AB INITIO CALCULATIONS OF DIELS–ALDER TRANSITION STRUCTURES FOR HETERO-DIENOPHILE ADDITIONS TO CYCLOPENTADIENE

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Transition states for the hetero-Diels–Alder addition of formaldehyde, formaldimine, diazene and nitrosyl hydride to cyclopentadiene were located with *ab initio* molecular orbital calculations. Asynchronous transition structures were located for the asymmetric hetero-dienophiles, whereas the symmetrical hetero-dienophile, *cis*-diazene, produced a synchronous transition structure. The relative reactivities are in good agreement with the LUMO energies of the hetero-dienophiles, and the transition states with the *exo* oxygen or nitrogen lone pairs have lower energies than the corresponding *endo* lone electron pair transition states. *Endo/exo* energy differences are much higher than in the addition of ethylene derivatives to cyclopentadiene.

INTRODUCTION

The Diels–Alder reaction is one of the most widely used synthetic methods for the preparation of organic compounds.[1] The reaction is highly regio- and stereospecific and consequently very desirable intermediates can be obtained.[2] Diels–Alder reactions that incorporate the formation of carbon–heteroatom bonds, useful as intermediates in natural product synthesis, are of special interest.[3]

These reactions are generally assumed to be concerted, asynchronous cycloadditions, but a stepwise mechanism is also possible for polar dienophiles or for acid-catalyzed processes. Although the all-carbon Diels–Alder reactions have been studied extensively,[4–6] there are only a few reports on the theoretical study of the hetero-Diels–Alder reactions (recently we have performed *ab initio* studies of hetero-dienophile additions to furan and 1,3-oxadiazole).[7,8] We have undertaken an extensive theoretical study of Diels–Alder reactions both with heteroatom-containing dienophiles and dienes; here we report our results on the non-aromatic all-carbon diene cyclopentadiene, which will be used as reference for a further study on some aromatic heterocyclic dienes (we have performed theoretical studies of the heterodienophile additions to aromatic heterocycles such as pyrrole,[9a] oxazole,[9b] pyrazole[9c] and

1,4-dioxabuta-1,3-diene[9d]). On the basis of the HOMO–LUMO interactions, energies of the reactants and the transition structures, the reactivity of the hetero-dienophiles towards cyclopentadiene will be discussed.

METHODS

Geometry optimization of the reactants prior to any *ab initio* calculations was performed with the PM3[10] method in MOPAC.[11] The transition states (the transition structure has to have only one imaginary frequency and that has become the major criteria for confirming the transition structure; for a perspective of the transition-state theory, see Ref. 12) were also located by PM3.[13] The structures of the reactants and the transition states obtained were then fully optimized at the RHF/3–21G theoretical level with GAMESS[14] *ab initio* program. Each transition state gave only one imaginary harmonic vibrational frequency, corresponding to the motion of the new C—C or C—X bonds.[12] The activation energies were estimated by single-point MP2/6–31G* calculations on the RHF/3–21G optimized geometries. One reason for choosing this model chemistry was that there are available theoretical studies at this level for other Diels–Alder reactions, thus making the comparison of

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the results possible.[15] Although the calculated acti-
vation energies at the MP2 level are probably under-
estimated by *ca* 10 kcal mol^{-1} (1 kcal = 4·184 kJ)
compared with MP3 and available experimental data,[6]
the activation energies reflect accurately the relative
reactivities of these dienophiles.

RESULTS AND DISCUSSION

The transition states were located for the reactions of
cyclopentadiene with formaldehyde, formaldimine, *cis*-
and *trans*-diazene and nitrosyl hydride. All reactions
studied except the reaction with formaldehyde have two
possible stereoisomers and both the *endo* and *exo*
stereoisomers were considered. The transition-state
structures are presented in Figure 1. All transition states
are for the concerted mechanism. In the reaction of
symmetrical dienophiles, symmetrical transition struc-
tures were obtained, but in all other cases asynchronous
transition-state structures were generated. Thus, the
transition state for ethylene addition to cyclopentadiene
is symmetrical with a new forming C—C bond length of
2·205 Å.[6] The transition state for the formaldehyde
addition to cyclopentadiene can be considered an excep-
tion, since it is practically synchronous ($\Delta r = 0·04$ Å)
with a shorter new forming C—C bond than in the eth-
ylene addition (Figure 1). The transition state is more
synchronous than in the case of formaldehyde addition
to buta-1,3-diene ($\Delta r = 0·135$ Å). The structural
characteristics of transition states 2 and 3 of for-
maldimine addition to cyclopentadiene are similar to
that from the formaldehyde reaction. Here again the
bond differences of the new forming bonds are smaller
(for 1 $\Delta r = 0·175$ Å and for 2 $\Delta r = 0·086$ Å) than in the
case of buta-1,3-diene ($\Delta r = 0·435$ and $0·284$ Å
respectively). The same kind of pattern was observed in
the case of the concerted transition-state structure 4 of
trans-diazene addition to cyclopentadiene. Again, 4 is
more synchronous ($\Delta r = 0·123$ Å) than the corre-
sponding transition state for the *trans*-diazene addition
to buta-1,3-diene ($\Delta r = 0·168$ Å).[7] However, the most
surprising differences come from the *endo* and *exo*
addition of *cis*-diazene to cyclopentadiene and buta-
1,3-diene (for a discussion of asynchronicity of the
transition structure of diazene addition to buta-1,3-
diene in relation to their energy calculated by the PM3
method, see Ref. 16). Both *endo* and *exo* transition-
state structures 5 and 6 are fully symmetrical, whereas
the corresponding transition-state structures in the
addition to buta-1,3-diene are unsymmetrical
($\Delta r = 0·129$ Å for the *exo* and $0·329$ Å for the *endo*
cis-diazene–buta-1,3-diene transition states).[7] The two
transition-state structures 7 and 8 for the concerted
addition of nitrosyl hydride to cyclopentadiene are also
more synchronous ($\Delta r = 0·149$ and $0·038$ Å respect-
ively) than the corresponding transition states with
buta-1,3-diene ($\Delta r = 0·209$ and $0·080$ Å, respectively).[7]

It is conceivable that the symmetry of the transition
structure has influence on the energy.[16]

The reactivity of the hetero-Diels—Alder reactions
can be determined by various physical properties of the
reactants. Frontier orbital theory[17] can explain, to
some degree, the reactivity of the reactants in the
chemical reactions. The HOMO and LUMO energies
are presented in Table 1. In terms of the frontier orbi-
tals, the Diels—Alder reaction of cyclopentadiene
appears to be controlled by the LUMO of the
dienophile, hence the most reactive dienophile is the
one with the lowest LUMO energy. In our case, the
most reactive dienophile is nitrosyl hydride with an
energy gap of only 0·39659 eV. The HOMO—LUMO
energy gap cannot explain the stereoselectivity of the
hetero-Diels—Alder addition with cyclopentadiene.
That can be explained with the energy barrier of the
reactions.

The calculated total energies for the reactants, the
transition states and the energies with respect to the
reactants for hetero-dienophile addition to cyclopenta-
diene are given in Tables 2 and 3.

According to the calculated MP2/6–31G*//RHF/
3–21G energies, formaldehyde and formaldimine (*exo*-
hydrogen addition) are less reactive than ethylene, even
though they have lower LUMO energies. One factor
that can explain the lower reactivity is the repulsive
interaction of the oxygen or nitrogen lone pair with the
filled π-orbital of cyclopentadiene, similar to the pro-
posed π-acetylene π-butadiene repulsion in the
Diels—Alder transition state.[18] The transition states of
formaldimine addition to cyclopentadiene 2 and 3 have
different energies. Structure 2 with an *endo* N—M bond
is predicted to have 4·6 kcal mol^{-1} lower activation
energy than the diastereomer 3 with an *exo* N—H
bond. This is considerably larger than was normally
observed in Diels—Alder reactions with substituted
ethylenes.[19] As expected on the basis of LUMO orbital
energies (Table 1), *trans*-diazene is more reactive than
acetylene, formaldehyde or formaldimine (Table 2).
The transition state reflects the above-discussed effect
of the nitrogen lone-pair repulsion with the π occupied
orbitals of cyclopentadiene. This can also explain why,
although the LUMO of *cis*-diazene is higher than of
trans-diazene, the activation energy is lower for the
endo hydrogen *cis*-diazene addition to cyclopentadiene
than the addition of *trans*-diazene. Actually, the
transition-state structure with *trans*-diazene 4 has
2·2 kcal mol^{-1} lower energy than the transition state
with *cis*-diazene 5, but because *trans*-diazene is
8·5 kcal mol^{-1} more stable (the *trans* form of diazene
is actually 6–7 kcal mol^{-1} more stable[20]) than the *cis*
isomer (according to MP2/6–31G* calculations), 4 has
a 6·3 kcal mol^{-1} higher activation barrier. Structures 5
and 6 represent stereoisomeric transition structures for
the *cis*-diazene addition to buta-1,3-diene. As men-
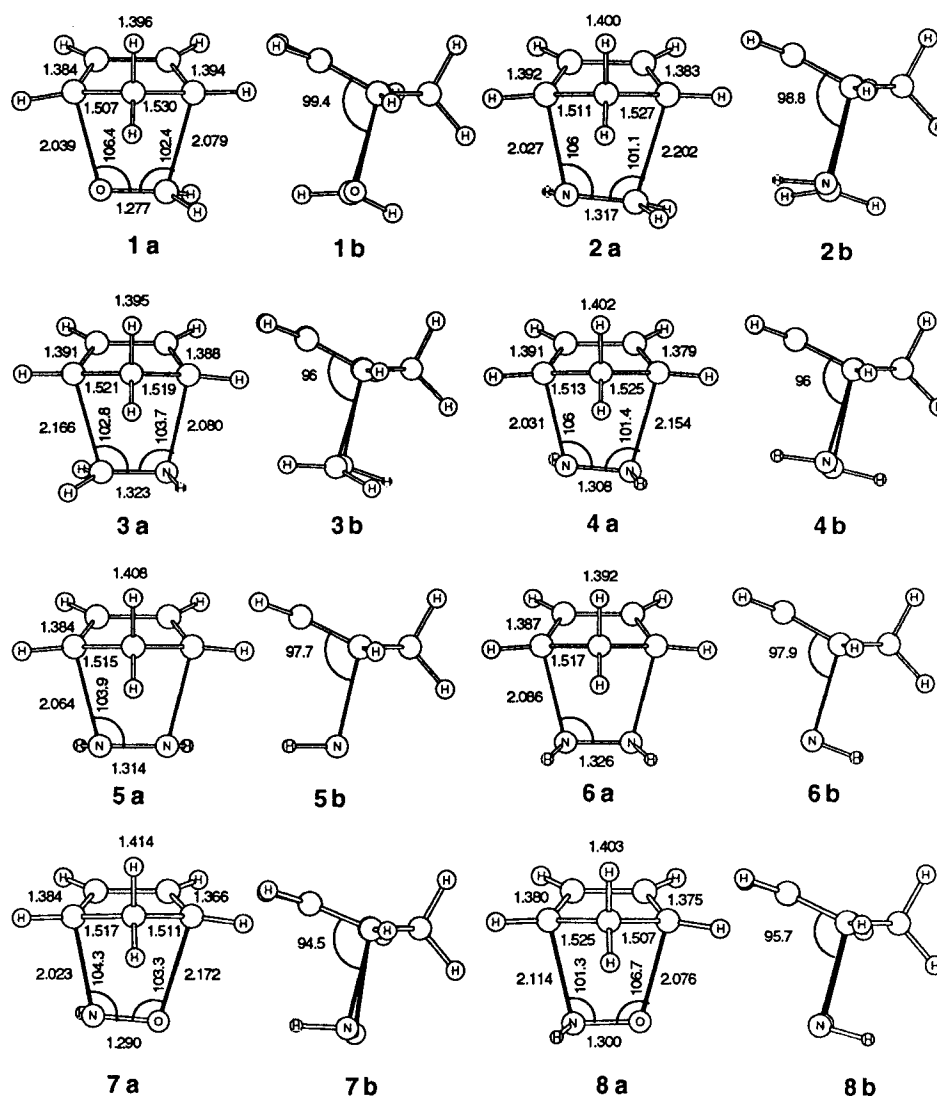tioned above, both structures are symmetrical. The *ab*

Figure 1. (a) Front and (b) side views of the transition-state structures for reaction of cyclopentadiene with hetero-dienophiles

Table 1. HOMO–LUMO energies (eV) of the reactants from a RHF/6–31G*//RHF/3–21G calculation

Reactant	HOMO	LUMO	ΔE_1	ΔE_2
Cyclopentadiene	-0.3062	0.1449		
Formaldehyde	-0.43982	0.13196	0.58472	0.46937
Formaldimine	-0.41750	0.16317	0.5624	0.46937
cis-Diazene	-0.38110	0.14771	0.526	0.45391
trans-Diazene	-0.38664	0.14689	0.53154	0.45309
Nitrosyl hydride	-0.42710	0.09039	0.572	0.39659

$\Delta E_1 = \text{LUMO}_{\text{diene}} - \text{HOMO}_{\text{dienophile}}$;
$\Delta E_2 = \text{LUMO}_{\text{dienophile}} - \text{HOMO}_{\text{diene}}$

initio calculations prefer by $11 \cdot 1$ kcal mol^{-1} the formation of the product with endo N—H bonds. That can again be explained by the repulsive interactions between the two occupied π molecular orbitals of cyclopentadiene with the lone pairs of the nitrogen atoms of cis-diazene in transition state 6. The two transition structures 7 and 8 of nitrosyl hydride addition to cyclopentadiene are almost synchronous and are predicted on the basis of LUMO energy of nitrosyl hydride to have lower activation barrier. The $7 \cdot 6$ kcal mol^{-1} endo preference is again caused by n–π repulsion in 8. The energy difference is lower than in the case of cis-diazene because in both stereoisomers 7 and 8, oxygen n–π

Table 2. Total energies (au) of reactants and transition states for the Diels–Alder reaction of cyclopentadiene with hetero-dienophiles

Species	RHF/3–21G	RHF/6–31G*//RHF/3–21G	MP2/6–31G*//RHF/3–21G
Cyclopentadiene	−191·7170797	−192·7913754	−193·4227822
Formaldehyde	−113·2218198	−113·8623871	−114·1676329
Formaldimine	−93·4947805	−94·00256453	−94·3129884
trans-Diazene	−109·3547665	−109·9924702	−110·3083725
cis-Diazene	−109·3423988	−109·978457	−110·2948632
Nitrosyl hydride	−129·0382903	−129·7832474	−130·1235817
1	−304·8990447	−306·5953157	−307·5697376
2	−285·1696252	−286·7564498	−287·7207100
3	−285·1600599	−286·7490355	−287·7134614
4	−301·0331997	−302·7196663	−303·7283985
5	−301·0294523	−302·7156831	−303·7249063
6	−301·0093517	−302·6981437	−303·7076965
7	−320·7365329	−322·5269796	−323·5541653
8	−320·7253835	−322·5157307	−323·5420616

Table 3. Calculated activation energies (kcal mol^{-1}) for the Diels–Alder reaction of cyclopentadiene with hetero-dienophiles

Dienophile	TS	RHF/3–21G		RHF/6–31G*//RHF/3–21G		MP2/6–31G*//RHF/3–21G	
Ethylene		30·1	(0·0)[c]	39·2	(0·0)[a,d]	10·6	(0·0)[b,d]
Formaldehyde	1	25·0	(−5·1)	36·7	(−2·5)	13·0	(2·4)
Formaldimine, *endo* H	2	26·5	(−3·5)	38·0	(−1·2)	9·4	(−1·2)
Formaldimine, *exo* H	3	32·5	(2·4)	42·7	(3·5)	14·0	(3·4)
trans-Diazene	4	24·2	(−5·9)	40·3	(1·1)	1·7	(−8·9)
cis-Diazene, *endo* H	5	18·8	(−11·3)	34·0	(−5·2)	−4·6	(−15·2)
cis-Diazene, *exo* H	6	31·4	(1·3)	45·0	(5·8)	6·2	(−4·4)
Nitrosyl hydride, *endo* H	7	11·8	(−18·3)	29·9	(−9·3)	−4·9	(−15·5)
Nitrosyl hydride, *exo* H	8	18·8	(−11·3)	36·9	(−2·7)	2·7	(−7·9)

[a] Data for RHF/6–31G//RHF/3–21G.
[b] Data for MP2/6–31G*//RHF/6–31G*.
[c] Ref. 6a.
[d] Ref. 6b.

repulsions are present, whereas in in structure **5** these repulsions do not exist.

It should be noted that the negative activation energies calculated by MP2/6–31G*//RHF/3–21G for the *endo* hydrogen *cis*-diazene and nitrosyl hydride additions (Table 2) do not mean that the reactions are activationless, but rather reflect the fact that the MP2 transition state occurs earlier along the reaction coordinate than the RHF transition state.

There is experimental evidence for the high stereoselectivity predicted by these calculations. It has been shown that some chiral α-chloro nitroso compounds add highly enantioselectively in some Diel–Alder reactions.[21]

CONCLUSION

All levels of *ab initio* calculations employed have shown that the considered hetero-dienophiles, except

formaldehyde, react much more readily than substituted ethylene in Diels–Alder cyclizations with cyclopentadiene. The activation energies are lower and there is a large preference for the heteroatom lone pair to be kept away from the diene π-orbitals. This method should be very useful for the preparation of hetero bicyclic compounds with defined configuration at the newly formed chiral carbon centers.

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