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Theoretical Study of the Facial Selectivity in Diels-Alder Reactions of 4,4-Disubstituted Cyclohexadienones

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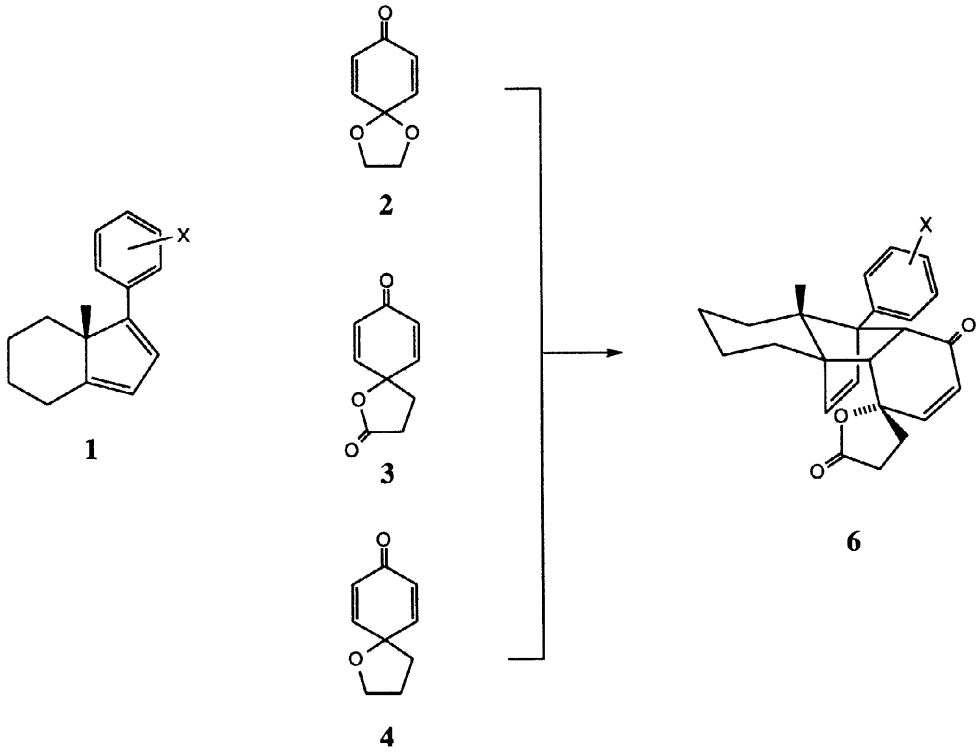
Abstract: PM3 and RHF/6-31G* calculations were performed for the Diels-Alder reactions of 1,5,5-trimethylcyclopentadiene with cyclohexadienone and a variety of 4-substituted and 4,4-disubstituted cyclohexadienone derivatives. The high stereoselectivity, observed experimentally for these systems by Winterfeldt *et al.*, arises from the lower steric demand of oxygen relative to methylene groups.

The Diels-Alder reaction is normally a concerted [4+2] cycloaddition with considerable synthetic utility. The reaction has been widely studied,[1,2] and the mechanistic aspects of this reaction have been much discussed and debated.[3] Recently, Winterfeldt *et al.*[4] studied the stereoselectivitiy in the Diels-Alder reactions of conformationally rigid bicyclic and polycyclic prochiral cyclopentadienes, such as **1**, with substituted cyclohexadienones (Scheme 1).



Scheme 1

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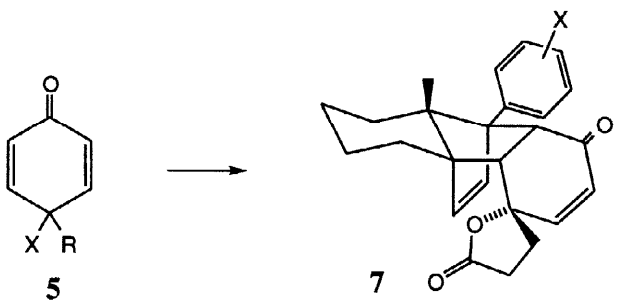
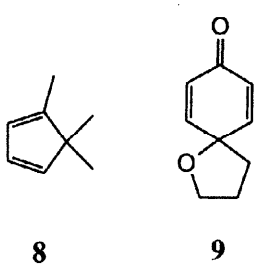
In the Diels-Alder reactions of spirolactones and spiroethers **2-4**, a single *endo* cycloadduct was always formed, corresponding to the orientation where the oxygen is closer to the π-system of cyclopentadiene (CPD), or *syn* to the newly forming bond.[5] Thus, when electronegative atoms (e.g., oxygen or fluorine) are substituents, they prefer this "inside" position. This type of stereoselective Diels-Alder reaction has found application in the synthesis of several marine natural products,[5c] with non-spiro 4,4-disubstituted cyclohexadienones as dienophiles, **5**. These cycloadditions are also highly facial-selective, but exhibit slower reaction rates. This deceleration was attributed to the higher steric demand of more conformationally mobile substituents.[5]

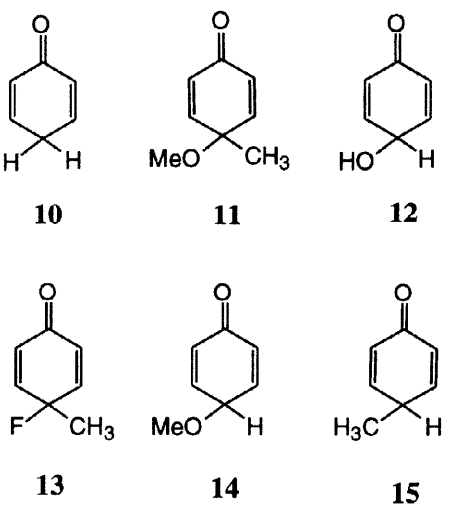


5 **7**

We undertook a general theoretical study of these Diels-Alder reactions to explain the inside preference of electronegative substituents. Herein we report our results for the reactions of 1,5,5-trimethylcyclopentadiene, **8**, a model for **5** and related dienes, with spiroether, **9**, and related dienophiles (**10**-**15**).



8 **9**



10 **11** **12**

13 **14** **15**

Methods

Semiempirical investigations were carried out at the PM3 level of theory, which is known to give a reasonable account of selectivity and relative reactivity for several concerted Diels-Alder reactions.[6] Initial calculations were performed using SPARTAN.[7] Geometry optimizations were carried out at the PM3 semi-empirical level using Gaussian 94.[8] Each transition structure gave only one imaginary harmonic vibrational frequency corresponding to the formation of new C–C bonds. The activation energies were estimated from RHF/6-31G* single point calculations on the PM3 optimized geometries.

Results and Discussion

To investigate the remarkable stereoselectivity and explain the substituent effects on the Diels-Alder reaction rates, we first compare the calculated activation energies and then analyze the geometries of the transition structures. The reaction mechanism is thought to be concerted but asynchronous. We located concerted transition structures for all reactions studied. Computational results and available experimental values[6] were compared whenever possible.

There are four possible isomers, **A-D**, (Figure 1) that can be formed in the Diels-Alder reaction between 1,5,5-trimethylcyclopentadiene and spiroether **9**. Calculated energies indicate that the transition states leading to **TS-C** and **TS-D**, resulting from of α-addition of the cyclopentadiene to the cyclohexadienone, are more stable than the isomers obtained in a β-addition (**TS-A** and **TS-B**). Thus, as was expected from the experimental studies,[4] **TS-C** is the most stable transition state. In every reaction involving spirolactones or spiroethers, only one cycloadduct (oxygen in inside position) was observed, in high yield.

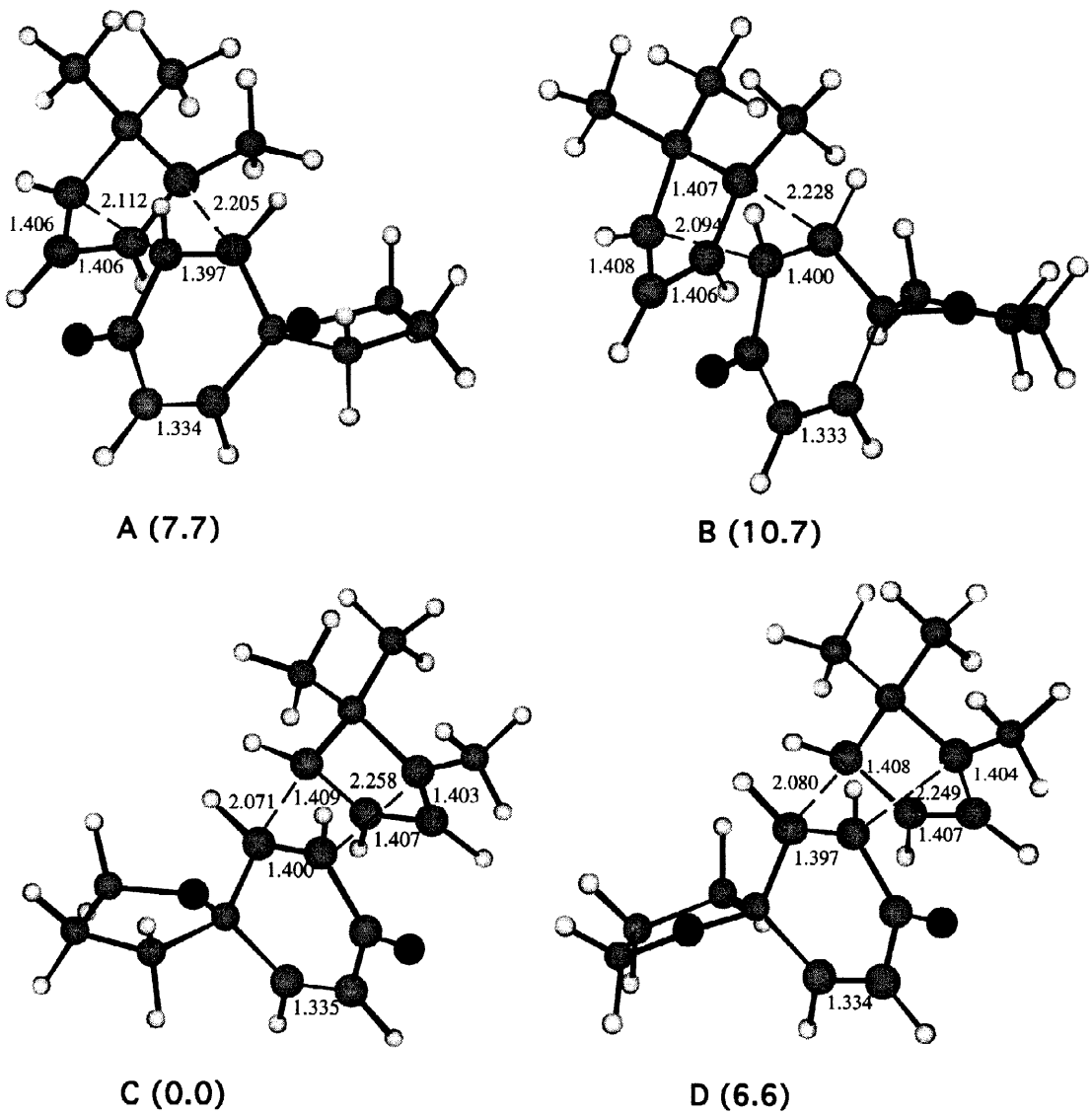


Figure 1. Transition structures for the reaction of 1,5,5-trimethylcyclopentadiene and **9**.

Our calculations reflect the high preference of the oxygen in the spiroether moiety to be placed in the "*endo*-inside" position. This inside preference is exhibited by the 6.6 kcal/mol difference between **TS-C** and **TS-D**, according to the energies obtained from the RHF/6-31G* single point energy calculations at the PM3 optimized geometries. The more stable transition structures **TS-C** and **TS-D** are more asynchronous than the two other possibilities, **TS-A** and **TS-B**. The isomer with the spiro-ether oxygen in the inside position, **TS-A**, is found to be more stable than **TS-B**.

The transition states for the reactions of dienophiles **10-12** are depicted in Figure 2. For dienophiles **11** and **12**, the inside is preferred. For the competition between the methoxy and methyl groups, **TS-F** and **TS-G**, respectively, OMe is favored by 3.0 kcal/mol. Furthermore, there is a 2.3 kcal/mol preference for OH over H (**TS-H** and **TS-I**).

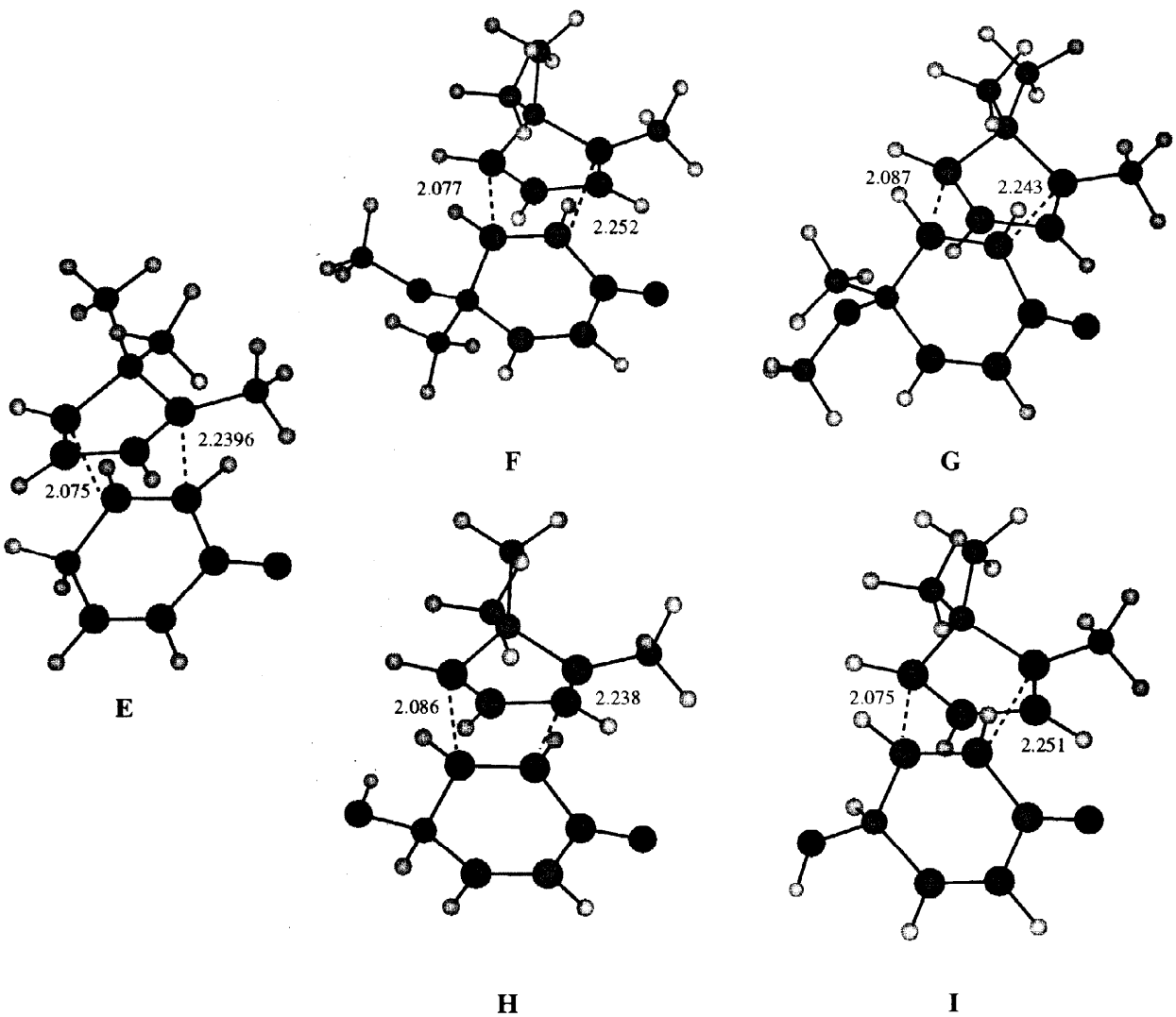


Figure 2. Transition structures for cycloadditions of dienophiles **10-12**. **F** and **H** are favored.

We also calculated a remarkable 8.0 kcal/mol preference for fluorine over a methyl group (**TS-J** and **TS-K**). Interestingly, for the substituent pairings MeO, H (**TS-L** and **TS-M**), or Me, H (**TS-N** and **TS-O**),

involving dienophiles **14** and **15**, *outside* preferences of 0.7 and 2.4 kcal/mol, respectively, are observed. These results also parallel the experimental observations for similar reactions.[4] These transition states are illustrated in Figure 3.

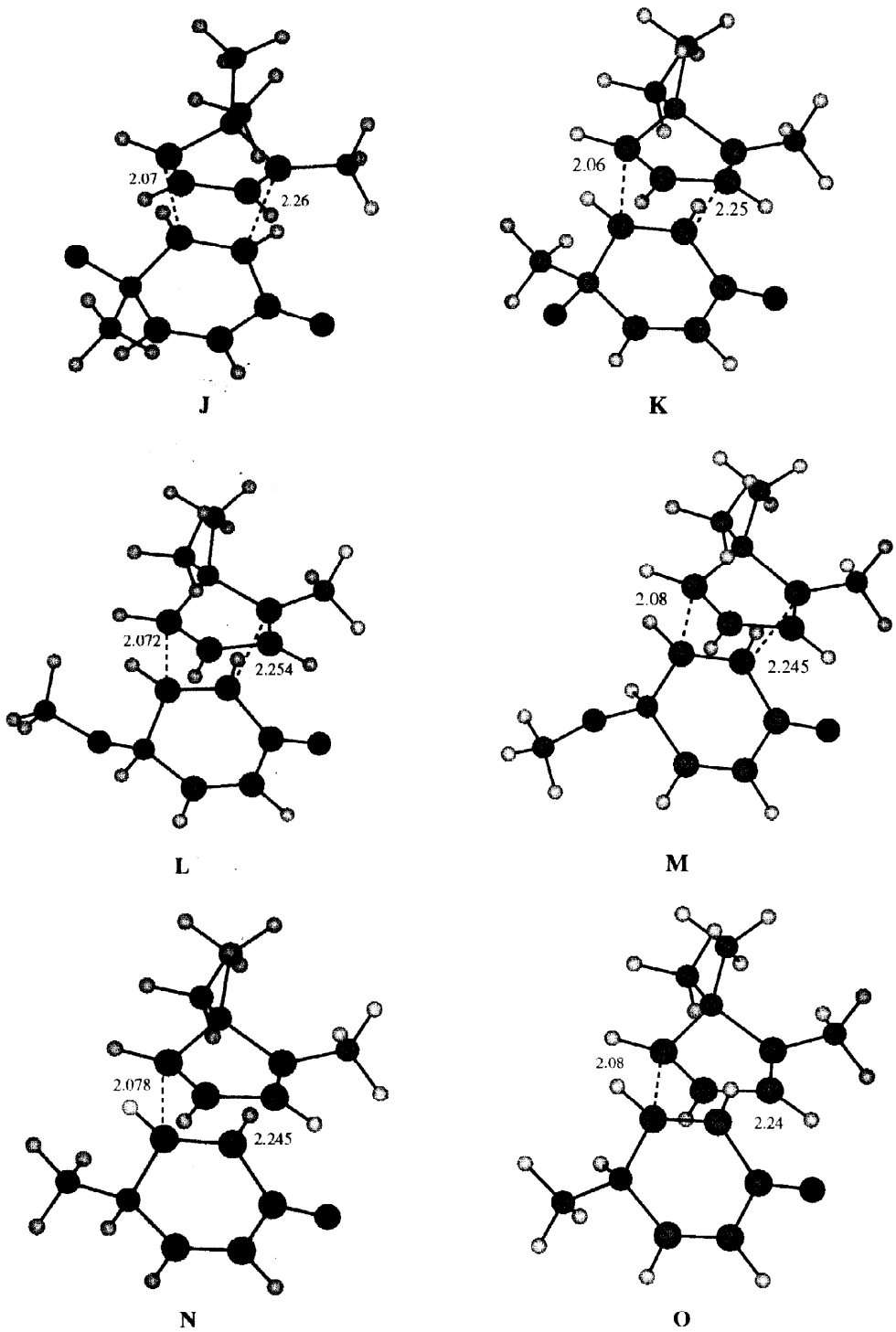


Figure 3. Transition structures for dienophiles **13**-**15**.

The predicted activation energies and calculated inside preferences for electronegative substituents are listed below in Table I. Clearly the calculations produce results which corroborate the available experimental data.

Table I. Predicted Activation Energies and Inside Preferences (kcal/mol).

				Activation Energies (Inside preferences)	
TS	**Dienophile**	**Substituent Stereochemistry**		**PM3**	**RHF/6-31G*//PM3**
A	*ortho*-spiro-tetrahydrofuran	O *endo*		44.8 (0.2)	57.6 (3.0)
B		O *exo*		45.0	60.5
C	*meta*-spiro-tetrahydrofuran	O *endo*		43.3 (0.3)	49.9 (6.6)
D		O *exo*		43.7	56.4
E	cyclohexadienone	—		42.6	52.5
F	4-methoxy-4-methylcyclohexadienone	MeO *endo*	Me *exo*	42.8 (1.3)	53.1 (3.0)
G		MeO *exo*	Me *endo*	44.0	56.1
H	4-hydroxycyclohexadienone	OH *endo*	H *exo*	39.9 (2.0)	48.5 (2.3)
I		OH *exo*	H *endo*	41.8	50.8
J	4-fluoro-4-methylcyclohexadienone	F *endo*	Me *exo*	41.5 (2.5)	47.7 (8.0)
K		F *exo*	Me *endo*	44.0	55.7
L	4-methoxycyclohexadienone	MeO *endo*	H *exo*	42.7 (-0.8)	49.8 (-0.7)
M		MeO *exo*	H *endo*	42.0	49.0
N	4-methylcyclohexadienone	Me *endo*	H *exo*	44.1 (-1.5)	55.2 (-2.4)
O		Me *exo*	H *endo*	42.6	52.8

Having established the adequacy of these models, we turned our attention to the origin of these preferences. For the reaction between 1,5,5-trimethylcyclopentadiene and spiroether **9**, cycloaddition occurs *anti* to the C–C bond at C4 and *syn* to CO. This orientation is similar to that rationalized by the Cieplak model for nucleophilic addition, which involves donation into a forming bond by the anti-periplanar donor.[12] Alternatively, the electron-withdrawing spiroether oxygen might be expected to increase the acceptor reactivity of the dienone most strongly in an antiperiplanar position.[10] However, we find no evidence for any difference in orbital interactions or asymmetry of the dienophile π-system, so this pattern is a coincidence, not the origin of stereoselectivity.

Wipf and Kim[11] analyzed the remarkable facial selectivity in nucleophilic additions to 4,4-disubstituted dienones, and found that electrostatic effects explain the selectivity observed for those systems. The close proximity of the spiroether oxygen to the π-system in CPD, and possible stacking interactions offers another potential explanation. However, comparison of the two electrostatic potential surfaces of CPD and the spiroether indicate that the high electron density on the oxygen of the spiroether and the π-system of the diene would cause electrostatic *repulsions* instead of attractions. While the avoidance of electrostatic repulsions was previously implicated for the exo-lone pair preference in heterodienophiles,[9] electrostatic repulsions are less important here than the steric interactions induced by the repulsion between the π-system and the methylene group.

When non-spiro cyclohexadienones are used as dienophiles, steric effects again govern the facial selectivity. The most reactive dienophile, **13**, is substituted by the largest number of electron-withdrawing groups (**TS-J**, Table I, Figure 3). There is a high preference for electronegative atoms to be in the inside position, as was evident from the activation energies for these cycloadditions. Hence, fluorine or methoxy groups on C-31 are located preferentially on the inside when Me is the other substituent [Figures **2** (**J**) and **3** (**F**)]. The inside preference is 8.0 kcal/mol for fluorine and 3.0 kcal/mol for the methoxy group (Table I).

In the case where OMe and Me groups are the substituents, **11**, the steric interactions of the methyl moiety are important enough to allow the OMe group to be in the inside position (Figure **3**, **F** and **G**). This is also the case when the methyl substitutuent is replaced by the much smaller hydrogen atom, **14** (**L** and **M**). The OMe outside preference, although weak (0.7 kcal/mol), is observed. We looked for the same effect when the methyl group was the C-31 substituent, **15** (**N** and **O**). A methyl group in the outside position is 2.4 kcal/mol more stable than on the inside according to single point energy calculations (Table I). In this position, the steric interactions between the methyl group and CPD are minimized. The transition states for reaction with dienophile **14** compared to those from dienophile **15** are more stable. The presence of the oxygen atom, which is more electronegative and has a smaller volume relative to a methyl group, stabilizes the transition state.

With the outside preference found for transition structures **O** and **N**, it is clear that when fluorine and Me are the substituents on C-31, (**J** and **K**) the transition state with fluorine inside and methyl outside, **TS-J**, is much more stable. The fluorine atom is also very small and electronegative compared to the methyl moiety, and the C–F bond (1.39 A) is comparable to C–O (1.43 A). Furthermore, the fluorine van der Waals radius (1.35 A) is very similar to that of hydrogen (1.20 A). If the substituents are OH and H (Figure **2**, **H** and **I**) the inside preference appears again. It is significant that the most unstable transition state is that with the methoxy group outside and the methyl inside, **G**. The magnitude of the steric interactions with the methyl inside makes it the most disfavored transition state.

Conclusion

We have thus demonstrated that the *endo*-selectivity of this reaction and the preference for the oxygen in the spiro moiety to be placed in the inside position arises from the high steric interactions between bulky substituents such as methyl, and the π-system and hydrogen atoms of CPD.

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