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Electrostatic Interactions between Substituents as Regioselectivity Control Elements in Diels−Alder Cycloadditions. A DFT Study of Cycloadditions of 1-Methoxy-4-trimethylsiloxy Dienes with Acrylonitrile

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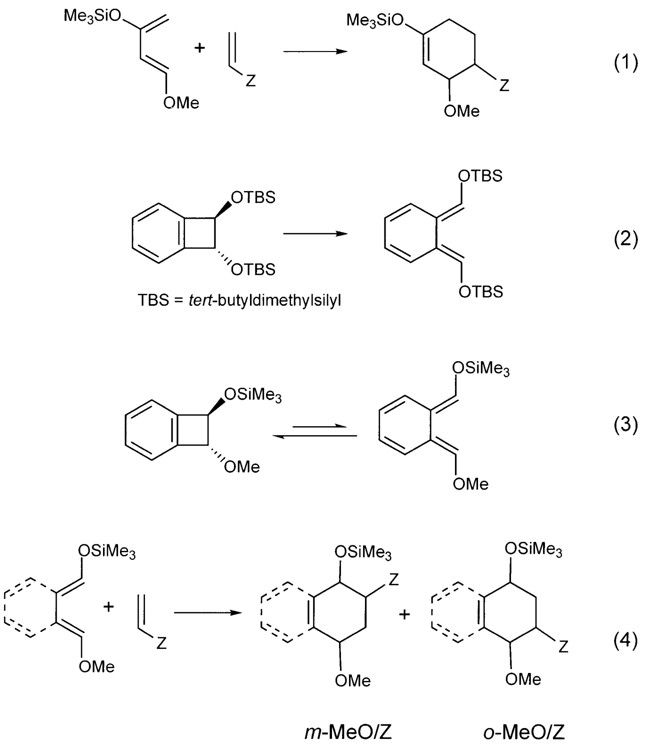
Received June 24, 2002

The regioselectivities of Diels−Alder reactions of 1-methoxy-4-trimethylsiloxy-1,3-butadiene and the corresponding *o*-xylylene with acrylonitrile were explored with density functional theory. The transition state of the reaction of the diene with acrylonitrile was studied in both the gas phase and in a low dielectric ($\epsilon = 2.247$) solvent. The regioselectivities of these reactions are predicted to be controlled by the direct electrostatic interactions between the diene and dienophile substituents. The electron-donating capacities of methoxy and trimethylsiloxy substituents are shown to be very similar and to not contribute to regioselectivity control. A prediction is made that the cycloadditions of the *o*-xylylene will be unselective, while 1-methoxy-4-trimethylsiloxy-1,3-butadiene will give a small preference (~5:1) in favor of the proximal methoxy and cyano groups. The thermochromic behavior of trans-disubstituted disiloxy benzocyclobutene was also explored.

Introduction

The frontier molecular orbital (FMO) model has proven to be useful for the understanding of regioselectivity of cycloadditions.[1] Electrostatic potentials have also been applied to understand regioselectivity,[2] and frontier molecular orbitals and electrostatic potentials usually mutually reinforce a common prediction. We describe a computational study of a new type of regiochemical control. We have found that the combination of electrostatic interactions and the conformations of substituents have a controlling influence on regioselectivity in a case where frontier molecular interactions exert negligible effects.

CHART 1



Alkoxy and trialkylsiloxy groups are widely used as diene activators in Diels−Alder cycloadditions. These are both good electron donors and can be transformed into a variety of other groups. Both alkoxy and trialkylsiloxy groups activate the remote terminus of an alkene or diene toward attack by the electrophilic terminus of a second cycloaddend. A classic example is Danishefsky's diene (eq 1). Here, both groups reinforce regioselectivity with unsymmetrical electron-deficient alkenes (eq 1, Z = electron-withdrawing group).[3] Danishefsky and co-workers have exploited the use of siloxy-substituted *o*-xylylenes in synthesis (e.g., eq 2).[4,5] Disiloxy benzocyclobutene[5] exhibits thermochromic behavior.[4] The appearance

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10.1021/jo020441w CCC: $22.00

of a yellow color occurs when the benzocyclobutene in eq 2 is warmed to room temperature in benzene solution. This yellow color is discharged when recooled or when exposed to a dienophile, as in eq 2. Consequently, the yellow color has been attributed to a low equilibrium concentration of the *o*-xylylene.

Professor Danishefsky cogitated about what the outcome would be if methoxy and trialkylsiloxy groups were placed in antagonistic positions (eq 3), so as to compete for regioselectivity control. Will the methoxy or the trialkylsiloxy dominate (eq 4)? In either a FMO sense or a classical nucleophilic-electrophilic sense, the better donor should end up proximal to the electron-withdrawing group to maximize the donor−acceptor interaction in the transition state. The silyl substituents stabilize β-electron deficiencies (e.g., cations) but can also stabilize α-electron-rich sites (e.g., anions).[6] It is not immediately obvious whether trimethylsiloxy (TMSO) is a better or poorer donor than methoxy (MeO). The Hammett substituent constants are $\sigma_m = 0.13$ and $\sigma_p = -0.27$ for TMSO and $\sigma_m = 0.12$ and $\sigma_p = -0.27$ for MeO.[7]

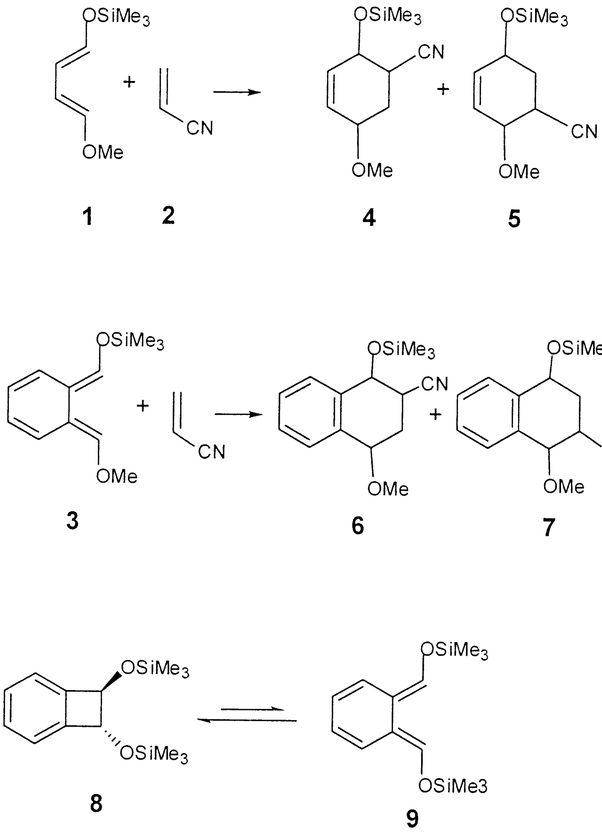
Due to the active interest in such molecules and the corresponding *o*-xylylene formed readily by ring opening of the corresponding benzocyclobutenes, we have explored reactions of these unsymmetrical dienes in Diels−Alder reactions with computational methods. We have identified both electrostatic and conformational effects that compete with FMO effects in controlling regioselectivity in these reactions. We also provide computational evidence for the thermochromic behavior of the trialkyl-substituted benzocyclobutene in eq 2 and confirm a low equilibrium concentration of the *o*-xylylene.

As model systems we chose the reaction of 1-methoxy-4-trimethylsiloxy-1,3-butadiene (**1**) with the typical unsymmetrical electron-deficient dienophile, acrylonitrile (**2**) (Scheme 1). The transition states to give the endo adducts, **4** and **5**, were investigated. The reaction of the corresponding *o*-xylylene (**3**) with the same dienophile to give the endo adducts, **6** and **7**, was also investigated. These reactions have not yet been studied experimentally, and in light of our predictions of zero to modest regioselectivity, it is not clear that there will be a need to test our predictions experimentally. Nevertheless, an interesting new regiochemical control element is found from this work. Bis(trimethylsiloxy)benzocyclobutene (**8**) was used to study the thermochromic behavior of benzocyclobutenes.

Methodology

Calculations were performed using Gaussian 98.[8] Density functional theory with the B3LYP functional and the 6-31G* basis set was used. Full geometry optimizations were carried out for reactants and transition states. Single-point calculations on the transition states were carried out using the 6-311+G* basis set. Time-dependent density functional theory (TDDFT) was used to determine UV/visible absorption energies. Each transition state gave one negative eigenvalue corresponding to the motion involving the formation of the new forming C−C bonds. Solvent effects on the transition states of 1-methoxy-4-trimethylsiloxy-1,3-butadiene with acrylonitrile and on the trans-disubstituted disiloxy compounds were calculated using the conductor polarizable continuum model (CPCM) for benzene.

SCHEME 1



Results and Discussion

The thermal chemistry and UV/visible absorption energies of **8** and the *o*-xylylene, **9**, are presented first. Then, the reactions between acrylonitrile and monosubstituted dienes are discussed, followed by the reactions of the disubstituted dienes, 1-methoxy-4-trimethylsiloxy-1,3-butadiene and the corresponding *o*-xylylene, with acrylonitrile.

Thermochromic Behavior of Bis(trimethylsiloxy)-benzocyclobutene. To explain the thermochromic behavior noted in eq 2, the interconversion of **8** and **9** was studied. The results for this system are presented in Figure 1. The benzocyclobutene, **8**, is more stable than the *o*-xylylene, **9**, by $\Delta H = 6.6$ and $\Delta G = 5.5$ kcal/mol. The activation energies for the conrotatory electrocyclic ring opening are calculated to be $\Delta H_a = 24.4$ and $\Delta G_a = 25.1$ kcal/mol. When solvated in benzene, the benzocy-

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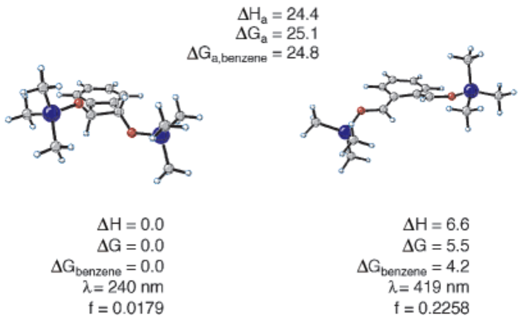


FIGURE 1. Computed transition energies and UV absorption wavelengths of bis(trimethylsiloxy)benzocyclobutene and the corresponding *o*-xylylene. Relative energies are in kcal/mol.

clobutene is predicted to be $\Delta G_{\text{benzene}} = 4.2$ kcal/mol more stable and $\Delta G_{\text{a,benzene}}$ for this reaction is 24.8 kcal/mol. The $\Delta G_{\text{benzene}}$ between **8** and **9** indicates that 0.08% of **9** will be present at 25 °C, or 0.24% in boiling benzene (78 °C).

The excitation energies were calculated using random phase approximation for a time-dependent density functional theory.[9] The calculated $S_0 \rightarrow S_1$ excitation energies of 5.16 eV for the benzocyclobutene and 2.96 eV for the *o*-xylylene correspond to UV absorptions at $\lambda = 240$ nm ($f = 0.0179$) and $\lambda = 419$ nm ($f = 0.2258$), respectively. The wavelength at which *o*-xylylene absorbs coincides with the absorption of violet light, so the molecule appears yellow; **8** should be colorless. Thus, the observed yellow color during the Diels–Alder reaction in eq 1 is expected to be due to the presence of a small concentration of the *o*-xylylene.

Cycloaddition of Terminal Monosubstituted Butadienes with Acrylonitrile. To determine which group is the better donor in these reactions, the Diels–Alder reactions between 1-methoxy-1,3-butadiene and 1-trimethylsiloxy-1,3-butadiene as dienes with acrylonitrile (**2**) as a dienophile have been studied. The syn and anti conformations of the substituent were investigated for both dienes. Figure 2 shows the calculated endo transition states for these reactions with a syn conformation of the substituent. For the ortho isomer and the syn conformation, the activation energy for reaction of the methoxydiene with acetonitrile is 14.5 kcal/mol, while for the reaction of siloxydiene the activation energy is 13.3 kcal/mol. The activation barriers for the formation of the meta regioisomers have been calculated also. The values are 19.8 and 18.9 kcal/mol for the methoxy- and siloxydienes, respectively. The ortho–meta activation energies differ by 5.3 kcal/mol for the methoxy case and 5.6 kcal/mol for the trimethylsiloxy. Both the lower E_a and higher regioselectivity indicate that the trimethylsiloxy group is a slightly better donor than the methoxy. For the anti conformers of the dienes, the ortho activation energies are 14.5 and 14.1 kcal/mol, while for the meta, the activation energies are 18.5 and 18.7 kcal/mol for methoxy and siloxy substituents, respectively.

Transition States for Cycloadditions of 1-Methoxy-4-trimethylsiloxy-1,3-butadiene and Acrylonitrile. Four conformers were optimized for the s-cis conformation of 1-methoxy-4-trimethylsiloxy-1,3-butadiene. Methyl vinyl ether and sterically unhindered derivatives have a syn (∠ C═COC = 0°) and an anti (∠ C═COC = 180°) conformation. These conformers both maintain overlap between the π-type lone pair on the π bond. The syn conformation minimizes electrostatic repulsion between the O lone pairs and the remote terminus of the alkene π bond and is lower in energy.[10] Because of the steric hindrance involving the trimethylsiloxy group, the minimum energy conformers of trialkylsiloxy alkene are anti, with a CCOSi dihedral angle of 180°.

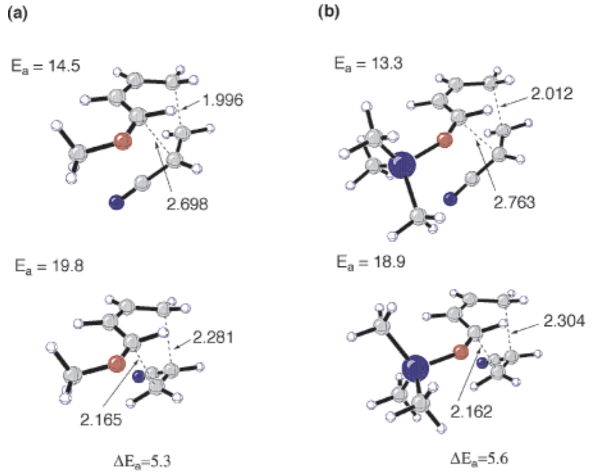
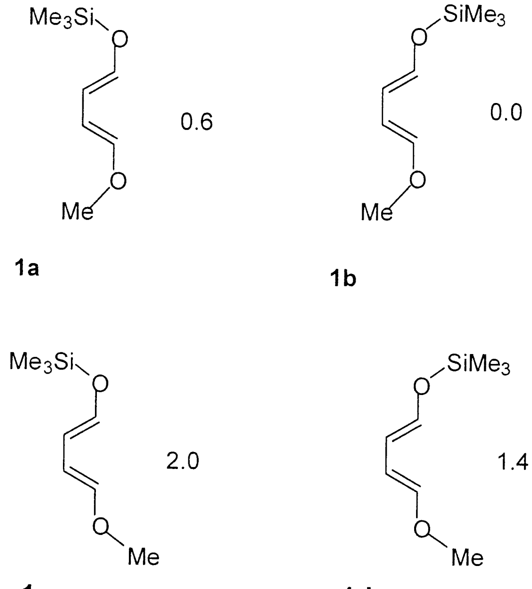


FIGURE 2. Computed transition structures for the reactions of acrylonitrile with (a) 1-methoxy-1,3-butadiene and (b) 1-trimethylsiloxy-1,3-butadiene. Relative energies are in kcal/mol, and distances are in Å.



1a **1b** **1c** **1d**

FIGURE 3. Conformers of *s-cis*-1-methoxy-4-trimethylsiloxy-1,3-butadiene. Relative energies are in kcal/mol.

The energies of the various conformations of diene **1** are gathered in Figure 3. The lowest energy conformer, **1b**, has a syn conformation of the methoxy and an anti

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conformation of the trimethylsiloxy. Conformer **1a** is 0.6 kcal/mol higher in energy than **1b**; the steric repulsion between the $-$OSiMe$_3$ group and H-2 of the diene in the syn conformer is more destabilizing than the electrostatic repulsion between the oxygen lone pair and the double bond in the anti conformer. Conformer **1c** is 2.0 kcal/mol higher in energy than **1b** due to the electrostatic repulsion between the lone pair of the oxygen of the $-$OMe group and the double bond and the steric repulsion between the $-$OSiMe$_3$ group and the H-2. Conformer **1d** is 1.4 kcal/mol higher in energy than **1b**, due to electrostatic repulsion between the σ lone pair of the $-$OMe group and the double bond.

All the conformers are energetically accessible. For each conformation there are two possible regioisomeric products and two possible stereoisomers (exo and endo). To understand the origin of the regioselectivity for this reaction, the endo transition states were studied. The diene **1** has four different conformations (Figure 3), and for each conformer there are two possible regioisomers. These are schematically represented in Figure 4. Each was found to be a saddle point on the potential hypersurface, with one negative eigenvalue. Single-point calculations on the transition states with a larger basis set (6-311+G*) give similar relative energies. Solvent effects on the transition states were predicted using CPCM calculations for benzene with a 6-31G* basis set. Full geometry optimizations were performed on **TS4** and **TS5**, and since significant changes in relative energies were not observed, single-point calculations were used to predict relative energies for all of the transition states.

The energetic differences among the transition states are not very large, and solvent effects of benzene are predicted to be insignificant. The transition state with the lowest energy, **TS4**, corresponds to the regioisomer where the CN from the dienophile is located nearest the $-$OMe group. The lowest energy transition state corresponding to the other regioisomer, **TS5**, is 1.0 kcal/mol higher in energy than **TS4**. Therefore, the *ortho*-MeO/CN is predicted to be the main product of the reaction, although the regioselectivity is predicted to be modest, on the order of 5:1.

The minimum energy transition state, **TS4**, corresponds to the lowest energy conformer of diene, **1b**. **TS5**, the lowest transition state for the *ortho*-Me$_3$SiO/CN regioisomer, corresponds not to the lowest energy conformer of the diene, **1b**, but to the highest one, **1c**.

The differences between conformational preferences of the transition states compared to those of the isolated reactants originate from electrostatic interactions taking place in the transition states. The CN group of the dienophile is partially negatively charged, especially in the vicinity of the nitrogen due to both π and *n* electrons. Electrostatic repulsion between an s lone pair of an oxygen of a diene substituent and the CN group is largest when the alkoxy or siloxy is anti; here, the oxygen lone pair and the N are in close proximity (Figure 5a). The opposite will occur in exo transition states.

The alkene π bond of the dienophile also has a negative electrostatic potential; therefore, there will be electrostatic repulsion between this π system and the lone pair of an oxygen, when they are in close proximity. The repulsion is largest when the alkoxy or silyloxy is syn (Figure 5b).

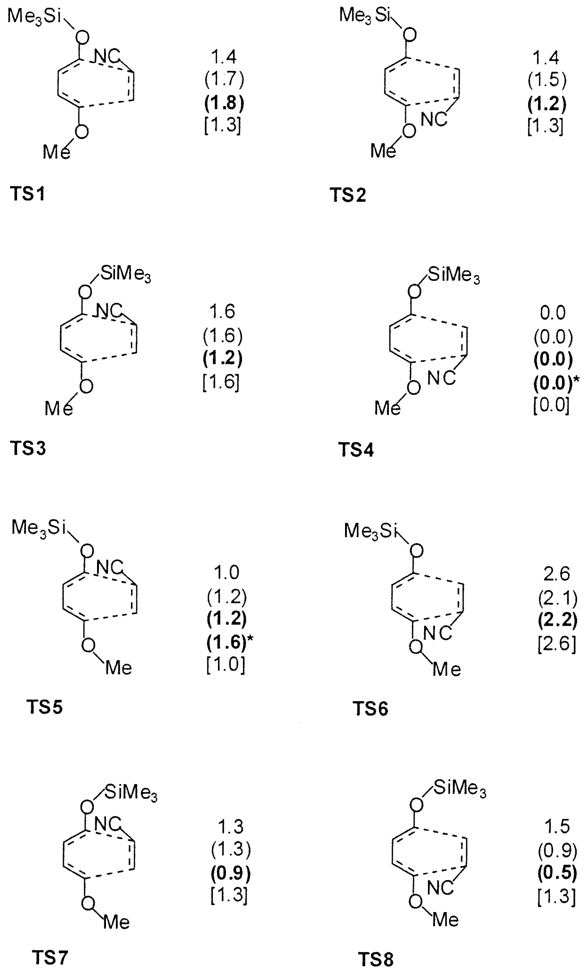


FIGURE 4. Schematic representation of the eight endo transition states for the reaction of 1-methoxy-4-trimethylsiloxy-1,3-butadiene with acrylonitrile. Energies (in kcal/mol) were calculated with the B3LYP/6-31G* level. Single-point calculation energies at the B3LYP/6-311+G* level are given in parentheses. CPCM single-point calculations with benzene and the B3LYP/6-31G* level are shown in bold parentheses (* indicates optimized energies). Values from simple additivity rules are in brackets.

For the odd-numbered transition states (corresponding to the *ortho*-Me$_3$SiO/CN regioisomer), the lowest energy transition state is **TS5**. It corresponds to the conformer **1c** of the isolated diene, which is the most energetic conformation. The transition state corresponding to the most stable conformation of the isolated diene, **1b**, is **TS3**. It is the highest transition state for this regioisomer, being 0.6 kcal/mol higher in energy than **TS5**. In **TS3**, both electrostatic respulsions are taking place: one between the CN and the lone pair of the trimethylsiloxy and the other between the π system of the acrylonitrile and the lone pair of the methoxy. However, these electrostatic repulsions are avoided in **TS5** (see Figure 6). Therefore, the energy differences are the result of the diene conformations and electrostatic interactions between substituents.

An approximate separation of the conformational and electrostatic factors influencing the regioselectivity can be made. We assume that the conformational preference in transition states is approximately half that of reac-

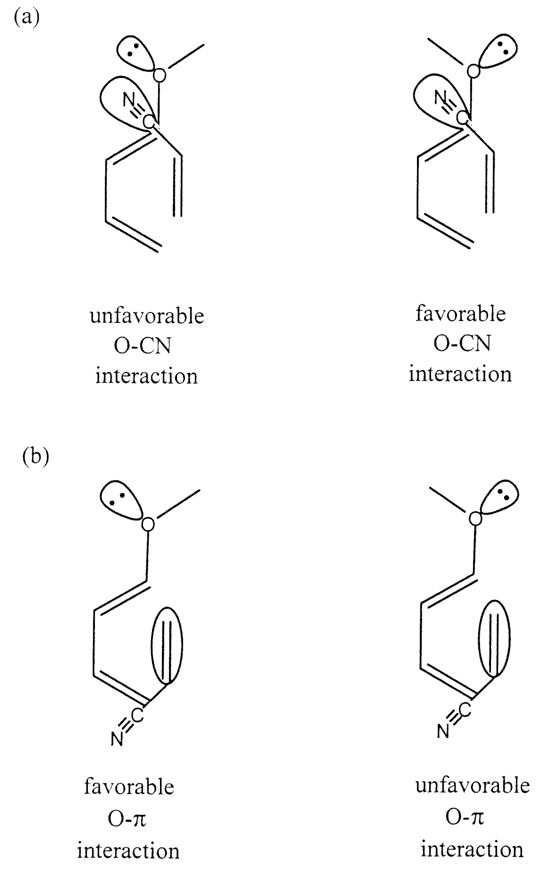


FIGURE 5. Schematic representation of the electrostatic interactions between the in-plane oxygen lone pair of the substituent and the negatively charged moieties of the acrylonitrile: (a) the CN group and (b) the double bond.

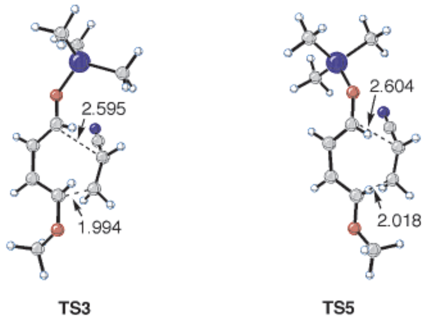


FIGURE 6. Computed transition structures for the reaction of 1-methoxy-4-trimethylsiloxy-1,3-butadiene with acrylonitrile giving the *ortho*-Me_3SiO/CN regioisomer. Distances are in Å.

tants (0.3 kcal/mol preference for anti $-OSiMe_3$ and 0.7 kcal/mol preference for syn −OMe).[10b] The unfavorable O−CN and O−π interactions are assumed to be 0.6 and 1.0 kcal/mol, respectively. With these quantities and an assumption of additivity, the energy changes for the transition states can be predicted. **TS4** corresponds to the minimum conformational energy, and both O−CN and O−π electrostatic repulsions are avoided. In the case of **TS6**, 0.3 kcal/mol has to be added due to the conformational change in the $-OSiMe_3$ group and 0.7 kcal/mol for the conformational change of the −OMe group (Figure 7). Electrostatic interactions of 1.0 kcal/mol for the O−π interaction and 0.6 kcal/mol for the O−CN interaction are added. The energy of **TS6** is predicted to be 2.6 kcal/mol higher than **TS4**, in excellent agreement with the computed value with 6-31G* and 0.5 kcal/mol too large with 6-311+G*. The same rules can be applied to predict the energies of the rest of the transition states with reasonable agreement, as indicated by the numbers in brackets in Figure 4.

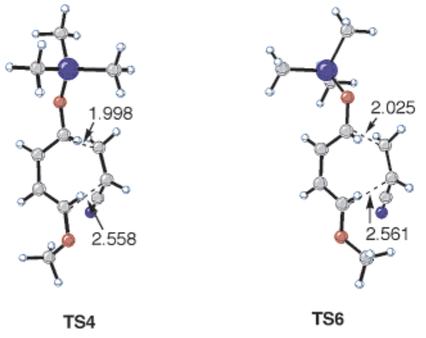


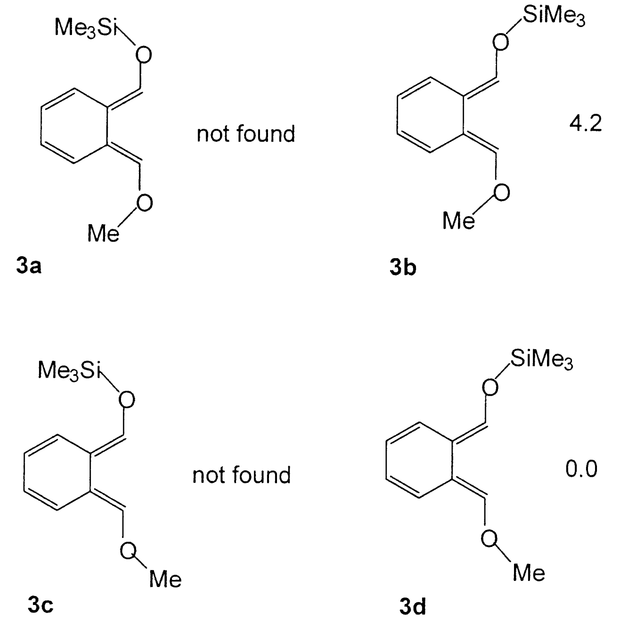
FIGURE 7. Two computed transition structures for the reaction of 1-methoxy-4-trimethylsiloxy-1,3-butadiene with acrylonitrile giving the *ortho*-MeO/CN regioisomer. Distances are in Å.

From these results we can say that the conformation of −OMe and $-OSiMe_3$ groups plays an important role in deciding the regiochemistry. The most stable conformation (corresponding to **1b**) gives the most favorable transition state, **TS4**. The *ortho*-MeO/CN regioisomer is predicted to be the main product of the reaction. The most energetic conformation (corresponding to **1c**) gives the lowest energy transition state found for the other regioisomer, **TS5**.

In the case of the exo transition states, assuming that the energy separation between conformational and electrostatic factors is the same as that for the endo transition states, a prediction on the regioselectivity can also be made. Now the siloxy or alkoxy groups will have less repulsion with cyano when the alkoxy or siloxy is syn. The lowest energy transition state is **TS4-exo**. It corresponds to the same minimum as that for the endo transition states but has a relative energy of 0.6 kcal/mol due to the introduction of an unfavorable O−CN interaction. **TS7-exo** and **TS8-exo** have the same predicted energy value of 0.7 kcal/mol, only 0.1 higher in energy than **TS4-exo**. Therefore, it is predicted that for the exo products, the *ortho*-MeO/CN will be only slightly dominant.

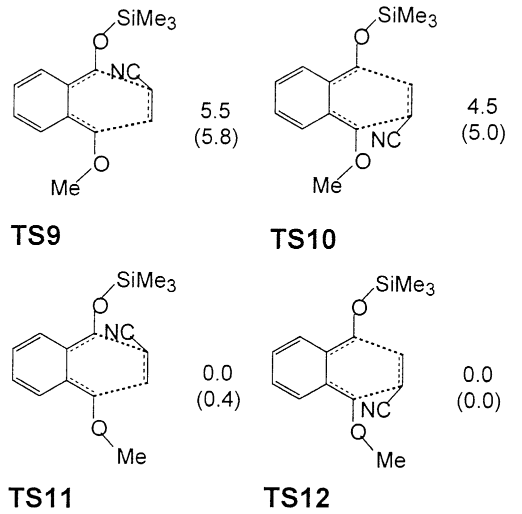
Cycloaddition of Disubstituted *ortho*-Xylylene with Acrylonitrile. The relative stabilities of *o*-xylylene conformers (*o*-quinone dimethide, **3**) are shown in Figure 8. The most stable conformer, **3d**, has the two oxygen lone pairs pointing toward the double bonds, unlike the most stable conformer from diene **1**. Here, steric effects override the electrostatic effects. Conformers **3a** and **3c** could not be located at all as energy minima.

The regioselectivity of the endo cycloaddition was explored. A schematic representation of each endo transition state is depicted in Figure 9. The conformation of the diene plays a key role in determining the energy of these transition states. The energetic difference between the conformers of the diene is so large that it cannot be overridden by the electrostatic interactions.



3a **3b** **3c** **3d**

FIGURE 8. Schematic representation of the various conformers of *o*-quinone dimethide. Relative energies are in kcal/mol.



TS9 **TS10** **TS11** **TS12**

FIGURE 9. Schematic representation of the four (endo) possible transition states for the reaction of *o*-quinone dimethide with acrylonitrile. Energies (in kcal/mol) were calculated at the B3LYP/6-31G* level. Single-point calculations at the B3LYP/6-311+G* level are given in parentheses.

TS11 and **TS12** have the same relative energy with 6-31G* and are only slightly different with 6-311+G*. **TS11** is a transition state corresponding to the *ortho*-Me_3SiO/CN regioisomer, whereas **TS12** corresponds to the *ortho*-MeO/CN regioisomer. Both transition states have the same conformation (corresponding to **3d**), and the electrostatic repulsions are similar. The reaction of *o*-xylylene, **3**, with acrylonitrile is predicted to give a very small preference for regioisomer **7**.

Contributions of conformational change and electrostatic interactions to the energy of the transition states are similar to those described earlier for the acyclic diene, except that the conformational change of the −OMe group to the syn conformer costs 4.5 kcal/mol. In **TS10**, both electrostatic repulsions are avoided, but it is 4.5 kcal/mol higher in energy than **TS12** because of the methoxy conformational energy. For **TS9**, the conformational change on the −OMe group raises the energy by 4.5 kcal/mol, and electrostatic repulsions involving both the cyano and alkene π raise the energy by 1.0 kcal/mol more, resulting in a total energy of 5.5 kcal/mol.

Conformational and electrostatic factors are expected to be similar for the exo and endo transition states. For the most favorable conformation of the diene, electrostatic repulsions are very similar in both regioisomers. Therefore, no regioselectivitiy is predicted for the exo products.

Conclusions

In summary, bis(trimethylsiloxy)benzocyclobutene is expected to exhibit thermochromic behavior; generation of *o*-xylylene upon warming gives rise to a yellow solution. For the main study on regioselectivity, the major product of the reaction of acrylonitrile with 1-methoxy-4-trimethylsiloxy-1,3-butadiene is predicted to be the regioisomer where the CN from the dienophile is near (ortho) the −OMe group. In the reaction with *o*-xylylene, either no selectivity or very low regioselectivity will be observed. FMO interactions do not have any significant influence on regioselectivity here, but electrostatic effects involving substituents have a significant influence on regioselectivity.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health, for financial support of this research. G.U. gratefully acknowledges NATO for financial support through a postdoctoral fellowship.

JO020441W