The Origin of *endo* Stereoselectivity in the Hetero-Diels–Alder Reactions of Aldehydes with *ortho*-Xylylenes: CH–π, π–π, and Steric Effects on Stereoselectivity

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Abstract: Theoretical studies of stereoselectivity have been carried out with B3LYP and MP2 calculations. The high *endo* selectivity of hetero-Diels–Alder reactions of *ortho*-xylylenes with acetaldehydes is shown to result from attractive CH–π interactions between alkyl groups of the aldehyde and the aromatic ring in the transition states of the reaction. For the hetero-Diels–Alder reactions of *ortho*-xylylenes with benzaldehyde, the stereoselectivity is shown to be mainly governed by the attractive π–π interactions between the phenyl rings of the benzaldehyde and the *ortho*-xylylene. MP2 calculations are necessary to reproduce the stabilizing dispersion interactions.

Keywords: ab initio calculations · cycloaddition · pi interactions · stacking interactions · stereoselectivity

Introduction

The hetero-Diels–Alder reaction has emerged as a powerful tool for the synthesis of six-membered heterocycles. The cycloaddition of electron-rich dienes with aldehydes and ketones are important methods in the process for synthesizing carbohydrates and other natural products. The Columbia and Sloan–Kettering groups have recently developed a family of *o*-xylylenes derived from benzocyclobutenes. These react under thermal conditions with aldehydes and selected imines to give cycloaddition products stereoselectively.[1, 2]

Cycloaddition reactions between *o*-xylylene derivatives and alkenes present high *endo* selectivity.[1, 3] The same *endo* preference has been found for the hetero-Diels–Alder reaction of *o*-xylylenes with the aldehydes tested.[2] This intriguing phenomenon complements previous stereochemical observations in Lewis acid catalyzed hetero-Diels–Alder reactions.[4] The *endo*/*exo* preference for the (hetero)-Diels–Alder reactions has been widely studied in the literature.[5, 6, 7] Despite this, there is no extensive agreement among the scientific community on the factors governing the stereoselectivity for these kind reactions.[8] Secondary orbital interactions (SOI) have been extensively invoked to explain the stereoselectivity of these reactions.[9] Nowadays, however, other well-known interactions are often invoked to explain the stereoselectivity (steric effects, electrostatic forces, hydrogen bonding, etc).[8]

We have explored the origin of stereoselectivity in the hetero-Diels–Alder reactions of *o*-xylylenes with acetaldehyde and benzaldehyde and have compared the experimental results for the same systems. Theoretical calculations using DFT (B3LYP) and post-HF (MP2) methods were performed to locate reactants and transition states along the reactions pathways. These results were used to analyze the effects that influence the *endo*/*exo* ratio. The reactions of 1,4-dihydroxy-1,3-butadiene with acetaldehyde and with benzaldehyde have been studied (Scheme 1 (1)), as well as the reactions of several disubstituted *o*-xylylenes with both aldehydes (Scheme 1 (2)).

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Methodology

Calculations were performed by using the Gaussian98 program.[10] The reactions where the dienophile is acetaldehyde were studied by using density functional theory, and the B3LYP functional. The 6-31G basis set was used for all atoms. Single-point energy calculations using the 6-31G(d)

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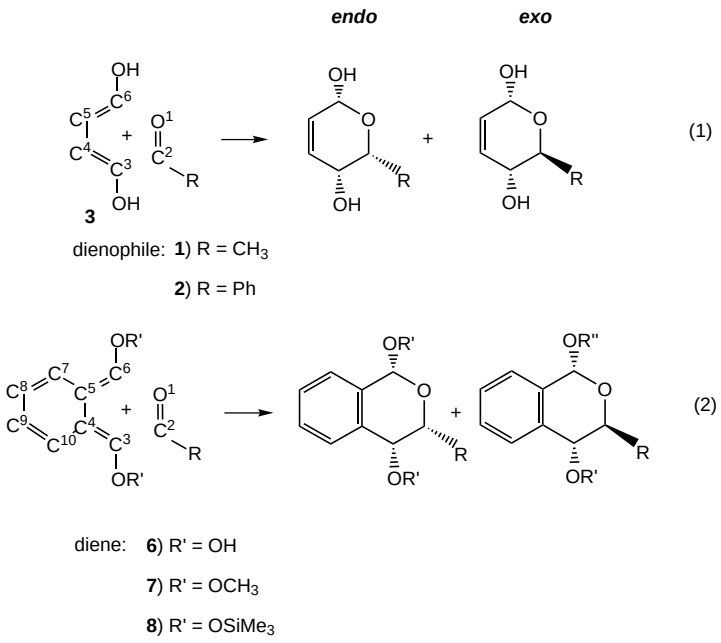


(1)

(2)

Scheme 1.

basis set on transition states were also performed. The *ortho*-xylylene/benzaldehyde reactions were studied by using DFT (B3LYP) and post-HF (MP2) methods. The 6-31G(d) basis set was used for all atoms. For each reaction, the reactants and transition states were fully optimized. Each transition structure gave only one imaginary harmonic vibrational frequency, corresponding to the motion involving formation of the new C–C and C–O bonds.

Results and Discussion

The experimental study of the hetero-Diels–Alder between several aldehydes and 1,2-*trans*-(*tert*-butyldimethylsiloxy)benzocyclobutene has been reported previously.[2] These reactions showed essentially complete *endo* specificity. These studies have now been extended to the reaction of acetaldehyde and benzaldehyde with 1,2-*trans*-dimethoxybenzocyclobutene, which has less bulky substituents.[11] *trans*-Dimethoxybenzocyclobutene reacts with acetaldehyde in [D_8]toluene at 60 °C. To avoid stereochemical scrambling that was observed upon chromatography, the adducts were directly oxidized to lactones which were analyzed by NMR spectroscopy. Only *endo* adducts were observed. The same benzocyclobutene reacts with benzaldehyde in [D_8]toluene at 60 °C. As before, only the *endo* adduct was observed.[11]

Benzocyclobutenes undergoes facile electrocyclic ring-opening to produce the corresponding *ortho*-xylylenes, which function as dienes in the hetero-Diels–Alder reactions with aldehydes (Scheme 1 (2)).[2, 11] The theoretical studies have been carried out using the corresponding *ortho*-xylylenes as dienes for the reactions. The results are presented in two sections. The first section describes the reactions of 1,4-dihydroxy-1,3-butadiene and dihydroxy-, dimethoxy-, and bis(trimethylsiloxy)-*o*-xylylenes with acetaldehyde. In the second section the reactions of the same dienes with benzaldehyde are described. Although both are rather simple aldehydes, acetaldehyde and benzaldehyde present entirely different challenges to theoretical analysis.

Diels–Alder reactions of acetaldehydes

The reaction of acetaldehyde (**1**) with 1,4-dihydroxy-1,3-butadiene (**3**) was studied first. The transition states for the reaction are presented in Figure 1. The C···O and C···C

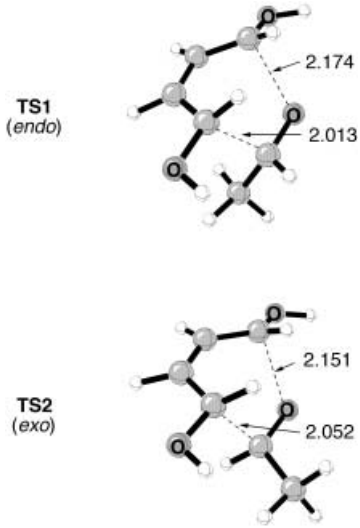
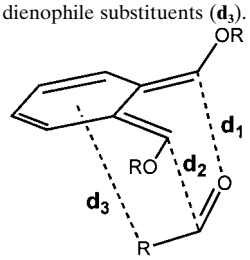


Figure 1. A view of the *endo* and *exo* transition states for the reaction of acetaldehyde with 1,4-dihydroxy-1,3-butadiene. Distances in Å.

forming bonds lengths are 2.174 and 2.013 Å for the *endo* transition state (**TS1**) and 2.151 and 2.052 Å for the *exo* transition state (**TS2**), respectively (Table 1). In both cases an asynchronous transition state has been found. This asynchro-

Table 1. Distances (in Å) at the transition states of the C···O ($\mathbf{d_1}$) and C···C ($\mathbf{d_2}$) forming bonds, and between the diene (center of forming benzene ring) and the dienophile substituents ($\mathbf{d_3}$).



		$\mathbf{d_1}$	$\mathbf{d_2}$	$\mathbf{d_3}$
1+**3**	**TS1**	2.174	2.013	3.292[a]
	TS2	2.151	2.052	–
1+**6**	**TS7**	2.297	2.203	3.794
	TS8	2.267	2.239	–
1+**7**	**TS9**	2.282	2.226	3.910
	TS10	2.268	2.222	–
1+**8**	**TS11**	2.356	2.194	3.778
	TS12	2.319	2.224	–

[a] Distance between the methyl carbon (dienophile) and the center of the forming double bond (diene).

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nous transition state is expected according to frontier molecular orbital theory. When the dienophile has two atoms differing in electronegativity (here carbon and oxygen) the LUMO has the highest coefficient on the less electronegative atom (carbon in this case). Hence, the diene HOMO/dienophile LUMO interaction is greater on the carbon atom than on the oxygen atom, thus promoting an asynchronous transition state.

The activation energies of the *endo* and *exo* pathways are 15.8 and 16.9 kcal mol^{-1}, respectively. The *endo* transition state is 1.1 kcal mol^{-1} lower in energy than the *exo* transition state. The calculations predict that the main product of the reaction of 1,4-dihydroxy-1,3-butadiene with acetaldehyde is the *endo* product. Vedejs et al.[12] demonstrated that thioaldehydes and cyclopentadiene react to give mainly the *endo* adducts, and that the trends with various substituents were consistent with stereoselectivity control by steric effects. In this case, steric effects should be small, since the substituents on the diene (two OH groups) and in the dienophile (a CH_3 group) are not bulky. The HOMO–LUMO primary interaction in both cases (*endo* or *exo*) is the same, so other secondary interactions must be responsible for the *endo* preference.

The Mulliken charge distribution indicate that the CH_3 moiety of acetaldehyde is slightly positively charged (charge is 0.01), while the carbons of the forming double bond of the diene are slightly negatively charged. The values of the charges for C^4 and C^5 are -0.07 and -0.14, respectively. Hence, in the case of the *endo* arrangement, there can be an electrostatic interaction between these two oppositely charged regions (the CH_3 moiety and the carbons of the forming double), which is lacking in the *exo* arrangement.

In the reaction of butadiene (**9**) with acetaldehyde (**1**) the diene is less negatively charged because of the absence of electron-donating hydroxy groups. Accordingly, the *endo* preference for this reaction should be smaller. The energies of activation for the *endo* and the *exo* pathways are 21.0 and 21.5 kcal mol^{-1}, respectively. The *endo* transition state (**TS3**) is more favorable than the *exo* transition state (**TS4**) by only 0.5 kcal mol^{-1}. The energy difference between the *endo* and the *exo* transition states is smaller than in the reaction of 1,4-dihydroxy-1,3-butadiene with acetaldehyde (1.1 kcal mol^{-1}). The Mulliken charges for C^4 and C^5 are -0.06 and -0.11, respectively, in the transition state. C^4 and C^5 are less negatively charged, the attractive interactions with the CH_3 moiety are smaller, and stereoselectivity drops.

The reaction of 1,4-dihydroxy-1,3-butadiene (**3**) with propene (**10**) has been also studied. In this particular case, the CH_3 moiety will not be so positively charged because the alkene is not electron-withdrawing. This should make the reaction much less stereoselective, if the reason given above is correct. In fact, the energy difference between the *endo* and *exo* transition states (**TS5** and **TS6**, respectively) is only 0.3 kcal mol^{-1}, with the *endo* transition state still the most favorable.

The details of geometries for these transition states are quite different from those obtained in previous theoretical studies carried out on the reaction of butadiene with formaldehyde.[13] Using RHF/3-21G it was found at that time that the transition state was nearly synchronous. The distance of the forming C···O bond (1.998 Å) was shorter than the distance of the C···C forming bond (2.133 Å). These different values were used to deduce that the reaction has a nearly synchronous transition state, since the equilibrium bond length of the C-O bond is shorter than that of the C-C bond. In the present study, the distances for the C···O and C···C forming bonds in the reaction of butadiene with acetaldehyde for the *endo* transition state are 2.101 and 2.057 Å, respectively. For the *exo* transition state these distances are 2.099 and 2.075 Å, respectively. The results reported here involve a method which is known to give more asynchronous and more reliable transition states geometries,[14] since DFT includes correlation energy, and a more flexible basis set may now be used.

The transition states for the reaction of acetaldehyde with butadiene-based dienes have the carbonyl groups twisted with respect to the termini of the diene. For instance, in the reaction of 1,4-dihydroxy-1,3-butadiene with acetaldehyde the O_1-C_2···C_3-C_6(diene) dihedral angles in the *endo* and *exo* transition structure are both -20°. The same tendency was found in the reaction of the butadiene with formaldehyde.[13] We believe the twisting is caused by electrostatic repulsion between the π system of the diene and the O lone pairs.[15]

Once the origin of the *endo* preference in the reaction of acetaldehyde with butadiene-based dienes was established, we studied the reactions of *o*-xylylenes with acetaldehyde. The *endo* and *exo* transition states found for the reaction of dihydroxy-*ortho*-xylylene (**6**) with acetaldehyde (**1**) are both asynchronous. In the *endo* transition state (**TS7**) the C···O forming bond length is 2.297 Å, and the C···C forming bond length is 2.203 Å. For the *exo* transition state (**TS8**) these distances are 2.267 and 2.239 Å, respectively. The charge transfer from the diene to the dienophile (based on the Mulliken charge distribution) is 0.23. Charges for the carbon, C^2, and oxygen, O^1, of acetaldehyde are 0.33 and -0.38, respectively, and for C^3 and C^6 in the diene are both 0.14. In the transition state the values become 0.27 and -0.51 for C^2 and O^1, and 0.14 and 0.32 for C^3 and C^6, respectively. In the transition state most of the charge transfer is to the oxygen of the acetaldehyde.

The reaction is highly exothermic. The energetic differences between the reactants and the products are practically the same for the *endo* and *exo* arrangements. In the case of the *endo* product, the reaction is exothermic by 48.1 kcal mol^{-1}, and for the *exo* product it is exothermic by 47.9 kcal mol^{-1}. The calculated activation energies for these reactions are very low, only 3.6 kcal mol^{-1} for the *endo* pathway, and 4.7 kcal mol^{-1} for the *exo* one. The *endo* transition state is preferred by 1.1 kcal mol^{-1}. Single-point calculations on these transition states using the 6-31G(d) basis set gave the same energetic difference between *endo* and *exo* transition states.

The Mulliken charge distribution for the groups not directly involved in the forming bonds indicate that the CH_3 moiety of acetaldehyde is slightly positively charged (+0.02 electrons), while the aromatic ring of the diene is slightly negatively charged in the transition state. The charges of the ring carbon atoms are $C^4 = 0.08$, $C^5 = 0.04$, $C^7 = -0.12$, $C^8 = -0.13$, $C^9 = -0.12$ and $C^{10} = -0.14$, respectively. The two carbon atoms

involved in the new forming double bond are slightly positive, while the other four carbon atoms of the ring are negatively charged. Hence, in the case of an *endo* arrangement, there is an electrostatic attraction between these two oppositely charged regions (the CH_3 moiety and the ring), which is lacking in the *exo* arrangement. The same justification is found for the *endo* preference here as in the reaction of acetaldehyde with butadiene-based dienes.

Additional quantum-mechanical calculations tested whether this electrostatic effect could cause the predicted stereoselectivity. The energy of interaction between acetaldehyde and a benzene ring was calculated. Benzene and the CH_3–CHO molecules were kept at the same geometry of the *endo* and *exo* transition states, and single-point energies were calculated. The interaction is more favorable for the *endo* arrangement by 0.6 kcal mol^{-1} than in the *exo*. Single-point calculations were also performed for benzene and methane in the same geometry that these fragments have in the *endo* and *exo* transition states. In this case (where the CH_3 moiety is not partially positive charged) the *exo* arrangement was more favorable by 1.6 kcal mol^{-1}. It appears that attractive electrostatic interactions between the CH_3 moiety of acetaldehyde, and the alkene of butadiene or the aromatic of benzene are responsible for the *endo* preference.

The reaction of the dimethoxy-*ortho*-xylylene (**7**) with acetaldehyde (**1**) has also been studied. This tests whether replacement of the hydroxyl H by an alkyl group alters the reaction pathway. Both *endo* (**TS9**) and *exo* (**TS10**) transition states are also asynchronous, giving a larger distance for the C···O than for the C···C forming distances bond. These values are 2.282 and 2.226 Å for the *endo* transition state and 2.268 and 2.222 Å for the *exo* transition state, respectively, all within 0.02 Å of the lengths for the dihydroxy case.

The activation energies for the *endo* and the *exo* pathways are 3.9 and 5.2 kcal mol^{-1}, respectively. The *exo* transition state is 1.3 kcal mol^{-1} higher in energy than the *endo* transition state, compared to 1.1 kcal mol^{-1} for the dihydroxy case. This difference is again 1.1 kcal mol^{-1} when single-point calculations on the *endo* and *exo* transition states using 6-31G(d) basis set. The OCH_3 groups therefore do not alter the stereochemical preference, and the electrostatic interaction between the aldehyde CH_3 moiety and the aromatic ring appears once more to be the main cause of the *endo* preference.

The reaction of the bis(trimethylsiloxy)-*ortho*-xylylene (**8**) with acetaldehyde (**1**) has been also studied (Figure 2). The transition states for the *endo* and *exo* pathways have been characterized. Both are asynchronous with the C···O forming bond lengths larger than the C···C forming bond lengths. In the case of the *endo* transition state (**TS11**) the C···O forming bond distance is 2.356 Å and the C···C forming bond distance is 2.194 Å. For the *exo* transition state (**TS12**) these forming bond distances are 2.319 and 2.224 Å, respectively. The energies of activation for this reaction over the *endo* and *exo* pathways are only 0.1 and 1.9 kcal mol^{-1}, respectively. The *exo* transition state is 1.8 kcal mol^{-1} higher in energy than the *exo* transition state. The energy difference between the *endo* and the *exo* transition states from single point calculation using the 6-31G(d) basis set is 1.9 kcal mol^{-1}. The $OSiMe_3$ groups do not alter the stereochemical preference, but increase the *endo* preferences for these reactions.

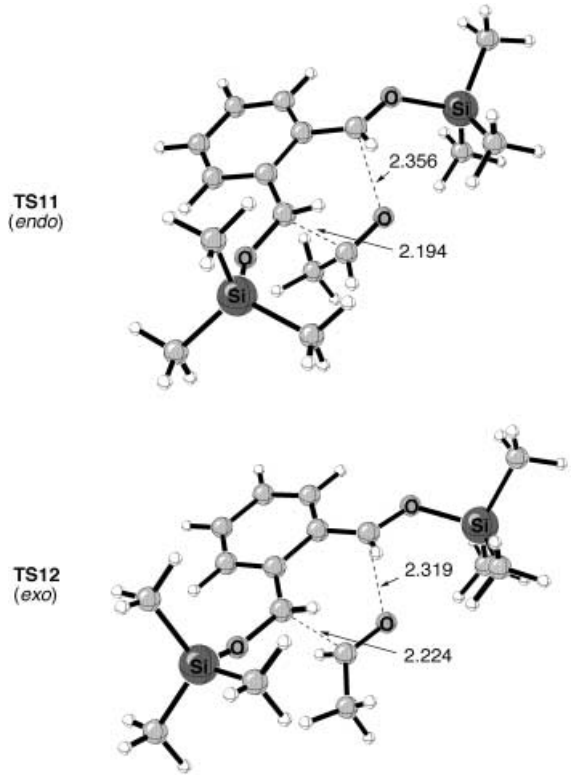

Figure 2. Views of the *endo* and *exo* transition states for the reaction of acetaldehyde with bis(trimethylsiloxy)-*ortho*-xylylene.

The results presented on the reactions of several *o*-xylylenes with acetaldehyde show that the *endo* transition states are always lower in energy than the *exo* ones. There is an *endo* preference for all the studied reactions so far. This is in very good agreement with the experimental values. The reactions of bis(*tert*-butyldimethylsilyl)-*ortho*-xylylene and dimethoxy-*ortho*-xylylene with acetaldehyde and other aliphatic aldehydes have been studied experimentally.[2, 11] For all of these reactions, the *endo* product was found to be the main product of the reaction.

The origin of the stereoselectivity can be attributed to the attractive electrostatic interaction between the CH_3 moiety of the acetaldehyde (slightly positively charged) and the aromatic ring of the *o*-xylylenes (slightly negatively charged). Moreover, as the OR substituent of the *o*-xylylene is made larger, the energy difference between the *endo* and the *exo* transition states becomes also larger. The energy differences for *o*-xylylene substituents. OH, OCH_3, and $OSiMe_3$ are 1.1, 1.3, and 1.8 kcal mol^{-1}, respectively. This is an indication that steric effects go in the same direction as electrostatic effects in controlling the stereoselectivity for the reactions of *o*-xylylenes with acetaldehyde.

Diels–Alder reactions of benzaldehyde

The study of the Diels–Alder reactions between benzaldehyde and the different *o*-xylylenes is presented in three subsections. In the first, a comparative study of the B3LYP

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and MP2 methodologies is described. In the second subsection, the activation energies for all of these reactions are discussed. The third subsection summarizes the factors governing the stereoselectivity of these reactions.

B3LYP versus MP2 methods: The reaction between benzaldedyde and the different *o*-xylylenes studied here is related to the structure of the benzene dimer,[16, 17] since similar interactions are expected to occur between the aromatic rings of the benzaldehyde and the *o*-xylylenes as in some of the benzene-benzene spatial arrangements. Dispersion interactions are one of the most important interactions for these systems. One of the simplest definitions of dispersion forces is: "The dispersive force is due to instantaneous dipoles which arise during the fluctuations in the electron clouds. An instantaneous dipole in a molecule can in turn induce a dipole in neighboring atoms, giving rise to an attractive inductive effect."[18] Theoretical studies on the benzene dimer and other systems[16a] show that dispersion interactions are not properly described by most of the DFT functionals normally used (B3LYP among them).[16a] MP2 calculations in turn, give more reliable results for the benzene dimer although they tend to overestimate the stabilization energy.[19] Hence, a comparative study with DFT (B3LYP/6-31G(d)) and post-HF (MP2/6-31G(d)) levels of theory has been carried out to evaluate their performance on the reactions under study.

For the reaction of benzaldehyde (**2**) with 1,4-dihydroxy-1,3-butadiene (**3**) the transition states for the *endo* and the *exo* pathways, calculated at B3LYP/6-31G(d) level, give an *exo* preference of 2.0 kcal mol^{-1}. Similar optimizations at the MP2/6-31G(d) level gives also an *exo* preference of 1.0 kcal mol^{-1} (Figure 3). Both methods give an *exo* preference, albeit the energy difference between the *endo* and the *exo* transition states is larger at the DFT level. Electrostatic repulsions between the forming double bond and the phenyl ring of benzaldehyde override attractive dispersion interactions.

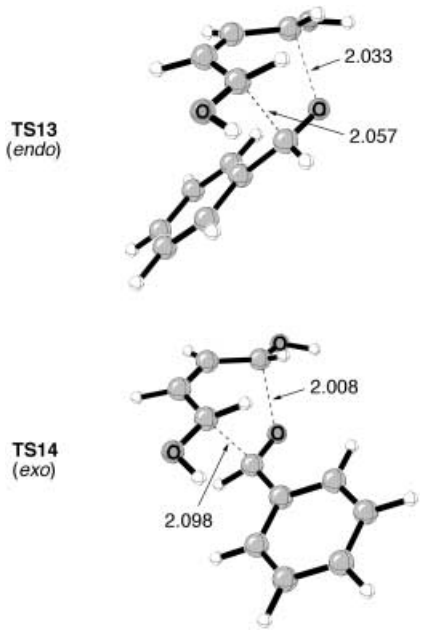

Figure 3. Views of the *endo* and *exo* transition states for the reaction of benzaldehyde with 1,4-dihydroxy-1,3-butadiene.

In the reaction of benzaldehyde (**2**) and dihydroxy-*ortho*-xylylene (**6**), where the dienophile is now an *o*-xylylene, the calculations of the *endo* and the *exo* transition states at the B3LYP/6-31G(d) level of theory give an *exo* preference of 2.8 kcal mol^{-1}. Calculations at the MP2/6-31G(d) level, however, gives an *endo* preference of 0.4 kcal mol^{-1}. Based on MP2 results the reaction is predicted to show a slight *endo* preference, whereas the B3LYP method shows a clear *exo* preference. MP2 calculations give more reliable results than B3LYP calculations when dispersion interactions are important. For this reaction, dispersion interactions are expected to be significant (especially in the *endo* pathway), since the structural arrangement of the aromatic rings of the benzaldehyde and *o*-xylylene are quite similar to the parallel-displaced form of the benzene dimer. The lack of the dispersion interactions in the B3LYP calculations is also reflected in the distance found between the two aromatic rings of the diene and the dienophile for the *endo* pathway. The distance between the centers of the two aromatic rings is 4.334 and 3.639 Å for the B3LYP and MP2 methods, respectively. The MP2 method (that includes dispersion interactions) shows a shorter distance between the aromatic rings in the *endo* transition state. As far the distance of the forming bonds is concerned, MP2 calculation shows an earlier and more asynchronous transition state. The C–O and C–C forming bond distances at the MP2 level for the *endo* transition state are 2.253 and 2.264 Å, respectively. The corresponding values at the B3LYP level are 2.162 and 2.260 Å, respectively. For the *exo* transition state these values are 2.235 and 2.304 Å at the MP2 level, and 2.162 and 2.289 Å, respectively.

For the reaction of benzaldehyde (**2**) and dimethoxy-*ortho*-xylylene (**7**) calculations at the B3LYP level give an *endo* preference of 0.2 kcal mol^{-1}. Calculations at the MP2 level give and *endo* preference of 2.2 kcal mol^{-1}. The results at the MP2 level of theory are in much better agreement with experiment, since the *endo* is the main product for this reaction.[11] The distance between the centers of the two aromatic rings at the B3LYP level is 4.314 Å. This distance is 3.650 Å at the MP2 level. A shorter distance between the centers of the aromatic rings at the MP2 level reflects the introduction of the dispersion interactions. The MP2 transition states are earlier than the B3LYP transition states. The values for the forming C–O and C – C bond distances at the MP2 level are 2.258 and 2.278 Å, respectively, for the *endo* transition state. The corresponding values at the B3LYP level are 2.177 and 2.251 Å, respectively. For the *exo* transition state these values are 2.208 and 2.292 Å at the MP2 level, and 2.154 and 2.225 Å at the B3LYP level, respectively.

For the reaction of benzaldehyde (**2**) and bis(trimethylsiloxy)-*ortho*-xylylene (**8**) calculations at the B3LYP level give an *endo* preference of 0.6 kcal mol^{-1}. Calculations at the MP2 level of theory give an *endo* preference of 1.9 kcal mol^{-1} (Figure 4). Once again, MP2 results are in much better agreement with experiment than B3LYP results, since experiments show the *endo* as the major product of the reaction.[2] Calculations at the MP2 level give a distance between the

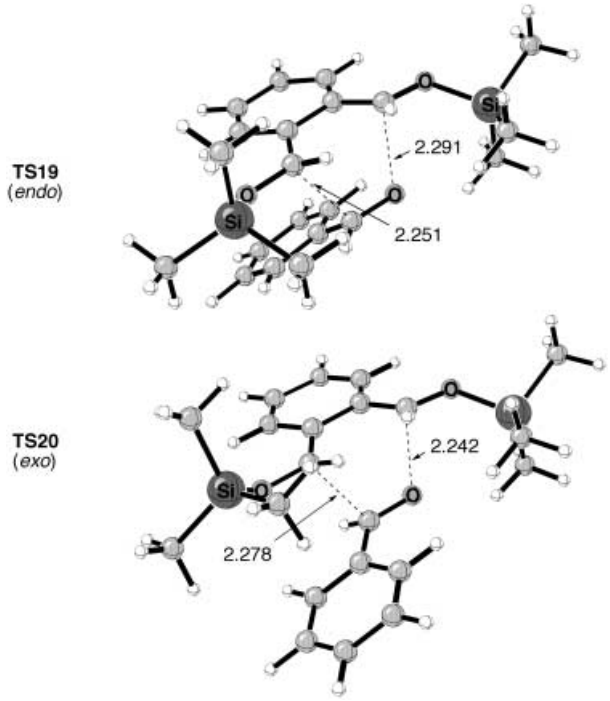

Figure 4. A view of the *endo* and *exo* transition states for the reaction of benzaldehyde with bis(trimethylsiloxy)-*ortho*-xylylene.

aromatic rings (3.728 Å) shorter than that from calculations at the B3LYP level (4.371 Å). MP2 transition states are earlier in the reaction path than the B3LYP ones. The distances for the forming C–O and C–C bonds in the *endo* transition state are 2.291 and 2.251 Å at the MP2 level, and 2.224 and 2.227 Å at the B3LYP level, respectively. For the *exo* transition state these values are 2.242 and 2.278 Å at the MP2 level, and 2.206 and 2.251 Å at the B3LYP level, respectively.

These results show that reactions between benzaldehyde and the different *o*-xylylenes are more properly described by MP2 than by B3LYP. Among the $\pi-\pi$ interactions between the aromatic rings, dispersion interactions are playing a key role in deciding the stereochemistry of these reactions. Hence, theoretical studies on systems where the interactions between aromatic rings (mainly dispersion interactions) play an important role are not well described using the B3LYP functional.

Activation energies: The hetero-Diels–Alder reactions studied here have substantially lower activation energies than the Diels–Alder reaction between 1,3-butadiene and ethene.[14] The *ortho*-xylylenes react very exothermically to restore aromaticity. Furthemore, the dienes studied here, all have two donor substituents, and the hetero-dienophile is electron-deficient.

The Diels–Alder reaction between 1,3-butadiene and ethene has been extensively studied using HF, post-HF and DFT methods.[14, 20] The experimental value for the energy of activation is 27.5 ± 2 kcal mol^{-1}.[21] Calculations including correlation energy at the MP2/6-31G(d) level give an energy of activation of 20.0 kcal mol^{-1},[22] which clearly underestimates the experimental value, while B3LYP/6-31G(d) calculations give an energy of activation of 24.8 kcal mol^{-1}.[14]

For the hetero-Diels–Alder between benzaldehyde (**2**) and 1,4-dihydroxy-1,3-butadiene (**3**) the energies of activation at the B3LYP/6-31G(d) level are 20.7 and 18.7 kcal mol^{-1} for the *endo* and *exo* pathways, respectively. The energies of activation calculated at the MP2/6-31G(d) level are 12.3 and 11.3 kcal mol^{-1} for the *endo* and the *exo* pathway, respectively. In this reaction, MP2 calculations give 7–8 kcal mol^{-1} lower activation energies than the B3LYP calculations. For the reaction of benzaldehyde (**2**) with dihydroxy-*ortho*-xylylene (**6**) the energies of activation for the *endo* and the *exo* pathways at the B3LYP/6-31G(d) level are 7.7 and 4.9 kcal mol^{-1}, respectively. The activation energies for the *endo* and the *exo* pathways at the MP2/6-31G(d) level are -4.0 and -3.6 kcal mol^{-1}, respectively. MP2 predicts that a complex of reactants is considerably more stable than the reactants. These reactant complexes are lower in energy than the transition states. The difference in the activation energies between the B3LYP and MP2 methods ranges from 8 to 12 kcal mol^{-1}. The activation energies for the reaction of benzaldehyde (**2**) with dihydroxy-*ortho*-xylylene (**7**) at the B3LYP/6-31G(d) level for the *endo* and the *exo* pathways are 8.0 and 8.2 kcal mol^{-1}, while the activation energies at the MP2/6-31G(d) level are -5.0 and -2.8 kcal mol^{-1}, respectively. The activation energy at the MP2 level is underestimated in the range of 11–13 kcal mol^{-1} compared to that calculated at the B3LYP level. For the reaction of benzaldehyde (**2**) and bis(trimethylsiloxy)-*ortho*-xylylene (**8**) the activation energies at the B3LYP level for the *endo* and the *exo* pathways are 6.3 and 6.9 kcal mol^{-1}, respectively, while these are -8.7 and -6.8 kcal mol^{-1}, respectively, at the MP2 level. The differences in activation energies between B3LYP and MP2 are around 15 kcal mol^{-1}.

MP2 activation energies are in general lower than B3LYP activation energies, in part due to overestimation of correlation energies.[14] The basis set superposition errors (BSSE) also decrease the activation energies. It has been shown that BSSE are larger at the MP2 level than at the B3LYP level for related systems.[23] For instance, the MP2 activation energy of the parent reaction between 1,3-butadiene and ethene with the large 6-311++G(d,p) basis set is 4.0 kcal mol^{-1} lower than the B3LYP value. For a smaller basis set this difference is even larger (around 5 kcal mol^{-1}). The calculated activation energies are probably better at the B3LYP level, although stereoselectivities are better predicted at the MP2 level.

A comparison of benzaldehyde reactions with different disubstituted-oxo *o*-xylylenes at the MP2 level: In this section, the reactions between benzaldehyde and the different *o*-xylylenes studied at the MP2 level of theory will be described in more detail.

The reaction of benzaldehyde (**2**) with 1,4-dihydroxy-1,3-butadiene (**3**) have both the *endo* (**TS13**), and the *exo* (**TS14**) less asynchronous than those with acetaldehyde (Table 2). The *exo* transition state is 1.0 kcal mol^{-1} lower in energy than the *endo* transition state. Theoretical calculations predict that the main product of the reaction is the *exo* product.

Steric effects involving the substituents are unlikely to cause the *exo* preference in this reaction, given that the hydroxyl groups are small. In the reactions of acetaldehyde,

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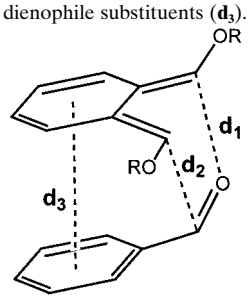
Table 2. Distances (in Å) at the transition states of the C···O ($\mathbf{d_1}$) and C···C ($\mathbf{d_2}$) forming bonds, and between the diene (center of forming benzene ring) and the dienophile substituents ($\mathbf{d_3}$).



		d_1	d_2	d_3
2+3	**TS13**	2.033	2.057	3.882[a]
	TS14	2.008	2.098	–
2+6	**TS15**	2.253	2.264	3.639
	TS16	2.235	2.304	–
2+7	**TS17**	2.258	2.278	3.650
	TS18	2.208	2.292	–
2+8	**TS19**	2.291	2.251	3.728
	TS20	2.242	2.278	–

[a] Distance between the center of the phenyl ring (dienophile) and the center of the forming double bond (diene).

the CH–π interactions between the diene and the dienophile are responsible for the *endo* preference. Here, however, the repulsive interaction between the π electrons of the aromatic ring of the benzaldehyde and the π orbitals of the forming double bond of the diene overrides any attractive interaction, and favors the *exo* transition state over the *endo* one.

In the reaction between benzaldehyde (**2**) and dihydroxy-*ortho*-xylylene (**6**) both the *endo* (**TS15**) and the *exo* (**TS16**) transition states are quite synchronous, since the C···O distances for both transition states are shorter than the C···C distances. The *endo* transition state is now favored by 0.4 kcal mol^{-1} over the *exo* transition state. Hence, theoretical calculations predict slightly *endo* preference for this reaction.

The π–π interactions between aromatic systems have been extensively described in the literature.[24] For the particular case of the benzene–benzene interactions,[16, 17] two different spatial orientations have been found as the most stables ones: T-shape and parallel-displaced. Whereas electrostatic quadrupole–quadrupole interactions are the main interaction stabilizing the T-shape spatial arrangement, dispersion interactions are the main ones stabilizing the parallel-displaced geometry. In the reaction of *o*-xylylene with benzaldehyde, similar π–π attractive interactions between the two six-membered aromatic rings in the *endo* transition state occur. In fact, these dispersion interactions are the principal contributors to the *endo* preference. The spatial orientation acquired by these aromatic rings in the *endo* transition state is quite similar to the parallel-displaced arrangement described for the benzene dimer.[16, 17]

In the reaction of dimethoxy-*ortho*-xylylene (**7**) with benzaldehyde (**2**) the *endo* (**TS17**) and the *exo* (**TS18**) transition states are quite synchronous. The energy difference between the *endo* and the *exo* transition states is 2.2 kcal mol^{-1}, with the *endo* favored. The agreement with experiment is excellent, since the *endo* product is found to be experimentally the main product for this reaction.[11]

Replacing the OH substituents by OCH_3 the stereoselectivity of the reaction shows a much greater preference for the *endo* transition state. The electronic changes introduced in the diene by replacing OH by OCH_3 are rather small. Instead, the OCH_3 is bulkier than the OH. It seems that the steric repulsions introduced favor the *endo* transition state over the *exo*. Notice that in the most stable conformation of the *o*-xylylene both OCH_3 substituents are *anti* to the double bond.[25] With the conformation adopted by the disubstituted *o*-xylylenes there is less steric repulsion in the *endo* than in the *exo* transition state.

In the reaction between benzaldehyde (**2**) and a bis(trimethylsiloxy)-*ortho*-xylylene (**8**) the *endo* (**TS19**) and the *exo* (**TS20**) transition states are quite asynchronous. The *endo* transition state is now 1.9 kcal mol^{-1} lower in energy than the *exo* transtion state. Hence, the product of the reaction predicted by theory is the *endo* product, in excellent agreement again with experiment. The reaction between benzaldehyde and bis(*tert*-butyldimethylsilyl)-*ortho*-xylylene gives complete *endo* specificity.

The energy difference between the *endo* and the *exo* transition states is larger when the *o*-xylylene substituents are OCH_3 or $OSiMe_3$ than when they are OH. The electronic effects introduced by replacing the OH groups by OCH_3 or $OSiMe_3$ are rather small, though their size is quite different. Hence, for the reaction of *o*-xylylenes with benzaldehyde, steric effects play some role in the stereoselectivity.

Conclusion

Attractive interactions between C–H bonds and π systems are well known from structural and conformational data.[26, 27] Sodupe et al.[28] identified CH–π interactions as an important factor in the *endo*-stereoselectivity of the Diels–Alder reaction of butadiene with cyclopropene.[29] We have discovered a related interaction stabilizing the *endo* transition state of cyclopropene dimerization.[30]

The attractive interactions of this type are generally attributed to a combination of dispersion forces (which stabilize van der Waals complexes), electrostatic, and polarization interactions.[31] In the current case, the electrostatic and polarization effects appear dominant, since the reaction of 1,4-dihydroxybutadiene with propene is predicted to give only a 0.3 kcal mol^{-1} preference for the *endo* transition state.

In the Diels–Alder reactions where the dienophile is acetaldehyde, stereoselectivity is caused by nonbonding interactions between the diene and the dienophile substituents. Attractive electrostatic and polarization interactions between the CH_3 moiety of the heterodienophile (slightly positive charged) and the aromatic ring of the diene (slightly negatively charged) are the main cause of the *endo* preference in this reaction.

For the Diels–Alder reactions of benzaldehyde, attractive interactions are also a combination of dispersion, polarization, and electrostatic interactions. Nevertheless, for this case, dispersion interactions between the aromatic rings of the

benzaldehyde and the *o*-xylylenes are dominant, being the main cause of the *endo* stereoselectivity found for these reactions. A comparative study of B3LYP and MP2 methodologies shows that MP2 results are in much better agreement with experiment for stereoselectivity comparisons. B3LYP methodology may be in error by a few kcal mol^{-1} for systems where dispersion interactions are playing an important role. However, B3LYP does give more reasonable average activation barriers, whereas these are systematically underestimated at the MP2 level.

Steric effects involving the *o*-xylylene substituents favor the *endo* transition state for the reaction of both acetaldehyde and benzaldehyde with *o*-xylylenes. Varying the size of the OR substituent on the *o*-xylylene modifies the stereoselectivity of the reaction, but all reactions favor the *endo* stereochemistry.

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