

# On the Origins of Diastereofacial Selectivity of [4 + 2] Cycloadditions in Cage-Annulated and Polycarbocyclic Diene/Dienophile Systems

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## ABSTRACT

$\pi$ -Facial diastereoselectivities in Diels–Alder reactions that involve  $\pi$ -facially differentiated cyclohexa-1,3-dienes, i.e., 3-substituted or 3–10-disubstituted hexacyclo-[10.2.1.0.2.110.4.90.4.140<sup>9,13</sup>]pentadeca-5,7-dienes have been investigated. Two types of reactions have been examined experimentally and theoretically: (i) reactions of cage-annulated,  $\pi$ -facially differentiated cyclohexa-1,3-dienes with  $\pi$ -facially symmetric dienophiles and (ii) reactions of  $\pi$ -facially symmetric dienes with cage-annulated,  $\pi$ -facially differentiated dienophiles.

## I. Introduction

The importance to synthetic organic chemists of thermal [4 + 2] cycloaddition processes, a reaction first announced by Diels and Alder in 1928,<sup>1</sup> is matched in importance only by the aldol reaction. Both reactions are facile, and each can be characterized to proceed by way of an aromatic transition state that possesses a cyclic array of six electrons (Figure 1). It is, therefore, not surprising that these two reactions are among the most important reactions in

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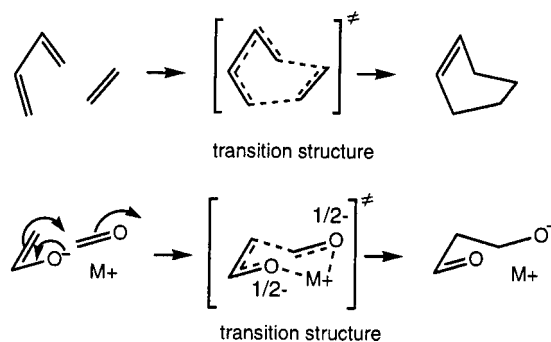


FIGURE 1. Diels–Alder and aldol reaction mechanisms that depict six-electron cyclic transition states.

organic chemistry. Each reaction has been utilized extensively to prepare optically active compounds in situations that demand rigorous stereoelectronic control. Indeed, the nature of the cyclic transition states, including their preferred conformations, provides the basis for this control. Thus, Diels–Alder reactions, which have found extensive application for the synthesis of carbocyclic<sup>2</sup> and heterocyclic<sup>3</sup> six-membered ring compounds, proceed by way of a boat transition structure. In contrast, aldol condensations, which can proceed by way of a chair or half chair transition structure, are employed in highly stereoselective syntheses of wide variety of alicyclic compounds.

Recently, our respective research groups, working individually and collaboratively, have focused upon the high degree to which  $\pi$ -facial selectivity (i.e., *diastereoselectivity*) has been observed to accompany kinetically controlled thermal Diels–Alder reactions between cage-annulated dienes or dienophiles in which one of the components contains nonequivalent  $\pi$  faces that are differentiated by the dissymmetry of a cage structure. This work was undertaken in an effort to improve our understanding of the factors that contribute to diastereoselectivity in these reactions and, thence, to determine the extent to which reaction specificity can be predicted by computational models.<sup>4</sup>

Two distinct situations have been examined experimentally and theoretically: (i) reactions of cage-annulated,  $\pi$ -facially differentiated cyclohexa-1,3-dienes with  $\pi$ -facially symmetric dienophiles (see Figure 2) and (ii) the opposite diene/dienophile configuration wherein  $\pi$ -facially symmetric dienes are allowed to react with cage-annulated,  $\pi$ -facially differentiated dienophiles. A variety of theoretical methods have been applied to these systems, as detailed in the examples that follow.

## II. Reactions of Cage-Annulated, $\pi$ -Facially Differentiated Cyclohexa-1,3-dienes with $\pi$ -Facially Symmetric Dienophiles

In our laboratories<sup>5,6,7</sup> and elsewhere,<sup>8,9,10</sup> 3-substituted- or 3–10-disubstituted hexacyclo[10.2.1.0.2.110.4.90.4.140<sup>9,13</sup>]pentadeca-5,7-dienes **1** and **2**<sup>11</sup> (Figure 2) were employed

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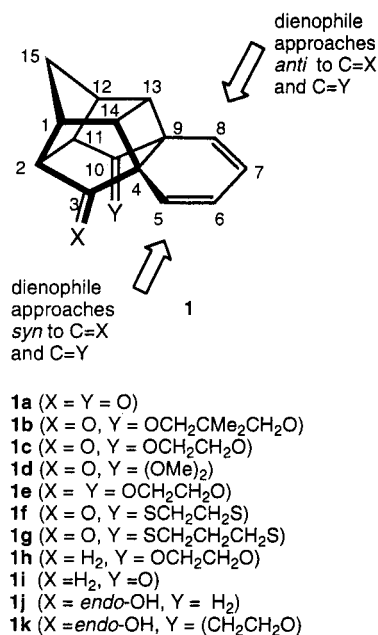


FIGURE 2.  $\pi$ -Facial selectivity in Diels–Alder cycloadditions to dienes **1** and **2**.

as the diene of choice. Diene **1** is prepared readily and inexpensively in two synthetic steps by starting with cyclopentadiene and 1,4-naphthoquinone.<sup>8,12</sup> Both **1** and **2** contain a structurally rigid cage moiety that renders the syn and anti  $\pi$  faces of the cyclohexa-1,3-diene moiety diastereotopically nonequivalent.

Diels–Alder cycloadditions of **1a** to moderately reactive,  $\pi$ -facially symmetric dienophiles such as *p*-benzoquinone,<sup>5,8</sup> methyl acrylate,<sup>5</sup> maleic anhydride,<sup>8</sup> and acrylonitrile,<sup>8</sup> proceed via predominant or even exclusive approach of the dienophile toward the syn  $\pi$  face of the diene. Similar results have been reported<sup>11</sup> for the corresponding Diels–Alder cycloadditions of similar dienophiles [i.e., *p*-benzoquinone, maleic anhydride, and dimethyl acetylenedicarboxylate (DMAD)] to diene **2** (X = Y = O). Ketone protecting groups (e.g., ketals) have been demonstrated to function as stereodirectors of syn/anti  $\pi$ -facial diastereoselectivity in Diels–Alder cycloadditions of **1b** and **1c** to DMAD.<sup>10</sup>

We have also investigated [4 + 2] cycloadditions that involve reaction of an unsymmetrically functionalized diene of the type **1** (X  $\neq$  Y) with an unsymmetrically functionalized dienophile (e.g., H<sub>2</sub>C=CHZ). Here, it should

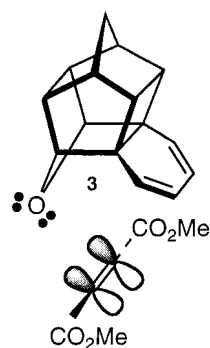


FIGURE 3. Interaction between an oxygen lone pair in **3** and a DMAD  $\pi$ -orbital.

be noted that in addition to syn/anti diastereoselectivity, the substituent, Z, in the resulting cycloadduct may reside on a carbon atom that lies *proximal* or *distal* to the C=X functionality in the diene, thereby resulting in as many as four possible Diels–Alder cycloadducts.

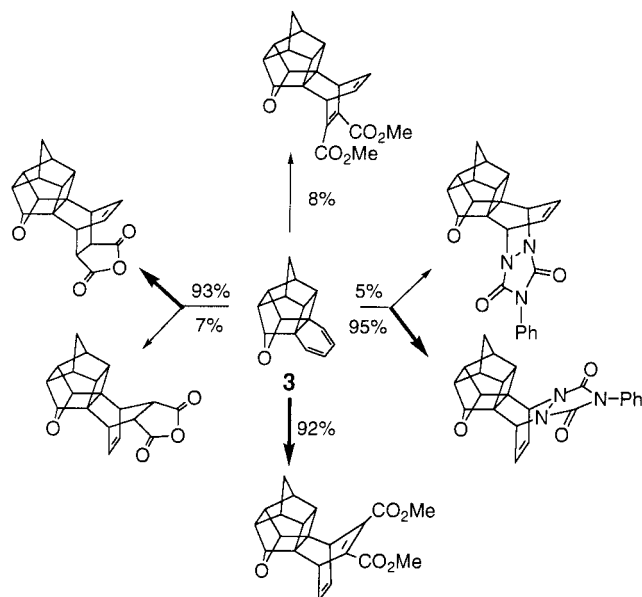
Diels–Alder cycloadditions of H<sub>2</sub>C=CHCO<sub>2</sub>Me to dienes **1c–1g** have been found to proceed with a high degree of syn  $\pi$ -facial diastereoselectivity but with only modest proximal/distal regioselectivity.<sup>5</sup> The results of fixed model molecular mechanics (MM2) transition-state calculations frequently account satisfactorily for the observed  $\pi$ -facial diastereoselectivities in these reactions. However, this level of theory is incapable of accounting for the more subtle proximal/distal regioselectivities that accompany reactions of this type.<sup>6</sup>

Attempts have been made to employ frontier orbital analysis with highest-occupied and lowest-unoccupied (HOMO/LUMO) orbital energies calculated by using semiempirical MO theory. However, such approaches fail to correlate the variation in HOMO/LUMO energies among dienes **1c–1g** with observed proximal/distal regioselectivities.

Compound **3** was synthesized and studied in an effort to examine the possibility that through-space electronic effects may affect facial selectivity.<sup>13</sup> This compound possesses a lone pair of electrons on the ether oxygen atom, which is centrally placed to interact with a dienophile as it approaches from the face of the diene anti to the cyclobutane group. In particular, this lone pair is positioned to interact with the  $\pi$  orbital of DMAD, which is orthogonal to the forming  $\sigma$  bonds (Figure 3).<sup>14</sup>

When **3** was allowed to react with DMAD, a strong preference (92%) for addition from the face of the diene syn to the cyclobutane group was observed (Figure 4). A similar preference has been observed for the corresponding reaction of **3** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). This observation contrasts with the results of the corresponding reactions of **3** with olefinic dienophiles, a typical example of which involves the use of maleic anhydride (MA).

These intriguing experimental results suggest the operation of electronic destabilization of the syn transition state for reactions of **3** with DMAD and PTAD. In addition, these results have prompted calculations of the transition states to be performed at the integrated molecular orbital–

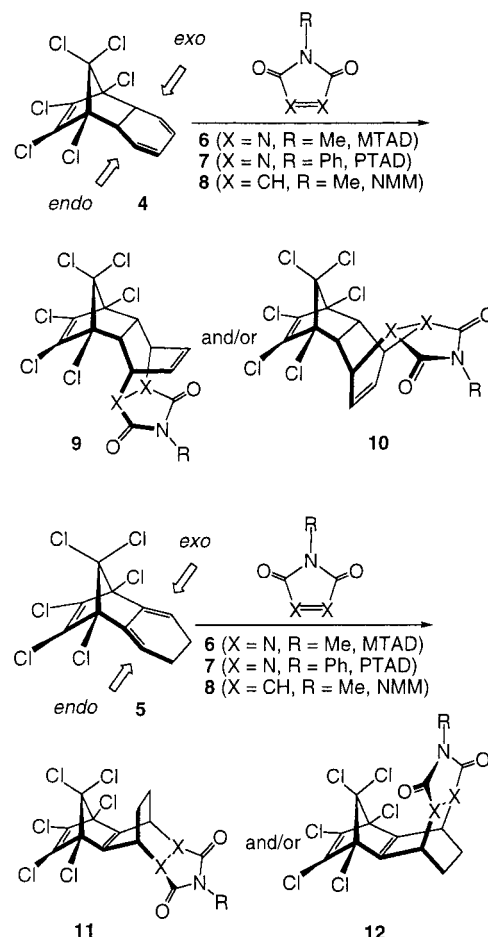


**FIGURE 4.** Diels–Alder reactions of **3** with dimethyl acetylenedicarboxylate (DMAD), 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), and maleic anhydride (MA).

molecular orbital (IMOMO) level of theory<sup>15</sup> that employs the G2MS computational procedure<sup>16</sup> and second-order Møller–Plesset (MP2) perturbation theory.<sup>17</sup> These calculations were carried out to test the hypothesis that the orthogonal alkyne  $\pi$  orbital of DMAD interacts in the transition state with the lone pair of the ether oxygen in **3**. It should be noted that this interaction is *not* present in the corresponding cycloaddition reaction of MA with **3**.

Diels–Alder cycloadditions to **3** are predicted at the IMOMO (G2MS:MP2) level of theory,<sup>5a</sup> using methods developed by Professor Keiji Morokuma, to afford syn:anti ratios of 99.9:0.1 for ethylene and 7.2:92.8 for acetylene. These results agree well with the corresponding experimental ratios of 93:7 and 8:92 for Diels–Alder cycloadditions of MA and DMAD, respectively, to **3**. Examination of the molecular orbitals for the Diels–Alder transition state reveals that the interaction of the perpendicular  $\pi$  orbitals of acetylene with the oxygen lone pairs destabilizes the syn transition state for acetylene cycloaddition. For the corresponding [4 + 2] cycloaddition to ethylene, cycloaddition proceeds predominantly via the less sterically hindered syn face. Higher level single point energy calculations for the reactions of **3**, performed by using Becke’s three-parameter hybrid method<sup>18</sup> with the Lee, Yang, and Parr correlation functional<sup>19</sup> and geometry-optimized with the 6-31G\* polarization basis set<sup>20</sup> (B3LYP/6-31G\*), afforded more accurate results with respect to the “benchmark” G2MS:MP2 values.

Overall, the integrated approach appears to offer a successful and viable method to study these relatively large Diels–Alder reactions, which otherwise could not be examined accurately. However, these high-level calculations require a correspondingly high level of expertise; thus, this approach may not appeal to the faint-of-heart! Most organic chemists find lower-level calculations easier



**FIGURE 5.** Diels–Alder reactions of **4** and **5** with 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), and *N*-methylmaleimide (NMM).

to handle and to interpret. For this reason, the studies described below, which require less highly specialized calculations, may prove to be more accessible to synthetic chemists. As indicated by the results described above, high-level calculations are required when low-level calculations provide inconclusive results or when special electronic effects might operate.

More recently, Diels–Alder cycloadditions of two isomeric, diastereofacially nonequivalent tricyclic dienes, i.e., **4** and **5** (Figure 5), to three symmetrical, highly reactive dienophiles, i.e., 4-methyl-1,2,4-triazoline-3,5-dione (MTAD, **6**), PTAD (**7**), and *N*-methylmaleimide (NMM, **8**), have been studied.<sup>21</sup> Significant differences between the reactivities and diastereofacial selectivities of dienes **4** and **5** toward dienophiles **6–8** were noted. Thus, diene **5** proved to be uniformly less reactive than **4** toward all dienophiles studied. The exclusive products formed via [4 + 2] cycloaddition of **4** to all three dienophiles possess the general structure **9** (Figure 5), i.e., those cycloadducts which result via exclusive approach of the dienophile upon the exo face of the diene. In contrast to this result, **5** afforded a mixture of cycloadducts, **11** + **12**, via each of its Diels–Alder cycloadditions to dienophiles **6–8**. Furthermore, the major product of each of these reactions results via endo approach of the dienophile upon the diene!<sup>21</sup>

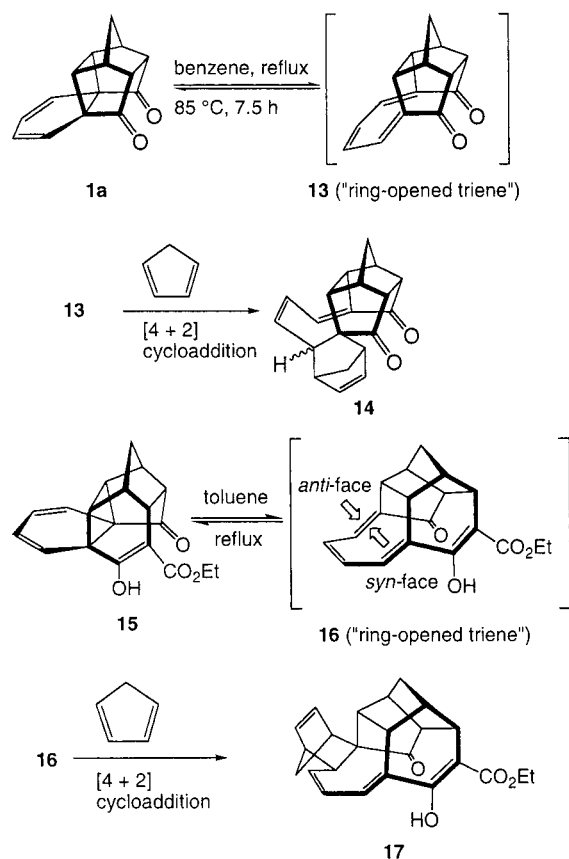
The experimentally observed  $\pi$ -facial diastereoselectivities of dienophiles **6–8** toward dienes **4** and **5** are mirrored by the results of semiempirical (AM1 Hamiltonian)<sup>22</sup> MO calculations. However, the relative lack of reactivity of diene **5** vis-à-vis **4** is *not* apparent when we compare the AM1-calculated activation barriers for Diels–Alder cycloaddition of each diene to NMM as dienophile. Importantly, the semiempirical (AM1)-calculated transition structures for Diels–Alder cycloaddition of both **4** and **5** with MTAD and with PTAD are *asynchronous*, whereas the computational results obtained for their corresponding Diels–Alder cycloadditions to NMM (**8**) suggest that these transition structures are *synchronous*.<sup>23</sup>

An improved understanding of the nature of these reactions is gained by application of higher levels of theory. Thus, the results of *ab initio* calculations performed at both the Hartree–Fock HF/3-21G\*<sup>24</sup> and B3LYP/6-31G\* levels of theory account for observed *syn/anti*  $\pi$ -facial diastereoselectivities and also for the observed relative reactivities of dienes **4** and **5** toward the various dienophiles studied. For example, the results of B3LYP/6-31G\* calculations indicate that the activation barrier associated with the Diels–Alder transition state that results via approach of MTAD toward the *exo* face of diene **4** [i.e., the transition state that leads to the formation of cycloadduct **10** (X = N, R = Me)] is favored vis-à-vis the corresponding *endo* approach transition state by  $\sim 10$  kcal mol<sup>-1</sup>. Importantly, *N*-methyl maleimide is seen to function as a reluctant dienophile toward dienes **4** and **5**. The calculated (B3LYP/6-31G\*) activation barriers associated with the transition states that lead to products **10** (X = CH, R = Me) and **12** (X = CH, R = Me) are  $\sim 19$  and 34 kcal mol<sup>-1</sup>, respectively.<sup>23</sup>

### III. Reactions of Cage-Annulated, $\pi$ -Facially Symmetric Cyclohexa-1,3-dienes with $\pi$ -Facially Differentiated Dienophiles

Our initial studies of these Diels–Alder cycloadditions employed **1a** as substrate; however, in this case, **1a** fulfilled the role of dienophile rather than diene! Compound **1a**, when refluxed in benzene solution ( $\sim 80$  °C), suffers thermal 6-electron distrotatory electrocyclic ring opening, thereby affording the corresponding cage-annulated triene, **13**, which can be trapped in situ by cyclopentadiene (Figure 6).<sup>5,26</sup> Similar behavior has been observed for **15**. When this compound is refluxed in toluene, electrocyclic ring opening occurs with concomitant formation of ring-opened triene **16**, which can be trapped in situ by cyclopentadiene (Figure 6).<sup>27a</sup>

It should be noted that symmetry-allowed electrocyclic 6-electron disrotation might afford two ring-opened trienes, i.e., **13a** and **13b** (Figure 7), either (or both) of which might be trapped in situ with cyclopentadiene and also might undergo thermal equilibration at 80 °C. We have investigated computationally two issues that relate to the generation and trapping of triene **13**, i.e., (i) the relative energetics of formation of **13a** vis-à-vis **13b** via electrocyclic ring-opening of **1a** and (ii) the relative energies



**FIGURE 6.** Electrocyclic ring opening of **1a** and of **15**, with subsequent Diels–Alder cycloaddition of cyclopentadiene to **13** and **16**, respectively.

of the various transition states that lead to the formation of Diels–Alder cycloadducts **14a** and **14b** that might result via in situ trapping of the ring-opened triene by cyclopentadiene.<sup>27b</sup>

Initially, the relative energetics of electrocyclic ring-opening of **1a** to **13a** and to **13b** were investigated by using semiempirical MO calculations (AM1 Hamiltonian). The results of these calculations indicate that formation of **13a** from **1a** is favored thermodynamically by  $\sim 24$  kcal mol<sup>-1</sup> and kinetically by  $\sim 22$  kcal mol<sup>-1</sup> relative to the corresponding ring-opening process that leads to the formation of **13b**.<sup>26</sup>

Next, the relative energetics of Diels–Alder cycloadditions of cyclopentadiene to **13a** that lead to the formation of **14a** and to **14b** were investigated computationally at the AM1 level of theory. Transition-state structures for these reactions were generated by applying restricted Hartree–Fock (RHF) theory. The results thereby obtained suggest both a thermodynamic ( $\sim 2.4$  kcal mol<sup>-1</sup>) and kinetic ( $\sim 1.7$  kcal mol<sup>-1</sup>) preference for formation of **14a** vis-à-vis **14b**. This prediction, borne out qualitatively by experiment,<sup>26</sup> demonstrates the usefulness of the simple low-level, user-friendly semiempirical method to obtain information of predictive value.

Dramatically different results were obtained when two electron-poor dienes, i.e., hexachlorocyclopentadiene (**18a**) and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (**18b**) were employed in Diels–Alder reactions with **1a**. Each

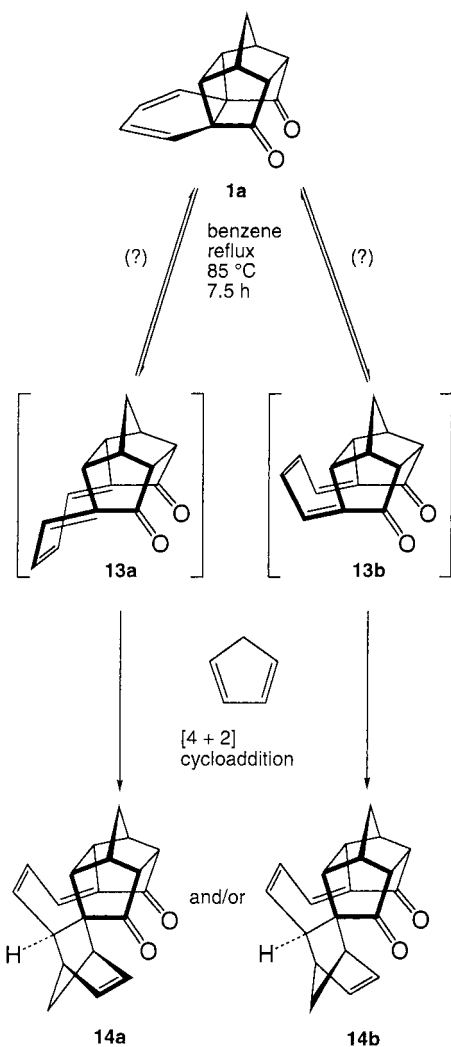


FIGURE 7. Stereochemistries of electrocyclic ring opening of **1a** and of subsequent Diels–Alder cycloaddition of cyclopentadiene to **13**.

reaction, when performed in refluxing xylene, afforded only one product (i.e., cycloadducts **19a** and **19b**, respectively, Figure 8). In each case, Diels–Alder cycloaddition occurred preferentially between the electron-poor diene (**18a** or **18b**) and one of the C=C double bonds in **1a** (electron-rich dienophile). The HOMO and LUMO associated with each reaction define an inverse-electron-demand Diels–Alder reaction.<sup>27</sup> Interestingly, cycloaddition occurs to afford **19a** and **19b**, respectively, despite the fact that the reaction temperature significantly exceeds the temperature at which **1a** undergoes electrocyclic ring-opening to **13a** (i.e.,  $\leq 85$  °C)!

Because of the symmetry properties of the diene and dienophiles in these reactions, it was necessary to investigate computationally the relative energetics of four modes of Diels–Alder cycloaddition, i.e., endo,anti; exo,anti; endo,syn; and exo,syn. The results of semiempirical MO calculations (AM1 Hamiltonian) performed for these four modes of Diels–Alder cycloaddition of **1a** to **18a** (Figure 9),<sup>28</sup> suggest that the transition state that leads to **19a** is preferred energetically vis-à-vis the corresponding transition states that would result via any

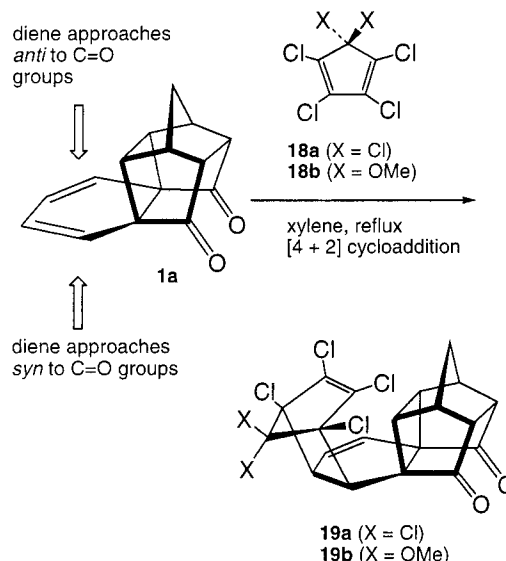


FIGURE 8. Reaction of **1a** as a dienophile.

of the remaining three cycloaddition modes. In addition, **19a** is the thermodynamically favored cycloadduct. It should be noted that the AM1-calculated HOMO–LUMO interactions are consistent with inverse-electron-demand Diels–Alder cycloaddition formalism.<sup>27</sup> The results of molecular mechanics (MMX) calculations<sup>29</sup> indicate that nonbonded steric interactions between the diene and the approaching dienophile play little or no role in determining the eventual outcome of the Diels–Alder cycloaddition that leads from **1a** to **16a**.

A final example of this category of Diels–Alder reaction is shown in Figure 10, wherein cyclopentadiene, by serving as a  $\pi$ -facially symmetric diene, is allowed to react with cage-annulated,  $\pi$ -facially differentiated dienophile **20**. In our hands, this reaction afforded a mixture of cycloadducts **21a** and **21b**, in which the former product predominates.<sup>30</sup> Calculation of the relative energetics of these two competing processes is in progress.

#### IV. Summary and Conclusions

Diels–Alder reactions between (i) various dienophiles and cage-annulated cyclohexa-1,3-dienes (i.e., systems **1**, **3**, **4**, and **5**) and (ii) various dienes and cage-annulated dienophiles (i.e., systems **1a** and **13**) have been investigated. The results of relevant molecular mechanics, semiempirical, and ab initio molecular orbital calculations generally are consistent with experiment and provide insight into the detailed mechanism of each of the reactions that has been investigated experimentally.

Development of a fundamental understanding of  $\pi$ -facial selectivity in Diels–Alder reactions offers a significant challenge to organic and theoretical chemists. The ability to conduct high-level calculations that include electron correlation is necessary if this goal is to be achieved in a timely and meaningful way. In the case of Diels–Alder cycloadditions of **3** with acetylenes, high-level calculations are required to establish the importance of the interaction between the perpendicular  $\pi$ -orbital

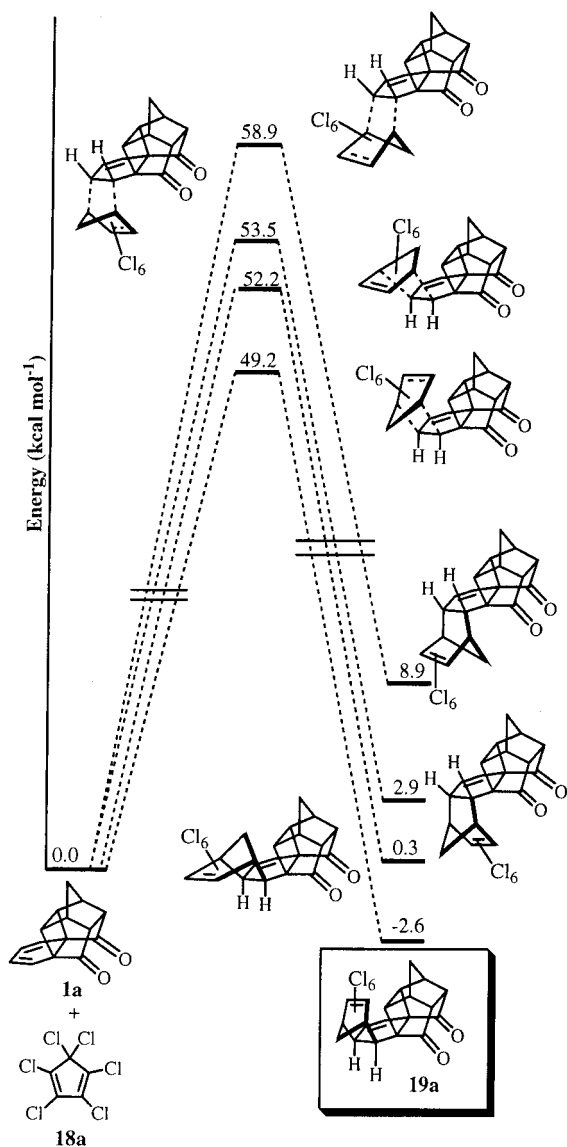


FIGURE 9. Calculated (AM1) energy profiles that correspond to four possible modes of Diels–Alder cycloaddition of hexachlorocyclopentadiene (**18a**, diene) to **1a** (dienophile).

of acetylene and the oxygen lone-pairs. This important electronic interaction selectively destabilizes the syn transition state for acetylene cycloaddition.

Despite the need in specialized cases for high level calculations, molecular mechanics, calculations in combination with semiempirical and ab initio molecular orbital calculations provide a simple and user-friendly method to predict stereoelectronic effects on Diels–Alder reactions between dienophiles and quite complicated cage-annulated cyclohexa-1,3-dienes (**1**, **3**, **4**, and **5**) and dienes and cage-annulated dienophiles (**1a** and **13**).

The success of high-level mixed methods suggest that within the next decade, theoretical calculations of transition states will become sufficiently rapid to enable organic chemists to predict  $\pi$ -facial selectivity in moderately complex systems. Incorporation of solvent (not a major complication in the case of those pericyclic reactions wherein charge effects are minimal) along with

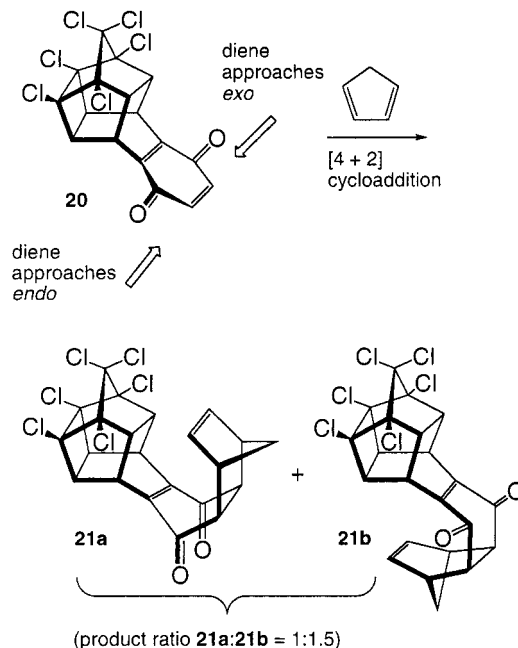


FIGURE 10. Reaction of **17** as a dienophile.

global minimum- and dynamics-related considerations constitute important issues that remain to be addressed constructively in the future. Meanwhile, we must rely upon the ingenuity of organic and theoretical chemists to continue to develop new generalizations that will increase our ability to render predictions that will prove of value to organic synthesis.

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