed HF/3-21G* transition state structural parameters of interest are shown in Figure 1. Thus, the newly-formed C···N bonds are developing to an equal extent in all cases studied; the C-N bond distances in the calculated transition states range between 2.12-2.27 Å.



1 + MTAD, *endo* TS | **1 + MTAD, *exo* TS** | **2 + MTAD, *endo* TS** | **2 + MTAD, *exo* TS**

1 + NMM, *endo* TS | **1 + NMM, *exo* TS** | **2 + NMM, *endo* TS** | **2 + NMM, *exo* TS**

Figure 1. Transition state geometries (distances in Å) for Diels-Alder cycloadditions of **1** and **2** to MTAD and NMM, calculated at the HF/3-21G* level of theory

The computational results indicate that MTAD is expected to approach diene **1** via its *exo* face. Indeed, the approach of MTAD via the *endo* face of **1** is calculated to be 15 kcal-mol^{-1} higher than via the alternative *exo* approach. On the other hand, analysis of the corresponding calculated activation barriers for Diels-Alder reaction of **2** with MTAD suggests that this dienophile is expected to approach diene **2** preferentially via its *endo* face. Here, the relative energy difference for approach of MTAD via the *exo* vs. the *endo* face of **2** is 5 kcal-mol^{-1} (see data in Table 2).

The computed activation barriers for Diels-Alder cycloadditions of dienes **1** and **2** with NMM clearly reveal that these reactions are expected to be much slower *vis-à-vis* the corresponding reactions of these dienes with MTAD and PTAD (see Table 2). The predicted high activation energy for diene **2** with NMM, computed at the HF/3-21G* level of theory, provides a cogent rationalization for the observed failure of this reaction.

Single-point calculations performed by using B3LYP/6-31G*//HF/3-21G* basis set[9] lead to much lower activation barriers for these reactions (see Table 2). The results thereby obtained permit us to rationalize the observed, virtually instantenous reaction of MTAD with diene **1**, since the activation barrier for this reaction is only 6.1 kcal-mol^{-1} at the B3LYP level of theory. Thus, this analysis predicts a greatly reduced energy gap between *exo* and *endo* modes of facial attack by MTAD upon diene **1** and **2** when compared to the results obtained at the HF/3-21G* level of theory.

The observed preferential approach of dienophiles in the case of diene **1** and **2** can be rationalized in terms of a combination of steric and electrostatic effects. Approach of MTAD toward the *endo* face of diene **1** leads to electrostatic repulsions between the chlorine atom lone-pairs in the Cl-C=C-Cl moiety located in the diene and the N-Me nitrogen atom lone-electron pair in the dienophile. Here, the relevant interatomic distances are 3.09 Å. In addition, the same C=C π-orbitals in the diene can also exert electrostatic repulsion toward the N-Me nitrogen atom lone-pair in the dienecophiile; here, the relevant interatomic distances are only 2.70 Å.

Approach of MTAD toward the *endo* face of diene **1** is expected to result in deleterious *steric* interactions between this dienophile and chlorine atoms that reside on the norbornene C=C double bond in diene **1**. In the case of approach by MTAD toward the *exo* face of **1**, the N=N nitrogen atoms in MTAD are removed from the *syn*-Cl atom in the apical dichloromethylene group in the norbornene moiety by 4.96 Å. Hence, destructive steric (and electorstatic) interactions are likely to be minimized when MTAD approaches toward the *exo* face of diene **1**.

The influence of steric and electrostatic effects exerted by Cl atoms has been studied.[10] In the case of diene **2**, approach of MTAD toward the *exo* face of **2** would lead to a transition structure in which the interatomic distance between the N-Me nitrogen atom in the dienophile and the *syn*-Cl atom in the apical CCl_2 group in the norbornene moiety is only 3.06 Å. This is expected to result in severe steric and electrostatic diene-dienophile repulsions that should result in destabilization of this transition state. For the corresponding approach of MTAD toward the *endo* face of diene **2**, the interatomic distance between the N-Me nitrogen atom in the dienophile and chlorine atoms that reside on the norbornene C=C double bond in diene **2** is somewhat greater in the transition structure, i.e., *ca.* 3.5 Å. Thus, destabilizing steric and electrostatic effects are likely to be less severe in the case of *endo* approach, which, accordingly, should be favored *vis-à-vis* the corresponding *exo* approach mode. NMM would also be expected to experience similar steric and electrostatic interactions with dienes **1** and **2**, respectively. Finally, the high activation barriers obtained for Diels-Alder reaction between MTAD and diene **2** via either *exo* or *endo* approaches is consistent with the observed sluggishness of this Diels-Alder reaction.

Frontier Molecular Orbital (FMO) Analysis. Additionally, FMO analysis was performed by using an ab initio HF/3-21G* basis set; the results thereby obtained appear in Table 3. The smaller the difference between HOMO-LUMO energies, the greater will be the stability of the forming filled MOs.[11] The data in Table 3 suggest that the smallest orbital energy difference occurs in all examples studied upon mixing of the HOMO of the diene with the LUMO of the dienophile. This result, which reflects the most favorable orbital interaction in the transition state, is consistent with expectations for a normal (rather than inverse) electron demand Diels-Alder reaction.[12]

Comparison of the energy differences ($\Delta E = E_{LUMO} - E_{HOMO}$) for Diels-Alder reactions of dienes **1** and **2** with the various dienophiles (Table 4) reveals a clear difference between them. The energy difference obtained for Diels-Alder reactions that involve NMM as dienophile is *ca.* 1eV higher than the corresponding reactions that involve MTAD and PTAD. This result is consistent with our experimental observation that NMM is less reactive than either MTAD or PTAD toward undergoing Diels-Alder cycloadddition to either dienes **1** or **2**.

Conclusions. AM1 and ab initio molecular orbital caculations have been performed in an attempt to rationalize the observed experimental results obtained for Diels-Alder reactions of dienes **1** and **2** with a variety of dienophiles (i. e., MTAD, PTAD, and NMM). The observed π–facial selectivities of these reactions are consistent with the results of AM1 calculations (see Table 1). However, the AM1-computed activation barriers appear generally to be high when compared with the corresponding activation energies that have been calculated at the HF/3-21G* and B3LYP/6-31G* levels of theory.

The AM1-calculated transition structures obtained for MTAD and PTAD with dienes **1** and **2** are both asynchoronous; however, AM1 calculations predict that the corresponding Diels-Alder reactions of **1** and **2** with NMM proceed via synchronous transition states. The results of AM1 calculations correctly predict that activation barriers for the preferred modes of MTAD and PTAD cycloadditions **1** are lower than those for the corresponding cycloadditions of these dienophiles to **2**. However, AM1 incorrectly predicts that the Diels-Alder reaction of **1** with NMM to afford **5b** should be a relatively facile process *vis-à-vis* the corresponding cycloadditions of **1** to MTAD and PTAD (Table 1).

Table 1. Calculated (AM1)[2a] enthalpies of activation for [4 +2] cycloadditions of dienes **1** and **2** with various dienophiles.

Diene	Dienophile	Diels-Alder Cycloadduct	ΔH$^{\neq}$ (AM1)[a] (kcal-mol^{-1})	Diene	Dienophile	Diels-Alder Cycloadduct	ΔH$^{\neq}$ (AM1)[a] (kcal-mol^{-1})
1	MTAD	3a	49.50	2	MTAD	6a	47.83
1	MTAD	3b	43.12	2	MTAD	6b	49.07
1	PTAD	4a	49.10	2	PTAD	7a	47.41
1	PTAD	4b	42.59	2	PTAD	7b	48.59
1	NMM	5a	45.40	2	NMM	*b*	44.92
1	NMM	5b	32.50	2	NMM	*b*	41.27

[a]Reference 2;[b]No reaction.

The foregoing experimental observations can be accounted for by the results of ab initio calculations performed at the HF/3-21G* level of theory. The activation barriers thus obtained are significantly lower in all the cases than those predicted on the basis of semi-empirical (AM1) calculations. The observed π-facial selectivities of these Diels-Alder reactions are in good agreement with the corresponding calculated results. The relative lack of diene reactivity of **2** *vis-à-vis* **1** is also evident upon inspection of the HF/3-21G*- and Becke 3LYP/6-31G*-calculated activation barriers for Diels-Alder reaction of each of these dienes with MTAD. Ab initio calculated activation barriers clearly reveal the reduced dienophilic reactivity of NMM compared to MTAD and PTAD. Finally, FMO analyses also reveal the reduced dienophilic reactvity of NMM *vis-à-vis* that of MTAD and PTAD. The computational results indicate that a combination of steric and electrostatic interactions appear to be the primary factors that control π-facial selectivities in the Diels-Alder cycloadditions studied herein .

Table 2. Activation barriers of transition states for dienes **1** and **2** with MTAD and NMM computed at HF/3-21G* and B3LYP/6-31G* levels of theory.

Diene	Dienophile[a]	Diels-Alder Cycloadduct	HF/3-21G* (kcal-mol^{-1})	B3LYP/6-31G*// HF/3-21G* (kcal-mol^{-1})
1	**MTAD**	**3a**	27.2	16.5
1	**MTAD**	**3b**	12.3	6.1
2	**MTAD**	**6a**	24.2	12.6
2	**MTAD**	**6b**	29.6	17.4
1	**NMM**	**5a**	47.1	34.7
1	**NMM**	**5b**	27.5	19.4
2	**NMM**	*b*	41.4	28.8
2	**NMM**	*b*	48.3	34.4

[a]MTAD = 4-methyl-1,2,4-triazoline-3,5-dione; NMM = *N*-methylmaleimide
[b]No reaction

Table 3. Energy differences ($\Delta E = E_{LUMO} - E_{HOMO}$), in eV, of the HOMO and LUMO orbitals of dienes **1** and **2** with respect to various dienophiles calculated at the HF/3-21G* level of theory.

Dienophile\Diene	1 (HOMO)	2 (HOMO)	1 (LUMO)	2 (LUMO)
MTAD (LUMO)	9.44	9.48		
MTAD (HOMO)			13.91	14.14
PTAD (LUMO)	9.23	9.27		
PTAD (HOMO)			12.15	12.38
NMM (LUMO)	10.43	10.48		
NMM (HOMO)			13.57	13.80

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