Pergamon

Tetrahedron 54 (1998) 6035–6050

TETRAHEDRON

What makes a Neutral Imino Dieneophile Undergo a Thermal, Non-catalysed, Diels-Alder Reaction?

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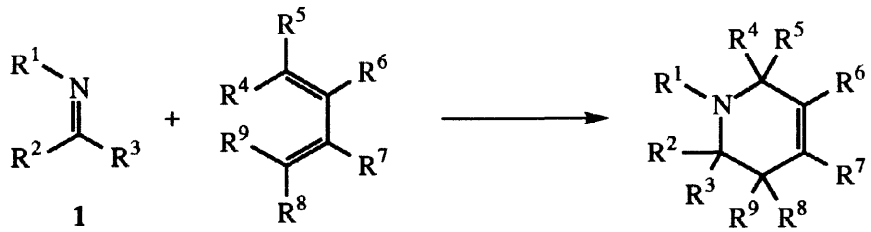
Received 17 March 1998; accepted 26 March 1998

Abstract: *Ab initio* calculations have been carried out at the MP2/6-31G* level of theory on the aza-Diels-Alder reaction of a range electron deficient imines (with sulfonyl and/or carbonyl substituents) with buta-1,3-diene. In all cases but one, an early cyclic transition-state could be located in which most often, the forming N-C bond was more fully formed than the forming C-C bond. However, examples were found in which this order of bond formation was reversed. Examination of HOMO-LUMO energy levels show that aza-Diels-Alder reactions are HOMO (diene)-LUMO (dienophile) controlled and that the most electron deficient imines should be more reactive than simple alkyl or aryl imines and imines possessing less electron withdrawing groups. Evidence is also found for *exo*-lone pair effects, but these effects become obscured by other stereoelctronic effects as electron withdrawing substituents are added to the imine.

Introduction.

The aza-Diels-Alder reaction[1] of an imine **1** with a diene **2** has become increasingly important over the last few years for the synthesis of tetrahydropyridine derivatives **3** (**Equation 1**)[2], largely because they can be readily converted into a wide range of natural product derivatives such as indolizidine alkaloids[3] and 1-aza carbohydrates[4].

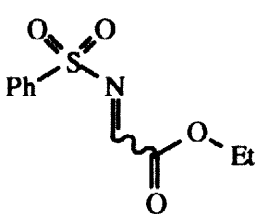
Equation 1.



1 **2** **3**

PII: S0040-4020(98)00284-1

The asymmetric synthesis of tetrahydropyridines **3** *via* asymmetric aza-Diels-Alder reaction[5] has also become an important goal to allow the preparation of chiral precursors of these natural products. Despite recent reports of high asymmetric induction in imine-based aza-Diels-Alder reactions using stoichiometric homochiral Lewis-acids[6], there have been no reports to date of successful catalytic Lewis-acid catalysed variants. Work has been underway in this area in our laboratories for some time[7], which has involved the development of homochiral Lewis-acid catalysed reactions of electron deficient N-sulfonylimino dienophiles such as **4**[8] but has failed to produce a solution to the problem of asymmetric induction arising from chiral catalysis in such processes[9]. Indeed, the problems of catalysing such reactions is highlighted by the fact that N-sulfonylimine **4** has been found to react rapidly with cyclopentadiene even at -100°C in the absence of any catalyst[9]. This surprising level of thermal reactivity clearly makes the development of new methods for the asymmetric induction of aza-Diels-Alder reactions difficult. It has therefore become our aim to gain a greater understanding of the electronic factors which govern this potentially synthetically important process.



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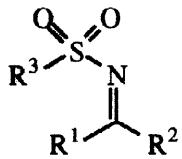
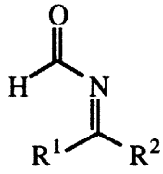


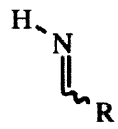
5

a; $R^1 = R^2 = H$, $R^3 = Me$
b; $R^1 = H$, $R^2 = CHO$, $R^3 = Me$
c; $R^1 = CHO$, $R^2 = H$, $R^3 = Me$
d; $R^1 = R^2 = H$, $R^3 = Ph$



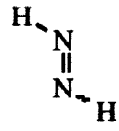
6

a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = CHO$
c; $R^1 = CHO$, $R^2 = H$
d; $R^1 = R^2 = CHO$



7

a; R = H
b; R = CHO



8

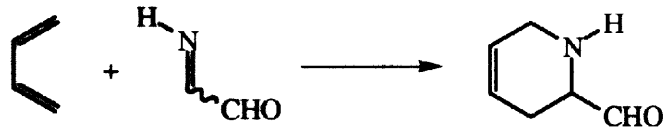
Although the mechanism[10,1] of the aza-Diels-Alder reaction is generally assumed to be a concerted, asynchronous cycloaddition, a stepwise, zwitterion- or radical-mediated mechanism can also occur with imines which are reacted under Lewis- or protic-acid catalysed conditions. Houk and co-workers have investigated hetero-Diels-Alder reactions from a theoretical aspect[11], including imino and imminium ion systems in some detail. This work clearly shows that aza-Diels-Alder reactions can occur, at least from a theoretical perspective, however, in order to probe the high level of reactivity of dienophile **4** and related systems further, theoretical study is necessary. In particular, an understanding of the reactivity of more electron deficient imines (non-imminium ion based) in aza-Diels-Alder reactions is required. Indeed, the most fundamental question to address would seem to be: what kinds of imines are able to undergo thermal, non-catalysed Diels-Alder reactions? In order to address this question, an *ab initio* study on imines related to **4**, *i.e.* **5** and their carbonyl substituted derivatives **6**. In this paper we discuss the results of this work, contrast these findings with experimental results and discuss the electronic effects of different electron withdrawing groups on the likely thermal reactivity of imino dienophiles in the Diels-Alder reaction.

Methods.

Approximate initial transition-state structures were generated for each set of reactants using an edited version[12] of the Diels-Alder transition-state MM2 force field[13] in MacroModel[14], followed by *ab initio*

optimisations, which was carried out at the restricted Hartree-Fock level using Gaussian 94[15]. For each reaction, the reactants, transition-state structures, and products were optimised with the 3-21G* basis set. Frequency calculations were performed on each transition-state structure and the results checked for a single imaginary vibrational frequency, corresponding to the motion forming the new C-C and C-N bonds for concerted transition-state structures. The activation energies were estimated from MP2/6-31G* point energy calculations on the structures previously optimised to the 3-21G* level. Both electron density and atomic orbitals were visualised using Molden 3.1[16] and optimised transition-state diagrams produced using Chem3D Plus[17].

Equation 2.

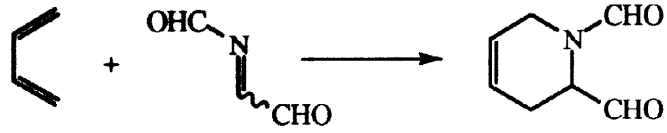


7b **9**

Equation 3.

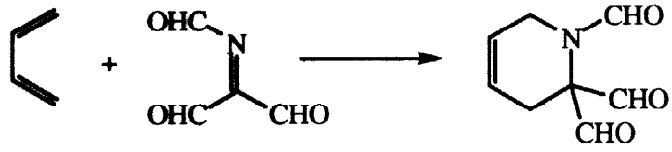
6a **10**

Equation 4.



6b/c **11**

Equation 5.

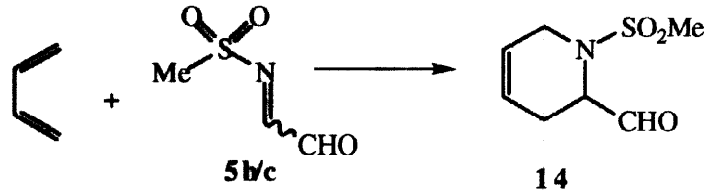


6d **12**

Equation 6.

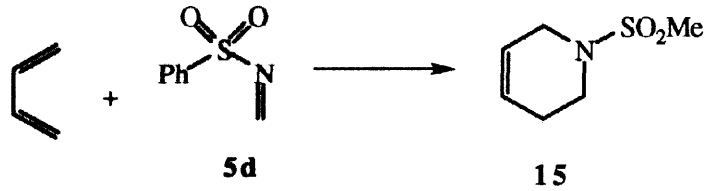
5a **13**

Equation 7.



5b/c 14

Equation 8.



5d 15

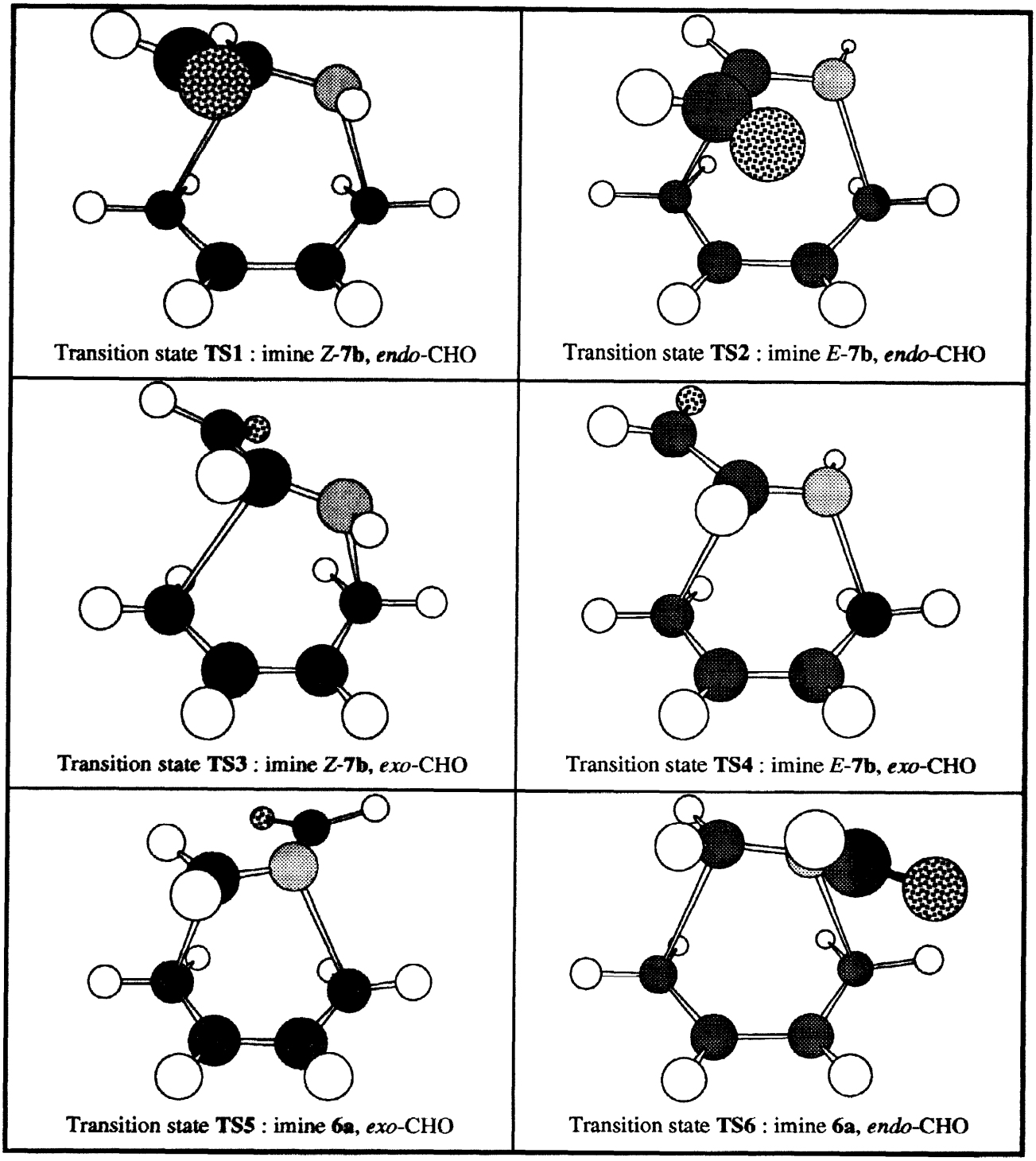
Results and Discussion.

The first stage in this study was to determine that the calculations of Houk could be accurately reproduced to check that our *ab initio* calculations were being carried out in a comparable manner to previous work. Thus, transition-states for the cycloaddition of formaldimine **7a** and diazines **8** with buta-1,3-diene were located and found to be reproduced exactly as those described[11]. Hence, a systematic search for each transition-state was then undertaken for imines **5a**, **5b**, **5c**, **5d**, **6a**, **6b**, **6c**, and **7b** with *cis*-buta-1,3-diene (as shown in **Equations 2-8**). In each case, and where relevant, both *endo*- and *exo*-orientations of the transition states of each of the imine substituents were calculated. The transition states located for each system are shown graphically in **Tables 1-4**, calculated energies in **Table 5**, relative energies of imines and products in **Table 6**, activation and reaction energies in **Table 7** (graphically shown also in **Figure 1**), and the corresponding HOMO-LUMO coefficients[18] in **Tables 8** and **9**. The only exceptional case studied, *i.e.* an imine-butadiene combination for which no transition state could be located, was for imine **5a** with an *exo*-orientation of the methylsulfonyl group, but with the methyl substituent orientated towards the diene [*i.e.* the rotamer of transition state **TS14** (**Table 3**) in which the N-S bond is rotated by ca. 180°].

Examination of HOMO-LUMO coefficients (**Tables 8** and **9**) show that all the electron deficient imines examined are predicted to react *via* HOMO(diene)-LUMO(dienophile)[18], which strongly parallels the observed reactivity all carbon Diels-Alder reactions. A frontier orbital treatment of the process shown in **Equation 1** alone, suggests that the most reactive system should the triply activated imine **6d**, followed by dialdehyde substituted imine **6c**, then the N-sulfonyl, C-aldehyde combination **5b**. N-sulfonyl substituents alone (*i.e.* **5a** and **5d**), provide the least activation towards cycloaddition, with the corresponding mono C-aldehyde and mono N-aldehyde systems **6a** and **7b** providing intermediate reactivity. This analysis fits broadly with observed reactivity[7,8,9] and suggests that carbonyl functions provide greater activation towards cycloaddition with buta-1,3-diene than sulfonyl functions and that these carbonyl functions have a greater activating effect when on the carbon end of the imine than the nitrogen end (for example, compare the reactivity of imines **6a** versus **7b**). Does this analysis using a frontier orbital approach explain reactivity in such systems better than analysis of activation energies?

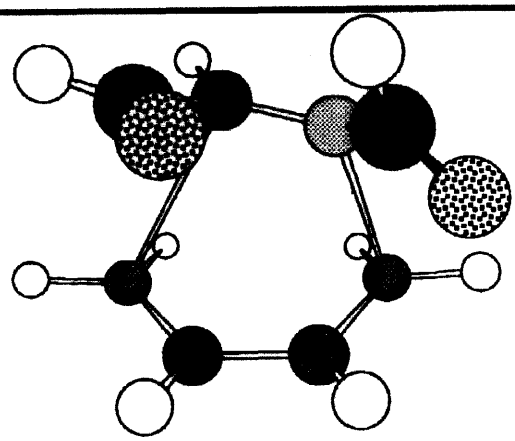
To answer this question, one needs to examine **Table 6** and **Figure 1**; inspection of these data allow analysis of the stereoelectronic effects which may be operative on the aza-Diels-Alder process of imines.

Table 1.

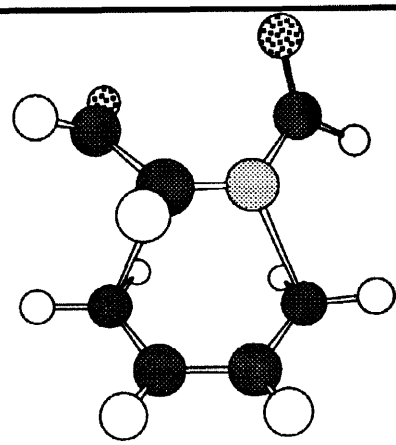


Of similar energies are transition states **TS9**, **7**, **17** and **11**, followed by **TS1**, according to their activation energies. A closer inspection of their corresponding transition state structures reveals (with the obvious exception of transition state **TS17**) that all the lower activation energy transition states have an *endo*-carbonyl function, with a C-carbonyl function having preference over an *endo* N-carbonyl function. This conclusion, taken in conjunction with the frontier orbital interpretation, can be explained by secondary orbital

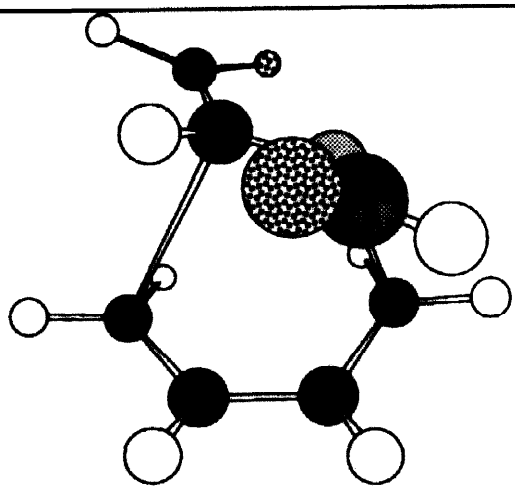
Table 2.



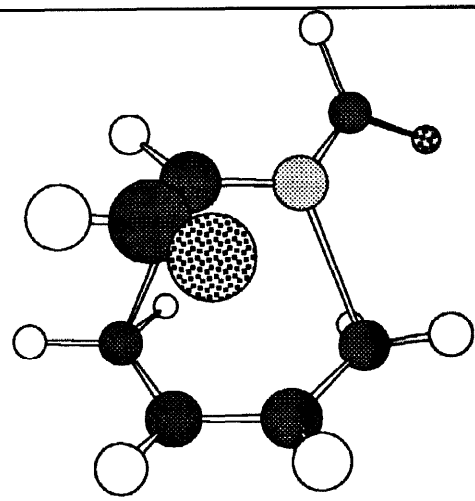
Transition state **TS7** : Z-imine **6c**, *endo*-C-CHO + *endo*-N-CHO



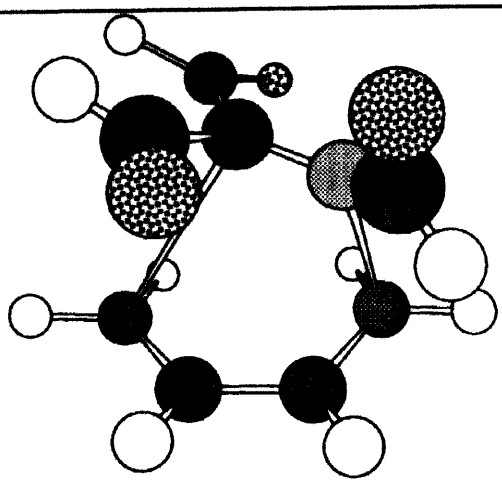
Transition state **TS8** : Z-imine **6c**, *exo*-C-CHO + *exo*-N-CHO



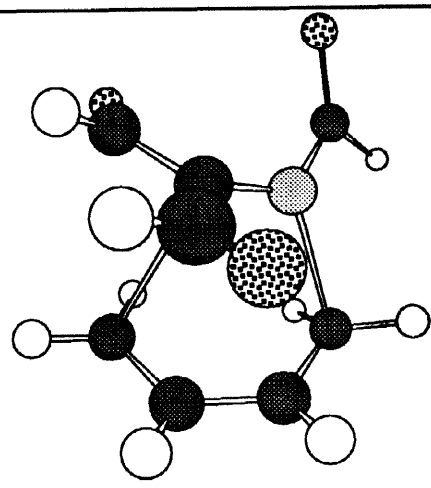
Transition state **TS9** : *E*-imine **6b**, *exo*-C-CHO + *endo*-N-CHO



Transition state **TS10** : *E*-imine **6b**, *endo*-C-CHO + *exo*-N-CHO

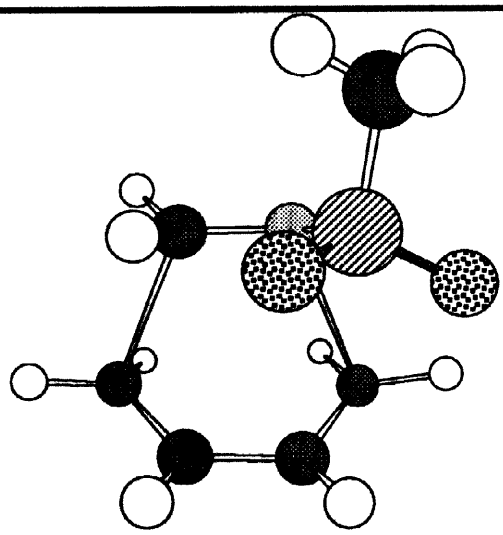


Transition state **TS11** : imine **6d**, *endo*-N-CHO

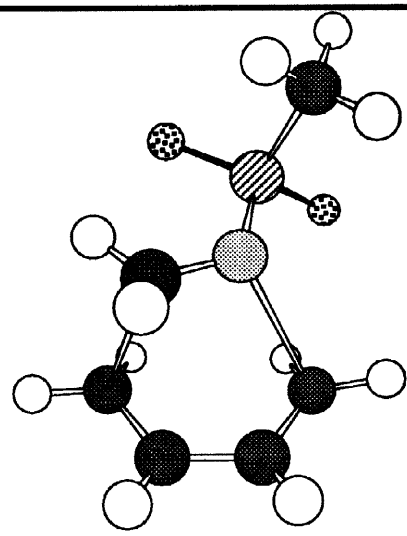


Transition state **TS12** : imine **6d**, *exo*-N-CHO

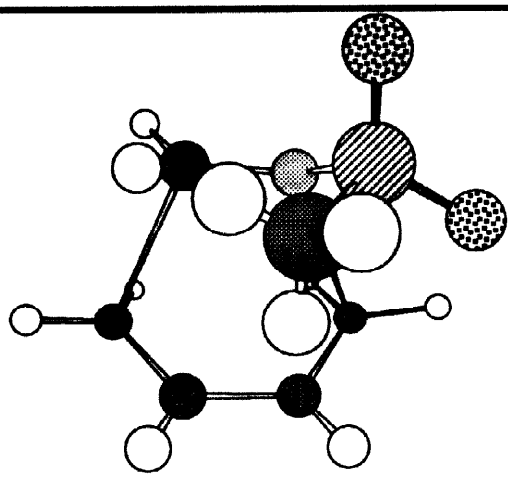
Table 3.



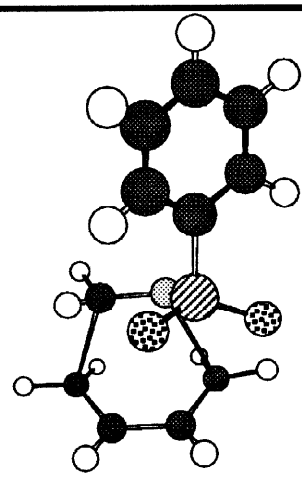
Transition state **TS13** : imine **5a**, *endo*-N-S=O



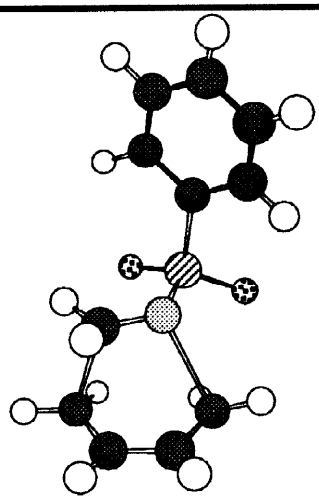
Transition state **TS14** : imine **5a**, *exo*-N-SO_2Me



Transition state **TS15** : imine **5a**, *endo*-N-S-Me

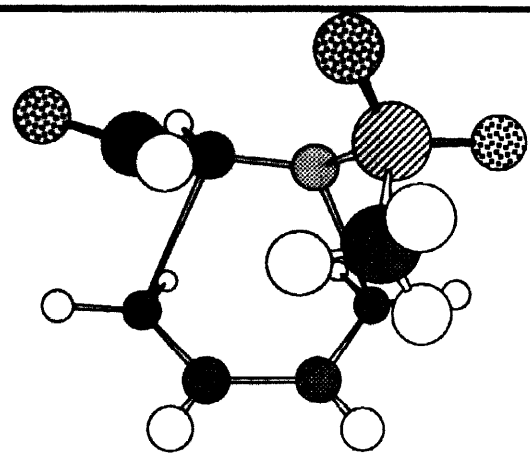


Transition state **TS16** : imine **5d**, *endo*-N-S=O

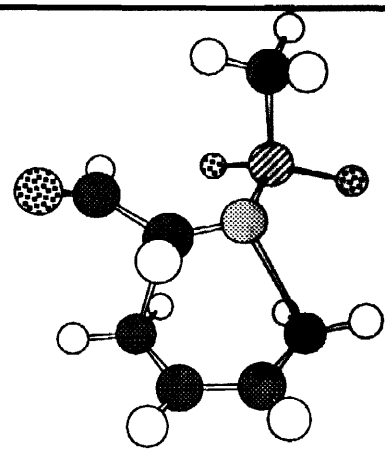


Transition state **TS17** : imine **5d**, *exo*-N-S-Ph

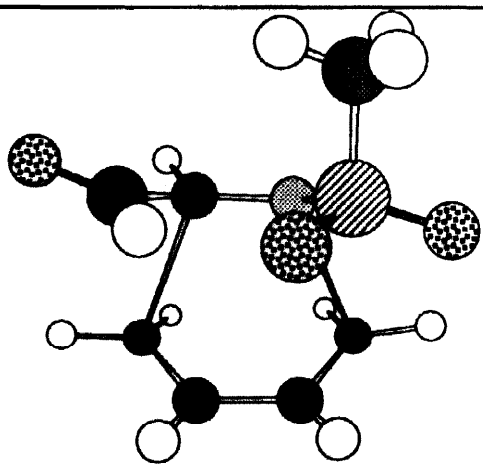
Table 4.



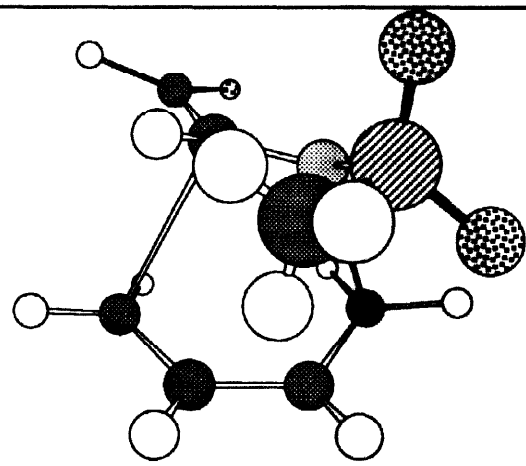
Transition state **TS18** : *Z*-imine **5c**, *endo*-N-S-Me + *endo*-C-CHO



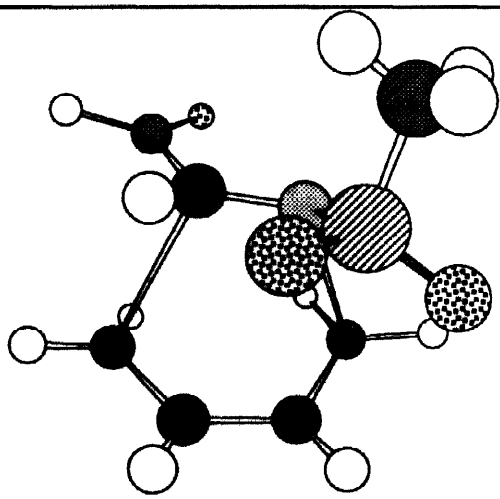
Transition state **TS19** : *Z*-imine **5c**, *exo*-N-S-Me + *exo*-C-CHO



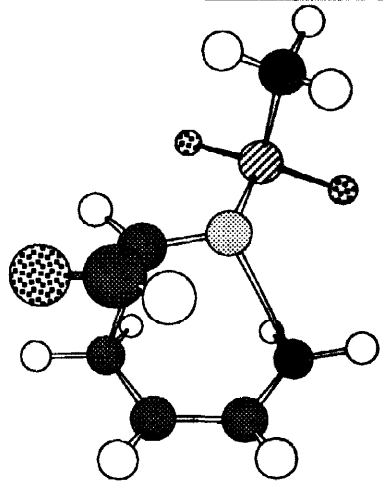
Transition state **TS20** : *Z*-imine **5c**, *endo*-N-S=O + *endo*-C-CHO



Transition state **TS21** : *E*-imine **5b**, *endo*-N-S-Me + *exo*-C-CHO



Transition state **TS22** : *E*-imine **5b**, *endo*-N-S=O + *exo*-C-CHO



Transition state **TS23** : *E*-imine **5b**, *exo*-N-S-Me + *endo*-C-CHO

Table 5. Table of calculated energies.

Transition state	Energy (3-21G*) (Hartrees)	Energy (6-31G*) (Hartrees)	ZPE (Hartrees/Part)	Energy (MP2) (Hartrees)	Corrected MP2 Energy
TS1	-359.60006	-361.61135	0.151108	-362.74753	-362.59642
TS2	-359.58377	-361.59571	0.150442	-362.73407	-362.58363
TS3	-359.59557	-361.60528	0.150762	-362.74241	-362.59165
TS4	-359.58974	-361.60201	0.150764	-362.73740	-362.58663
TS5	-359.59769	-361.61106	0.149859	-362.73964	-362.58978
TS6	-359.59831	-361.61325	0.150574	-362.74138	-362.59080
TS7	-471.68932	-474.33661	0.160955	-475.77434	-475.61338
TS8	-471.67238	-474.32197	0.160194	-475.75901	-475.59882
TS9	-471.69177	-474.33957	0.160896	-475.77440	-475.61351
TS10	-471.67886	-474.32964	0.160004	-475.76613	-475.60613
TS11	-583.77128	-587.04093	0.170732	-588.79907	-588.62834
TS12	-583.75967	-587.04316	0.170394	-588.78957	-588.61918
TS13	-830.85367	-835.08484	0.182534	-836.53866	-836.35613
TS14	-830.85212	-835.08460	0.182417	-836.54352	-836.36111
TS15	-830.83950	-835.07006	0.182129	-836.53060	-836.34847
TS16	-1020.30257	-1025.59100	0.240391	-1027.67611	-1027.43573
TS17	-1020.30052	-1025.59060	0.240337	-1027.69212	-1027.45178
TS18	-942.91635	-947.78629	0.191951	-949.54887	-949.35692
TS19	-940.93027	-947.79858	0.192405	-949.55739	-949.36498
TS20	-942.93469	-947.79998	0.192516	-949.56350	-949.37098
TS21	-942.92455	-947.79043	0.192359	-949.55979	-949.36743
TS22	-942.93865	-947.80488	0.192663	-949.57152	-949.37886
TS23	-942.93733	-947.80865	0.192005	-949.56679	-949.37479

Table 6. Table of Relative Energies of reactant imines and product aza-Diels-Alder adducts.

Equation number	Energy of imine (structure) (kJ/mol)	Total energy of reactants (kJ/mol)	Energy of product (kJ/mol)
2	-207.27467 (**7b**)	-362.60331	-362.66351
3	-207.28387 (**6a**)	-362.61251	-362.69421
4	-320.28880 (**6b** or **c**)	-475.61744	-475.70306
5	-433.29438 (**6d**)	-588.63302	-588.70905
6	-681.05315 (**5a**)	-836.38179	-836.44255
7	-872.12719 (**5d**)	-1027.45583	-1027.51764
8	-794.06344 (**5b** or **c**)	-949.39208	-949.45307

overlap in these transition states, causing a lowering of the transition state energies. However, the fact that transition state **TS9** has only a slightly lower activation energy than **TS7**, suggests that the steric demand of a *Z*-dienophile is sufficient to perturb both N- and C-carbonyl functions from adopting an *endo*-orientation. This is further shown by **TS11**, which having three carbonyl functions, can not avoid less favourable stereoelectronic interactions, despite the combined activation of the three electron withdrawing groups. This dienophile (*i.e.* **6d**) does however prefer to adopt a transition state in which two carbonyl functions are *endo* in the transition state. This being the case, how does one explain the extreme experimental reactivity of dienophile **4** with cyclopentadiene and the *exo*-selectivity with respect to the ester group?

Table 7. Table of calculated activation and reaction energies.

Transition state	Energy activation (Hartrees)	Energy activation (kJ mol^{-1})	Energy reaction (Hartrees)	Energy reaction (kJ mol^{-1})
TS1	0.00690	18.1	0.06019	158.0
TS2	0.01968	51.7	0.06019	158.0
TS3	0.01167	30.6	0.06019	158.0
TS4	0.01668	43.8	0.06019	158.0
TS5	0.02272	59.7	0.08171	214.5
TS6	0.02170	57.0	0.08171	214.5
TS7	0.00406	10.7	0.08562	224.8
TS8	0.01862	48.9	0.08562	224.8
TS9	0.00393	10.3	0.08562	224.8
TS10	0.01131	29.7	0.08562	224.8
TS11	0.00469	12.3	0.07603	199.6
TS12	0.01384	36.4	0.07603	199.6
TS13	0.02566	67.4	0.06076	159.5
TS14	0.02068	54.3	0.06076	159.5
TS15	0.03332	87.5	0.06076	159.5
TS16	0.02011	52.8	0.06173	162.1
TS17	0.00404	10.6	0.06173	162.1
TS18	0.03516	92.3	0.06098	160.1
TS19	0.02710	71.2	0.06098	160.1
TS20	0.02110	55.4	0.06098	160.1
TS21	0.02465	64.7	0.06098	160.1
TS22	0.01730	45.4	0.06098	160.1
TS23	0.01320	34.7	0.06098	160.1

The closest transition states to that which would be involved in the observed reaction of **4** with cyclopentadiene studied here, are transition states **TS18-23**. The lowest activation energy is that found for **TS23**, *i.e.* the transition state which combines both an *endo*-C-carbonyl function and an *exo*-sulfonyl function, with the methyl group orientated away from the transition state. While this can be viewed as being surprising in light of the observed stereocontrol in this reaction (*i.e.* reaction of **4** with cyclopentadiene produces solely the *exo*-ester product), it may be indicative of the limitations of this kind of molecular orbital interpretation of such processes. Specifically, if the reaction of an imine such as **5c** were highly reversible, thermodynamic effects could control the reaction outcome, *i.e.* even though **TS23** is predicted to have a lower activation energy than **TS22** and the reaction could be driven to completion *via* **TS22** rather than **TS23**, by the fact that in the product (*i.e.*, **16**, if cyclopentadiene were used) would have a *pseudo*-equatorial (*exo*) carbonyl function which would be thermodynamically more favourable than the corresponding *pseudo*-axial (*endo*) product (*i.e.* **17**). This possibility is further supported by the anomalous result eluded to above, *i.e.* that **TS17** appears as one of the lowest energy transition states; if this reaction were also highly reversible, one might predict that despite the very low activation energy, the reaction equilibrium favours starting materials, rather than the products. This possible reversibility of the reaction is confirmed by examining the relative energies of formation of the imines. It is noticeable from **Tables 6** and **7** that N-sulfonyl imines in general are more thermodynamically stable compared to their carbonyl substituted counterparts (*i.e.* imines **5a-d** versus imines **7b** and **6a-d**, **Table 6**). Additionally, the overall energies of reaction are all relatively low

Figure 1.

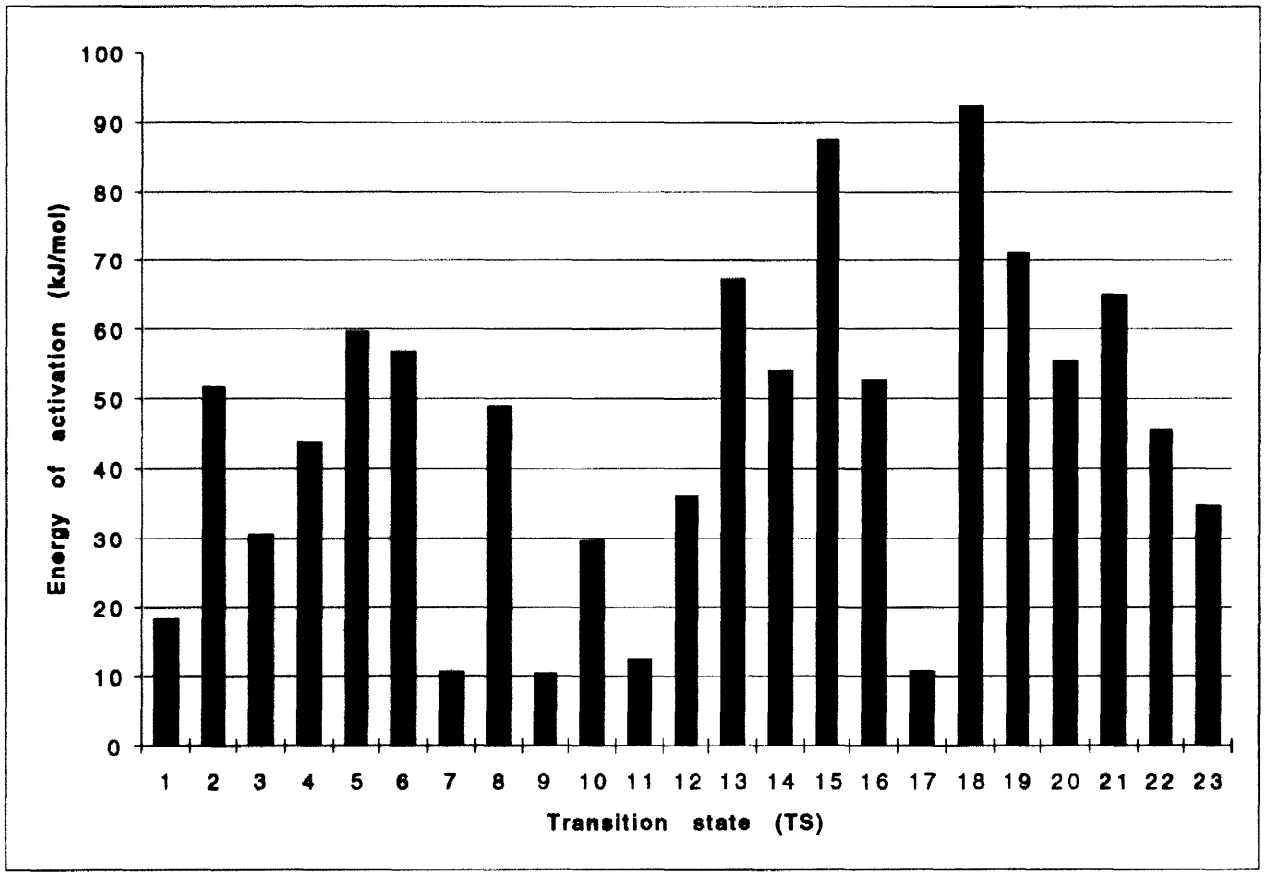


Table 8. Table of HOMO / LUMO energies.

	HOMO energy	LUMO energy
cis-butadiene	-0.32023	0.18754
Equation 2	-0.41261	0.08466
Equation 3	-0.41533	0.08800
Equation 4	-0.42367	0.03319
Equation 5	-0.40655	0.00988
Equation 6	-0.42884	0.10092
Equation 7	-0.43718	0.03387
Equation 8	-0.35954	0.09729

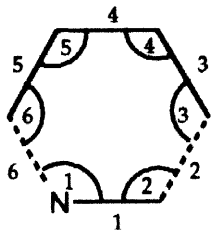
Table 9. Table of HOMO / LUMO energies relative to *cis*-butadiene.

	LUMO diene/ HOMO imine	HOMO diene / LUMO imine
Equation 2	0.60015	0.40489
Equation 3	0.60287	0.40823
Equation 4	0.61121	0.35342
Equation 5	0.59409	0.33011
Equation 6	0.61638	0.42115
Equation 7	0.62472	0.35410
Equation 8	0.54708	0.41752

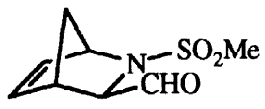
Table 10. Table of calculated transition state bond angles (see **Figure 2** for numbering key).

Transition state	1 (Degrees)	2 (Degrees)	3 (Degrees)	4 (Degrees)	5 (Degrees)	6 (Degrees)
TS1	113.8	105.7	95.1	123.6	121.4	100.0
TS2	113.8	104.6	95.0	123.6	121.0	108.9
TS3	113.2	105.3	92.9	123.7	120.9	107.6
TS4	113.6	103.9	103.9	124.0	121.5	99.3
TS5	107.8	109.4	98.3	123.2	120.4	100.5
TS6	113.4	107.5	98.8	123.2	121.0	98.4
TS7	113.8	105.8	94.8	123.4	121.9	98.1
TS8	113.9	105.4	96.1	123.0	120.6	104.2
TS9	112.8	104.3	99.1	123.7	120.3	97.8
TS10	113.3	104.1	95.3	123.5	121.1	105.1
TS11	114.1	102.3	88.7	124.1	122.5	98.0
TS12	115.1	101.9	93.1	123.2	121.5	107.4
TS13	109.3	110.9	100.4	122.6	120.7	96.9
TS14	107.2	109.3	97.3	123.9	120.6	99.6
TS15	111.7	108.7	100.7	122.9	120.8	98.5
TS16	108.1	101.8	92.9	114.2	113.6	88.5
TS17	117.9	91.3	87.7	121.1	121.7	104.3
TS18	113.2	107.0	100.8	129.1	121.4	99.4
TS19	108.3	107.5	96.1	123.5	120.5	98.7
TS20	111.1	108.8	100.3	122.3	120.8	96.9
TS21	112.2	106.0	96.0	123.6	121.7	97.9
TS22	114.0	100.5	96.5	122.4	119.3	96.4
TS23	108.9	109.5	99.5	123.3	120.7	98.6

Figure 2. Key to angle and bond labelling.



(approximately 160 kJ mol^{-1}) compared to the di- and tri-carbonyl substituted imines (reaction energies in the range 200-225 kJ mol^{-1}), supporting the possibility of greater reversibility in the reaction involving N-sulfonyl imines.



16

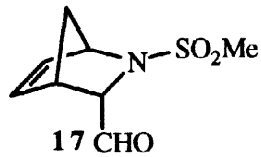


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Table 11. Table of transition state bond lengths (see **Figure 2** for numbering key).

Transition state	1 (Å)	2 (Å)	3 (Å)	4 (Å)	5 (Å)	6 (Å)
TS1	1.307	2.438	1.362	1.399	1.385	1.918
TS2	1.314	2.340	1.371	1.390	1.384	1.949
TS3	1.307	2.508	1.361	1.400	1.389	1.890
TS4	1.309	2.332	1.372	1.392	1.381	1.969
TS5	1.342	2.026	1.383	1.395	1.361	2.270
TS6	1.311	2.259	1.367	1.399	1.371	2.089
TS7	1.303	2.445	1.359	1.401	1.374	2.012
TS8	1.308	2.267	1.370	1.396	1.368	2.089
TS9	1.305	2.452	1.360	1.403	1.379	1.994
TS10	1.307	2.310	1.371	1.395	1.372	2.080
TS11	1.299	2.694	1.349	1.412	1.377	1.947
TS12	1.305	2.497	1.360	1.399	1.377	1.986
TS13	1.335	2.097	1.375	1.396	1.364	2.243
TS14	1.344	2.019	1.385	1.395	1.359	2.319
TS15	1.319	2.197	1.370	1.398	1.368	2.153
TS16	1.287	2.313	1.341	1.455	1.342	2.183
TS17	1.342	2.031	1.383	1.396	1.359	2.308
TS18	1.312	2.266	1.366	1.401	1.369	2.131
TS19	1.338	2.073	1.384	1.394	1.360	2.310
TS20	1.382	2.169	1.374	1.394	1.369	2.185
TS21	1.308	2.413	1.365	1.399	1.378	2.032
TS22	1.317	2.323	1.367	1.396	1.374	2.086
TS23	1.338	2.044	1.385	1.394	1.359	2.323

Examination of bond angles and bond lengths in each of the transition states (**Tables 10 and 11**) clearly show all the located transition states are more or less skewed, as found by Houk for aldimine[11]. However, in that case, the newly forming nitrogen-carbon bond was more formed in the transition state than the carbon-carbon bond (*i.e.* bond 6 was more formed than bond 2, **Figure 2**). In the case of electron deficient imines activated by carbonyl groups, the nitrogen carbon bonds are more fully formed in the transition states, but N-sulfonyl substituents have the effect of lengthening the newly forming carbon-nitrogen bonds in some cases (**TS13, 14, 17, 18, 19, 20**, and **23**). It is noticeable that the latter transition states (**TS19, 20 and 23**), which are both N-sulfonyl and C-carbonyl substituted, are not all *exo*-transition states with respect to the sulfonyl substituent (**TS20** being the exception). The picture is similar with N-sulfonyl susbstituents alone (both *endo*- and *exo*-transition states **TS13** and **14** show longer C-N than C-C bonds), however the combination of *endo*-lone pair repulsion[11] and stereoelectronic repulsion between the sulfonyl oxygens and diene hydrogens could be to blame for the abnormal transition state skewing. These observations do suggest however, that for certain orientations of N-sulfonyl substitutents on the imine, and depending upon the carbon susbstitutent orientation, there is little assistance for transition state formation, suggesting that limited secondary orbital overlap *via* the sulfonyl S=O bonds does not occur. Indeed, the fact that *exo*-orientations of the sulfonyl group produce lower energy transition states also supports this conclusion.

Houk's study[11] of imine based systems found clear evidence for an *exo*-lone pair effect (*vide supra*); an effect which favoured *exo*-orientation of the imine dienophile nitrogen lone pair, presumably due to stereoelectronic repulsion between the diene π-orbitals and the nitrogen lone pair. A similar effect also seems

to be operative for some of the electron deficient systems examined here, however, the effect becomes less important as other stereoelectronic effects become more demanding. The clearest case is not surprisingly for the C-formyl imines which produce transition states **TS1-4**. For the pair of *endo*-transition states **TS1** and **TS2**, the only difference is the orientation of the nitrogen lone pair; **TS1** has an *exo*-lone pair and **TS2** an *endo*-lone pair. The effect of this change is to raise the activation energy of the reaction by approximately 24 kJmol^{-1}; a substantial rise which reflects the added instability of the transition state due to repulsion between the *endo*-nitrogen lone pair and diene, and in this case, between the nitrogen lone pair and C-formyl oxygen. It is difficult in the case of these two transition states to differentiate between these two repulsions, *i.e.* which contributes most to the 24 kJmol^{-1} activation energy increase? Examination of the next pair of transition states (*i.e.* **TS3** and **TS4**), clarifies the situation to some extent. In these two cases, the C-formyl group of the dienophile is *exo* and each transition state differs only in the orientation of the nitrogen lone pair. The *endo*-lone pair orientation is still less stable again, but only by 13 kJmol^{-1}. Since the nitrogen lone pair to C-formyl oxygen repulsion may be taken as approximately constant between the pairs **TS1** and **TS2**, and **TS3** and **TS4**, one may estimate that orientation of the nitrogen lone pair into the *endo*-position, destabilises the transition state by the order of 11 kJmol^{-1}. The situation becomes much less clear with N-formyl substuents, *i.e.* producing transition states **TS5** and **TS6** respectively, since these two transition states are not particularly favourable and one can not separate lone pair orientation effects from the effect of changing the N-formyl orientation. Indeed, the entire situation with respect to the effect of the lone pairs becomes blurred as further substituents are added; an extreme example can be seen by looking at transition states pair **TS7** and **TS8**, which differ in energy by 38 kJmol^{-1}. The highest energy transition state, **TS8** does have the less favourable *endo*-orientated lone pair. However, the transformation of **TS7** to **TS8** also involves the movement of both C- and N-substituents from an *endo*- to an *exo*-orentation. Clearly, the effects of moving both C- and N-susbstitutents into positions where secondary orbital overlap is not possible is likely completely to outweigh any lone pair effects. Certainly, by the time N-sulfonyl substitutents are added, one finds that *endo*-lone pair orientation is not at all unfavourable in comparison to placing the stereoelectronically demanding N-sulfonyl group in the more favourable *exo*-position (see **TS23** for example which has a lower activation energy than transition states **TS18-23**).

Summary.

The location of transition states which are could be involved in the aza-Diels-Alder reaction involving imino dienophiles by *ab initio* methods provides an insight into why electron withdrawing substituents are necessary to achieve thermal cycloaddition with butadiene. Calculation of HOMO-LUMO energies shows that the thermal cycloaddition is HOMO(diene)-LUMO(dienophile) for all electron deficient imines examined and that iit is expected that generally the more electron withdrawing groups added, the more reaction the imine towards aza-Diels-Alder reaction. Carbonyl (formyl) substituents are more activating than sulfonyl functions and the effect adding the electron withdrawing group to the carbon-end of the dienophile is greater than adding the electronc withdrawing group to the nitrogen-end. Secondary orbital overlap is an important factor for all carbonyl-susbtituted imines, *i.e.* producing a stabilising effect on the transition state. In contrast, however, sulfonyl groups do not seem to to be able to cause transition state stabilisation when orientated into the *endo*-position. Lone pair effects are apparent in the less substituted transition states, however, as more

stereoelectronically demanding groups are added to the dienophile, the repulsive effect of *endo*-lone pair orientation becomes less significant.

Such studies of the rules that govern imine cycloaddition reactivity are important for the successful use of imino dienophiles in the aza-Diels-Alder reaction and help to clarify what is a remarkably difficult reaction to predict. Further studies to examine the effects of Lewis-acid activation and hence the development of suitable catalysts are underway.

Acknowledgements.

We thank the MacroModel support group of Professor W.C. Still (Columbia University, New York) for helpful discussions, together with Mr Brett Beno (K.N. Houk's research group, Department of Chemistry and Biochemistry, University of California, Los Angeles) and Dr. D.J. Fox (Gaussian Inc.). We thank Professor W.C. Still for a copy of MacroModel and finally, Dr Alan Hinchliffe (Chemistry Department, UMIST) for extremely helpful advice and discussions.

Supplementary Material.

All supplementary material, including the MM2 force fields and all calculated structure files can be accessed and downloaded from the following web site: http://uchsg11.ch.umist.ac.uk/model/index.htm, or by direct contact *via* email to a.whiting@umist.ac.uk .

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