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Density Functional Study of π Facial Selectivity in Diels−Alder Reactions

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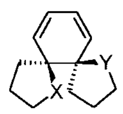
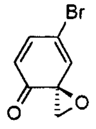
Facial selectivity is an important aspect of Diels−Alder (DA) cycloadditions.[1] In most cases, when heteroatoms are involved, the relative percentage of one of the adducts exceeds 90%. In usual experimental conditions, this indicates that the reaction-path leading to this adduct is favored by more than about 1.3 kcal/mol. Several factors have been invoked to explain facial selectivity, but the interpretations are difficult when several competitive interactions occur. Kraus[2] proposed a method based on the molecular electrostatic potentials of the reactant structures: electrostatic maps are computed for the two π faces of the reactant, and the preferred approach can be visualized. Hehre[3] suggested to consider the nucleophilicities of the two reactant π faces. However, these methods are not very reliable, and studies based on transition structures (TS) should be preferred.[4] In a study of cyclopentadiene derivatives, Fallis[1a] invoked an hyperconjugation of σ bonds with the developing incipient bonds and, for similar compounds, Poirier[5] proposed an explanation based on diene deformation energies. In a detailed investigation on dimerization of substituted cyclopentadienes, Trost[4d] considered the substituent effect on the LUMO of the dienophile. It is likely that these various interpretations are not completely independent. Recently, the high selectivity observed in DA reactions on dispiro 1,3-cyclohexadienes **A**[6] or spiroepoxydienone **B**[7] was interpreted in terms of electrostatic and steric interactions.



A (X,Y = O, CH$_2$)



B

Taking into account the restricted conformational mobility of dienes **A** and **B** which should be attractive to better understand the factors governing facial selectivity, density functional calculations on two model reactions involving these dienes have been carried out. The interactions occurring in the *syn* and *anti* TS's were examined, and a model is now proposed to account for the observed facial selectivity. Some typical experimental results concerning these dienes are recalled in Table 1.

As we focus on facial selectivity, the reactants are simplified. In all the cycloadditions involving **A** or **B**, the *syn*/*anti* ratios are high (more than 9/1) whatever the dienophile. Thus, we use ethylene as dienophile in this theoretical study. In addition, **A** and **B** are simplified and we study the model reactions (reactions 5 and 6, Scheme 1). We performed calculations with the Becke3LYP density functional method[8] as implemented in the Gaussian 94 package.[9] The B3LYP method is computationally efficient and has been proven recently to provide accurate results for DA reactions.[6f,6g] Interaction energies are corrected for Basis Set Superposition Error (BSSE) using the counterpoise method[10] with standard basis set up to 6-311+G(d,p). The transition structures were optimized using the Synchronous Transit-Guided Quasi-Newton method as implemented in Gaussian 94.[11] In each case, the fully optimized transition structures are characterized by one and only one negative eigenvalue of the Hessian. No account has been made of zero point energy corrections. Such corrections are usually neglected when barrier heights of similar reactions are compared.

Results and Discussion

The *syn* and *anti* TS's of (5) and (6) were located at B3LYP/6-31G(d,p) level. Total energies and barrier heights are collected in Table 2. Calculations at the ab initio RHF/3-21G level are included in Table 2 for comparison.[12] The B3LYP-optimized transition structures of (5) are depicted in Figure 1. These calculations are consistent with

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Table 1. Experimental Results for DA Reactions with A and B Dienes

reaction	diene + dienophile	% *syn*[a]	exptl conditions	ref
(1)	**A** (X = O, Y = O) + NPM[b]	100	Δ, 72 h	6
(2)	**A** (X = O, Y = CH_2) + NPM[b]	92	150000 psi, 72 h	6
(3)	**B** + styrene	100	rt, 24 h	7
(4)	**B** + ethyl vinyl ether	100	rt, 72 h	7

[a] *syn* to oxygen atom. [b] *N*-Phenylmaleimide.

Scheme 1. Model Reactions (5) and (6)

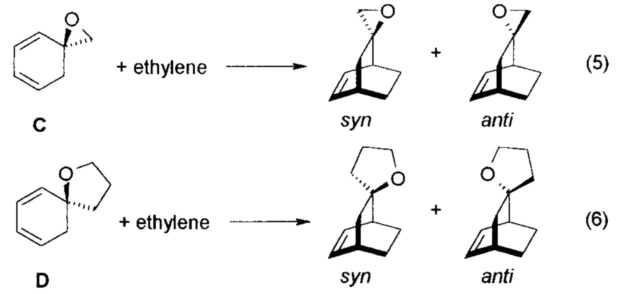

Table 2. Total Energies (hartrees) for Reactants and Transition Structures for (5) and (6) Model Reactions (barrier heights in kcal/mol in parentheses)

	RHF/3-21G	B3LYP/6-31G**/ RHF/3-21G[a]	B3LYP/6-31G**
ethylene	−77.60099	−78.59122	−78.59198
diene **C**	−342.58482	−346.69432	−346.69845
diene **D**[b]	−420.28075	−425.34999	−425.35362
syn-TS (5)	−420.13437	−425.25172	−425.25641
	(32.3)	(21.2)	(21.4)
anti-TS (5)	−420.12956	−425.24956	−425.25409
	(35.3)	(22.6)	(22.8)
syn-TS (6)[b]	−497.82680	−503.90552	−503.90973
	(34.5)	(22.4)	(22.5)
anti-TS (6)[b]	−497.81866	−503.90217	−503.90638
	(39.6)	(24.5)	(24.6)

[a] Single point energy calculations at RHF/3-21G geometries. [b] Two conformers are obtained for the five-membered ring of diene **D** and of (6)-TS's. Only the lowest energy conformer results are reported.

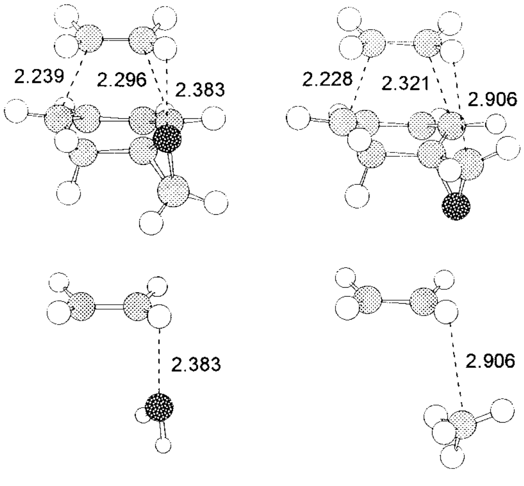

Figure 1. B3LYP/6-31G(d,p) *syn* and *anti* (5)-transition structures and the corresponding **C*syn*** and **C*anti*** clusters (selected distances in Å).

experimental results since in each case the *syn* approach is favored, and the *syn* and *anti* barrier heights differ by more than 1.3 kcal/mol. As expected, the barrier heights are significantly lowered upon inclusion of electron correlation. At this stage, a better understanding of the factors governing facial selectivity in these two model reactions is possible. Our basic assumption is that facial selectivity results from direct interactions between the spiro group of the diene and the dienophile moiety. These interactions will be subsequently referred to as proximate-substituent interactions.

Table 3. Proximate-Substituent Interactions (kcal/mol) Calculated for (5)- and (6)-Transition Structures (see text) and BSSE Corrected Values in Parentheses

proximate-substituent interaction	B3LYP/ 6-31G(d,p)	B3LYP(6-311+G(d,p)/ B3LYP/6-31G(d,p)
$\Delta E_{\mathbf{C}syn}(5)$	−1.0 (+0.5)	0.0 (+0.2)
$\Delta E_{\mathbf{C}anti}(5)$	+0.6 (+1.5)	+1.3 (+1.4)
$\Delta E_{\mathbf{C}syn}(6)$	−1.5 (+0.1)	−0.4 (−0.1)
$\Delta E_{\mathbf{C}anti}(6)$	+1.5 (+2.3)	+2.2 (+2.3)

Proximate−Substituent Interactions. To quantify these interactions, we used the following method: Two clusters denoted **C*syn*** and **C*anti*** are constructed from the *syn* and *anti* TS's: In each case, the ethylene moiety is retained. In **C*syn***, all atoms of the diene moiety are removed except for the oxygen atom and the two carbon atoms bonded to it. These two carbon atoms are replaced with hydrogen atoms. The resulting H_2O molecule was optimized at the same level of calculation but constraining the H−O−H bond angle to the value of the C−O−C bond angle in the diene moiety. **C*anti*** was constructed in a similar way. All atoms of the diene moiety were removed except for the CH_2 bonded to the six-membered ring and the two atoms bonded to this methylene. These two later atoms are then replaced with hydrogen atoms, and the two C−H bonds thus formed are shortened to the average value between the two C−H bonds of this CH_2 group. **C*syn*** (respectively **C*anti***) is constituted of a C_2H_4 moiety and a H_2O (respectively CH_4) moiety. The **C*syn*** and **C*anti*** clusters of (5) are shown in Figure 1 together with the corresponding TS's. The proximate-substituent interaction energy is calculated as the difference in total energies between the cluster and the two moieties calculated independently, namely:

$$\Delta E_{\mathbf{C}syn} = E(\mathbf{C}\boldsymbol{syn}) - [E(\mathrm{H_2O}/\mathbf{C}\boldsymbol{syn}) + E(\mathrm{C_2H_4}/\mathbf{C}\boldsymbol{syn})]$$

$$\Delta E_{\mathbf{C}anti} = E(\mathbf{C}\boldsymbol{anti}) - [E(\mathrm{CH_4}/\mathbf{C}\boldsymbol{anti}) + E(\mathrm{C_2H_4}/\mathbf{C}\boldsymbol{anti})]$$

where $E(\mathbf{C}syn)$, $E(\mathrm{H_2O}/\mathbf{C}syn)$ and $E(\mathrm{C_2H_4}/\mathbf{C}syn)$ are the total energies of the **C*syn*** cluster, the H_2O and the ethylene moieties of **C*syn***, respectively (and similar definitions for **C*anti***). For such interactions, BSSE corrections are justified and are reported in Table 3. The positive sign of the $\Delta E_{\mathbf{C}anti}$ values can be unambiguously assigned to the Pauli repulsion between the CH_4 and C_2H_4 moieties in the **C*anti*** clusters. As expected, the BSSE corrected values are slightly higher than the uncorrected values. On the other hand, our results are less conclusive about the interactions in the **C*syn*** clusters. Actually, the uncorrected interaction energies are negative but the BSSE corrected values are slightly positive. It is known that BSSE corrections using the counterpoise method are very approximate.[13] A better

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[13] Gutowski, M.; VanDuijneveldt, F. B.; Chalasinski, G.; Piela, L. *Mol. Phys.* **1987**, *61*, 233.

approach is to enlarge the basis set with the hope for some convergence in the results. We have performed energy calculations with the extended 6-311+G(d,p) basis set on the 6-31G(d,p) TS's. The values reported in Table 3 indeed indicate that the BSSE corrections significantly decrease from the 6-31G(d,p) level to the extended 6-311+G(d,p) level. In addition, the interaction energy in the **C*syn*** clusters is nearly 0 kcal/mol in both (5)- and (6)-TS's (+0.2 and −0.1 kcal/mol, respectively). This result was not expected since the Mulliken charges on the oxygen atom and on the H atom of the ethylene moiety (−0.47e and +0.14e in the (5)-*syn*-TS and −0.53e and +0.14e in the (6)-*syn*-TS at 6-31G(d,p) level) looked consistent with an attractive electrostatic interaction. Such an interpretation for *syn* facial selectivity on similar compounds has already been proposed indeed.[6,7] However, the H- - -O distances in the *syn*-TS's (2.383 and 2.316 Å in the (5)- and (6)-TS's respectively) are significantly less than the sum of the VdW radii (2.70 Å[14]). At such distances, the exchange term of the interaction energy is likely to compensate or exceed the electrostatic component.

The $\Delta E_{\mathbf{C}syn}$ and $\Delta E_{\mathbf{C}anti}$ interaction energies may be compared with the difference between the *syn* and *anti* barrier heights. For this purpose, we calculated

$$\Delta(\Delta E) = \Delta E_{\mathbf{C}anti} - \Delta E_{\mathbf{C}syn}$$

$\Delta(\Delta E)$ values obtained for (5) and (6) are 1.6 and 3.0 kcal/mol, respectively. They can be compared with the differences between the *syn* and *anti* barrier heights (1.4 and 2.1 kcal/mol for (5) and (6), respectively). These values show that the proximate−substituent interactions as modeled in the **C*syn*** and **C*anti*** clusters account for a large amount of the difference between the *syn* and *anti* barrier heights. Thus, the assumption that facial selectivity in (5) and (6) is controlled by these proximate interactions is reasonable.

The interaction energies derived for (6) are consistent with the experimental results for (1) and (2) in Table 1. Let us suppose additivity for the two five-membered rings in **A**. In (2), a repulsive CH_2 replaces an oxygen atom in (1). Then, the barrier height for (2) should be greater than the one for (1) by about 0.1 + 2.3 = 2.4 kcal/mol. This result is consistent with the high-pressure involved in (2). In addition, the difference between the *syn* and *anti* barrier heights in (1) is expected to be approximately 2.4 + 2.4 = 4.8 kcal/mol whereas it is only about 2.4 kcal/mol in (2). This observation may be compared with the better selectivity in (1) with respect to (2). This analysis shows that the calculated increments for model reaction 6 can be used to interpret the facial selectivity for reactions 1 and 2 in Table 1. It is likely that these increments can be used to interpret the facial selectivity for other DA cycloadditions, provided that the spiro-group (i.e., the group that allows to distinguish between the two π surfaces) remains unchanged. For instance, it is expected that any substituent lying in the plane of the diene (or the dienophile) do not change dramatically the facial selectivity.

Geometrical Aspects. Some geometrical aspects of our TS's can be pointed out. Among them, we consider the "out of plane" angles of the C and O atoms (denoted X) of the epoxide (or five-membered ring) bonded to the carbon atom (denoted C') of the cyclohexadiene moiety.[15] These "out of plane" angles are shown in Figure 2. In the *anti* TS's, the OOP of C changes from 17.9° in (5) to 43.6° in (6). This is consistent with an increasing steric repulsion and therefore a higher $\Delta E_{\mathbf{C}anti}$ value. Turning now to the *syn* TS's, the increase of the oxygen OOP is less important (from 35.9° in (5) to 52.8° in (6)). This is also reflected by the small decrease of the ethylenic H to oxygen distance (see above). Such C−H- - -O interactions were considered in crystal packing studies and geometrical criteria were proposed to identify hydrogen bonds.[16] According to these criteria, the present C−H- - -O interactions involved in the *syn* TS's cannot be classified as hydrogen bonds. The H- - -O distances are slightly too short, and the C−H- - -O angles deviate too much from linearity (116.4° in *syn*-(5)-TS and 117.6° in *syn*-(6)-TS).

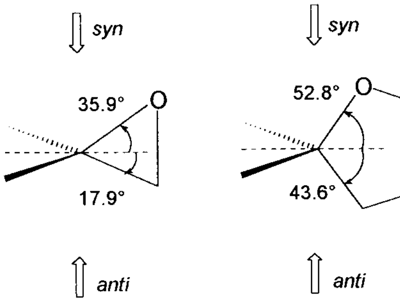

Figure 2. "Out of plane" angles (in degrees) in the spiro-group of (5)- and (6)-TS's.

Concluding Remarks

The calculations presented in this paper are in satisfying agreement with the experimental results. These B3LYP calculations using double-ζ plus polarization functions basis set provide reliable results for π-facial selectivity in DA reactions. A modelization of proximate-substituent interactions in (5)- and (6)-TS's supports that steric effects and C−H- - -O interactions govern facial selectivity. From this model, the *anti* approach is clearly disfavored by steric interactions. On the other hand, the C−H- - -O proximate−substituent interactions occurring in the *syn* approach are slightly more subtle. Even though the net charges on the oxygen atom and the ethylenic H atom induce some electrostatic attraction, the distance between these two atoms is rather short, and therefore the exchange term compensates the electrostatic component. The resulting interaction is about 0 kcal/mol making the *syn* approach more favorable. Concerning the electron correlation treatments in theoretical studies of substituent effects in DA reactions, a remark seems appropriate. Studies at RHF level are generally assumed to provide acceptable results since the number of active electron pairs does not change when modifying the substituent. Then, the correlation energy should be nearly constant. In the present study, however, the electron correlation may play a significant role through proximate-substituent interactions (i.e., not involving

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[14] Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

[15] The "out of plane" angle of X is the angle between the C'−X bond and the plane defined by C' and the two carbon atoms of the cyclohexadiene moiety bonded to it.

[16] (a) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441. (b) Desiraju, G. R. *Crystal Engineering. The Design of Organic Solids*; Elsevier: Amsterdam, 1989; pp 142−164. (c) Steiner, T. *Chem. Commun.* **1997**, 727.

active electrons). The electron correlation treatment modifies the balance between ionic and covalent components in the wave function. A general tendency is a decrease in the net atomic charges and lowered electrostatic interactions. Some care is necessary to extend our calculated ΔE_{Csyn} values to other dienophiles than ethylene. As noted above, the electrostatic component of the *syn* proximate-substituent interaction is a significant part of the interaction. Therefore, the acidity of the ethylenic H atom has to be considered.

Supporting Information Available: Cartesian coordinates of the computed structures (B3LYP). This material is available free of charge via the Internet at http://pubs.acs.org.

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