Electrostatic Effects in 1,3-Dipolar Cycloaddition Reactions to Chiral Allyl Ethers: a Rationale for the Experimentally Observed Diastereoselectivities

Rita Annunziata, Maurizio Benaglia, Mauro Cinquini and Laura Raimondi*

Centro CNR and Dipartimento di Chimica Organica e Industriale

Università degli Studi di Milano

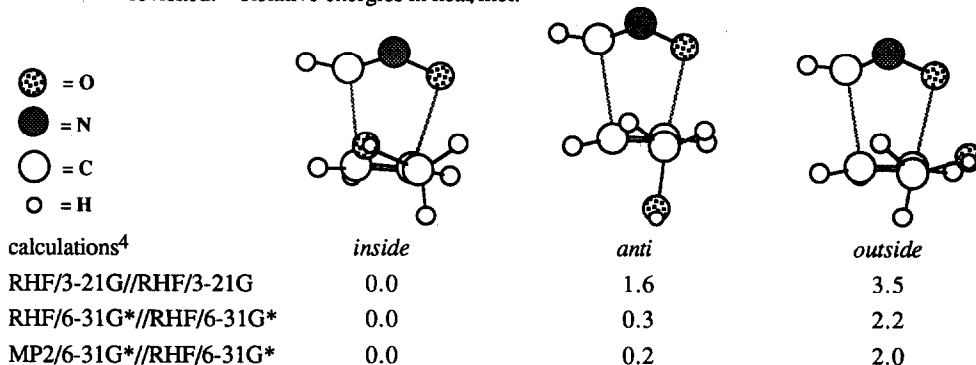via Camillo Golgi, 19

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Abstract: Semiempirical (PM3) and *ab initio* (RHF/3-21G) transition structures for 1,3-dipolar cycloadditions of 5 different dipoles to alkenes were analyzed; the differences in 1,3-dipole charge distribution offer a rationale for the different stereoselectivities experimentally observed in the reactions with chiral allyl ethers.

1,3-Dipolar cycloaddition of nitrile oxides to chiral alkenes has recently become a very popular approach to the regio- and stereocontrolled synthesis of polyfunctionalized organic molecules.[1] A great deal of theoretical attention has been paid to the mechanism of this reaction, now fully investigated and understood,[2a] and force field methods have been developed to account for the observed stereoselectivities.[3]

Recently a re-examination of the so-called "inside alkoxy effect" in nitrile oxide cycloadditions[3a,b] showed that electrostatic interactions between the nitrile oxide oxygen and the allylic oxygen seem to play a major role in determining the stereochemical outcome of these reactions;[3d] in the transition structure for the cycloaddition of fulminic acid to allyl ethers the oxygen-*inside* and the oxygen-*anti* conformations have almost the same energy at the MP2/6-31G*//RHF/6-31G* level,[4] the latter being only 0.2 kcal/mol less stable. The *outside* conformer however is 2.0 kcal/mol higher than the *inside*, due to the electrostatic repulsion between dipole and dipolarophile oxygens (Figure 1).

On this basis we reasoned that electrostatic effects, together with steric effects, may be at the origin of the different stereoselectivities observed in cycloaddition reactions of several 1,3-dipoles to chiral alkenes.[1] The experimentally determined sense of stereoselection in the reaction of different dipoles with chiral allyl ethers depends mainly on the substitution at the allylic stereocenter of the olefin, the effect of the nature of the 1,3-dipole being limited to tuning the actual extent of diastereofacial selectivity. In Scheme 1 are shown three different 1,3-dipoles reacting with the same chiral alkene;[1,5-7] several other examples, at least for nitrile oxide and nitrone cycloadditions, are known in the literature.[1,3,6,7]

Figure 1. T.S.s for the fulminic acid plus allyl alcohol cycloaddition : the "inside alkoxy effect" revisited.[3d] Relative energies in kcal/mol.

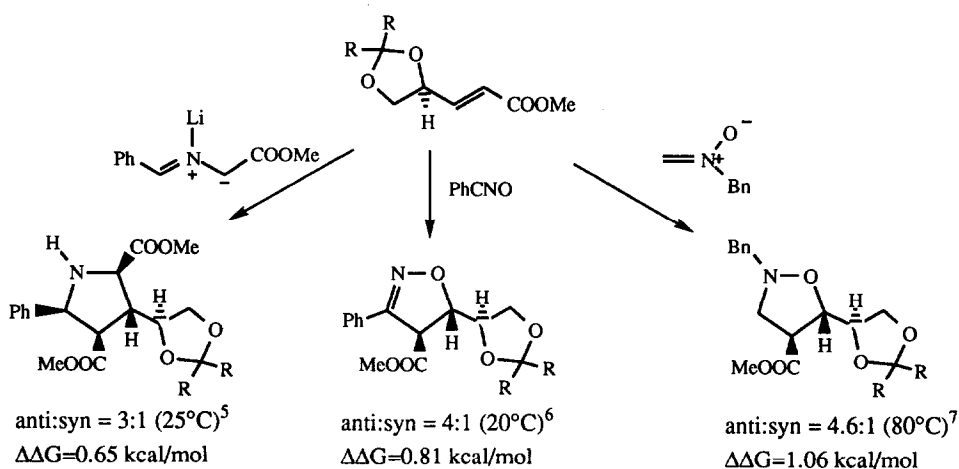| calculations[4]	*inside*	*anti*	*outside*
RHF/3-21G//RHF/3-21G	0.0	1.6	3.5
RHF/6-31G*//RHF/6-31G*	0.0	0.3	2.2
MP2/6-31G*//RHF/6-31G*	0.0	0.2	2.0

The aim of this project was to evaluate the point charge distribution on the transition structures for various 1,3-dipolar cycloaddition reactions to ethylene (the simplest alkene), and to compare these charge distributions with the experimentally observed diastereoselectivities in the corresponding cycloadditions to chiral allyl ethers. If a relation exists, it should be possible, once given the point charges in a transition structure, to predict the extent of stereoselectivity.

The transition structure **A** for the reaction between fulminic acid (the simplest nitrile oxide) and ethylene was located by Brown in 1985[8] at the RHF/3-21G level of theory.[4] The corresponding T.S. for nitrone cycloaddition **B** was studied by Bernardi et al. with MCSCF methods and the 4-31G basis set;[2a,4] for sake of comparison, we relocated this transition structure at the RHF/3-21G level.[9] The two structures **A** and **B** are shown in Figure 2, together with significant geometrical data.

We studied also the T.S.s for the cycloaddition to ethylene of three more 1,3-dipoles (azomethine ylide, diazomethane, nitrilimine). In these cases, the negatively charged atom in the dipole moiety is not an

Scheme 1. Experimental diastereoselectivities for 1,3-dipolar cycloadditions of different dipoles to the same chiral alkene; only *anti* isomers are shown for simplicity.

anti:syn = 3:1 (25°C)[5]
ΔΔG=0.65 kcal/mol

anti:syn = 4:1 (20°C)[6]
ΔΔG=0.81 kcal/mol

anti:syn = 4.6:1 (80°C)[7]
ΔΔG=1.06 kcal/mol

Figure 2. RHF/3-21G transition structures for nitrile oxide and nitrone cycloadditions to ethylene.

<center>A   B</center>
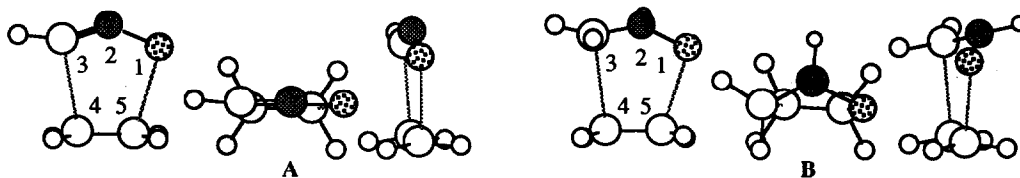
<center>bond distances (Å)</center>

O_1-N_2	1.315		O_1-N_2	1.365
N_2-C_3	1.163		N_2-C_3	1.294
C_3-C_4	2.265		C_3-C_4	2.316
C_4-C_5	1.354		C_4-C_5	1.360
O_1-C_5	2.181		O_1-C_5	2.081

<center>bond angles (degrees)</center>

O_1-N_2-C_3	138.8		O_1-N_2-C_3	116.8
N_2-C_3-C_4	99.2		N_2-C_3-C_4	95.0
C_3-C_4-C_5	99.3		C_3-C_4-C_5	96.4
O_1-C_5-C_4	105.8		O_1-C_5-C_4	107.4
N_2-O_1-C_5	96.8		N_2-O_1-C_5	99.1

<center>dihedral angles (degrees)</center>

O_1-N_2-C_3-C_4	0.0		O_1-N_2-C_3-C_4	53.0
N_2-C_3-C_4-C_5	0.0		N_2-C_3-C_4-C_5	28.8
C_3-C_4-C_5-O_1	0.0		C_3-C_4-C_5-O_1	-2.7
N_2-O_1-C_5-C_4	0.0		N_2-O_1-C_5-C_4	-21.7
C_3-N_2-O_1-C_5	0.0		C_3-N_2-O_1-C_5	-53.5

oxygen (as in transition structures **A** and **B**), but a carbon for azomethine ylide (**C**) or a nitrogen for diazomethane and nitrilimine transition structures (**D**, **E**). Transition structures **C** - **E** were first located with semiempirical methods (PM3),[10,11] than optimized at the RHF/3-21G level[4] starting from the semiempirical geometry. All semiempirical calculations were performed using the MOPAC 5.0 package;[10b] *ab initio* calculations were run using the program GAMESS.[13] RHF/3-21G transition structures for azomethine ylide (**C**), diazomethane (**D**) and nitrilimine (**E**) reactions with ethylene, together with significant geometrical data, are reported in Figure 3. A full vibrational analysis was performed on all transition structures located with *ab initio* and semi empirical procedures. The one and only one imaginary frequency found in all cases corresponded to the symmetric stretch of the two forming bonds, thus confirming the nature of concerted transition structure for all these stationary points.[4,11] Significant geometrical data for PM3 transition structures **A**, **C**, **D** and **E** are reported in ref. 14.

Transition structures **A** , **C** and **D** possess C_s symmetry; in **A** and **D** the symmetry plane is the one containing the forming five-membered ring, while in **C** the symmetry plane is orthogonal to the one containing the two forming bonds and contains the nitrogen atom of the dipole moiety. T.S.s **B** and **E** have C_1 symmetry; in **E**, however, the forming five membered ring is almost planar as for the corresponding diazomethane plus ethylene reaction (T.S. **D**). Transition structure **C** is remarkably early, the forming bonds being 2.479 Å (Figure 3); the corresponding PM3 structure is slightly later along the reaction coordinate (forming bond length = 2.243 Å).[14]

In transition structures **B** and **C** two modes of approach, *endo* and *exo*, are possible when the alkene is unsymmetrically substituted. The *endo* approach is favored over the *exo* one,[1] at least for steric reasons:

Figure 3. RHF/3-21G transition structures C-E for azomethine ylide, diazomethane and nitrilimine cycloadditions to ethylene.


	C		D		E
		bond distances (Å)			
N_1-C_2	1.332	N_1-N_2	1.140	N_1-N_2	1.312
C_2-C_3	2.479	N_2-C_3	1.332	N_2-C_3	1.166
C_3-C_4	1.344	N_1-C_5	2.232	N_1-C_5	2.280
		C_3-C_4	2.226	C_3-C_4	2.363
		C_4-C_5	1.363	C_4-C_5	1.350
		bond angles (degrees)			
C_2-N_1-C_5	126.3	N_1-N_2-C_3	144.2	N_1-N_2-C_3	143.1
N_1-C_2-C_3	91.8	N_2-C_3-C_4	93.1	N_2-C_3-C_4	96.3
C_2-C_3-C_4	102.0	C_3-C_4-C_5	103.9	C_3-C_4-C_5	99.6
		N_2-N_1-C_5	97.0	N_2-N_1-C_5	94.7
		N_1-C_5-C_4	101.7	N_1-C_5-C_4	105.3
		dihedral angles (degrees)				
C_2-C_3-C_4-C_5	0.0	N_1-N_2-C_3-C_4	0.0	N_1-N_2-C_3-C_4	-11.8
C_2-N_1-C_5-C_4	58.5	N_2-C_3-C_4-C_5	0.0	N_2-C_3-C_4-C_5	1.5
N_1-C_2-C_3-C_4	23.2	N_1-C_5-C_4-C_3	0.0	N_1-C_5-C_4-C_3	-2.6
		N_2-N_1-C_5-C_4	0.0	N_2-N_1-C_5-C_4	-6.6
		C_3-N_2-N_1-C_5	0.0	C_3-N_2-N_1-C_5	13.2

this clearly appears from the inspection of the distances between the ethylene hydrogens and the dipole hydrogens, as shown in Figure 4. The effect is somehow enhanced by the non-parallel plane fashion of approach between the reactants, in analogy with Diels-Alder reactions.[15]

What about point charges for T.S.s **A - E**? Semiempirical and *ab initio* programs calculate by default the so-called Mulliken charges. Mulliken population analysis[16] has found widespread application in evaluating atomic point charges, because of its computational simplicity; however, this method has been recently criticized for its poor performance.[17] In particular, it was found that Mulliken charges are strongly sensitive to the size of the basis set employed in the *ab initio* calculation;[18] moreover, the charges so obtained are sometimes unreasonable when a high dipolar character is expected in the molecule under examination, as indeed can be the case for 1,3-dipolar transition structures.

Some other methods have been studied to overcome these problems; in particular, the use of the program CHELPG[19] provides atomic charges fitting the calculated electrostatic potential, that can be directly obtained at any point from the *ab initio* molecular wavefunction. This method seems to be reliable and independent of the molecule orientation (this was a major problem of the first version of the program, named CHELP).[19] Indeed, the differences between point charges calculated with the two methods are noticeable

Figure 4. A comparison between RHF/3-21G transition structures **B** and **C**.

B   C
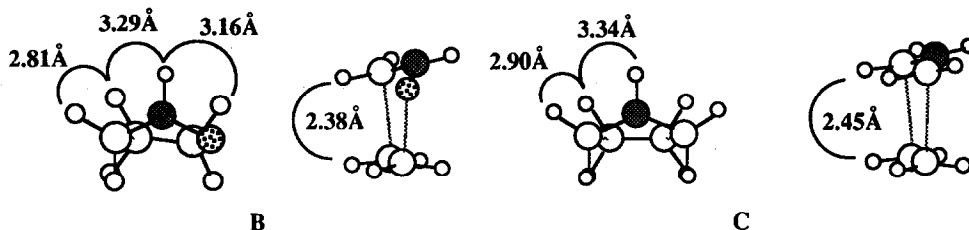
(see Figure 5). The atomic charges are shown only for the heavy atoms on the dipole moieties (O, N, C). An interesting feature, however, is revealed by the analysis of all the atomic charges, both on the heavy atoms and the hydrogens: there is almost no charge transfer from the 1,3-dipoles to the ethylene. In each of the transition structures, at all levels of theory, the sum of all the atomic charges for each reactant amounts almost to zero.

Either considering Mulliken or CHELPG charges, experimental data can indeed find a rationale. Both oxygenated 1,3-dipole moieties (T.S.s **A** and **B**) have a strong negative charge on the incoming oxygen; this charge is more negative in the T.S. for nitrone cycloaddition **B**; thus nitrones would be more *anti* selective than nitrile oxides. The difference between the two dipoles is enhanced by using the CHELPG method, that seems to give a better agreement with the bulk of experimental data (cf Scheme 1).[1,3a-b,6,7] For transition structure **C** the situation is less straightforward. CHELPG charges for azomethine ylide cycloadditions would suggest a diastereoselectivity intermediate between those obtained in nitrone and nitrile oxide reactions (cf T.S.s **A** and **B**). From Mulliken charges, however, a lower selectivity is expected, as indeed is experimentally found (cf Scheme 1).[1,5] Thus, Mulliken charges seem to be more reliable in this case while less reliable for nitrile oxide and nitrone reactions!

Figure 5. Mulliken and CHELPG charges of RHF/3-21G transition structures A - E.

[CHELPG charges]
(Mulliken charges)

A   B

C   D   E
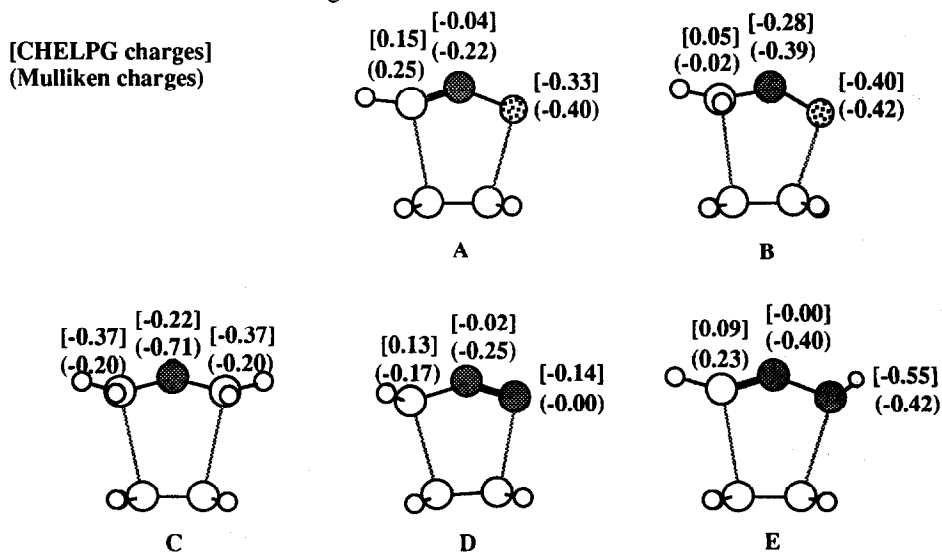
However, some more factors must be taken into account. First of all, in Scheme 1 we compared three different 1,3-dipole cycloadditions featuring the same chiral alkene to emphasize that the nature of the stereocenter on the dipolarophile really plays the major role in determining the stereochemical outcome of the reaction. To the best of our knowledge, the alkene shown in Scheme 1 is the only one that has been reacted with all these three different 1,3-dipoles; thus this is the only case for which a direct comparison is possible between nitrile oxide, nitrone and azomethine ylide reactivities,[1] while nitrile oxide and nitrone reactions can be directly compared in several other cases.[1,3a-b,6,7] This means that the major *anti* selectivity of nitrones compared to nitrile oxides is well documented, while the same cannot be said for the nitrile oxide *vs.* azomethine ylide reactions.[1]

Moreover, steric factors are not accounted for in the calculated T.S.s for the cycloadditions to ethylene, while experimental results derive obviously from a balance of both steric and electronic effects. Steric requirements of the substituents on the alkene moiety in T.S. **C** can strongly affect the diastereoselectivity in azomethine ylide reactions: the reaction with the (E)-alkene shown in Scheme 1 is completely *endo* selective, and this forces the alkoxy-bearing substituent in the crowded *exo* region (Figure 4). The steric requirements of the allylic stereocenter may be affected by the unfavorable interaction with the two *inside* hydrogens on the dipole, concurring in the tuning of the *anti / syn* ratio. Another weakness of the direct comparison between T. S. **C** and the experimental data reported in Scheme 1 is the extreme simplicity of the azomethine ylide moiety considered in the calculations when compared to the real 1,3-dipole derived from glycine: the substituents on the azomethine ylide may alter the charge distribution in the transition structure. We are currently investigating computationally both these two hypotheses.

From the point charges reported in Figure 5, by considering Mulliken and CHELPG results, it can be anticipated that diazomethane cycloadditions on chiral allyl ethers should be almost stereorandom, since T.S. **D** is basically not charged at the terminal nitrogen of the 1,3-dipole (Mulliken charges), or bears a low negative charge in that position (CHELPG charges). Nitrilimine cycloadditions, on the other hand, should allow a high degree of *anti* stereoselection since in T.S. **E** the terminal nitrogen is strongly negatively charged. Experimental evaluation of diastereoselectivity in the cycloadditions of these two 1,3-dipoles is currently in progress in our laboratories.

Computational procedures.

PM3 hamiltonian was used as implemented in MOPAC 5.0;[10] transition structures were located through a multistep procedure, first optimizing all variables with the exception of the two forming bonds, then optimizing all variables with the option NLLSQ and finally refining the structure with the option PRECISE. A full vibrational analysis was performed (FORCE): the results were analyzed also with the aid of the program DRAW 2.0.[20] As starting geometries the known *ab initio* transition structures were utilized for T.S.s **A**[8] and **B**[2a] (in the latter case without any success, at least using PM3 hamiltonian).[11] Transition structure **C** was located by modifying *ab initio* T.S.s structures **A** and **B**. Transition structures **D** and **E** were located starting from Sustmann's semi empirical T.S. for diazomethane plus ethyl vinyl ether cycloaddition.[10c]

Ab initio transition structures **C**, **D** and **E** were located using the program GAMESS,[13] starting from the corresponding PM3 T.S.s, while T.S. **B** was relocated at the RHF/3-21G level starting from the MCSCF/4-31G transition structure.[2a] First the hessian was computed at the RHF/3-21G level, then a full

optimization at this level provided the desired transition structures. The hessian was analytically calculated each 5 steps, thus providing a good evaluation of the PES curvature. Finally, a full vibrational analysis was performed to ensure the nature of concerted transition structures for these stationary points.[4]

Mulliken charges were obtained from the standard outputs both from MOPAC[10b] and GAMESS[13] packages. CHELPG[19] charges were obtained from a GAUSSIAN 88[21] checkpoint file, giving no limit for the maximum number of points in the grid and no scaling factor for the van der Waals radii. The distance between the points in the grid was set to 0.5 Å, and the maximum distance of a point to the closest atom to 2.8 Å.

MOPAC and GAMESS calculations were run on a Digital Vaxstation 3100. GAUSSIAN 88 single point and CHELPG calculations were performed on a Convex C 3820 at the Centro Interuniversitario Lombardo Elaborazione Automatica (CILEA). All geometrical data for transition structures **A** - **E** are obtainable from the authors.

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11. We were unable to locate any transition structure for the nitrile oxide reaction with ethylene using the AM1 hamiltonian,[12] while we were successful using PM3.[10a] On the other hand, the corresponding transition structure for nitrone reaction was not a stationary point on the PM3 potential energy surface.[4] An AM1 study on nitrone cycloaddition reactions, however, has recently appeared in the literature: Pascal, Y. L.; Chanet-Ray, J.; Vessiere, R.; Zeronal, A. *Tetrahedron* **1992**, *48*, 7197.

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14. significant PM3 geometrical data for T.S.s **A**, **C**, **D** and **E** (for the numbering system, see Figures 2 and 3):
    A: bond distances (Å): O_1-N_2, 1.226; N_2-C_3, 1.228; C_3-C_4, 2.062; C_4-C_5, 1.372; O_1-C_5, 2.145; bond angles (degrees): O_1-N_2-C_3, 136.7; N_2-C_3-C_4, 100.4; C_3-C_4-C_5, 103.7; O_1-C_5-C_4, 101.2; N_2-O_1-C_5, 98.0; dihedral angles (degrees): O_1-N_2-C_3-C_4, 0.0; N_2-C_3-C_4-C_5, 0.0; C_3-C_4-C_5-O_1, 0.0; N_2-O_1-C_5-C_4, 0.0; C_3-N_2-O_1-C_5, 0.0.
    C: bond distances (Å): N_1-C_2, 1.356; C_2-C_3, 2.243; C_3-C_4, 1.362; bond angles (degrees): C_2-N_1-C_5, 120.7; N_1-C_2-C_3, 93.6; C_2-C_3-C_4, 102.8; dihedral angles (degrees): C_2-C_3-C_4-C_5, 0.0; C_2-N_1-C_5-C_4, 55.9; N_1-C_2-C_3-C_4, 24.8.
    D: bond distances (Å): N_1-N_2, 1.152; N_2-C_3, 1.359; N_1-C_5, 2.224; C_3-C_4, 2.187; C_4-C_5, 1.361; bond angles (degrees): N_1-N_2-C_3, 140.3; N_2-C_3-C_4, 95.2; C_3-C_4-C_5, 104.4; N_2-N_1-C_5, 98.2; N_1-C_5-C_4, 101.9; dihedral angles (degrees): N_1-N_2-C_3-C_4, 0.0; N_2-C_3-C_4-C_5, 0.0; N_1-C_5-C_4-C_3, 0.0; N_2-N_1-C_5-C_4, 0.0; C_3-N_2-N_1-C_5, 0.0.
    E: bond distances (Å): N_1-N_2, 1.282; N_2-C_3, 1.212; N_1-C_5, 2.182; C_3-C_4, 2.237; C_4-C_5, 1.356; bond angles (degrees): N_1-N_2-C_3, 138.5; N_2-C_3-C_4, 96.8; C_3-C_4-C_5, 103.4; N_2-N_1-C_5, 99.0; N_1-C_5-C_4, 102.1; dihedral angles (degrees): N_1-N_2-C_3-C_4, -6.7; N_2-C_3-C_4-C_5, 1.8; N_1-C_5-C_4-C_3, 0.7; N_2-N_1-C_5-C_4, -3.2; C_3-N_2-N_1-C_5, 7.2.

15. This means that the 1,3-dipole and the ethylene are planar in the transition structure as in their ground states, but that the two planes of the reactants are not parallel to each other (cf data in Figures 2 and 3 for T.S.s **B** and **C** respectively). This is in analogy with the computational results for the Diels-Alder and the etero Diels-Alder reactions:
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17. For a discussion on methods to determine point charges, see for instance: Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. and references therein. See also ref. 19.

18. About the dependence of Mulliken population analysis upon the basis set utilized in the calculations, we must remark that for T.S.s **A**, **C**, **D** and **E**, when located at PM3 level[12], the Mulliken charges were completely different from those at RHF/3-21G level, despite the strong similarity in the geometries. The major difference was for the charge on the central atom in the dipole moiety. PM3 Mulliken charges: **A**: O_1, -0.42; N_2, 0.56; C_3, -0.40. **C**: N_1, 0.58; C_2, -0.49. **D**: N_1, -0.25; N_2, 0.39; C_3, -0.32. **E**: N_1, -0.36; N_2, 0.40; C_3, -0.34. We were not able to locate any T.S. corresponding to **B** on the PM3 potential energy surface.[11]

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