J. Org. Chem. **1997,** *62,* 8687−8692 **8687**

Inverse Electron Demand Diels−Alder Reactions: Cycloaddition of Enol Ethers and Enamines with 4-Substituted 6-Nitrobenzofuroxans and a Nitroethylene Model. An *ab Initio* and Semiempirical Theoretical Study

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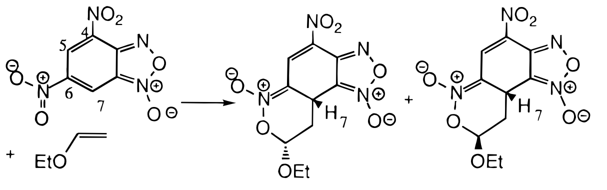
Received May 13, 1997[⊗]

The stereochemistry of the cycloaddition of nitroethylene, as a model of 6-nitrobenzofuroxans, with ethenol and vinylamine has been studied at the ab initio DFT level. MO analysis reveals that these inverse electron demand Diels−Alder reactions are under frontier orbital control. A one-step reaction pathway involving a dissymmetrical transition state is favored relative to a two-step mechanism in which the intermediate has essentially a diradical character. Study of reactions of a series of 4-substituted 6-nitrobenzofuroxans with various enol ethers and enamines at the semiempirical AM1 level shows that in these instances a stepwise mechanism involving a short-lived diradical intermediate is likely to occur. Relative rates and stereoselectivities of these reactions as a function of the nature of reactants is discussed.

Introduction

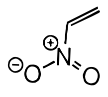
In classical Diels−Alder cycloadditions,[1] the main MO interaction occurs between the high-energy HOMO of an electron-rich diene and the low-energy LUMO of an electron-poor dienophile.[2,3] However, inverse electron demand Diels−Alder (IEDDA) reactions may also occur in some instances and have been the subject of recent investigations.[3,4] In such reactions, a diene or, more frequently, an heterodiene[5] with a low-energy LUMO interacts with the HOMO of an electron-rich dienophile.[3,6,7]

Recently, we discovered that 4,6-dinitrobenzofuroxan (DNBF) reacts with ethyl vinyl ether to give a diastereomeric mixture of dihydrooxazine *N*-oxide cycloadducts 1 (eq 1).[8] Interestingly, this regiospecific condensation is also stereoselective regarding the relative positions of the ethoxy group, and the ring hydrogen H_7 (**1** *trans*/**1** *cis* = 4/1) was best accounted for in terms of an IEDDA cycloaddition. This will involve the heterodienyl fragment constituted by the 6-NO_2 group and the conjugated 6,7-double bond of DNBF and the enol ether dienophile (eq 1). In this paper, we present a theoretical study which confirms the IEDDA mechanism of this condensation and related ones.



1 *trans* 1 *cis* (eqn. 1)

In a first approach, ab initio calculations have been carried out on a simple model reaction, namely, that of nitroethylene (**2**) with ethenol (**3a**). In particular, the role of the olefin substituent will be discussed by comparison with the reaction of **2** with vinylamine (**3e**). Then, the reactions between methyl vinyl ether (**3b**) and 6-nitrobenzofuroxans possessing various 4-R_2 substituents (**4a**−**f**) were considered at the semiempirical level. Finally, similar level calculations were carried out on the reactions of DNBF (**4a**) with the substituted olefins **3a**−**f**. With **3f**, the reactions with the heterodiene **4g** possessing the π-donor substituent OH has also been studied. MO perturbations have been analyzed in order to establish whether this family of reactions is frontier orbital controlled, as is generally the case in classical Diels−Alder reactions, or not.[2]



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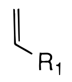
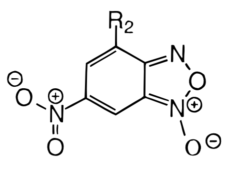


3

a : R_1 = OH
b : R_1 = OMe
c : R_1 = $OSiH_3$
d : R_1 = $OSiMe_3$
e : R_1 = NH_2
f : R_1 = NMe_2



4

a : R_2 = NO_2 (DNBF)
b : R_2 = CN
c : R_2 = SO_2CF_3
d : R_2 = SO_2H
e : R_2 = CF_3
f : R_2 = H
g : R_2 = OH

Calculation Methods

Ab initio calculations were performed using the GAUSSIAN 94 series of programs.[9] The standard basis sets 3-21G** and 6-31G** were used at the SCF level and at the DFT level for the latter one. In this case, the Becke three-parameter/Lee−Yang−Parr technique[10] (B3-LYP) was used. This DFT has

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[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1997.

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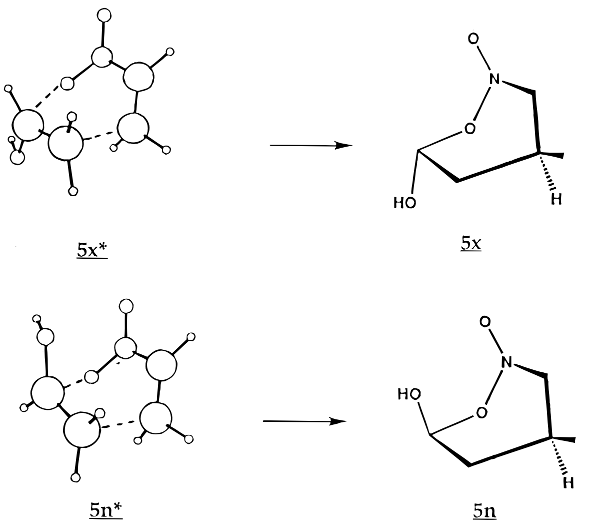


	5n*		5x*	
	C-O	C-C	C-O	C-C
SCF/3-21G**	2.26	2.06	2.23	2.05
DFT/6-31G**	2.39	1.94	2.36	1.96
CAS/3-21G**	2.54	1.65		
AM1	2.36	1.97	2.35	1.87

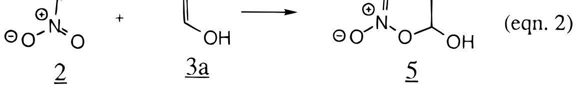
Figure 1. Calculated (DFT/6-31G**) *endo* (**5n***) and *exo* (**5x***) TSs for the cycloaddition of nitroethylene (**2**) with ethenol (**3a**). In the lower part, the C−O and C−C bond lengths are reported for various calculation levels.

been recently found to be suitable for this kind of system.[11] For comparison of the concerted and the two-step mechanism, the latter involving an intermediate diradical, CASSCF/3-21G** calculation were performed, with an active space including the two HOMOs and the two LUMOs of π symmetry (20 configurations).

Semiempirical calculations were performed at the AM1 level, using either GAUSSIAN 94 or MOPAC[12] series of programs, with Dewar's parameters.[13] A HOMO−LUMO CI was used for a proper description of the states having a diradical character.

Results and Discussion

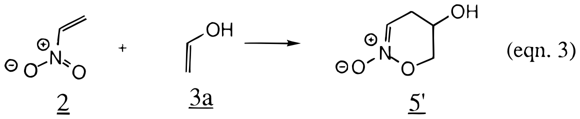
Concerted Reaction of Nitroethylene (2) with Ethenol (3a). The transition state for the one-step reaction (eq 2)



has been optimized at various calculation levels, both in *endo* and *exo* approaches, according to the geometry displayed in Figure 1, and the corresponding energies are reported in Table 1.

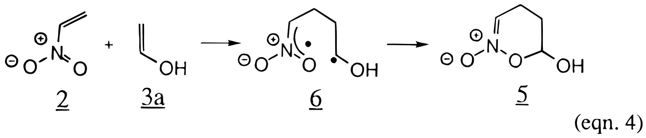
It can be seen in Figure 1 that the *endo* **5n*** and *exo* **5x*** TSs are respectively connected to the **1** *trans* and **1** *cis* isomers (see eq 1). Whatever the calculation method used, the TS appears to be characteristic of a concerted asynchronous mechanism, with the developing C−C bond beeing shorter than the C−O one.[14−18] The *endo* TS is found at a lower energy than the *exo* one. Their energy difference, ranging from 0.1 kcal mol^{-1} (AM1) to 0.8 kcal mol^{-1} (SCF/3-21G**), is 0.3 kcal mol^{-1} at the highest level of calculation (DFT/6-31G**). From the Arrhenius relation, and assuming equal frequency factors for both *endo* and *exo* reaction rate constants, the experimental relative yield of **1** *trans* and **1** *cis* involves a difference of ca. 0.4 kcal mol^{-1} in TS energies. This is in good agreement with the calculated values. The endo TS **5n*** lies at 17.7 kcal mol^{-1} and at 19.6 kcal mol^{-1} at the AM1 and the SCF/3-21G** levels, respectively, but drops to 13.2 kcal mol^{-1} at the DFT/6-31G** level. These results indicate a strong reactivity at room temperature.

The regiospecificity of the reaction has been studied by optimizing the *endo* **5′n*** and *exo* **5′x*** TSs for the formation according to eq 3 of the "para" regioisomers **5′** (see Table 1).



The *endo* approach is again favored over the *exo* one, by 0.2 kcal mol^{-1} at the highest calculation level (DFT/6-31G**) though it appears to be disfavored at the SCF/3-21G** by 1.4 kcal mol^{-1} levels. Nevertheless, this reaction requires high activation energies (34 or 29.4 kcal mol^{-1} at these two levels, respectively); therefore it may be expected to be very unefficient.

Diradical Mechanism of the Reaction of Nitroethylene (2) with Ethenol (3a). Since diradical mechanisms are frequently suggested as reasonable competitors with the one-step reaction,[15−18] the following reaction path (eq 4) was studied at the CASSCF/3-21G** level, such a calculation method being required by the essentially multiconfigurational nature of the diradical states.[19] The results are reported in Table 1 and summarized in Figure 2.



The intermediate of structure **6** was first optimized in the "zig-zag" conformation **6a**. This entity indeed appears as being purely diradical, with a negligible contri-

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Table 1. Reference Absolute Energies (au) and Relative Energies (kcal mol^{-1}) of TSs (E*) Above Reactant Energies

	SCF/3-21G**	E*SCF/3-21G**	DFT/6-31G**	E*DFT/6-31G**	CASSCF/3-21G**	E*^{a} CASSCF/3-21G**	E* AM1
2	−279.906 83		−283.092 65				
3a	−152.070 27		−153.812 77				
5n*	−431.945 89	19.6	−436.884 43	13.2	−431.999 74^b	−2.7	17.7
5x*	−431.944 56	20.4	−436.883 94	13.5			17.8
5′n*	−431.922 01	34.6	−436.858 59	29.4			
5′x*	−431.924 15	33.2	−436.858 23	29.6			
6*					−431.990 73	3.4	
6a					−431.994 38^c	0.6	
6b					−431.995 49	0.0	
3e			−133.954 29				
7n*			−417.034 13	8.0			11.5
7x*			−417.030 38	10.4			12.7

[a] Diradical **6b** as reference energy (see also Figure 2). [b] At the CASSCF (6,6) level: −432.027 74 au. [c] At the CASSCF (6,6) level: −432.029 68 au.

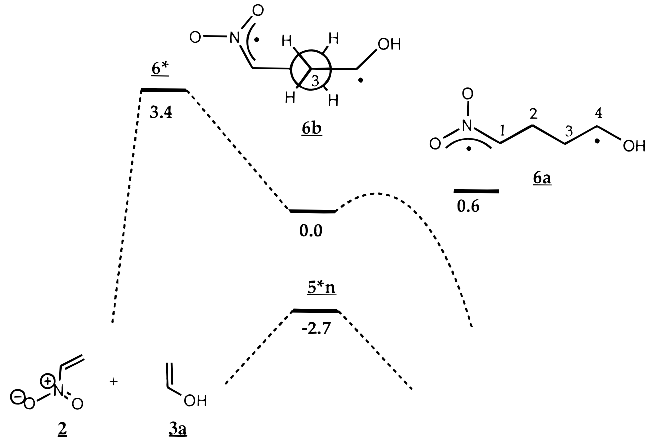
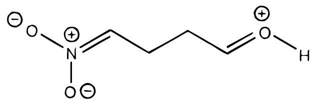


Figure 2. Comparison between one-step (endo approach) and two-step reaction for the cycloaddition of nitroethylene (**2**) with ethenol (**3a**).

bution of the following zwitterionic form (commonly encountered in the literature):[5,18]



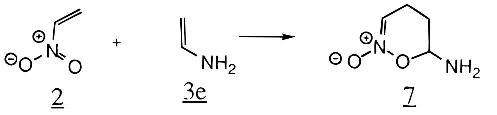
As a matter of fact, the neat charge of the heteroatoms and adjacent carbon atoms are nearly the same (within 0.01) as that found in the reactants, except for one of the oxygen atoms of the nitro group (dissymmetrical in this conformation) which is 0.30 in **6a** vs 0.27 in nitroethylene (**2**) and for the carbon adjacent to this group which is 0.23 in **6a** vs 0.16 in **2**. Indeed, the lowest excited state of the diradical **6a** with a vertical energy of 25 kcal mol^{-1} is not zwitterionic but corresponds to an excitation of the −CHNO$_2$ moiety. In fact, though the presence of a solvent is likely to stabilize a zwitterionic state, it is not expected to become the ground state. Such a situation is only encountered in the cases of very dissymmetrical species allowing the stabilization of both anionic and cationic sites, in very polar solvents, as reported by Sustmann and Siking.[18] In addition, the reactions with DNBF have been carried out in methylene chloride, a solvent of weak dielectric constant, and one can then assume than the diradical ground state in such a solvent is the same as that calculated in the gas phase.

The **6b** conformation, in which the C$_2$−C$_3$ bond is eclipsed with both p MOs bearing the unpaired electrons was then optimized. This **6b** conformation is directly correlated to the reactants **2** and **3a** upon elongation of C$_2$−C$_3$. In this process, a TS has been found at 3.4 kcal mol^{-1} above **6b**. The *endo* TS, **5n***, for the one-step process was optimized at 2.7 kcal mol^{-1} under **6b**. We note that this TS is strongly dissymmetrical, with a C$_2$−C$_3$ bond length of 1.65 Å, close to its equilibium value in the product (1.54 Å), and a rather long C$_4$−O bond (2.54 Å). At this level of calculation, the reaction is thus likely to occur via a one-step mechanism.

Indeed, the relative energies required by both mechanism are very close one another and should depend on the calculation method. CASSCF is known to favor diradical species, and this trend must increase with the size of the active space. As a landmark, a single-point calculation has been performed on the TS **5n*** and the diradical **6a** at the (6,6) CASSCF level (175 configurations). In this case, diradical **6a** is stabilized by 0.0280 au vs 0.0353 au for TS **5n*** (see footnote in Table 1) so that the diradical becomes more stable than **5n*** by 1.2 kcal mol^{-1}.

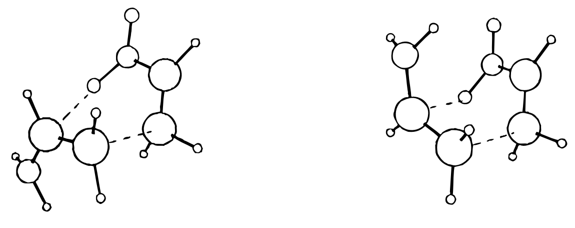
For these reasons, the formation of a diradical cannot be ruled out but this entity is expected to be very short-lived, since its cleavage requires an activation of the same order of magnitude as that of the rotational barriers. Under these conditions, either the diradical is formed in a conformation which does not allow the ring closure, and it is likely to give back the reactants before closure, or the geometry of approach of the reactants is favorable to the one-step asynchronous reaction and yields the product.

Concerted Reaction of Nitroethylene (2) with Vinylamine (3e). Enamine compounds, as electron-rich olefins, are good candidates for IEDDA condensation.[5] The reaction of nitroethylene (**2**) with vinylamine (**3e**) was thus studied, at the higher level of calculation, DFT/6-31G**, and only for the "ortho" regioisomers **7**:



(eqn. 5)

The **7n*** and **7x*** TSs corresponding to the *endo* and the *exo* approaches, respectively, are displayed in Figure 3, and the corresponding energies are reported in Table 1. First, we note that the *endo*/*exo* selectivity is enhanced with respect to enol addition, since the difference in TS energy is 2.4 kcal mol^{-1}, and second, we observe that the *endo* reaction only needs a 8.0 kcal mol^{-1} activation energy. The enamine **3e** is thus expected to be very reactive. The TS is more reactant-like than that for the enol addition, with relatively long distances between the atoms to be bonded: 2.71 Å for CO and 1.96 Å for CC.



7x*   7n*

	7n*		7x*	
	C-O	C-C	C-O	C-C
DFT/6-31G**	2.71	1.96	2.57	1.98
AM1	2.77	1.91	2.58	1.91

Figure 3. Calculated (DFT/6-31G**) *endo* (**7n***) and *exo* (**7x***) TSs for the cycloaddition of nitroethylene (**2**) with vinylamine (**3e**).

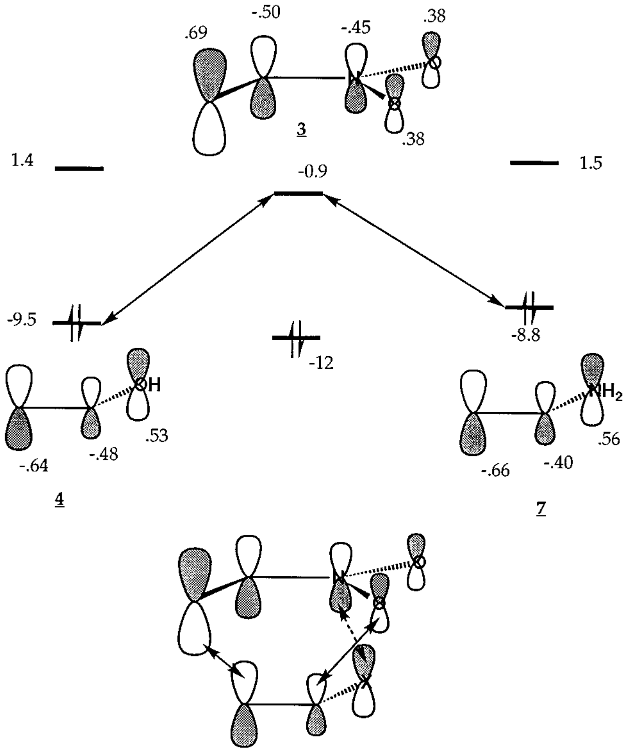


Figure 4. Frontier MO perturbation schemes for concerted cycloadditions of nitroethylene (**2**) with ethenol (**3a**) and vinylamine (**3e**) (AM1, MO energies in eV).

The results are quite similar at the semiempirical AM1 level: the endo approach is preferred by 1.2 kcal mol^{-1} over the exo one; the required activation is 11.5 kcal mol^{-1} for the endo TS, which has a CO distance of 2.77 Å and a CC distance of 1.91 Å. As previously found for enol addition, AM1 calculations enhance the dissymmetry of the TS, but they agree qualitatively with the higher level calculations. In both cases enamine addition is found to be faster and more stereoselective than enol addition.

Frontier Orbital Study. The frontier orbital interaction diagram is displayed in Figure 4. The main HOMO–LUMO interaction occurs between the LUMO of the heterodiene **2** and the HOMO of the dienophiles **3a** or **3e**. These reactions appear to be under frontier control as it is the case for most of "classical" Diels–Alder cycloadditions.[2] The regioselectivity is interpreted by the main interaction between atoms of each moiety having the higher coefficient in the frontier MO's. The *endo*/*exo* stereoselectivity can be explained by a favorable in-phase secondary MO interaction between a nitrogen atom of **2** and an heteroatom, O or N, of the dienophiles **3a** or **3e**. Examination of the MO coefficients and the HOMO–LUMO energy difference is consistent with the fact that enamine addition is faster and more stereoselective than enol addition.

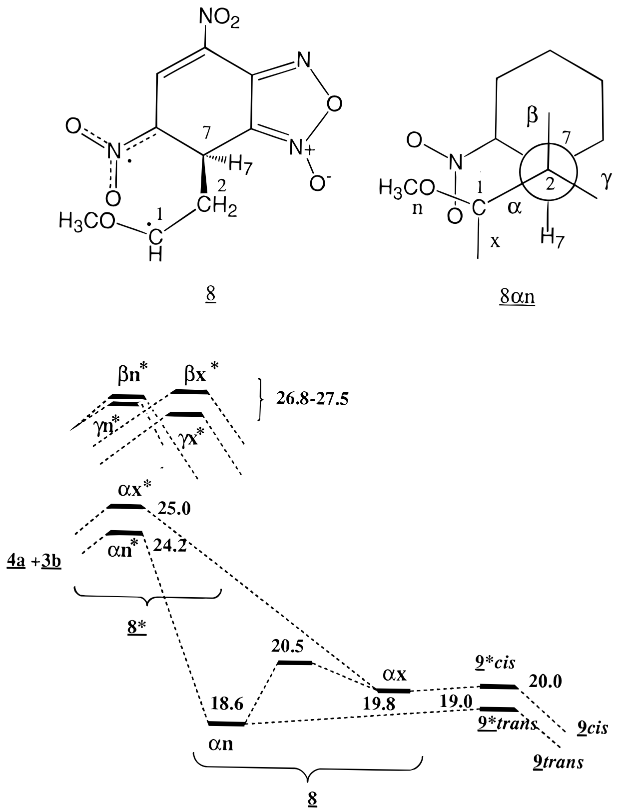
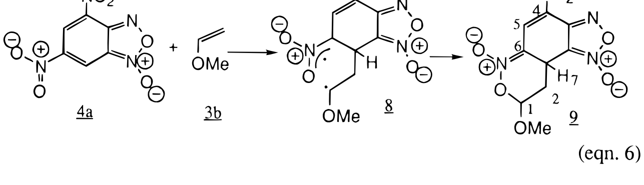


Figure 5. Reactions paths in the two-step cycloaddition of DNBF (**4a**) with methyl vinyl ether (**3b**), according to the approach conformation (see text).

Reaction of 4,6-Dinitrobenzofuroxan (DNBF) (4a) with Methyl Vinyl Ether (3b). The reaction of DNBF (**4a**) with methyl vinyl ether (**3b**) giving the cycloadducts **9** *trans* and **9** *cis*, according to the relative positions of the methoxy group and the ring junction hydrogen H_7, has been studied at the AM1 level. Any attempt to characterize a one-step TS has failed, using either automatic search or "manual" exploration. Apparently, this area of the potential energy surface exhibits a very flat maximum in which a saddle point cannot be clearly determined.

Thus, the two-step reaction path (eq 6) has been investigated systematically.



(eqn. 6)

The diradical **8** can be formed *a priori* in several conformations described in the upper part of Figure 5. In the Newman view in the C_2–C_7 axis, the carbon C_1 may occupy one of the three α, β, or γ position in the various staggered conformers. For each of these con-

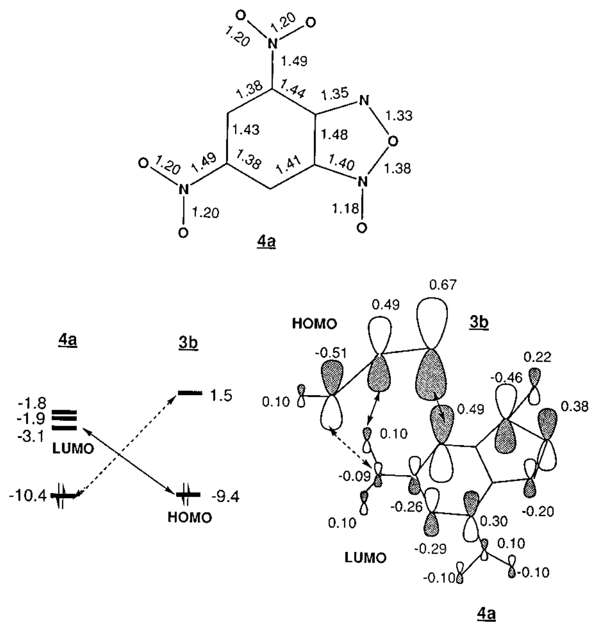


Figure 6. Upper part: optimized geometry (AM1) of DNBF (**4a**). Lower part: HOMO–LUMO interaction of **4a** with methyl vinyl ether (**3b**).

formers, the methoxy group can be in the *endo* (n) or *exo* (x) position with respect to the NO_2 group. The conformer of Figure 5 will be thus labeled αn. In the lower part of Figure 5 are displayed the crucial features of the reaction profile. The TSs for the formation of the diradical **8** in its various conformations are labeled in the same way as for **8** and marked by an asterisk. The formation of both α conformers is favored over the β and γ ones, with the αn *endo* conformer being itself favored over the αx *exo* one by 0.8 kcal mol^{-1}. The relative orders of magnitude of the activation energies indicate that only the two latter ones may be in competition. Cyclization of **8an** and **8ax**, into the **9** *trans* and **9** *cis* adducts, respectively, requires only a negligible activation energy (<0.4 kcal mol^{-1}), while the **8ax** → **8an** conversion needs 0.7 kcal mol^{-1}. Accordingly, the closure of the diradical is faster than its *endo*/*exo* interconversion, and thus, the overall reaction rate and the **9** *trans*/**9** *cis* ratio are mainly controlled by the energies of the αn* and αx* TSs. Finally, although an energy minimum corresponding to the diradical structure is found along the reaction coordinate, this reaction appears to be concerted but very asynchronous, since the diradical is too short-lived to undergo any conformation change. This result is supported by the fact that AM1 is known to favor stepwise mechanisms over concerted ones.[20]

As compared with the nitroethylene (**2**) – enol **3a** reaction, which requires 17.7 kcal mol^{-1}, the 4,6-dinitrobenzofuroxan (**4a**) appears less reactive than **2**. This could be partly due to the loss of aromaticity that the reaction involves, though this aromaticity is lowered in DNBF, **4a**, by ring substituents. As a matter of fact, the optimized geometry of **4a** (Figure 6) exhibits a marked bond length alternance in the phenyl ring.

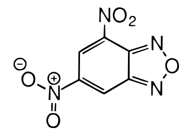
The quasi-concerted character of the reaction allows for rationalization in terms of frontier orbital interactions of the reactants. Indeed, the MO interaction diagram in Figure 6 agrees with calculation results: a secondary in-phase overlap occurs between the HOMO of **3b** and the LUMO of **4a**, thus favoring the *endo* approach over the *exo* one. Nevertheless, the coefficient involved on the nitrogen atom is small (0.10). Moreover, the LUMO+1 and LUMO+2 of **4a** lie very close to the LUMO; they could play an important role since they bear larger coefficients (>0.2) on the nitrogen atom.

Table 2. Influence of Various R_1 and R_2 Substituents on Reactivity and Selectivity of the Cyclocondensation between the Dienophiles 3a–f with the Heterodienes 4a–g and 3b with 4′a (See Also Figure 7)

3			4					
R_1	a_1[a]	b_1[b]	R_2	a_2[a]	b_2[b]	E^*[c]	ΔE^*[d]	LU–HO[e]
OH (**3a**)	0.70	−0.48	NO_2 (**4a**)	0.49	−0.09	25.2	0.6	6.5
OMe (**3b**)	0.67	−0.51	NO_2 (**4a**)	0.49	−0.09	24.2	0.8	6.3
$OSiH_3$ (**3c**)	0.69	−0.49	NO_2 (**4a**)	0.49	−0.09	18.1	0.2	6.3
$OSiMe_3$ (**3d**)	0.70	−0.49	NO_2 (**4a**)	0.49	−0.09	13.5	−0.7	6.0
OMe (**3b**)	0.67	−0.51	H (**4f**)	0.45	−0.13	29.3	0.9	7.0
OMe (**3b**)	0.67	−0.51	SO_2H (**4d**)	0.50	−0.09	23.3	0.2	6.4
OMe (**3b**)	0.67	−0.51	SO_2CF_3 (**4c**)	0.52	−0.07	20.3	0.4	6.0
OMe (**3b**)	0.67	−0.51	CF_3 (**4e**)	0.48	−0.10	26.0	0.6	6.6
OMe (**3b**)	0.67	−0.51	CN (**4b**)	0.47	−0.10	26.8	0.6	6.6
NH_2 (**3e**)	0.66	−0.57	NO_2 (**4a**)	0.49	−0.09	16.3	0.5	5.8
NMe_2 (**3f**)	0.58	−0.60	NO_2 (**4a**)	0.49	−0.09	14.4	−0.6	5.5
NMe_2 (**3f**)	0.58	−0.60	H (**4f**)	0.45	−0.13	21.9	−0.1	6.2
NMe_2 (**3f**)	0.58	−0.60	OH(**4g**)	0.41	−0.12	19.7	0.3	6.1
OMe (**3b**)	0.67	−0.51	NO_2 (**4′a**)	0.52	−0.11	21.5	0.2	6.3

[a] Coefficients of frontier orbitals involved in the formation of the C–C bond (see also Figure 7). [b] Coefficients of frontier orbitals involved in the *endo*/*exo* selectivity (see also Figure 7). [c] Activation energy (kcal mol^{-1}) for the formation of the *endo* diradical (see also Figure 5). [d] $E^*_{exo} - E^*_{endo}$ (kcal mol^{-1}) energy difference. [e] LUMO–HOMO energy difference (eV, see also Figure 7).

Influence of Substituents on the Rate and the Stereoselectivity of the Reaction between 3a–f and 4a–g. Various substituted reactants have been studied to emphasize the influence of R_1 fragments of the dienophiles **3a–f** and the influence of R_2 substituents in the heterodiene **4a–g**, including an electron donor substituent, i.e., R_2 = OH (**4g**). In addition, it would be of interest to examine the *N*-oxide influence, by comparing the reactivity of **4a** with that of the deoxygenated homolog, namely, the 4,6-dinitrobenzofurazan (**4a′**).



4a'

According to the above discussion, the crucial step controlling the rate and the selectivity of the reaction is the formation of the diradical. Thus, the structure and energy of the TS in this diradical formation reaction, in its αn and αx conformations (cf. Figure 5), have been calculated at the AM1 level. The results are reported in Table 2. The energy of the *endo* TS (E^*) has been taken as an index of the reaction rate, whereas ΔE, the energy difference between the *endo* and *exo* TSs, is a characteristic of the *cis*/*trans* selectivity of the reaction. Table 2 also reports frontier MO features depicted in Figure 7, i.e., the HOMO–LUMO gap corresponding to the main MO interaction, the MO coefficients of the primary interaction involved in the bond formation, and the MO coefficients involved in the secondary interaction responsible for the *endo*/*exo* energy difference.

Though the order of magnitude of ΔE^* (**4a–3b**) is consistent with experimental values (cf. supra), some ΔE^*

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(20) Ciolowsky, J.; Sauer, J.; Hetzenegger, J.; Karcher, T.; Hierstetter, T.; *J. Am. Chem. Soc.* **1993**, *115*, 1353.

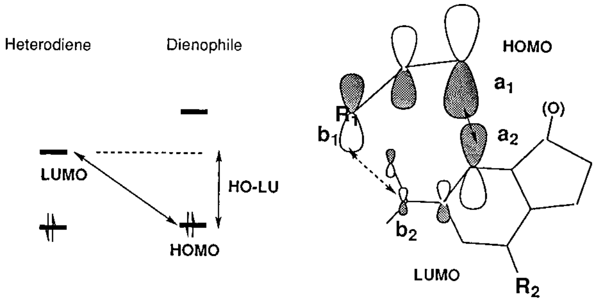

Figure 7. Main MO parameters controlling the reaction of heterodienes **4** with dienophiles **3**.

are so close to one another that inversions cannot be ruled out; we thus only report general trends.

Regarding, first, the heterodiene: (i) The influence of a R_2 withdrawing substituent is observed when comparing E^* in both couples **4a**–**f**+**3b**. Replacement of R_2 = H (**4f**) by $R_2 = NO_2$ (**4a**) lowers the activation energy by ca. 5 kcal mol^{-1}. This observation is consistent with the decrease of the HOMO–LUMO gap and increase in the a_2 coefficient (Figure 7) by the NO_2 group. (ii) If we compare the influence of the electron-withdrawing R_2 groups along the series **4a**–**e** in the cycloaddition with the same **3b** dienophile, only **4c** ($R_2 = SO_2CF_3$) appears more reactive than **4a** ($R_2 = NO_2$), but this goes with a weaker stereoselectivity. (iii) Removing the oxygen atom from the five-membered ring (**4a′**) increases the reactivity with the dienophile **3b** but there is concomitantly a decrease in the selectivity.

Looking now at the influence of the dienophile structure, the following remarks can be made. (iv) In the enol **3a** and the enol ether series **3b**, **3c**, **3d**, the reactivity with DNBF (**4a**) increases, as expected, with the increasing donor character of the olefinic R_1 substituent:[21] **3a** (R_1 = OH), **3b** (R_1 = OMe), **3c** ($R_1 = OSiH_3$), **3d** ($R_1 = OSiMe_3$). Simultaneously, the *trans*:*cis* cycloadducts ratio decreases along the sequence **3a**–**3d**. That the *cis* cycloadduct is predicted to be the major compound in this latter case is not surprising, since it should be the result of a steric hindrance between the bulky (trimethylsilyl)oxy group and the DNBF moiety in the *endo* TS, rather than of a change in the MO perturbation scheme. (v) Enamines **3e** and **3f** are found to be more reactive than enol and enol ethers, in agreement with our preceding ab initio level calculations on the simple models. An inversion of the selectivity is again observed with the hindered **3f**. (vi) Since enamines are likely to be much more reactive than enol ethers, one can expect that an electron-withdrawing R_2 substituent is no longer necessary to observe the enamine cycloaddition. Indeed, with the R_2 = OH donor substituent **4g**, the activation energy (E^* = 19.7 kcal mol^{-1}) is lower than in the reference couple **4a** + **3a** (E^* = 25.2 kcal mol^{-1}). Nevertheless, the reaction is found to be less stereoselective. (vii) The calculated E^* values are consistent with available experimental results. Enamines (E^* = 14.4 kcal mol^{-1}) are stronly reactive.[22] On the contrary, no reactivity, at room temperature, has been observed[22] between **4f** and **3b** (E^* = 29.3 kcal mol^{-1}). Calculation results allow us to expect a stronger reactivity of **4a** with trimethylsilyl ether **3d** (E^* = 13.5 kcal mol^{-1}) than with methyl ether **3b** (E^* = 24.2 kcal mol^{-1}).[23]

Some of the preceding features may be rationalized in terms of frontier interaction. For example, the reactivity, characterized by E^*, roughly follows the decreasing order of the HOMO–LUMO gap. The prevision of the stereoselectivity on the simple basis of the secondary interaction coefficients, "b_2" and "b_1" seems more problematic. The increased amount of trans product with **4f** + **3b** with respect to **4a** can be explained by the greater "b_2" coefficient (0.13 vs 0.09). Nevertheless, counterexamples can be found: the enamine **3e** has a greater "b_1" coefficient (0.57) than **3b** (0.51), but a weaker selectivity in the cycloadducts formation with **4a**.

A possible 4 + 2 reaction involving the 4-NO_2 group in **4a**, in competition with the 6-NO_2 one, has not been investigated. Nevertheless, one can remark that the LUMO coefficient of C_5 is only 0.29, as compared with 0.49 for the carbon in position 7 which is thus expected to be more reactive. On the other hand, one can imagine the possibility of the addition of a second molecule of dienophile on the adduct **1**. Examination of the LUMO of this species shows that its energy difference with the HOMO of the dienophile **3b** is 7.2 eV; this difference is 6.3 eV for the couple **4a** + **3b**. The addition of a second enol molecule is thus expected to be slower than addition of the first one. These qualitative remarks are in good agreement with experimental findings. As a matter of fact, the reaction of DNBF with ethyl vinyl ether diluted in CH_2Cl_2 only yields to the monoadduct **1**,[8] whereas a second addition is observed when ethyl vinyl ether is used as a solvent.[8]

Conclusion

Regarding a simple IEDDA model studied, namely, nitroethylene (**2**) with ethenol (**3a**), ab initio calculations show that this reaction is pericyclic with a dissymmetrical TS. A two-step reaction, with an intermediate of essentially diradical character, constitutes a less favorable reaction path. This reaction, as well as the other model studied (nitroethylene (**2**) and vinylamine (**3e**)) is frontier controlled for rate and stereoselectivity.

Dealing with reactions of DNBF and related compounds **4**, on various dienophiles **3**, AM1 calculations suggest a stepwise mechanism with a short-lived diradical intermediate. The rate of these reactions is under frontier MO control but their stereoselectivity cannot always be easily rationalized in these terms and thus requires a full calculation.

The study of cycloadditions of the heterodienes **4** with the dienophiles **3** shows that the highest *trans*:*cis* ratio for the adducts is obtained for **4a** ($R_2 = NO_2$) with **3b** (R_1 = OMe). Nevertheless, this ratio could be reversed when introducing a bulky subtituent on the dienophile, like in **3d** ($R_1 = OSiMe_3$). Enamines appear more reactive than enol ethers, and for these dienophiles, the presence of a strongly electron-withdrawing substituent R_2 on the heterodiene is no longer necessary.

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[22] Hallé, J. C.; Vichard, D.; Terrier, F.; to be published.

[23] Hallé, J. C.; Vichard, D.; Terrier, F.; work in progress.