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Concerted vs Stepwise Mechanism in 1,3-Dipolar Cycloaddition of Nitrone to Ethene, Cyclobutadiene, and Benzocyclobutadiene. A Computational Study

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The problem of competition between concerted and stepwise diradical mechanisms in 1,3-dipolar cycloadditions was addressed by studying the reaction between nitrone and ethene with DFT (R(U)B3LYP/6-31G*) and post HF methods. According to calculations this reaction should take place via the concerted cycloaddition path. The stepwise process is a viable but not competitive alternative. The R(U)B3LYP/6-31G* study was extended to the reaction of the same 1,3-dipole with cyclobutadiene and benzocyclobutadiene. The very reactive antiaromatic cyclobutadiene has an electronic structure that is particularly disposed to promote stepwise diradical pathways. Calculations suggest that its reaction with nitrone represents a borderline case in which the stepwise process can compete with the concerted one on similar footing. Attenuation of the antiaromatic character of the dipolarophile, i.e., on passing from cyclobutadiene to benzocyclobutadiene, causes the concerted 1,3-dipolar cycloaddition to become once again prevalent over the two-step path. Thus, our results suggest that, in 1,3-dipolar cycloadditions that involve normal dipolarophiles, the concerted path (Huisgen's mechanism) should clearly overwhelm its stepwise diradical (Firestone's mechanism) counterpart.

Introduction

The cycloaddition of nitrones with olefins is one of the most studied reactions among all the 1,3-dipolar cycloadditions,[1] and the resulting isoxazolidines have been increasingly used as starting compounds for building more complex molecules.[2]

In the context of our studies on the mechanism of this reaction[3,4] we decided to start a computational investigation on the reaction between the parent nitrone and the highly reactive cyclobutadiene[5,6] with the aim of assessing whether a concerted process is preferred over a stepwise diradical mechanism.

The proposal, by Firestone[7] in the 1970s, of a diradical stepwise mechanism for 1,3-dipolar cycloadditions triggered a hot controversy between this author and Huisgen, who strongly and convincingly supported the concerted mechanism.[8] The latter mechanism eventually emerged as the only mechanism that satisfactorily explains all the experimental observations (such as isotope effects, activation parameters, solvent effects, selectivity, reactivity sequences, etc.), in particular the strict stereospecificity that as a rule characterizes these reactions.[9−11]

There is now a general consensus that 1,3-dipolar cycloadditions follow, as a rule, a concerted path.[9−11] The most documented and convincing exceptions have been discovered by Huisgen.[12a] However, these examples are confined to the realm of stepwise via dipolar intermediate mechanisms[12a−c] and not to that of stepwise via diradical intermediate processes. While several examples of stepwise diradical processes are known in the field of Diels−Alder reactions,[13] no convincing experimental examples of this mechanism have been reported so far for 1,3-dipolar cycloadditions.[12d]

On the computational side several ab initio MO calculations have been carried out on 1,3-dipolar cycloaddi-

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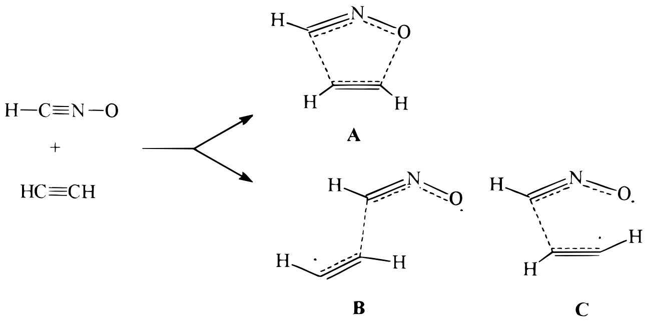
Scheme 1



tions,[14−29] but only two of them have specifically addressed the problem of the possible competition between the Firestone's and the Huisgen's mechanisms.[17,18]

First Hiberty et al.[17] compared the two mechanisms for the reaction of formonitrile oxide with acetylene (Scheme 1) by using restricted and unrestricted HF methods with 4-31G basis set and final energy estimates with a multireference iterative perturbational technique. They concluded that the extended (anti) diradical transition structure **B** lies 3.6 kcal/mol below the concerted structure **A** (Scheme 1).

Robb et al.[18] contended that the method used by Hiberty et al.[17] artificially favored the diradical path and reinvestigated this reaction by MCSCF methods that, in their opinion, should allow a balanced comparison between the two mechanisms. With CASSCF(4,4) (using the 4-31G basis set) they found that the concerted TS **A** is preferred over the anti diradicaloid TS **B** by 4.7 kcal/mol, while the energy gap in favor of the concerted path is larger (i.e., 8.4 kcal/mol) in the reaction of fulminic acid with ethylene.

Recently, in a B3LYP study of the 1,3-dipolar cycloaddition involved in the dimerization of methanethial *S*-oxide, Arnaud et al.[28] located a very asynchronous "concerted" TS (with two bonds partially formed), which is connected to both the cyclic final product (according to RB3LYP IRC) as well as to a syn diradical intermediate (according to UB3LYP IRC). The two paths involve the same TS. This TS is definitely more stable than the diradicaloid TS leading to the anti diradical.

Thus, computational results reported so far indicate that the concerted process (i.e, **A**) should prevail over the stepwise mechanism via an anti diradicaloid TS (i.e., **B**). Distinction between the concerted and the stepwise mechanism, via a syn diradicaloid TS (i.e., **C**), seems to be more elusive.

To support viability of a stepwise process, we remind that 1,3-dipoles, in particular those of the allyl type, have some diradical character.[30−33] For example, Yamaguchi and Houk classified nitrones as 1,3-dipoles with very weak diradical character (2%),[31] while a value as high as 44% was evaluated by Hiberty.[33] However, it has also been stressed[34−36] that even a very high diradical character of the 1,3-dipole does not necessarily result in a stepwise process. In the case of nitrone cycloaddition more than the diradical character of the starting nitrone, it is worth emphasizing the high stability of the nitroxide moiety[37] (present in the diradical intermediates and incipient in TSs leading to them) as a possible factor that might favor the stepwise process.

Cyclobutadiene exhibits not only the well-known high antiaromatic character (which is responsible for its high reactivity) but also a peculiar reactive biradical nature.[38] Moreover, in the reaction of nitrone with cyclobutadiene, there should be no sizable "energy of concert", which usually makes the concerted path favored over the stepwise diradical mechanism.[39a] Cyclobutadiene cannot benefit from maintenance of a closed-shell structure and the potential energy of a diradical intermediate should lie well below that of reactants (nitrone + cyclobutadiene).

The latter observations should make it clear that the reaction of nitrone with cyclobutadiene lends itself as a reaction in which the stepwise process has a real possibility to win competition with the concerted process.

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Here we report the computational study of this reaction and, for sake of comparison, of the cycloaddition of nitrone with ethene and benzocyclobutadiene, respectively.

Computational Methods

Recent explorations of quantum chemical procedures, with the aim of assessing their reliability in describing potential surfaces of pericyclic reaction[39−41] and competition between concerted and stepwise processes (e.g., in Diels−Alder reactions),[39a,40] allowed the authors to conclude that the B3LYP/6-31G* method is adequate for this task.

To validate this conclusion also in the field of 1,3-dipolar cycloadditions we have reinvestigated the prototype reaction of nitrone with ethene not only with the RB3LYP/6-31G* (for closed-shell species) and UB3LYP/6-31G* (for open-shell species) methods but also, for purpose of comparison, with CAS(6,5)/6-31G* and QCISD/6-31G* methods (full geometry optimization). The geometries obtained by all these approaches were used for single point evaluation of transition structure energies with the QCISD(T)/6-31G* (with RHF and UHF reference) and CCSD(T)/6-31G* (coupled cluster with single and double excitations and a perturbative estimate of triple excitations) methods.[42]

A well-known problem for UB3LYP/6-31G* calculations is that wave functions for the optimized singlet open-shell species can exhibit some degree of spin contamination as a result of the use of nonexact functionals. In the present study, the $\langle S^2\rangle$ values range from 0.3 to 1.1 for diradicaloid TSs while they are ~1.0 for diradical intermediates. Thus, the corresponding wave functions are not pure singlet ($\langle S^2\rangle = 0$) but contain a triplet ($\langle S^2\rangle = 2$) component[43] [i.e., $\Psi_{(UB)} = c_S\,{}^1\Phi + c_T\,{}^3\Phi$]. The problem of spin contamination removal from UB3LYP wave functions has not satisfactorily been solved yet, and in particular it is not clear to what extent this procedure can improve the quality of the DFT potential energy surface.[44] We have used the approximate spin projection procedure proposed by Yamaguchi et al.:[45]

$$^{1}E_{(SC)} = {}^{1}E_{(UB)} + f_{SC}\,[{}^{1}E_{(UB)} - {}^{3}E_{(UB)}]$$

$$f_{SC} = c_T^{\,2}/(1 - c_S^{\,2}) \approx {}^{1}\langle S^2\rangle/({}^{3}\langle S^2\rangle - {}^{1}\langle S^2\rangle)$$

However, Houk et al.[39a] have demonstrated, on the basis of a H_2 dissociation study, that this spin-correction procedure leads to overestimation of the stability of pure singlet states and suggested that the true energy of these states actually lies between the spin-contaminated and spin-projected singlet energies and closer to the former. Moreover, Schlegel showed that B3LYP potential energy curves have the correct shape, when compared to the full CI ones, for bond dissociation and concluded that one should not use spin projected DFT calculations.[44a] Finally, also Cremer pointed out that “contrary to an orbital-based method a density-based method is less sensitive to the triplet contamination, which indicated that it is not justified to use in this case an orbital-based method such as spin-projection to get a noncontaminated state”.[44b]

All calculations were performed with the GAUSSIAN 98 suite of programs.[46] Geometries of reactants, oriented complex, intermediates, transition structures and products (Scheme 2, Figures 1 and 2) were fully optimized at the RB3LYP/6-31G* and UB3LYP/6-31G* level for closed- and open-shell species, respectively.

Critical points have been characterized by diagonalizing the Hessian matrices calculated for the optimized structures. Transition structures have only one negative eigenvalue (first-order saddle point) with the corresponding eigenvector involving the formation of two bonds in the concerted cycloaddition and only one bond (either C−C or C−O bond) in the stepwise reaction. The stability of all the wave functions was positively tested.

Vibrational frequencies in the harmonic approximation were calculated for all B3LYP/6-31G* optimized structures and used, unscaled, to compute both the zero point energies and activation parameters (Tables 1, 3, 4, 6, and 7). For the prototype system (nitrone + ethene), also CASSCF(6,5)/6-31G* vibrational frequencies were computed on CASSCF(6,5)/6-31G* optimized structures (Tables 2 and 4).

Solvent effects on Gibbs free energies were evaluated with the polarizable continuum model[47a] (in the CPCM version,[47b] which takes into account not only electrostatic but also cavitation, dispersion and repulsion effects) for benzene and dichloromethane solutions by single point calculations with unrelaxed gas-phase geometries.

Results and Discussion

Prototype System: Reaction of Nitrone with Ethene. Recent studies (by B3LYP/6-31G*, B3LYP/6-31+G* and MP2/6-31G* methods)[23,24] on the reaction of nitrone with ethene has been focused only on the concerted process. According to Cossìo et al.[24] the TS of this reaction shows a strong aromatic character.

Robb et al.[18] addressed, several years ago, the concerted stepwise problem in nitrone + ethene reaction by CASSCF(4,4) calculations (with the 4-31G basis set). They took into account only four electrons of two π orbitals of the reacting system and neglected the nitrone

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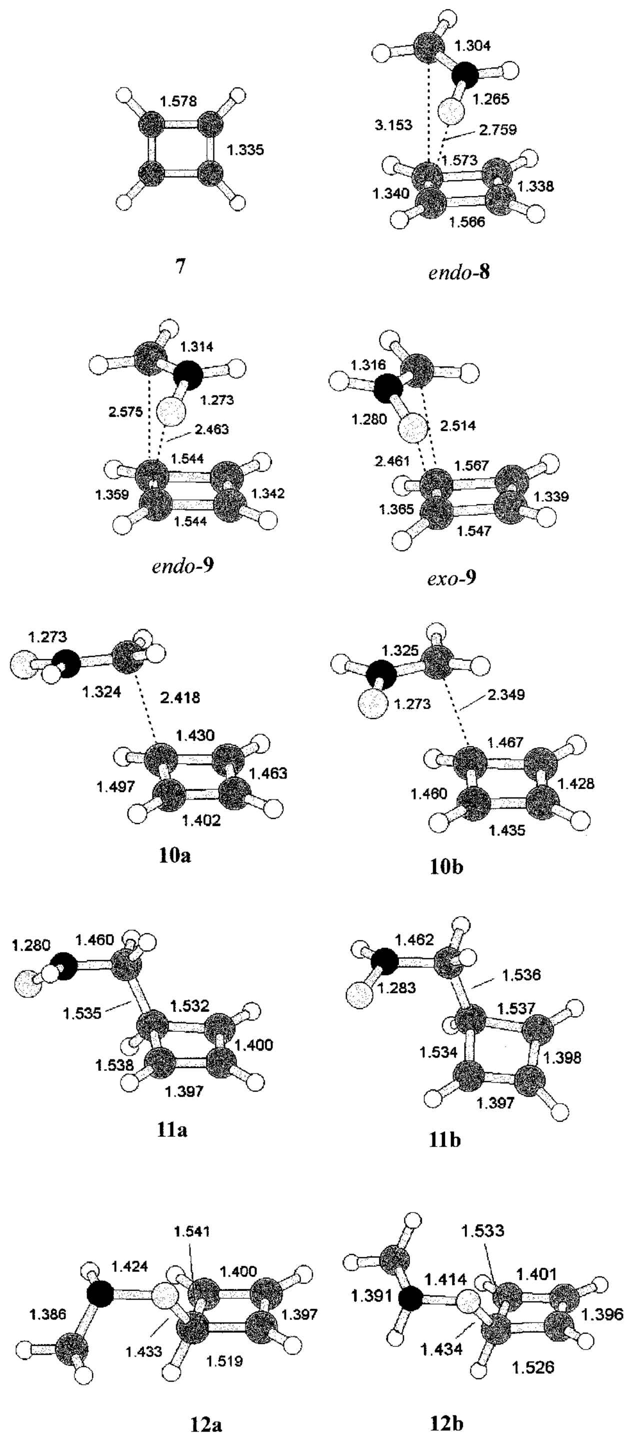
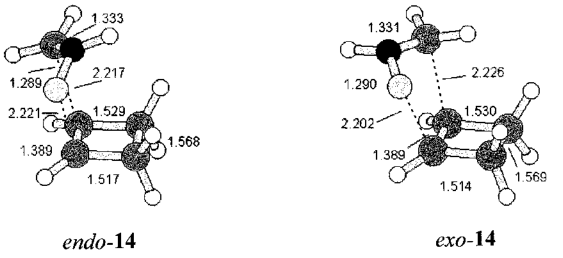


7 *endo*-**8** *endo*-**9** *exo*-**9** **10a** **10b** **11a** **11b** **12a** **12b**

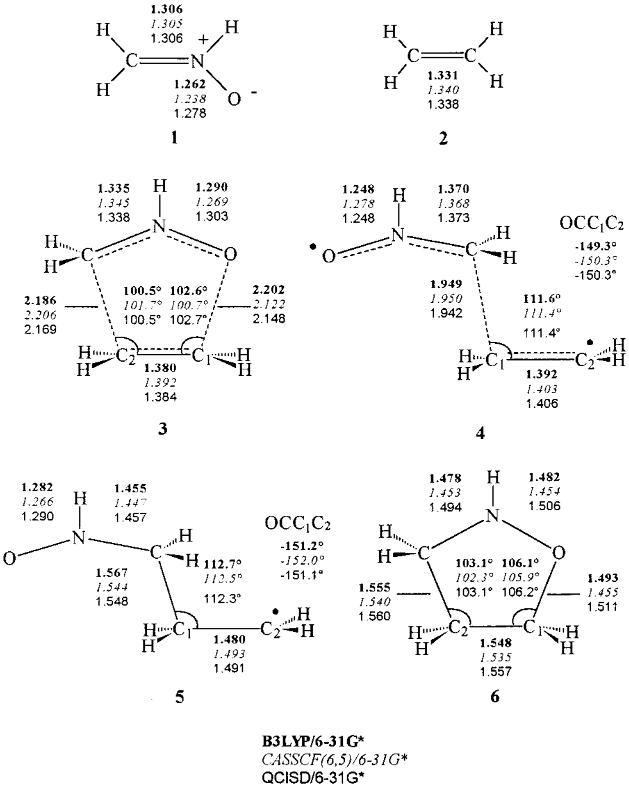
Figure 1. Optimized (B3LYP/6-31G*) cyclobutadiene (**7**) and nitrone + cyclobutadiene transition structures (**8**−**12**) (bond lengths in Å).



endo-**14** *exo*-**14**

Figure 2. Optimized (B3LYP/6-31G*) transition structures (**14**) (bond lengths in Å) for cycloaddition of nitrone to cyclobutene.

Scheme 2



lower energy π orbital, which was assumed to remain doubly occupied. At that time CASSCF calculations were considered to treat both mechanisms on the same footing, but later on it became progressively evident that these calculations overestimate the stability of diradical (open-shell) species relative to that of closed-shell species. Notwithstanding this bias in favor of the stepwise process, the concerted TS was found to lie below the diradicaloid anti TS by 5.1 kcal/mol.

We also carried out MCSCF calculations on the two competing paths, but with a more extended basis set (6-31G*) and by including also the nitrone lower π orbital [i.e., with CASSCF(6,5), to take into account all the electrons directly involved in the reaction]. Likewise, the two mechanisms (with full geometry optimization of all structures) were studied with both the R(U)QCISD/6-31G* and R(U)B3LYP/6-31G* theories.

It is gratifying that, as shown in Scheme 2, the R(U)B3LYP/6-31G* geometries are remarkably close to those obtained with the more time-consuming R(U)QCISD/6-31G* method. In particular, B3LYP TSs exhibit forming bonds that are only slightly longer than the corresponding bonds in the QCISD TSs. Also CASSCF structures do not show strong differences with respect to the other two methods, that is, geometries do not heavily depend on the calculation level. The latter observation made us confident on the reliability and accuracy of the energies obtained with high level post HF methods (such as QCISD(T)/6-31G* and CCSD(T)/6-31G* methods) by single point calculations on the mentioned (B3LYP, QCISD and CASSCF) geometries. The refined energies obtained in this way (Table 3) allow us to evaluate the performance of the R(U)B3LYP/6-31G* and CASSCF(6,5)/6-31G* methods on the problem under study.

Table 1. B3LYP/6-31G* and QCISD/6-31G* Energies, B3LYP/6-31G* Entropies, and $\langle S^2 \rangle$ Values for Stationary Points for Nitrone plus Ethene Cycloaddition

molecule	E_{B3LYP} (au)	ZPE_{B3LYP} (au)	S_{B3LYP} (eu)	$\langle S^2 \rangle_{B3LYP}$	E_{QCISD} (au)
1	−169.793 491	0.045 367	59.71	0	−169.311 428
2	−78.587 457	0.051 219	55.08	0	−78.313 352
3	−248.362 733 2	0.100 216	72.21	0	−247.598 695
4	−248.347 997 3	0.098 040	76.56	0.468	−247.579 634
5	−248.362 401 1	0.098 819	78.08	0.944	−247.606 736
6	−248.356 332 8	0.105 115	71.45	0	−247.345 291

Table 2. CASSCF(6,5)/6-31G* Energies and Entropies for Stationary Points for Nitrone plus Ethene Cycloaddition

molecule	E_{CAS} (au)	ZPE_{CAS} (au)	S_{CAS} (eu)
1 + **2**	−246.904553[a]	0.101361[b]	114.8[c]
3	−246.8659789	0.106306	71.74
4	−246.8572142	0.104388	76.11
5	−246.87161572	0.105040	79.97
6	−246.9739083	0.112809	70.40

[a] Nitrone and ethene are 10 Å apart. [b] Sum of individual ZPEs. [c] Sum of individual entropies.

As for the absolute electronic activation energies (Table 3, values in square brackets) the concerted reaction barrier (i.e., the energy of **3** relative to reactants) is only slightly underestimated (by roughly 2 kcal/mol) by the RB3LYP calculations. This finding is in agreement with previous observations that emphasized the good performance of the B3LYP/6-31G* method but with tendency to underestimate barrier heights.[48,49] Likewise, the UB3LYP method also underestimates (by ~3 kcal/mol) the barrier for the diradicaloid TS **4**, with respect to those evaluated with higher level methods. Things become much worse after spin correction, which gives rise to a large reduction in energy barrier (by 5.4 kcal/mol) for **4**.

On the other hand, from inspection of Table 3, it is quite clear that the CASSCF method strongly overestimates absolute electronic activation energy for TS **3** (by 11 kcal/mol) and also, to a reduced extent, that for **4** (by 6 kcal/mol).

But how do B3LYP and CASSCF methods perform in evaluating competition of the concerted with the stepwise path?

The barrier height of **4** relative to that of **3**, predicted by B3LYP methods without spin-correction, compares well with those predicted by QCISD(T) and CCSD(T). For example, the R(U)B3LYP result (9.3 kcal/mol) is sandwiched by those of CCSD(T)/6-31G*//B3LYP/6-31G* (9.6 kcal/mol) and QCISD(T)/6-31G*//QCISD/6-31G* (8.9 kcal/mol) (Table 3). On the basis of these methods the concerted mechanism via **3** should largely overcome the stepwise process via **4**, and this conclusion also holds if Gibbs free energy (Table 4) is considered. In previous studies authors took into account only electronic energy, completely neglecting contribution of molecular motions. Actually, both ZPE (by ~1.4 kcal/mol) and entropy (by ~4 eu.) favor the diradical over the concerted path, and the Gibbs free energy gap between the two paths is smaller than the corresponding potential energy difference (7.0 vs 9.3 kcal/mol). Moreover, also solvent effects, evaluated by the CPCM method, further slightly reduce this gap (by 1.3 kcal/mol in dichloromethane and by 0.2 in benzene).[50] The latter observations warn one to be careful in comparing concerted vs stepwise mechanisms only on the basis of relative electronic energies, as the contribution of molecular motions and solvent effects is far from being negligible and in borderline cases can switch the mechanism from concerted to stepwise.

The small energy difference between the intermediate diradical **5** and TS **3**, predicted by B3LYP calculations (0.2 kcal/mol), is comparable to that obtained with all post-HF methods (−0.4−1.1 kcal/mol) but UQCISD(T)//CAS (−3.1 kcal/mol). Anyway, all calculations indicate that diradical **5** is much less stable than the starting reactants.

Predictions by the CASSCF(6,5))/6-31G* method clearly demonstrate the tendency by this theory to favor the diradicaloid or diradical open-shell systems over closed-shell structures. In fact, the potential energy preference of TS **3** over TS **4** decreases to 5.5 kcal/mol (from ~10 kcal/mol obtained with other methods), and now **5** is more stable than **3** by 3 kcal/mol (in agreement with the UQCISD(T)//CAS value). Dominance of concerted **3** over diradicaloid **4** is maintained also, even if attenuated, at the free energy level (by 3.4 kcal/mol). Thus, it is gratifying that our results, with the use of improved CASSCF calculations and with inclusion of molecular motions contributions, confirm the previous conclusion by Robb et al. on the prevalence of **3** over **4**.

Introduction of spin correction into UB3LYP data completely broke down the accord of the B3LYP with other methods and strongly reduces the prevalence of **3** over **4**. *If we trust energetics obtained with higher level methods we can state that Yamaguchi procedure significantly errs in the case of diradicaloid TSs for nitrone cycloaddition (in accord with criticisms mentioned above)*[44] *and that uncorrected UB3LYP values have to be used to adequately describe the stepwise process.*[51]

Moreover, it is important to stress that diradicaloid **4**, even after the 5.4 kcal/mol stabilization from spin-correction, lies above concerted **3** (both at the potential and the free energy levels, Tables 3 and 4) and that introduction of solvent effects[50] does not reverse this stability order.

It is definitely concluded that, according to calculations, the Huisgen's concerted mechanism clearly overcomes the stepwise Firestone's mechanism in the nitrone + ethene reaction.

Moreover, we feel that, despite the problem of spin correction, R(U)B3LYP methods at present provide the most reasonable tool, as far as both reliability and computational time are concerned, to computationally investigate the problem of concertedness in the 1,3-dipolar cycloadditions.

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(48) Bach, R. D.; Glukhovtsev, M. N.; Gonzales, C.; Marquez, M.; Estevez, C. M.; Baboul, A. G.; Schlegel, H. B. *J. Phys. Chem. A* **1997**, *101*, 6092 and references therein.

(49) Görling, A.; Trickey, S. B.; Gisdakis, P.; Rösch N. In *Topics in Organometallic Chemistry*; Brown, J., Hofmann, P., Eds.; Springer: Heidelberg, 1999; Vol. 4, pp 109−163.

(50) The solvent effect on the energy of the transition structures, evaluated by the CPCM method at B3LYP/6-31G* level, in dichloromethane and benzene, respectively, is **3** −4.3 and −1.1 kcal/mol; **4** −5.6 and −1.3 kcal/mol; **5** −5.7 and −1.5 kcal/mol; *endo*-**9** −4.4 and −0.7 kcal/mol; *exo*-**9** −6.2 and −0.1 kcal/mol; **10a** −5.8 and −0.9 kcal/mol; **10b** −5.8 and −1.0 kcal/mol; *endo*-**16** −4.8 and −0.4 kcal/mol, *exo*-**16** −6.2 and −1.0 kcal/mol; **17a** −6.5 and −0.9 kcal/mol; **17b** −-5.9 and −0.8 kcal/mol; **17c** −6.6 and −1.1 kcal/mol.

(51) However, one could argue that B3LYP calculations actually strongly underestimate the energy difference between **4** and **3** and that this error is compensated by increase in energy of **4** induced by spin contamination. Spin contamination removal causes this drawback to emerge.

Table 3. Relative Electronic Energies (kcal/mol) for the Diradical Transition Structure 4 and the Diradical Intermediate 5 with Respect to Concerted Transition Structure 3 and (square brackets) with Respect to Reactants[a,b]

	method							
molecule	B3LYP	CAS(6,5)	QCISD(T) //CAS	UQCISD(T) //CAS	QCISD(T) //B3LYP	QCISD(T) //QCISD	CCSD(T) //CAS	CCSD(T) //B3LYP
3	0.0[11.4]	0.0[24.2]	0.0[13.4]	0.0[13.4]	0.0[13.2]	0.0[13.5]	0.0[13.3]	0.0[13.1]
4	9.3[20.7] (3.8)[a]	5.5[29.7]	10.5[23.9]	11.5[24.9]	9.7[22.9]	8.9[22.3]	10.4[23.7]	9.6[22.7]
5	0.2[11.6] (−1.9)[a]	−3.5[20.7]	0.6[14.0]	−3.0[10.3]	1.1[14.3]		−0.4[13.0]	−0.2[12.8]

[a] In parentheses are reported spin-corrected relative energies (kcal/mol). [b] B3LYP stands for R(U)B3LYP/6-31G*. The 6-31G* basis set was used for all calculations.

Table 4. Relative Gibbs Free Energies[a] (kcal/mol) for the Diradical Transition Structure 4 and the Diradical Intermediate 5 with Respect to Concerted Transition Structure 3

molecule	B3LYP	CAS(6,5)
3	0.0[22.0][b]	0.0[38.8][b]
4	7.0(1.6)[c]	3.4
5	−1.6(−3.8)[c]	−5.8

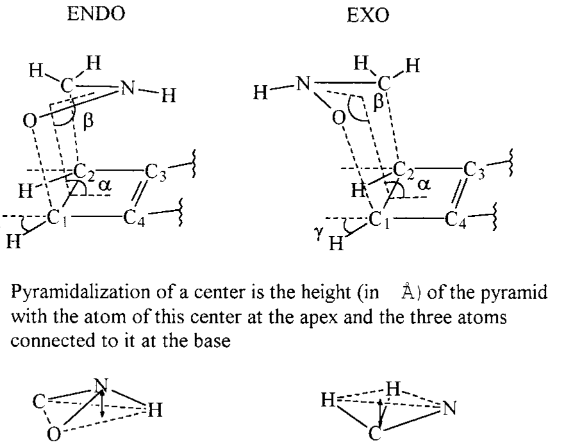
[a] Harmonic approximation assumed. [b] In square brackets are reported absolute activation free energies (kcal/mol) for **3**. [c] In parentheses are reported spin-corrected relative energies in kcal/mol.

Table 5. Dihedral and Plane Angles (deg) and Pyramidalization (Å) of Concerted Transition Structures 9 and 14[a]

	endo-**9**	*endo*-**14**	*exo*-**9**	*exo*-**14**
α	89.9	105.2	96.6	104.7
β	111.5	125.9	126.1	127.9
γ	12.5	24.6	19.8	25.3
C−N−O	124.0	119.3	123.7	119.9
N pyr[b]	0.098	0.188	0.099	0.176
C pyr[b]	0.096	0.193	0.121	0.196

[a] See Scheme 3. [b] pyr = pyramidalization.

Scheme 3



Pyramidalization of a center is the height (in Å) of the pyramid with the atom of this center at the apex and the three atoms connected to it at the base

Reaction of Nitrone with Cyclobutadiene. Geometries of Intermediates and Transition Structures.

Exploring the RB3LYP/6-31G* potential energy surface for the nitrone-cyclobutadiene reaction we located a minimum corresponding to the oriented complex *endo*-**8**[52] and two first-order saddle points corresponding to concerted TSs *endo*-**9** and *exo*-**9** (Figure 1).

Cyclobutadiene is a very reactive compound so that also its reaction with nitrone should be very fast and very exothermic. On the basis of the Hammond postulate one can anticipate that this reaction should exhibit significantly earlier TSs than those for reactions of related “normal” olefins (e.g., TSs *endo*-**14** and *exo*-**14** for cyclobutene, Figure 2). Indeed, this expectation is borne out by (i) longer incipient bond lengths (Figures 1 and 2), (ii) lower pyramidalization of the C and N nitrone centers and larger CNO angle (Table 5), and (iii) smaller out of plane distortion of the olefinic hydrogens [i.e., γ, Scheme 3 and Table 5] in TSs **9** than in the corresponding TSs **14**.

Noteworthy geometrical features of *endo*-**9** are the perpendicular orientation of the forming bonds with respect to the cyclobutadiene plane (i.e., $\alpha = 90°$, Scheme 3 and Table 5) as well as the almost parallel orientation of the heavy atom planes of the two reactants (dihedral angle = 22°). These features are unique for the cyclobutadiene reaction. In fact, in *endo*-**14** the incipient bonds are inclined outside ($\alpha = 105°$) and the nitrone plane tilting with respect to the cyclobutene plane (as a result of an upward shift of the nitrone nitrogen atom) is now more pronounced (dihedral angle = 42°).

The characteristic geometrical overlap between the reactant partners in *endo*-**9** is even more enhanced in the oriented complex *endo*-**8** [$\alpha = 85.3°$ (Table S1); dihedral angle between the reactant planes = 14.3°].

Then we explored the potential energy surface with the UB3LYP/6-31G* method and located four minima corresponding to anti diradical intermediates **11a**, **11b**, **12a** and **12b** (Figure 1). We were not able to locate diradical intermediates with a syn geometry (i.e., intermediates with a geometry very similar to that of adducts but with the C−O bond completely broken).

Structures **11a** and **11b** originate from a cyclobutadiene attack to the nitrone carbon with formation of the sole C−C bond and lie much lower in energy (by 30 kcal/mol, Table 6) than **12a** and **12b** deriving from attack at the nitrone oxygen with formation of the sole C−O bond. In all of these intermediates the radical center located on the former cyclobutadiene moiety is highly stabilized by conjugation, while the second unpaired electron is much more stabilized when it is located on the oxygen atom (as in **11a**,**b**) than when it is located on the carbon atom (as in **12a**,**b**). It is well-known that nitrones can act as a very efficient trap for radicals, which only attack the nitrone carbon with formation of the very stable nitroxide moiety.[37]

The energy gap between diradicals **11** and **12** is very high and it should certainly give rise to a large energy gap between the transition structures leading to them. Thus, we focused our study on the search of the sole TSs, i.e., **10a** and **10b**, leading to the former intermediates.

The two diradicaloid TSs **10a** and **10b** exhibit C−C bond lengths slightly shorter (by 0.15 Å) than those in the corresponding concerted TSs. These open-shell tran-

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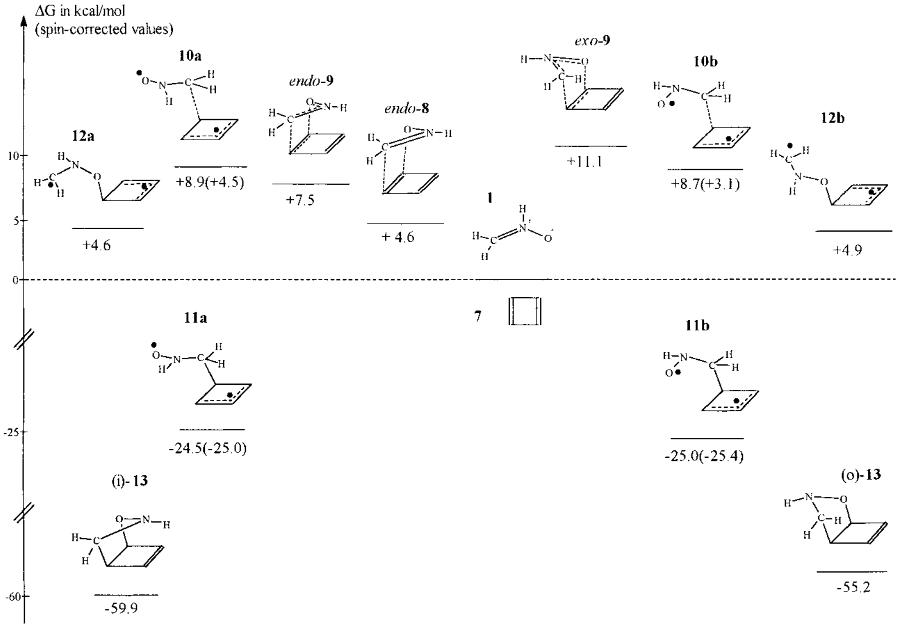
(52) An oriented complex was located by Sustmann et al.[23] on the potential energy surface of the reaction of nitrone and ethylene with the B3LYP, MP2 and HF methods (always by using a 6-31G* basis set). It is more stable than reactants by ~2.0 kcal/mol.

Scheme 4



sition structures present a very high spin separation, i.e., a strong diradical character that is almost has high as that of **11a**,**b**.

Wave functions of **10a**,**b** and **11a**,**b** are not pure singlet but are spin-contaminated by the higher lying triplet. The $\langle S^2 \rangle$ value for all these species is close to 1.0 (Table S2), indicating that we are in the presence of ~1:1 mixture of the two states.

The ring closure of diradical **11** (or **12**) to final isoxazolidines **13**[54] is certainly very fast, much faster than reversion to reactants, and consequently it is of no relevance for the concerted-stepwise problem.

Energetics. The free energy levels for all the stationary points located by us on the potential energy surface of nitrone-cyclobutadiene reaction are depicted in Scheme 4 with the separate reactants as reference. Other thermodynamic parameters for this reaction are reported in Table 6.

The oriented complex *endo*-**8**[52] is a minimum that lies 3.2 kcal/mol below reactants on the potential energy surface (the favor decreases to 1.4 kcal/mol if enthalpy is considered) while it is less stable (by 4.6 kcal/mol) than reactants at the free energy level, being disfavored by entropic factors.[53]

This complex can evolve to the final isoxazolidine passing through the concerted endo TS, i.e., *endo*-**9**, along what is the most favored of the two concerted pathways. Actually, the electronic activation energy and activation enthalpy for the latter TS are negative (−2.5 and −1.2 kcal/mol, respectively); however, it is a true first-order saddle point slightly higher in energy than *endo*-**8**. The free activation enthalpy for *endo*-**9** is small but positive owing to the contribution of sizable negative activation entropy.

Table 6. Relative Electronic Energies (Δ*E*), Spin-Corrected Electronic Energies (in parentheses, ΔE_{SC}), Enthalpies (Δ*H*), Entropies (Δ*S*), Gibbs Free Energies (Δ*G*), and Spin-Corrected Gibbs Free Energies (in parentheses, ΔG_{SC}) of Intermediates, Transition Structures, and Products for the Reaction of 1 with 7[a]

molecule	ΔE (ΔE_{SC})	ΔH	ΔS	ΔG (ΔG_{SC})
endo-**8**	−3.2	−1.4	−20.1	+4.6
endo-**9**	−2.5	−1.2	−29.2	+7.5
exo-**9**	+0.9	+2.3	−29.2	+11.1
10a	+4.0 (−0.4)	+3.2	−19.1	+8.9 (+4.5)
10b	+3.6 (−2.1)	+2.9	−19.4	+8.7 (+3.1)
11a	−35.1 (−35.6)	−32.6	−27.1	−24.5 (−25.0)
11b	−35.5 (−35.8)	−32.9	−26.8	−25.0 (−25.4)
12a	−4.3	−3.2	−26.1	+4.6
12b	−3.7	−2.5	−24.6	+4.9
(i)-**13**	−75.8	−70.8	−36.4	−59.9
(o)-**13**	−70.7	−65.8	−35.7	−55.2

[a] Harmonic approximation assumed; energies in kcal/mol, entropy in cal/(mol K); standard state (298.15 K) of the molar concentration scale (gas in ideal mixture at 1 mol/L, P = 1 atm); Δ*H*, Δ*G* are the molar relative enthalpy and free enthalpy; Δ*S* is the molar relative entropy. For conversion from 1 atm standard state to 1 mol/L standard state (both for gas phase) the following contributions need to be added to standard enthalpy, free enthalpy and entropy, respectively: $-RT$, $RT \ln R'T$, $-R \ln R'T - R$ where R' (0.082) is the value of R constant given in (L atm)/(mol K). For a reaction with A + B = C stoichiometry at 298 K, the corrections for Δ*H*, Δ*G*, and Δ*S* amount to 0.59 and −1.89 kcal/mol and 8.34 cal/(mol K), respectively. Δ*S* includes statistical reaction factors.

The antiaromatic destabilization of the cyclobutadiene ground state is fully reflected in the low barriers for endo and exo TSs, which are much lower (by >10 kcal/mol) than normal barriers in nitrone 1,3-dipolar cycloadditions (e.g., $\Delta E^{\ddagger}$ for endo and exo TSs of the reaction of cyclobutene with nitrone are 11.6 and 11.3 kcal/mol, respectively). The endo TS, *endo*-**9**, is much more stable than its exo counterpart, *exo*-**9** (by ~3.5 kcal/mol; notice that in the reaction of nitrone with cyclobutene the endo TS is less stable than the exo one by 0.36 kcal/mol) and, as mentioned in the preceding paragraph, exhibits an unusually ordered structure with the nitrone fragment disposed over and almost parallel to the cyclobutadiene fragment.

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(53) It should be realized that removal of BSSE would certainly reduce but might even reverse the potential energy gap between reactants and *endo*-**8**.

(54) The isoxazolidines (i)-**13** [(i) conformation] and (o)-**13** [(o) conformation] can easily convert into each other by ring flipping and nitrogen inversion: Gandolfi, R.; Grünanger, P. Partially Saturated Polynuclear Isoxazoles. In Grünanger, P.; Vita Finzi, P. *Isoxazoles*, Part 2; Wiley-Interscience: New York, 1999.

Obviously it is tempting, to explain geometry and energy of *endo*-**9**, to invoke a strong secondary orbital interaction, $\text{LUMO}_{\text{nitrone}}-\text{HOMO}_{\text{cyclobutadiene}}$, between the nitrone nitrogen center and the cyclobutadiene C_3-C_4 double bond, reminiscent of the more popular Diels–Alder secondary orbital interactions. We will discuss this aspect in due time,[4] but for now it is important to emphasize that a quantitative evaluation of chemical interactions indicates that secondary orbital interactions cannot be held responsible for the stability of the endo TS. Actually in *endo*-**9** orbital interactions involving the nitrone nitrogen center and the cyclobutadiene C_3-C_4 double bond are small.[4]

Both the radical centers in the anti diradicals **11** experience an efficient conjugative stabilization that explains why formation of these two intermediates is exothermic. Diradicals **11a** and **11b** can easily afford (i)-**13** and (o)-**13**,[54] respectively, by rotation around the new C−C bond followed by ring closure. This process can be preceded or accompanied by a fast equilibration of the two diradicals through rotation around the C−N bond ($\Delta E^{\ddagger} = 1.76$ kcal/mol).

However, what about the stability of diradicaloid TSs (**10a** and **10b** leading to **11a** and **11b**) with respect to that of their concerted competitors, namely, *endo*-**9** and *exo*-**9**?

Inspection of Table 6, considering the uncorrected (for spin-contamination) values for **10a** and **10b**, shows that the potential energy and enthalpy of concerted TSs **9** is lower than that of their diradicaloid counterparts **10** but the difference, in particular considering *exo*-**9**, is far from being dramatic. Activation entropy strongly favors (by 10 eu) the stepwise over the concerted mechanism, thus counterbalancing activation enthalpy. It is certainly not surprising that the more flexible acyclic TSs **10** are entropically preferred over the cyclic more ordered TSs **9**. However, in the cyclobutadiene reaction this effect is unexpectedly higher; actually it is twice that evaluated for the reactions of nitrone with ethene and benzocyclobutadiene, respectively. As a result activation Gibbs free energy values (gas phase) (Table 6 and Scheme 4) indicate that only concerted *endo*-**9** overwhelms, by ca. 1.2−1.4 kcal/mol, diradicaloids **10a** and **10b** (whose stability is very similar), which in turn, are more stable than concerted *exo*-**9** by ∼2.4 kcal/mol. A close context between *endo*-**9** and **10a**,**b** can be anticipated for condensed phase reactions given that solvent effects stabilize the latter TSs with respect to the former one (by 0.2 and 1.4 kcal/mol, respectively, in benzene and dichloromethane).[50]

Removal of spin contamination gives rise to a small change in the energy of diradicals **11a**,**b**, but it induces a strong decrease (∼4.5 kcal/mol) in energy for the diradicaloids **10a**,**b**. Spin contamination of TSs **10** is almost the same as that of intermediates **11,** but the singlet−triplet energy gap is substantial (∼4.0 kcal/mol, with the triplet state at higher energy) in the case of **10** while in the case of **11** it is very low (Table S2).

The free energy of both **10a** and **10b**, evaluated by using spin corrected electronic energy, is definitely lower than that of *endo*-**9** and *exo*-**9**. However, we have already stressed that Yamaguchi's method leads to overcorrection and that the uncorrected B3LYP values in the reaction of nitrone with ethene nicely (and much better than corrected values) reproduce the results of higher levels calculations.

In conclusion, our computational results suggest that the reaction of nitrone with cyclobutadiene represents a borderline reaction in which stepwise and concerted paths can be contemporarily viable in a true competition with each other.

The "antiaromatic" cyclobutadiene offers the stepwise process particularly favorable conditions. To define to what extent attenuation of the "antiaromaticity" of the dipolarophile can influence stepwise vs concerted competition we examined the reaction of benzocyclobutadiene with nitrone.

Reaction of Nitrone with Benzocyclobutadiene. Geometries of Intermediates and Transition Structures. The potential energy profile of the reaction of nitrone with benzocyclobutadiene is similar to that of the reaction of nitrone with cyclobutadiene. In fact, two first-order saddle points corresponding to concerted transition structures, i.e., *endo*-**16** and *exo*-**16** (Scheme 5 and Figure S1), were characterized with the RB3LYP/6-31G* method even if no endo oriented complex (of the type *endo*-**8**) could be located.

TSs **16** exhibit C−O and C−C forming bond lengths shorter than those of the corresponding cyclobutadiene TSs. These and other geometry details such as pyramidalization of nitrone nitrogen and carbon atoms, as well as the relative disposition of the two reactants, are midway between the "normal" values for nitrone-cyclobutene and those for the nitrone-cyclobutadiene reaction.

As for the open-shell structures we limited our UB3LYP/6-31G* search to diradical intermediates resulting from attack of benzocyclobutadiene to nitrone carbon, i.e., **18**. As a result of the lower symmetry of benzocyclobutadiene with respect to that of cyclobutadiene, we located four minima with the carbon−carbon bond fully formed, i.e., the anti singlet diradicals **18a**−**d**. They look very similar to **11a**,**b** and can easily convert into each other by rotation around the new C−C bond and/or rotation around the former nitrone C−N bond.

We managed to locate only three, i.e., **17a**−**c**, out of the four conceivable diradicaloid TSs on the pathway to **18a**−**d**. Despite numerous attempts, TS **17d** (which should lead to the diradical intermediate **18d**) escaped localization and the system always collapsed to the concerted *exo*-**16**. The $\langle S^2\rangle$ values for the diradical minima **18a**−**d** are, as for intermediates in the cyclobutadiene reaction, very close to 1.0, while the singlet and triplet states have very similar energies. In the case of diradicaloid transition structures $\langle S^2\rangle$ values varies from 0.43 and 0.30 for **17a** and **17b**, respectively, to 0.72 for **17c**, but the singlet−triplet (the latter less stable) energy gaps for these structures are quite higher (16.2, 19.4 and 9.5 kcal/mol, respectively) than those for **10a,b** (∼4.0 kcal/mol) (Table S3).

Energetics. The presence of the condensed benzene system in benzocyclobutadiene certainly lowers the antiaromaticity of the cyclobutadiene moiety in this compound with respect to parent cyclobutadiene, thus explaining why the energy barriers for the concerted cycloadditions of the former are higher (by ∼5 kcal/mol, Table 7) than those of the latter. However, benzocyclobutadiene is still predicted to be a very reactive dipolarophile in the reaction with nitrones, with the endo TS, *endo*-**16**, preferred over the exo TS, *exo*-**16**, by 2.3 kcal/mol (preference reduced to 1.7 and 1.0 kcal/mol in benzene and dichloromethane solution, respectively).[50]

Scheme 5

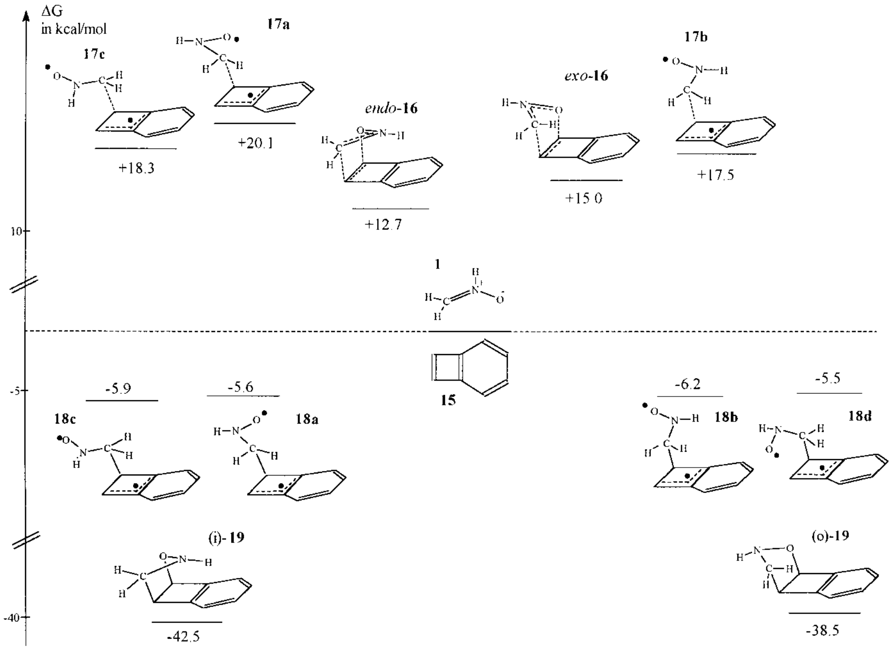

Table 7. Relative Electronic Energies (ΔE), Spin-Corrected Electronic Energies (in parentheses, ΔE_{SC}), Enthalpies (ΔH), Entropies (ΔS), Gibbs Free Energies (ΔG), and Spin-Corrected Gibbs Free Energies (in parentheses, ΔG_{SC}) of Intermediates, Transition Structures, and Products for the Reaction of 1 with 15[a]

molecule	ΔE (ΔE_{SC})	ΔH	ΔS	ΔG (ΔG_{SC})
endo-**16**	+1.9	+3.3	−31.6	+12.7
exo-**16**	+4.3	+5.6	−31.6	+15.0
17a	+11.6 (+7.3)	+12.0	−26.9	+20.1 (+15.8)
17b	+8.9 (+5.5)	+9.6	−26.4	+17.5 (+14.1)
17c	+10.3 (+5.0)	+10.0	−26.4	+18.3 (+13.0)
18a	−15.9 (−16.0)	−13.9	−27.8	−5.6 (−5.7)
18b	−16.6 (−16.8)	−14.5	−27.9	−6.2 (−6.4)
18c	−16.1 (−17.1)	−14.0	−27.6	−5.9 (−7.0)
18d	−15.9 (−15.9)	−13.9	−28.7	−5.5 (−5.5)
(i)-**19**	−58.0	−53.6	−37.1	−42.5
(o)-**19**	−53.6	−49.3	−36.4	−38.5

[a] See footnote in Table 6.

The reaction of benzocyclobutadiene with nitrone is strongly exothermic in the formation of the final isoxazolidines **19**, and also the diradical intermediates **18** are more stable than the educts.

More important for our problem is the observation that (using uncorrected potential energies for diradicaloid TSs **17**) the concerted processes, in particular *endo*-**16**, emerge as clearly dominant over the stepwise reactions. This is particularly true at the enthalpy level, but the clear-cut choice between the two kind of processes is carried over to the free energy level (Scheme 5), even if somewhat attenuated since the entropic factors promote (by 5 eu; $T\Delta S = 1.5$ kcal/mol) the diradical path. Introduction of solvent effects[50] does not substantially change the scenery as it leaves the concerted TS *endo*-**16** favored by ≥3.6 kcal/mol over the diradicaloid TSs **17**.

Thus, the diradical mechanism (in this reaction where the conditions that can induce it, although present, are less extreme) seems to be no more able to efficiently compete with the concerted process.

Once again spin correction strongly lowers the energy of diradicaloid TSs **17a**−**c**, while it is almost negligible for the energy of diradicals **18a**−**d**. However, taking into account considerable overcorrection in the Yamaguchi procedure, we can confidently anticipate prevalence of the concerted over the diradical paths in the nitrone-benzocyclobutadiene reaction.

Conclusions

Our study by R(U)B3LYP/6-31G* and post-HF methods demonstrates that in the reaction of nitrone with ethene product formation should take place via the concerted cycloaddition path. The stepwise process is a viable but not competitive alternative.

In the case of the reaction of nitrone with the very reactive antiaromatic cyclobutadiene, a dipolarophile whose electronic structure is particularly disposed to promote stepwise diradical pathways, R(U)B3LYP/6-31G calculations suggest that we are in the presence of a borderline case in which the stepwise process can compete with the concerted one on similar footing.

Attenuation of the antiaromatic character of the dipolarophile, i.e., on passing from cyclobutadiene to benzocyclobutadiene, causes the concerted 1,3-dipolar cycloaddition to become once again prevalent over the two-step path.

Thus, our computational results join previously reported computational data and the elegant and convincing arguing by Huisgen, mostly based on experimental observations and qualitative theory, in making one confident that 1,3-dipolar cycloadditions with normal dipolarophiles will follow a concerted mechanism via an aromatic transition state.

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Supporting Information Available: Singlet and triplet electronic energies, ⟨S^2⟩ values, corrections to enthalpy, corrections to Gibbs free energy, and entropies for all transition structures reported. Figures for nitrone-benzocyclobutadiene transition structures reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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