An ab Initio Study of Facial Selectivity in the Diels−Alder Reaction

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Abstract: Facial selectivities in the Diels−Alder reactions of 5-substituted 1,3-cyclopentadienes with a variety of dienophiles are predicted reliably at the ab initio HF/6-31G* level. The ranges of activation energies for syn addition are large relative to those for anti addition, which are all similar to the activation energy for cyclopentadiene itself. Partitioning the activation energy into diene deformation, dienophile deformation, and diene−dienophile interaction energies shows that the major factor in determining facial selectivity is in the energy required to deform the diene into its transition state geometry. Deformation of the 5-fluoro-, 5-hydroxy-, and 5-amino-1,3-cyclopentadienes into their syn transition state geometries is predicted to require less energy than deformation of cyclopentadiene itself, which is in accord with experimental observation of syn addition with these dienes. The first definition of an ab initio steric factor is presented which correlates very well with syn activation energies. This indicates that facial selectivity with these dienes is primarily due to steric hindrance between the dienophile and the plane-nonsymmetric groups on the diene. However, we have also identified a significant lone pair−lone pair interaction with the reacting nitrogens when the dienophile is 1,2,4-triazoline-3,5-dione.

Introduction

There are many instances in synthesis in which facial selectivity has been exploited to produce a Diels−Alder adduct with high diastereoselectivity.[1] Synthetic planning has invariably relied on crude estimates of the difference in steric hindrance on either side of a plane-nonsymmetric diene or dienophile, but the success of the synthetic endeavors is testimony to the accuracy of this simple basis of prediction. On the other hand, when theoretical and experimental work was directed specifically at the question of facial selectivity, reactions involving three types of cyclic dienes were discovered to proceed in a manner that appeared to defy steric control. As a result, alternative rationalizations were developed based on what might loosely be called stereoelectronic phenomena. Paquette[2] and others[3] suggested that orbital mixing leads to a tilting of the π orbitals in isodicyclopentadiene, and this is the source of its facial selectivity.[2] Brown and Houk claimed that this selectivity could also be explained by torsional effects at the transition state.[4] Ginsburg[5] showed that addition syn to carbonyl groups might arise by favorable admixture of dienophile lone-pairs into the carbonyl LUMO's. A recent "contrasteric" reaction by De Lucchi's group might have been explained in a similar way.[6] On the other hand, a remote oxygen function can direct addition anti to itself by a closed-shell repulsion mechanism.[7]

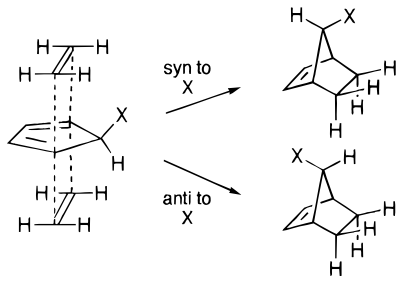

Figure 1. Definition of syn and anti addition.

The simplest dienes to which dienophiles add preferentially syn to the larger group are 1,3-cyclopentadienes (Figure 1) substituted at C5 by an oxygen,[8] fluorine,[9] or chlorine.[10−13] Dienes with amine[12] and carboxylic sub-

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stituents[14] also show marked tendencies for syn addition. When the substituent at C5 is a sulfide there is little facial selectivity.[12,15] Other heteroatoms, such as silicon,[16] selenium,[15] bromine,[11,13] iodine,[11,13] and more oxygenated sulfur-containing functional groups[12] direct addition almost exclusively anti to the heteroatom. We demonstrated that facial selectivity with dienes of this type is the same in inverse-electron-demand reactions as it is in normal Diels−Alder reactions.[17] 1,3-Cyclohexadiene with cis oxygen functions at C5 and C6 can also show facial selectivity that appears to be at variance with a simple steric argument,[18] whereas additions to benzene oxide are clearly not controlled by a stereoelectronic effect.[19] Facial selectivity is believed to be controlled by steric interactions with cyclopentadienes and dienes in six-membered rings that are substituted with alkyl groups.[20−22]

The hypotheses that have been proposed to explain facial selectivity with substituted cyclopentadienes can be classified as those that should have ground-state manifestations and those that should not. In terms of the former, Japanese workers have favored various forms of orbital mixing within the diene as the causative phenomenon.[14,15,23] Kahn and Hehre[24] suggested that a facially nonequivalent diene would have a more nucleophilic face which should be more reactive toward an electrophilic dienophile, but this hypothesis has been rebutted.[25] The importance of any phenomenon observable in the reactant diene is now questionable in the light of photoelectron spectral data.[26] Causative phenomena that would be manifested in the transition state include: favorable orbital overlap between the dienophile and the heteroatom of the diene;[27] steric and/or torsional effects, as have been postulated based on computational work for some hydrocarbon dienes[4,21] and for benzene oxide;[19] attractive van der Waals and London dispersion forces;[10] and the hyperconjugative effect, initially proposed by Cieplak to explain carbonyl reactions,[28] that was extended by Macaulay and Fallis[12] to Diels−Alder reactions. Although this last effect has since been used to rationalize other Diels−Alder results,[9,29] AM1 calculations by Werstiuk and Ma[30] and ab initio calculations by Poirier and co-workers[31] suggest that the "Cieplak effect" cannot be significant in the Diels−Alder reactions of these cyclopentadienes.

We present here a comprehensive ab initio examination of the Diels−Alder reactions of 5-substituted 1,3-cyclopentadiene derivatives (Figure 1).[31] This leads to an explanation of the facial selectivity in the reactions of cyclopentadienes that is consistent will all the experimental evidence.

Computational Methods

The MUNGAUSS[32a,b] program, with a few exceptions,[32c] was used to optimize fully all structures at the HF/6-31G* level of theory.[33] Reactant structures were obtained using the Optimally Conditioned method of Davidon,[34] and transition state geometries were determined using a minimization of sum-of-squares method.[35] Any incompletely converged structures were further optimized by Pulay's DIIS method.[36] Conformationally mobile groups were allowed to assume their lowest energy forms in both the reactants and the transition states. (In many instances, the conformation of lowest energy for the substituent was different in the diene and in the corresponding syn or anti transition states.) Facial selectivities are reported as the percentage of syn addition, as approximated by: $(1 + E^{\Delta E_{act.}/RT})^{-1} \times 100\%$, where $\Delta E_{act.}$ is the difference between the activation energies for the syn

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Table 1. Calculated Facial Selectivity Data for 5-Substituted 1,3-Cyclopentadienes with Ethylene

C5 substituent	calcd[a] facial selectivity (% syn addition)	$\Delta E_{act.}$[b] (kJ/mol)	E_{diene}^{def}[b] (kJ/mol)	E_{dphile}^{def}[b] (kJ/mol)	S_{CX}[c] (eÅ^2)	S_{CX}/R_{CX} (Å)
H	50	0.00	0.00	0.00	0.7346	1.0128
BH_2	0.5	13.28	17.37	0.36	0.8750	1.3617
CH_3	20	3.47	8.01	−2.40	0.7508	0.9960
NH_2	95	−7.17	−1.80	−1.12	0.6340	0.7778
OH	99	−10.50	−0.55	−4.64	0.5302	0.6158
F	100	−25.27	−13.22	−4.47	0.4345	0.4783
SiH_3	0	26.70	30.30	−2.24	1.0406	1.5253
PH_2	0.1	16.69	23.81	−2.63	1.0017	1.2830
SH	11	5.14	15.09	−3.61	0.9426	1.0752
Cl	71	−2.20	7.76	−5.37	0.8789	0.8990
GeH_3	0	28.07	31.50	−3.55	1.1657	1.5999
AsH_2	0	23.46	30.38	−2.97	1.1669	1.4327
SeH	2	10.17	20.22	−3.41	1.1154	1.2232
Br	7	6.49	16.62	−6.08	1.0752	1.0509
SnH_3	0	38.37	40.67	−3.50	1.3782	1.9256
SbH_2	0	35.50	40.25	−2.82	1.3750	1.7339
TeH	0	20.38	28.59	−2.88	1.3468	1.4895
I	0.1	18.02	26.95	−5.97	1.3388	1.3035

[a] T = 298 K. [b] Calculated as syn–anti energies. [c] e = charge in atomic units.

and anti additions (T = 298 K). Localized molecular orbitals (LMO's) were obtained by the Boys localization method[37] in which the σ and the π contributions were allowed to mix.

Results and Discussion

Comparison with Experiment. The Diels–Alder reactions with ethylene as the dienophile shown in Figure 1 were examined at the HF/6-31G* level of theory with eighteen X groups, including hydrogen.[38] Table 1 provides the computed facial selectivities[39] along with pertinent energetic and structural parameters. Furthermore, the Diels–Alder reactions of eight substituted dienes were also studied using three quite different dienophiles: acetylene, maleimide, and 1,2,4-triazoline-3,5-dione (TAD), and the corresponding data[39] can be found in Table 2. The activation energies for the reactions with maleimide and, especially, TAD are lower than those with ethylene and acetylene. For example, the activation energies for the reaction of cyclopentadiene with acetylene, ethylene, maleimide, and TAD are 180, 166, 130, and 95 kJ/mol, respectively. What is more important is that with each dienophile the range of activation energies is significantly larger for syn additions than for anti additions. This is especially true with the less reactive dienophiles. For instance, for ethylene the activation energies for syn addition range from 139 to 210 kJ/mol, whereas for anti addition the range is 164 to 172 kJ/mol. The activation energy for the reaction of ethylene with cyclopentadiene is 166 kJ/mol. The narrow range of activation energies for anti addition is not consistent with facial control by the "Cieplak effect," in which selectivity would be a function of the σ-donating ability of the group on C5 that is anti to the incoming dienophile. The calculated facial selectivities are in excellent agreement with the available experimental data (Table 3), even though the latter were obtained in different solutions at a variety of temperatures and sometimes with more elaborate dienes and dienophiles. This clearly demonstrates that calculations at the HF/6-31G* level can be reliably used to probe facial selectivity.[31]

Orbital Mixing. The orbital mixing rule[23] predicts that the lone pairs on the C5 substituent can perturb the π-HOMO of the diene, and this was proposed to be responsible for enhancing attack on the face of the diene syn to some substituents. Kato, Inagaki, and coworkers[15c] extended this idea to a range of substituted cyclopentadienes, for which they obtained orbital energies and coefficients using the STO-3G basis set, and n-π mixing was predicted to tilt the π orbitals in directions that might favor addition to one face or the other. Our own higher level MO data confirm minor distortions in the π orbitals in the directions reported by Kato et al. However, the analysis provided by Kato et al., even with their STO-3G data,[15c] indicates that substituents such as PH_2, AsH_2, and Br should favor syn addition. The data in Tables 1 and 2 (and their own PM3 data with maleic anhydride as the dienophile[15c]) indicate that these dienes must react almost exclusively by anti addition, so Kato et al. admitted that, at least with Br- and I-substituted cyclopentadienes, steric hindrance must dominate over any orbital distortion effect.[15c] The photoelectron spectroscopic work by Werstiuk[26] could discern no significant correlation between substituent and π-HOMO energies. Therefore, we have concluded that there is no reason to expect orbital mixing effects to play a significant role in determining facial selectivity with 5-substituted cyclopentadienes.

Electronegativity and Geometry. Even though it seems unlikely that orbital mixing effects play a significant role, other electronic phenomena cannot be discounted. If an electronic contribution is important at the transition state, some correlation between facial selectivity and a gross electronic property, such as electronegativity, should be expected. In Figure 2 the activation energies for syn additions with ethylene are plotted against the electronegativities[40] of the C5 substituents, and a correlation is obvious (r^2 = 0.83).

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(38) X refers to the substituent at C5 of 1,3-cyclopentadiene. The C–X bond refers to the bond from C5 of 1,3-cyclopentadiene to the central atom of the substituent.

(39) Individual activation energies computed at the Hartree–Fock level must contain systematic errors, but syn-anti ratios are ideally suited for comparison because of the isodesmic relationship of facial diastereoselectivity.

Table 2. Calculated Facial Selectivity Data for 5-Substituted 1,3-Cyclopentadienes with Acetylene, Maleimide and TAD

C5 substituent	calcd[a] facial selectivity (% syn addition)	acetylene $\Delta E_{act.}$[b] (kJ/mol)	acetylene E_{diene}^{def}[b] (kJ/mol)	acetylene E_{dphile}^{def}[b] (kJ/mol)
CH_3	29	2.21	6.73	−2.52
NH_2	99	−12.16	−4.02	0.23
OH	100	−20.06	−7.93	3.27
F	100	−13.98	−10.57	−2.63
SiH_3	0.1	17.92	27.50	−2.78
Cl	14	4.60	7.97	−4.87
Br	0.7	12.42	16.02	−6.00
I	0	20.67	25.18	−6.13

C5 substituent	calcd[a] facial selectivity (% syn addition)	maleimide $\Delta E_{act.}$[b] (kJ/mol)	maleimide E_{diene}^{def}[b] (kJ/mol)	maleimide E_{dphile}^{def}[b] (kJ/mol)
CH_3	13	4.73	8.17	−2.06
NH_2	100	−10.53	5.22	−5.10
OH	100	−17.28	−0.69	−3.59
F	100	−29.01	−14.22	−3.06
SiH_3	0	28.73	31.03	−2.12
Cl	88	−5.00	6.53	−3.95
Br	33	1.74	14.66	−4.98
I	0.1	16.26	24.64	−5.09

C5 substituent	calcd[a] facial selectivity (% syn addition)	TAD $\Delta E_{act.}$[b] (kJ/mol)	TAD E_{diene}^{def}[b] (kJ/mol)	TAD E_{dphile}^{def}[b] (kJ/mol)
CH_3	69	−1.96	2.02	−2.39
NH_2	100	−20.65	−9.24	−1.67
OH	100	−33.45	−13.47	−0.61
F	100	−11.36	−12.94	−2.25
SiH_3	0.1	16.79	20.96	−3.25
Cl	7	6.30	1.71	−4.29
Br	0.8	11.81	7.37	−5.49
I	0.1	18.50	13.61	−6.03

[a] T = 298 K. [b] Calculated as syn-anti energies.

Table 3. Experimental Facial Selectivity Data for 5-Substituted 1,3-Cyclopentadienes

substituent	dienophile	% syn addition	reference
CH_3	*N*-phenylmaleimide	40	20d
CH_3	4-phenyl-TAD	79	20d
NH_2[a]	*N*-phenylmaleimide	100[b]	12
$OCOCH_3$	ethylene	100	8a
F	dimethyl acetylene-dicarboxylate	100	9
$Si(CH_3)_3$	methyl acrylate	0	16b
SH[a]	*N*-phenylmaleimide	55[b]	12
SCH_3	nitroso compound	28	15e
SPh	*N*-phenylmaleimide	30	15d
SPh	4-phenyl-TAD	14	15d
Cl	*N*-phenylmaleimide	79	13
Cl	4-phenyl-TAD	42	13
SePh	*N*-phenylmaleimide	0	15a
Br	*N*-phenylmaleimide	15	13
Br	4-phenyl-TAD	4	13
I	*N*-phenylmaleimide	0	13
I	4-phenyl-TAD	0	13

[a] 1,2,3,4,5-Pentamethyl-1,3-cyclopentadiene analog. [b] % Syn versus a 5-methyl substituent.

Side-on views of the transition structures for cyclopentadiene with the four dienophiles are shown in Figure 3. Important steric interactions at the transition state would be expected to result in some geometrical differences. With any dienophile, the geometries of the transition states, for both syn and anti addition and regardless of diene substituent, are remarkably similar in the region of the diene moiety, the dienophile, and the incipient σ bonds. For instance, the incipient bonds for additions of ethylene with all the dienes in Table 1 are between 2.2273 Å (syn addition with SH) and 2.1699 Å (anti addition with SnH_3). With acetylene, these bond lengths range from 2.2087 Å (syn addition with NH_2) to 2.1709 Å (anti addition with SiH_3). With maleimide the range is from 2.2286 Å (syn addition with SH) to 2.1756 Å (anti addition with SiH_3), and with TAD the range is from 2.1423 Å (syn addition with NH_2) to 2.0520 Å (syn addition with PH_2). The amount of rehybridization at the primary reacting carbons of the diene in the transition state is evidenced by the decrease in the C3−C4−C5 bond angles. Decreases in this angle range from 4.68° (syn addition with Br with ethylene) to 1.10° (anti addition with I with TAD). Similarly, the transition structure of a dienophile changes only slightly with a change of C5-substituent. For example, the C=C bond in ethylene ranges from 1.3878 Å (anti addition with SnH_3) to 1.3772 Å (syn addition with OH), which can be compared to 1.3170 Å for ethylene itself. The N=N bond in TAD ranges from 1.2989 Å (anti addition with SiH_3) to 1.2862 Å (syn addition with F), which can be compared to 1.2145 Å for TAD itself. In contrast, a geometrical parameter that does show significant differences is the C1−C5−X angle (θ) in the syn transition state. There are more modest differences in the C1−C5−H angles in the anti transition states. There is a definite correlation ($r^2 = 0.67$) in the plot of activation energy for syn addition of ethylene versus the change in this angle ($\Delta\theta$) from the reactant diene to the transition state (Figure 4). (The small range of activation energies for anti addition would be responsible for an almost horizontal line in Figure 4.) Figure 4 shows that generally the Diels−Alder reaction

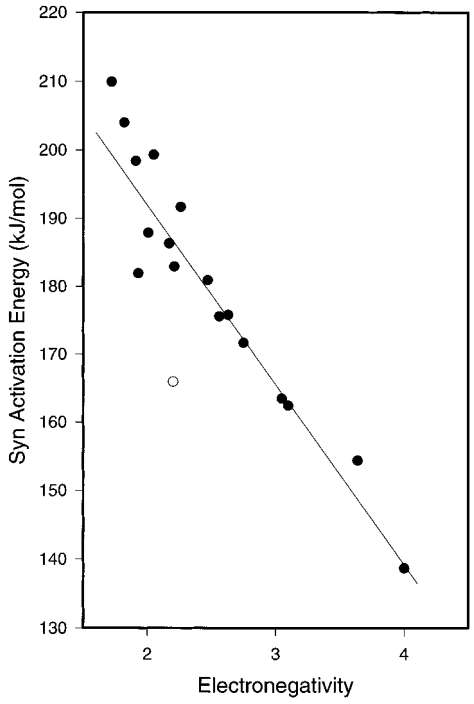

Figure 2. Syn activation energy as a function of the electronegativity (○ = cyclopentadiene).

(40) Boyd, R. J.; Edgecombe, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 4182−4186. For hydrogen and fifth Period atoms: Allred, A. L.; Rochow, E. G. *J. Inorg. Nucl. Chem.* **1958**, *5*, 264−268.

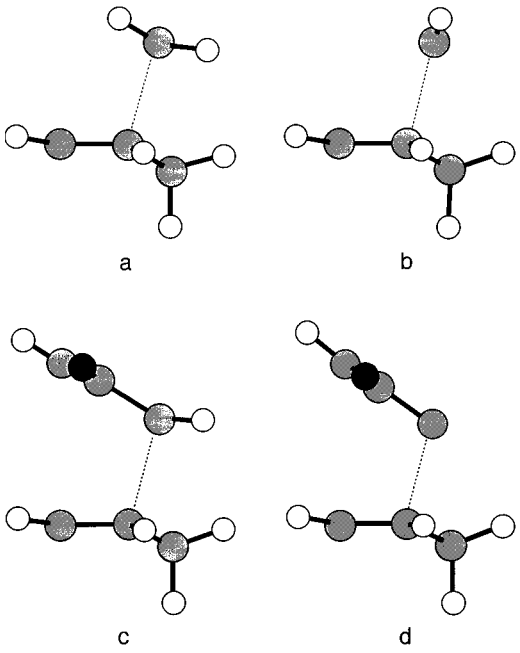

Figure 3. Side-on views of the transition structures for cyclopentadiene with (a) ethylene, (b) acetylene, (c) maleimide, and (d) TAD as dienophiles. Incipient bonds are indicated by broken lines.

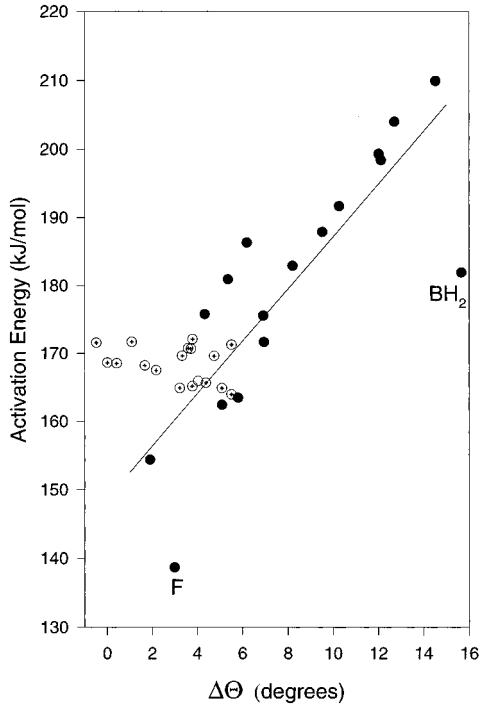

Figure 4. Activation energy as a function of the change in the C1−C5−X angle facing the dienophile (● = syn addition, ⊕ = anti addition and ○ = cyclopentadiene).

occurs preferentially on the face that experiences the smaller $\Delta\theta$. Against a fairly constant activation energy for anti addition, a substituent composed of a larger atom shows a greater $\Delta\theta$ in syn addition, and thus it has a greater tendency for anti addition. However, the energetic cost of angular change cannot be related to $\Delta\theta$ in a straightforward way. Nevertheless, Figures 2 and 4 indicate that both electronic and simple size considerations may be important in governing facial selectivity.

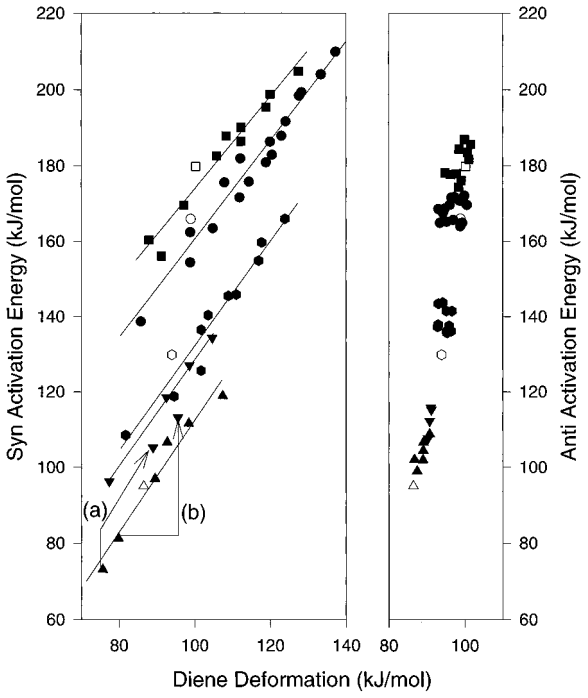

Figure 5. Activation energy as a function of diene deformation energy (● = ethylene, ■ = acetylene, hexagon = maleimide, ▼ = TAD with halogen-substituted cyclopentadienes, ▲ = TAD with other substituted cyclopentadienes, open symbols = cyclopentadiene). The arrows indicate the displacement of the OH (a) and NH_2 (b) points to the rotational maxima.

Partitioning Activation Energy. In an effort to circumscribe the control of facial selectivity more clearly, each activation energy, $E_{act.}$, was partitioned[41] as follows:

$$E_{act.} = E^{def}_{diene} + E^{def}_{dphile} + E^{int}$$

where E^{def}_{diene} and E^{def}_{dphile} are the "deformation energies" for the diene and dienophile, respectively. These are the energies required to deform the addends into their transition state geometries, and they were determined by single-point HF/6-31G* calculations. Thus, E^{def}_{diene} should largely reflect the energy associated with $\Delta\theta$ as well as other torsional strain within the diene at the transition state. E^{int} is the "interaction energy" between the diene and the dienophile at the transition state, i.e., the remainder after subtracting both deformation energies from the activation energy. The partitioned energies are presented in Tables 1 and 2 as differences between syn and anti. The plots of E^{def}_{diene} (Figure 5), E^{def}_{dphile} (Figure 6), and E^{int} (Figure 7) versus activation energies are extremely revealing. Diene deformation energies tend to decrease with increasing dienophile reactivity, regardless of facial selectivity (Figure 5). However, the diene deformation energies for syn additions have wide ranges (for instance, 61.3 kJ/mol with ethylene as the dienophile), and show excellent correlation with the activation energies ($r^2 = 0.95$, 0.95, and 0.94 for ethylene, acetylene, and maleimide, respectively, with slopes of 1.3, 1.2, and 1.4, respectively). In contrast, the diene defor-

(41) This approach has been used in an MM2 examination of the Diels−Alder reactions of isodicyclopentadiene[3] and in a MP4SDQ/4-31G study of the Diels−Alder reaction of 1,3-butadiene with acetylene: Coxon, J. M.; Grice, S. T.; Maclagan, R. G. A. R.; McDonald, D. Q. *J. Org. Chem.* **1990**, *55*, 3804−3807.

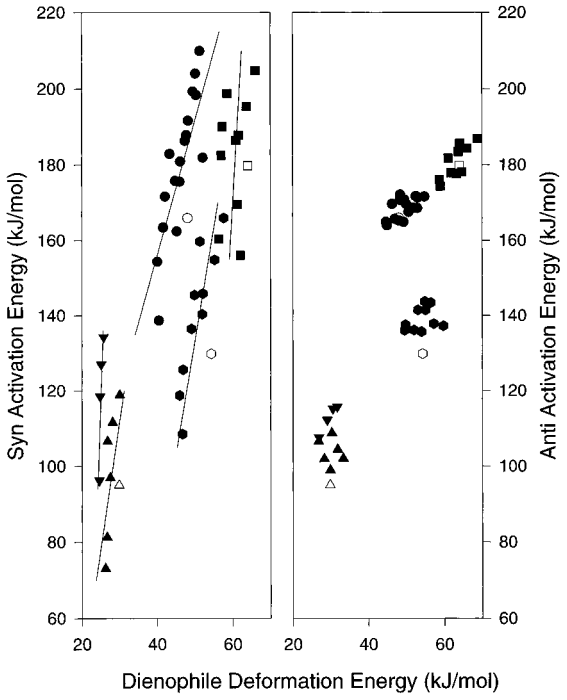

Figure 6. Activation energy as a function of dienophile deformation energy (● = ethylene, ■ = acetylene, hexagon = maleimide, ▼ = TAD with halogen-substituted cyclopentadienes, ▲ = TAD with other substituted cyclopentadienes, open symbols = cyclopentadiene).

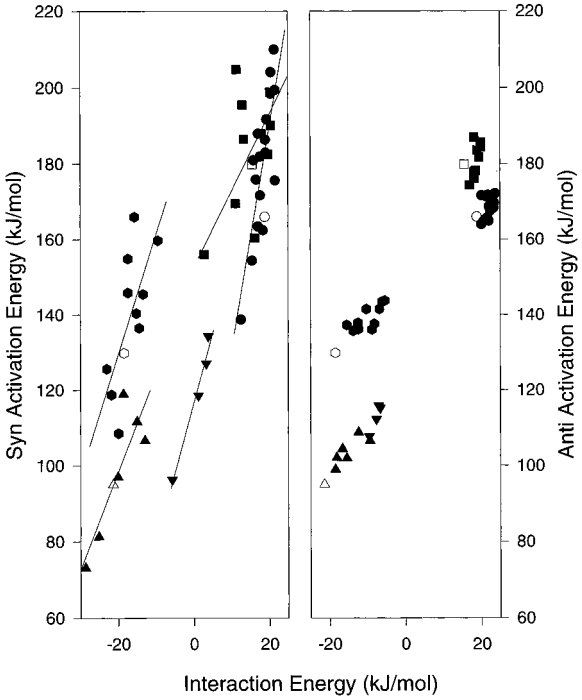

Figure 7. Activation energy as a function of diene−dienophile interaction energy (● = ethylene, ■ = acetylene, hexagon = maleimide, ▼ = TAD with halogen-substituted cyclopentadienes, ▲ = TAD with other substituted cyclopentadienes, open symbols = cyclopentadiene).

mation energies for anti additions have small ranges (for instance, only 8.5 kJ/mol with ethylene), clustering about the values for cyclopentadiene itself. The $E^{\mathrm{def}}_{\mathrm{diene}}$ plot for TAD indicates that syn additions with this dienophile are of two types. The halogen-substituted dienes fall along a line ($r^2 = 1.00$, slope = 1.4) of higher activation energy than all the other dienes ($r^2 = 0.96$, slope = 1.5), including unsubstituted cyclopentadiene. This parallels our recent experimental finding in which 4-phenyl-TAD showed a reluctance for syn addition to a halogen (cf. Table 3) that could not be accounted for by simple steric considerations.[13] We suggested that this might be due to filled-orbital repulsion (nitrogen lone pairs with halogen lone pairs) similar to that seen by Coxon and co-workers[7] in a very different carbonyl-substituted diene system. It can be demonstrated computationally that this significant contributor to facial selectivity is seated in the substituent lone pairs. Consider the OH- and NH_2-substituted dienes. In their transition states for syn addition with TAD, the substituents are in staggered conformations, with a hydrogen directed toward the dienophile. Although they are rotational maxima, the staggered conformations of the OH and NH_2 substituents in which a lone pair is directed toward TAD leads to activation and diene deformation energies that are significantly higher. These two conformationally altered substituents are now closer to the line with the halogens (Figure 5).

For all dienophiles, the ranges of $E^{\mathrm{def}}_{\mathrm{dphile}}$ for both syn and anti additions are very narrow compared to the ranges of $E^{\mathrm{def}}_{\mathrm{diene}}$ for syn addition (Figure 6). As can be seen in Figure 7, the more reactive dienophiles, maleimide and TAD, have negative values for the interaction energy, i.e., at the transition states for both syn and anti additions the diene−dienophile interactions are attractive, whereas for ethylene and acetylene these interactions are all repulsive. Also, the ranges for E^{int} are somewhat wider for maleimide and TAD than for ethylene and acetylene, but overall the ranges of the interaction energies are much narrower than the ranges for the diene deformation energies. Therefore, of the three partitioned components of the activation energy, $E^{\mathrm{def}}_{\mathrm{diene}}$ is by far the most important factor in determining facial selectivity, regardless of dienophile. The degree of diene deformation must be determined to some extent by the steric demands of the dienophile, but with dienophiles of similar steric bulk but different reactivity one should nevertheless expect similar facial selectivity. This is consistent with studies in which dienes have been reacted with a number of dienophiles.[13,17,20]

Deformation of the fluorine- and oxygen-substituted cyclopentadienes into their syn transition state geometries requires very much less energy than that required to deform unsubstituted cyclopentadiene. This is also true, but to a lesser extent, for the nitrogen- and chlorine-substituted cyclopentadienes. This is the reason for the predominant addition of dienophiles to the syn faces of these dienes. The next step is then to determine why a hydrogen atom in the syn position should require a higher diene deformation energy than fluorine, oxygen, nitrogen, or chlorine.

Definition of a Steric Factor. A steric interaction must be inevitable between the incoming dienophile and either the C5 substituent during syn addition, or the C5 hydrogen during anti addition. The interaction energy is almost independent of the face of addition, so it can be hypothesized that the facially distinct component of the interaction between the diene and the dienophile has translated very largely into diene deformation at the transition state. Nevertheless, it would still be a steric interaction between the diene and the dienophile that

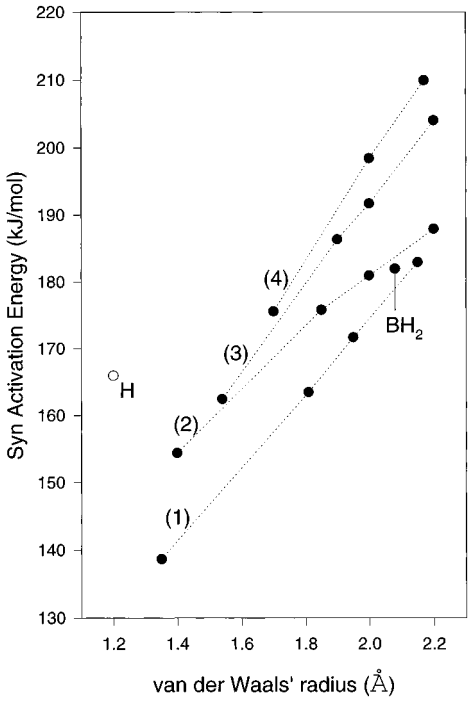

Figure 8. Syn activation energy as a function of the van der Waals radius of the central atom of the C5 substituent ((1) for Group 7A, (2) for Group 6A, (3) for Group 5A, and (4) for Group 4A).

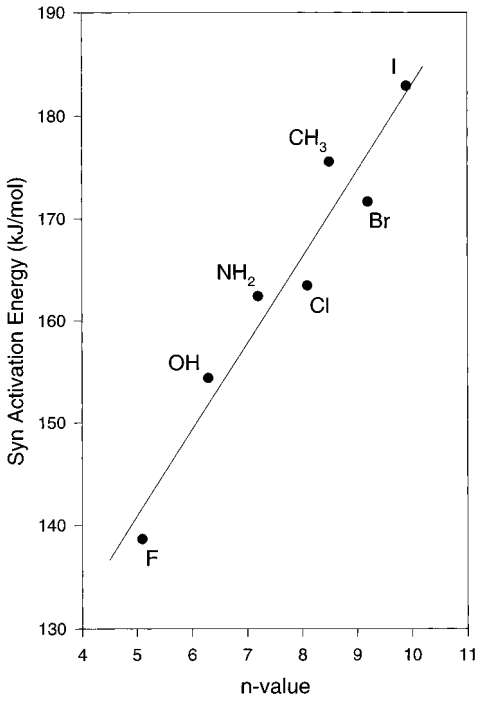

Figure 9. Syn activation energy as a function of the *n*-value of the C5 substituent.

determines the facial selectivity. Steric hindrance is a function of both size and distance. There are many empirical measures of size (e.g. *A*-values, *n*-values, *P*-values, Tafts's E_S, and van der Waals radii and volumes).[42] All of these show some correlation with the activation energies for syn addition, but all have serious failings. First, many of the empirical estimates are not available for the full range of substituents. The second problem can be illustrated with the plot of the data with ethylene versus the van der Waals radii of the various C5 atoms (Figure 8). In this plot each periodic Group shows its own straight-line relationship. However, the activation energy for the reaction of unsubstituted cyclopentadiene is anomalously high relative to the van der Waals radius for hydrogen. Reliance on the existing empirical measures of size would lead to the erroneous prediction that facial selectivity should always favor addition anti to the C5 substituent. The best measure of size, based on the available data, appears to be *n*-values[42a] (Figure 9, $r^2 = 0.93$).

The use of a computed estimate of size would obviate the first problem with the empirical estimates of size. At the transition state the geometry of the diene–dienophile association (Figure 3) is such that it is the C5–X bond, rather than just X, that faces the dienophile. Thus, a useful computed property would be some measure of bond size. The size of an orbital has been modeled as the second moment of the orbital at its centroid of charge.[43] We calculated the size, S_{CX}, of C5–X bond from the LMO (Ψ_{CX}) of that bond at its centroid of charge ($\langle\Psi_{CX}|r|\Psi_{CX}\rangle$) *in the reactant diene*:

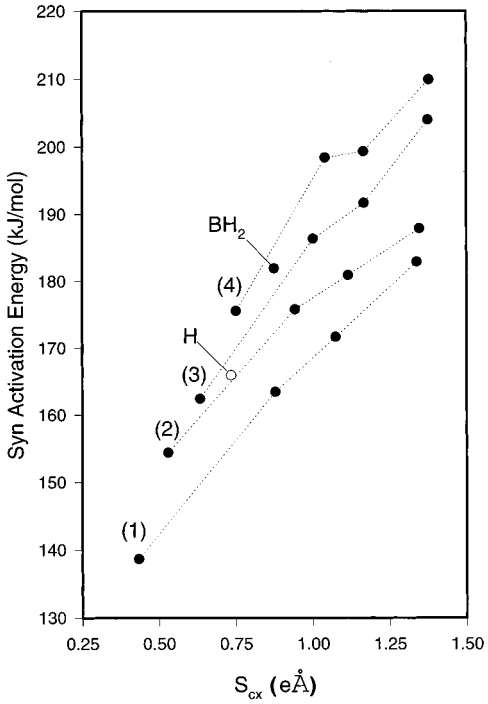

Figure 10. Syn activation energy as a function of the C5–X bond size for the reactant diene ((1) for Group 7A, (2) for Group 6A, (3) for Group 5A and (4) for Group 4A).

$$S_{CX} = \langle\Psi_{CX}|r^2|\Psi_{CX}\rangle_{\langle\Psi_{CX}|r|\Psi_{CX}\rangle}$$

Plots of these bond sizes versus activation energies of syn addition (Figure 10) show periodic straight-line relationships similar to those of van der Waals radii (Figure 8), but to extend an estimate of size to an estimate of steric hindrance must also take into account position. This can be accomplished by proposing S_{CX}/R_{CX} as a *computationally estimated steric factor* in which R_{CX}

(42) (a) Förster, H.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 429–441. (b) Gallo, R. *Prog. Phys. Org. Chem.* **1983**, *14*, 115–163.
(43) Robb, M. A.; Haines, W. J.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1973**, *95*, 42–48.

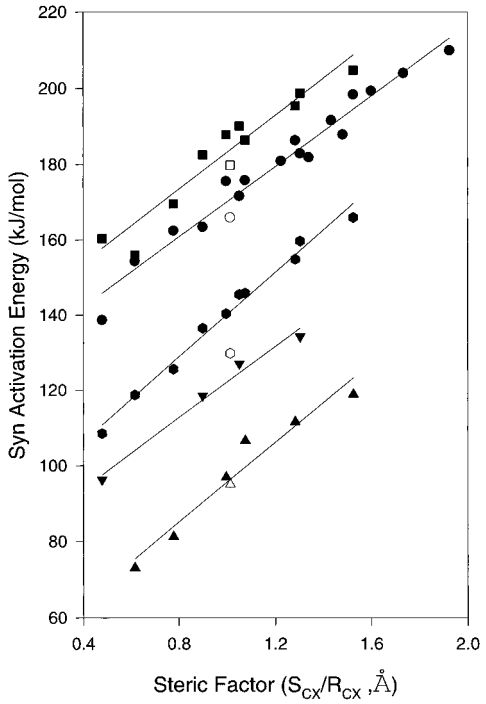

Figure 11. Syn activation energy as a function of the computed steric factor (● = ethylene, ■ = acetylene, hexagon = maleimide, ▼ = TAD with halogen-substituted cyclopentadienes, ▲ = TAD with other substituted cyclopentadienes, open symbols = cyclopentadiene).

is the distance from C5 to the centroid of charge of C5−X. The resulting steric factor appropriately has the unit of length. Note that R_{CX}, as well as incorporating a positional component, introduces an electronic component into steric hindrance since R_{CX} must be intimately related to the electronegativity (cf. Figure 2) of the substituent. For all four dienophiles, the plot of activation energy versus the computed steric factor (Figure 11) gives an excellent correlation (r^2 = 0.96, 0.92, 0.95, 0.98, and 0.95 for ethylene, acetylene, maleimide, TAD (with halogen-substituted cyclopentadienes), and TAD (with other substituted cyclopentadienes), respectively) for all the cyclopentadienes, *including cyclopentadiene itself*. The fact that facial selectivity for substituents as different as F and SnH_3 can be accounted for simply by the steric factor of C5−X eliminates the possibility of a significant role for any kind of secondary effect in the control of facial selectivity with the carbon-based dienophiles. Thus, the C5−Cl bond has a smaller steric factor than a C5−H bond, which correctly accounts for a preference for syn addition to 5-chloro-1,3-cyclopentadiene.[13] However, with TAD the halogen data reflects a significant additional steric contribution of lone pair-lone pair interaction. Nevertheless, with carbon-based dienophiles, the steric factor accounts remarkably well for the facial selectivity although hydrogen atoms and/or lone pairs on the central atom of the substituent are ignored. This implies that the conformation of the substituent contributes much less to facial selectivity than does the nature of the C5−X bond.

Conclusions

Facial selectivity in the Diels−Alder reactions of 5-substituted 1,3-cyclopentadienes is determined very largely by steric hindrance between the substituent on C5 and the incoming dienophile. At the transition state, facial preference is in the difference in energy required to deform the diene into its syn or anti form, and this is manifested mainly in differences in the angles about C5. A computed steric factor, S_{CX}/R_{CX}, derived from the size and relative position of the centroid of charge of the C5−X bond, is in excellent agreement with the calculated facial selectivities, which in turn are in good agreement with experiment. With different dienophiles, facial selectivity is predicted to be sensitive predominantly to the amount of steric hindrance between the dienophile and the C5 substituent. For dienophiles with lone-pairs on the reacting centers, such as TAD, the orientation of lone pairs on the substituent of the diene becomes important. Poor dienophiles have destabilizing diene−dienophile interaction energies. More reactive dienophiles react via transition states with lower deformation energies and with attractive interactions between diene and dienophile.

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