Computational study of the stereoselectivity profiles of the Diels-Alder cycloaddition reactions of cyclopentadiene and butadiene with cyclopropenes

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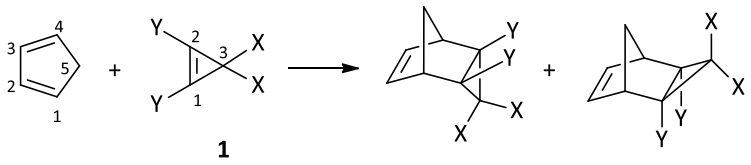
Abstract: The *endo* and *exo* stereoselectivities of the Diels-Alder (DA) cycloaddition reactions of 3,3-disubstituted cyclopropenes with butadiene and cyclopentadiene, the latter for the first time, were investigated by means of density functional and quantum chemical calculations for a comparison. To establish distinction between the selectivites, activation free energies were systematically estimated in the gas phase and also under solvent effects. The differential activation free energies clearly predict exclusive *endo* configuration of the products formed from the reaction of the unsubstituted cyclopropene with butadiene and cyclopentadiene. However, the results were found to be markedly different for the substituted cyclopropenes from the available experimental selectivities. It was also discovered that butadiene and cyclopentadiene are markedly different in their respective stereospecific product yields, nevertheless the difference between the two is only a methylene group. The failure of the differential activation free energy approach to predict the experimental stereoselectivities of the DA reactions of several perhalocyclopropenes with cyclopentadiene is probably due to yet insufficient development of the various theoretical models dealing with the *endo* and *exo* DA preferences.

1. **INTRODUCTION**

The experimental *endo* and *exo* stereoselectivities of the DA cycloaddition reactions of cyclopentadiene with cyclopropene **1a**, cyclopropenone acetal **1b**, perfluorocyclopropene **1c**, 1,2-dichloro-3,3-difluorocyclopropene **1d** and 1,2-dibromo-3,3-difluorocyclopropene **1e** are given in Scheme 1. While **1a** (CH_2Cl_2, 0 °C)[1] and **1c** ($CDCl_3$, 25 °C)[3,4] form the *endo* adduct exclusively, **1d** and **1e** generate only the *exo* adduct (CCl_4, 0 °C)[3] and **1b**[2] exhibits

no selectivity for furnishing an equal mixture of both the adducts at 25 °C under no solvent conditions. The corresponding reactions of butadiene with the cyclopropenes **1a**,[1,6] **1b**,[2] **1c**,[5] **1d**[7] and **1e**[7] are also reported in the literature. The stereochemistry of the reaction of **1c** has not been firmly secured. Among the rest, **1a** adds *endo* and the others *exo* exclusively.



1a, X = H, Y = H; *endo*:*exo* = 100 : 0
1b, X = **-**O(CH$_2$)$_3$O**-**, Y = H; *endo*:*exo* = 50:50
1c, X = F, Y = F; *endo:exo* = 100:0
1d, X = F, Y = Cl; *endo:exo* = 0:100
1e, X = F, Y = Br; *endo:exo* = 0:100

Scheme 1**.** The experimental *endo* and *exo* selectivities of the DA cycloaddition reactions of the cyclopropenes **1a**–**e** with cyclopentadiene

The stereoselectivities of the DA reactions of unsubstituted and substituted butadienes with unsubstituted, 3-substituted and 3,3-disubstitiued cyclopropenes have been the subject of several computational investigations in the recent past. For instance,

(a) Jursic has studied the reaction of cyclopropene with butadiene at the B3LYP/6-31G(d) density functional level and concluded that the *endo* transition state (TS) structure was 2.0 kcal/mol lower in energy than the corresponding *exo* TS structure due to the Secondary Orbital Interactions (SOI) between the methylene hydrogen of cyclopropene and the developing π-bond in butadiene.[8]

(b) Fujimoto and co-workers have studied the reaction of cyclopropene with a range of substituted butadienes and concluded that the electrostatic interactions between the reactants also contributed to the stereoselectivity along with the SOI.[9]

(c) Poirier and Burnell have investigated the reactions of cyclopropene and 3-BH_2/CH_3/SiH_3/NH_2/PH_2/OH/SH/F/Cl substituted cyclopropenes with butadiene at the B3LYP/6-31++G(d)//HF/6-31++G(d) level and concluded that there was no contribution of the SOI to the stereoselectivity.[10]

(d) Gosse and Poirier have studied the reaction of butadiene with 3,3-disubstituted cyclopropenes (the substituents were CH_3, SiH_3, NH_2, PH_2, OH, SH, F and Cl) at the B3LYP/6-31++G(d) level and observed that the *exo* TS structure was consistently favored over the corresponding *endo* TS structure.[11]

(e) Lewandowski and Houk have very recently studied the reactions of cyclopropene, 3-substituted cyclopropenes and 3,3-disubstituted cyclopropenes with butadiene at the M06-2X/6-31+G(d) density functional level and suggested that factors such as hyperconjugation, electrostatic and steric effects also contributed along with the SOI to the stereoselectivity.[12] This study was inspired by the experimental selectivities of the DA reactions of the cyclopropenes **1a**-**e** with cyclopentadiene. However, cyclopentadiene was never used in the calculations.

A similar investigation of the DA reactions of cyclopentadiene with 3,3-disubstituted and also 1,2,3,3-tetrasubstituted cyclopropenes has not been reported till date. We, therefore, have calculated the activation free energies ($\Delta G^{\ddagger}$) of the reactions of both cyclopentadiene and butadiene with the cyclopropenes **1a**–**e** to: (a) compare the stereochemical features while the difference is that of only a methylene group and (b) assess how well the stereoselectivities calculated for cyclopentadiene corresponded with the experimental stereoselectivities.

We demonstrate herein that (a) the stereochemical results obtained for the reactions of cyclopropenes with butadiene are significantly different from those with cyclopentadiene and (b) the differential activation energy does not always corroborate with the experimental selectivity.

2. COMPUTATIONAL METHODS

All the structures, geometry optimizations and TS structure searches were carried out using the global hybrid meta-GGA M06-2X density functional and 6-31+G(d) basis set.[13] Quantum chemical calculations at the second order perturbation theory MP2/6-31G(d) level[14] were carried out for comparison. The optimized structures were verified as minima or first order saddle points on their potential energy surfaces by harmonic vibrational frequency analysis. Calculations at the gold standard CCSD/6-31G(d)//MP2/6-31G(d) level (full optimization) and CCSD(T)/6-31G(d)//MP2/6-31G(d) level (single point calculation) were also carried out to compare the results obtained at other levels of theory. The solvation effects of dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$) and carbon tetrachloride (CCl_4) were estimated using the Conductor Polarized Continuum Model (CPCM).[15] Calculations were carried out using the Gaussian 09 suite of programs.[16]

3. RESULTS AND DISCUSSION

The activation free energies of the *endo* and *exo* TS structures for the reactions of the cyclopropenes **1a**–**1e** with cyclopentadiene are given in Table 1. While the cyclopropene **1a** is predicted to undergo exclusive *endo* addition, the perfluorocyclopropene **1c** is predicted for predominantly *exo* addition. In contrast, the acetal **1b** is predicted to furnish an equal mixture of the two products. Like **1b**, both 1,2-dichloro-3,3-difluorocyclopropene **1d** and 1,2-dibromo-3,3-difluorocyclopropene **1e** are also predicted to form mixtures, but predominating in the *endo* product. All the reactions are highly exergonic, ranging from 17–31 kcal/mol. While the predictions for **1a**

and **1b** corroborate well with the experiments, they contrast the observed exclusive *endo* selectivity for **1c** and *exo* selectivities for both **1d** and **1e**.

Table 1**.** Activation free energies ($\Delta G^{\ddagger}$) and enthalpy changes ($\Delta G_{endo/exo}$), kcal/mol, for the gas phase DA reactions of **1a**–**e** with cyclopentadiene and butadiene at the M06-2X/6-31+G(d) level and 298.15 K

cyclopropene	reaction with cyclopentadiene				reaction with butadiene		
	$\Delta G^{\ddagger}_{endo}$	$\Delta G^{\ddagger}_{exo}$	k_{endo}:k_{exo}	$\Delta G_{endo/exo}$	$\Delta G^{\ddagger}_{endo}$	$\Delta G^{\ddagger}_{exo}$	k_{endo}:k_{exo}
1a	20.84	24.98	>99:1	-29.7/-31.4	20.64	23.20	98:2
1b	27.07	27.22	55:45	-19.4/-24.2	26.27	23.21	1:99
1c	27.87	25.56	<2:98	-21.6/-26.7	28.97	26.41	2:98
1d	26.59	26.85	60:40	-17.6/-21.8	28.62	26.88	5:95
1e	20.26	21.19	80:20	-23.2/-28.0	23.76	21.96	5:95

The TS structure data for the corresponding reactions with butadiene, also given in Table 1, allows a comparison with the data for the reactions with cyclopentadiene. While the reaction of **1a** with butadiene is exclusively *endo*, like the reaction with cyclopentadiene, the cyclopropenes **1b**–**e** are predicted for predominant to exclusive *exo* selectivities. The exclusive *exo* selectivity predicted for the reaction of **1b** with butadiene contrasts the dismal selectivity with cyclopentadiene. Also, in contrast to the predominant *exo* selectivities for the reactions of **1d** and **1e** with butadiene, the corresponding reactions with cyclopentadiene are predicted to generate mixtures predominating in the *endo* products.

It is clear from the above discussion that the stereoselectivity features discerned for the DA reactions of the cyclopropenes **1a**–**e** with butadiene are generally different from those with cyclopentadiene. This difference underlines the contribution, steric and/or electrostatic, of the additional methylene group in cyclopentadiene.

Question arises as to why at all the TS approach failed at predicting the experimental exclusive *endo* selectivity for **1c** and also the *exo* selectivities for **1d** and **1e** in their reactions with cyclopentadiene. Is the global hybrid meta-GGA M06-2X density functional inappropriate at handling halogen-containing molecules?[17] We chose to carry out the above calculations using the MP2/6-31G(d) wave functional for comparison. The results are collected in Table 2. A comparison of the data in the Tables 1 and 2 readily reveals that both the levels of calculation are qualitatively very similar. The exclusive *endo* selectivity of **1c** and the *exo* selectivities of **1d** and **1e** remain, therefore, unexplained.

Table 2**.** Activation free energies ($\Delta G^{\ddagger}$) and enthalpy changes ($\Delta G_{endo/exo}$), kcal/mol, for the gas phase DA reactions of **1a**–**e** with cyclopentadiene calculated at the MP2/6-31G(d) level and 298.15 K

cycopropene	$\Delta G^{\ddagger}_{endo}$	$\Delta G^{\ddagger}_{exo}$	k_{endo}:k_{exo}	ΔG_{endo}	ΔG_{exo}
1a	15.94	20.44	>99:1	-34.8	-36.5
1b	19.71	19.86	56:44	-25.4	-30.4
1c	21.59	19.62	4:96	-25.0	-30.7
1d	18.39	18.82	68:32	-23.8	-28.7
1e	13.78	14.36	73:27	-28.8	-34.0

Table 3**.** Activation energies ($\Delta E^{\ddagger}$), kcal/mol, for the gas phase DA reactions of **1a**–**e** with cyclopentadiene from calculations the CCSD/6-31G(d)//MP2/6-31G(d) level and 298.15 K

cycopropene	$\Delta E^{\ddagger}_{endo}$	$\Delta E^{\ddagger}_{exo}$	k_{endo}:k_{exo}
1a	14.16	18.32	>99:1
1b	18.85	18.67	46:54
1c	20.38	17.96	08:92
1d	18.54	18.69	54:56
1e	14.65	14.95	57:43

We also chose to perform calculations of the ground and TS structures at CCSD/6-31G(d)//MP2/6-31G(d) level to estimate the stereoselectivity profile. The data is collected in Table 3. The stereoselectivity levels of the DA reactions of the cyclopropenes **1a**–**c** are much the same as at other levels of theory. However, the cyclopropenes **1d** and **1e** are predicted for near no selectivity which is against the experimental results. The results obtained from single point calculations at CCSD(T)/6-31G(d)//MP2/6-31G(d) level (see Table 3S in SI) are very similar. Thus, the CCSD level calculations also failed at predicting the experimental stereoselectivities of the DA reactions of the cyclopropenes **1c**–**e**.

In search of a rationale, we also considered the effect of solvents on stereoselectivity. The TS structure calculations were carried out to study the effect of CH_2Cl_2 on the reaction of **1a,** $CHCl_3$ on the reaction of **1c**, and CCl_4 on the reactions of **1d** and **1e**. The corresponding activation free energies are given in Table 4. It is to be easily seen that the overall trend, including the level of stereoselectivity, remained more or less the same as in the gas phase calculation in each instance. The solvent, therefore, does not have any controlling influence on the stereoselectivities of the DA reactions studied herein.

Table 4**.** Activation free energies ($\Delta G^{\ddagger}$), kcal/mol, for the DA reactions of **1a** in CH_2Cl_2, **1c** in $CHCl_3$, and **1d** and **1e** in CCl_4 with cyclopentadiene calculated at the M06-2X/6-31+G(d) level and 298.15 K

cycopropene	solvent	$\Delta G^{\ddagger}_{endo}$	$\Delta G^{\ddagger}_{exo}$	k_{endo}:k_{exo}
1a	CH_2Cl_2	20.43	24.69	> 99:1
1c	$CHCl_3$	27.92	25.59	>2:98
1d	CCl_4	25.45	25.72	60:40
1e	CCl_4	19.28	20.19	80:20

The preferential formation of the *endo* product in DA reactions has been attributed to the Secondary Orbital Interactions (SOI) between the atoms of the two reactants that are not bonded in the TS structure.[18,19] The

bonding interaction of the forming π bond between the two internal sp^2 carbons of the diene (cyclopentadiene or butadiene) and a substituent orbital on the dienophile (cyclopropene) in the *endo* TS structure constitutes the SOI as shown in Figure 1a for the reaction of **1a** with cyclopentadiene. Such an interaction, of course, does not exist in the *exo* TS structure. *In the present context, the endo addition of **1b** is SOI-neutral, that of **1c** somewhat repulsive as shown in Figure 1b, and those of **1d** and **1e** slightly, if at all, repulsive*. The $\pi_{C=C} \rightarrow \pi^*_{C=C}$ interactions between the two reactants leading to the formation of the two new σ bonds constitute the primary interactions required for the DA reaction itself to take place and, as such, do not contribute to the stereoselectivity. Hyperconjugation, electrostatic and steric effects also contribute to the stereoselectivity as observed by Lewandowski and Houk.[12]

Among all the interactions, it is conceivable that a given interaction is more important than others for a given pair of reactants. Also, an argument applicable to a given pair of reactants need not necessarily be applicable to another pair of reactants. In the instance involving the DA reaction of a 3,3-disubstituted cyclopropene, the steric effects arising from the *syn* C3-substituent must necessarily be important in both the *endo* and *exo* TS structures. Further, depending on the nature of the substituent, the electrostatic interaction of the *syn* C3-substituent in cyclopropene with the *syn* methylene-H of cyclopentadiene in the *exo* TS structure, as shown in Figure 2, must also be important.

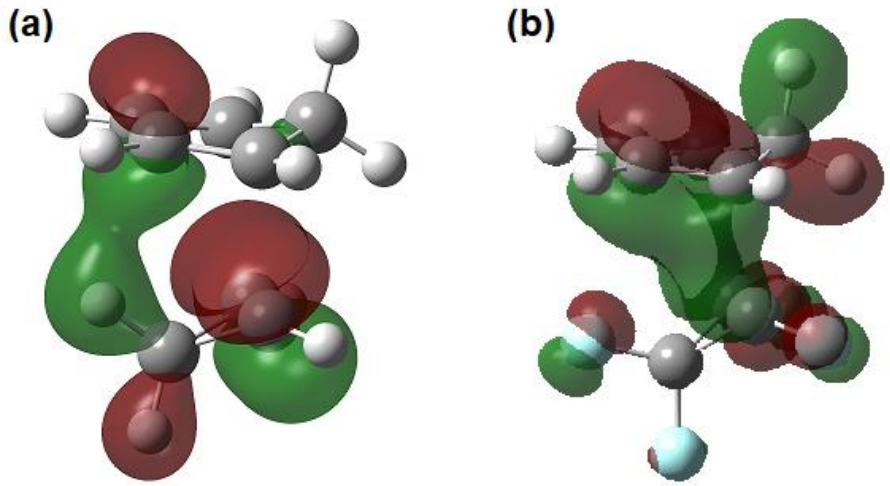


Figure 1. Molecular orbital of the TS structure for the *endo* DA addition of cyclopentadiene with (a) **1a** showing the constructive SOI between the *syn* methylene σ_{CH} and the forming π bond between the two internal sp^2 carbons of cyclopentadiene and (b) **1c** showing the repulsive SOI between the lone pair orbital of *syn* methylene-F and the forming π bond

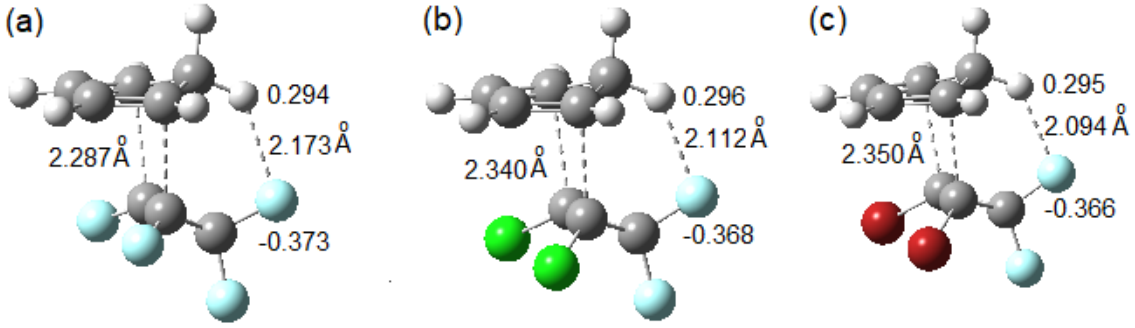


Figure 2. The electrostatic interactions between the negatively charged F and the positively charged *syn* methylene-H in the *exo* TS structures for the DA reactions of (a) **1c**, (b) **1d** and (c) **1e** with cyclopentadiene

It is significant to note that as the length of the forming σ bond increases from 2.287 Å to 2.340 Å to 2.350 Å, the distance between the *syn* methylene-H and the *syn* cyclopropene-F decreases from 2.173 Å to 2.112 Å to 2.094 Å in (a), (b) and (c), respectively. In contrast, the NBO charges on the interacting atoms changed marginally. The electrostatic interaction, therefore, supports *exo* selectivity. *The presence of electrostatic interactions in the exo*

*TS structures together with the absence of SOI in the endo TS structures do explain the observed exo selectivities of **1d** and **1e**. However, the similar electrostatic interaction coupled with the somewhat repulsive SOI in the endo TS structure predicts exo selectivity of **1c**, which contradicts the experiment.* An all-applicable unified rationale is therefore not available.

It is generally understood that all the possible interactions, constructive or otherwise, are ingrained in the TS structure and, hence, the differential activation free energy *($\Delta\Delta G^{\ddagger}$)* must predict well the level of stereoselectivity on further translation to the kinetic spread of products[20] for irreversible processes such as the present DA reactions. The failure of $\Delta\Delta G^{\ddagger}$ in predicting the experimentally observed DA stereoselectivities of **1c–e** with cyclopentadiene is bothersome. It appears that the various theoretical models dealing with the *endo* and *exo* DA preferences are not sufficiently developed even today to allow sound predictions in such (complicated) situations.

4. CONCLUSION

The application of differential activation free energy to the kinetic spread of the *endo* and *exo* products from the irreversible DA cycloaddition reactions of cyclopentadiene with perfluorocyclopropene **1c**, 1,2-dichloro-3,3-difluorocyclopropene **1d** and 1,2-dibromo-3,3-difluorocyclopropene **1e** failed at predicting the experimental stereoselectivities at different levels of theory. The TS approach favors *exo* selectivity against the *endo* observed for **1c** and formation of mixtures, predominating in the *endo* isomer, in contrast to the exclusive *exo* selectivities observed for **1d** and **1e**. Also, the stereoselectivities of the DA reactions of cyclopentadiene to substituted cyclopropenes are generally different from that of butadiene.

The failure of the differential activation energy at correctly predicting the experimental selectivities of the DA reactions of **1c**, **1d** and **1e** with cyclopentadiene leaves us to also conclude that the various theoretical models dealing with the stereoselectivities of the DA reactions are not sufficiently developed to allow sound predictions in complicated situations.

ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates of the optimized substrates, transition state structures, Gibbs' free energies and total electronic energies (PDF, 33 pages)

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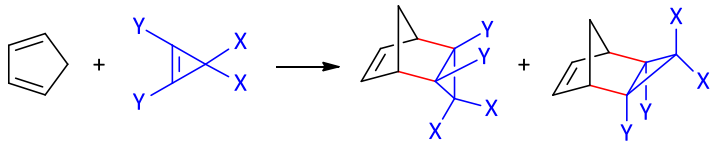
The endo/exo stereoselectivity of the Diels-Alder reaction of cyclopentadiene with substituted cyclopropenes is generally different from that of butadiene. Also, calculations at different levels of theory fail to predict the experimental selectivity of halogen-substituted cyclopropenes in reactions with cyclopentadiene.



endo adduct *exo* adduct