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anti-Diradical Formation in 1,3-Dipolar Cycloadditions of Nitrile Oxides to Acetylenes

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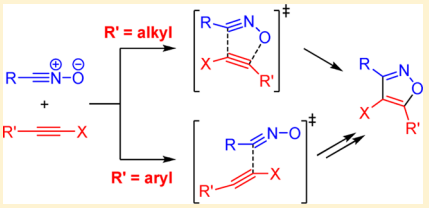
Supporting Information

ABSTRACT: By means of high level quantum chemical calculations (B2PLYPD and CCSD(T)), the mechanisms of the reaction of nitrile oxides with alkenes and alkynes were investigated. We were able to show that in the case of alkenes, regardless of the chosen substituents, the concerted mechanism is always energetically favored as compared to a two-step process, which runs through an *anti*-diradical species. In the case of alkynes, the concerted mechanism is favored only for the reaction of alkyl-substituted acetylenes. For aryl-substituted acetylenes, the activation barrier toward the *anti*-diradical is equal to or lower than the activation barrier of the concerted reaction. This reversal of the reaction paths is not only limited to nitrile oxides as dipolarophiles. Conditions favoring the *anti*-diradical path are the presence of a triple bond in both the 1,3-dipole and the dipolarophile and additionally an aryl substituent attached to the alkyne. The featured energy relationships between the reaction paths are able to explain the experimentally observed byproducts of the reaction of nitrile oxides with arylacetylenes. The discovered differences for the preferred reaction path of 1,3-dipolar cycloadditions to acetylenes should be of considerable interest to a broader field of chemists.

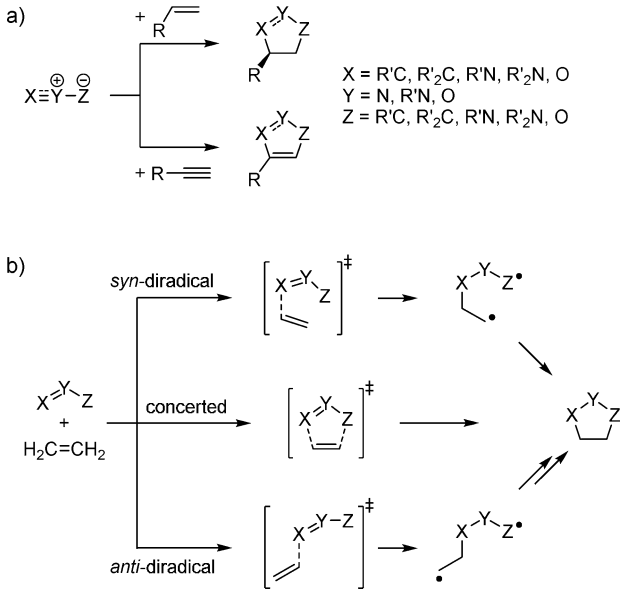


INTRODUCTION

1,3-Dipolar cycloaddition is a general and powerful method for the synthesis of heterocycles.[1] Now it is utilized in almost all areas of chemistry, including materials chemistry,[2] drug discovery,[3] and chemical biology.[4] The origin of the systematic studies of 1,3-dipolar cycloadditions goes back to the late 1950s when Rolf Huisgen examined the addition of diazoalkanes to strained double bonds.[5] These investigations led to a generalization and classification of 1,3-dipolar cycloaddition.[5] 1,3-Dipolar compounds contain at least one heteroatom, and they can be described by at least one structure, which includes a positive and a negative charge (dipole). Furthermore, they can be divided into propargylic and allylic species. In the former case, the 1,3-dipoles have two sets of degenerate π orbitals in a linear structure; the central atom is in general nitrogen. In the second case, the 1,3-dipoles are isoelectronic to the allyl anion, and the central atom is in general an oxygen or nitrogen atom. The second component in 1,3-dipolar cycloadditions is called a dipolarophile and could be an alkene, an alkyne, or a polyvalent heteroatom-containing group. The cycloaddition of alkenes and alkynes to 1,3-dipoles including possible combinations from first-row atoms is shown in Scheme 1a.

Regarding the mechanism of 1,3-dipolar cycloaddition, there was a vigorous debate.[6] On the basis of kinetic and especially stereochemical results, Huisgen postulated a concerted, although sometimes asynchronous, mechanism.[6b] On the basis of the same experimental data, Firestone suggested a stepwise *syn*-diradical mechanism.[6a] In this case, a σ bond is first formed preferentially (Scheme 1b). The resulting *syn*-diradical is a short-lived intermediate and undergoes a cyclization before

Scheme 1. (a) General 1,3-Dipolar Cycloaddition and Possible X, Y, and Z Combination from First-Row Atoms; and (b) Concerted and Stepwise Mechanisms for 1,3-Dipolar Cycloadditions



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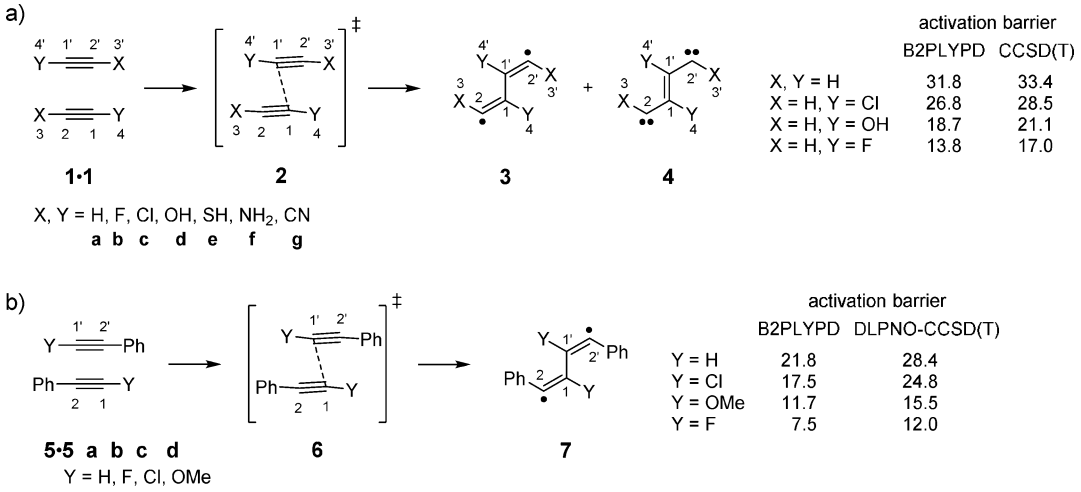
Scheme 2. (a) Dimerization of Substituted Alkynes 1·1 to Diradicals 3 and Dicarbenes 4; and (b) Dimerization of Substituted Phenylacetylenes 5·5 to Diradicals 7



a rotation around the newly formed σ bond takes place. Here too, retention of the stereochemical information occurs. The stepwise mechanism, which proceeds via a long-lived *anti*-diradical, was ruled out due to the stereochemical results. Experimental evidence for the concerted mechanism has been provided by stereospecific cycloadditions of *para*-nitrobenzonitrile oxide to *cis*-1,2-dideuterioethylene and *trans*-1,2-dideuterioethylene.[7] In this case, one might have expected the putative diradical mechanism. Comprehensive comparisons of stepwise (*anti*-diradical) and concerted transition states using modern computational methods show that the concerted pathways are favored over the stepwise,[8] as described by Huisgen.[6b] Because of these high-level calculations and due to the experimental data, the current doctrine is that 1,3-cycloaddition reactions proceed via a concerted mechanism. According to the current state of scientific knowledge, neither the *anti*- nor the *syn*-diradicals are intermediates during 1,3-cycloadditions.

Recently, we have dealt with the dimerization of alkynes **1**, wherein the *trans*-1,4-diradicals **3** are formed as intermediates.[9] We could show that the reaction course strongly depends on the substituents bonded to the alkyne.[10] Substituents with high electronegativity (F, OH, Cl) lead to a decrease of the activation barrier as well as the reaction energy, if they are attached directly to the reactive carbon atoms of the acetylene (C1 and C1′ in Scheme 2a).[10a] For example, the activation energy of the dimerization of acetylene (**1a**, X = H, Y = H) is 33.4 kcal/mol according to CCSD(T) calculations (Scheme 2a).[10a] The replacement of the hydrogen atoms at the reaction centers C1 and C1′ by Cl, OH, or F leads to a lowering of the activation barrier to 28.5, 21.1, and 17.0 kcal/mol.[10a] An explanation for this phenomenon is given by Bent's rule. It states that atoms direct hybrid orbitals with more p character toward more electronegative elements.[11] In addition, we could show that NH_2 and OH groups, which are bonded to the C2 and C2′ centers, lead to the fact that, in addition to the diradicals **3**, the corresponding singlet dicarbenes **4** can be formed.[9c]

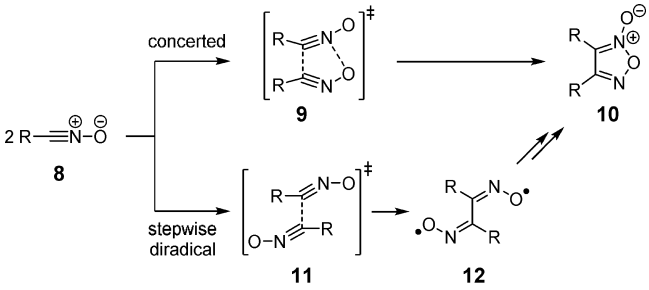
Furthermore, we showed that phenyl groups, which are bound to the C2 and C2′ centers, additionally reduce the activation barrier, because the resulting diradicals **7** are stabilized by conjugation with the phenyl groups (Scheme 2b).[10a] The combination of two stabilizing factors (electronegative substituent at C1 and C1′ as well as a phenyl group at C2 and C2′) strongly decreases the activation energy. For example, the reaction barrier of the dimerization of phenylmethoxyacetylene (**5d**) amounts to only 15.5 kcal/mol using DLPNO-CCSD(T) calculations.[10a] This is only about one-half of the activation energy of acetylene (**1a**). Therefore, the introduction of suitable substituents can lead to a drastic reduction of the activation energy concerning the formation of *anti*-diradicals.

The question arises whether suitable substituents can lead to such a strong decrease of the activation barrier for the *anti*-diradical mechanism that this mechanism is preferred as compared to the concerted one. A search of quantum chemical studies of 1,3-dipolar cycloadditions shows that the aspect of the substituents of 1,3-dipoles and dipolarophiles has been almost completely ignored. In this Article, we want to examine the dependence of the two mechanisms (concerted and *anti*-diradical) on the substituents of the alkyne, alkene, and 1,3-dipolar molecules.

RESULTS AND DISCUSSION

a. Model Study on Substituent Effects in the 1,3-Dipolar Cycloaddition of Nitrile Oxides. Because of the large number of different 1,3-dipolar reactions, it was necessary in a first step to limit the study to only one or two types of reactions. We chose substituted alkenes and alkynes as dipolarophiles, because these represent the most commonly used dipolarophiles. When selecting the 1,3-dipolar compound, we decided to use nitrile oxides (**8**). They easily dimerize to form the furoxans **10**.[5b] Here again, there are two possible

Scheme 3. Dimerization of Nitrile Oxides 8 to Furoxans 10



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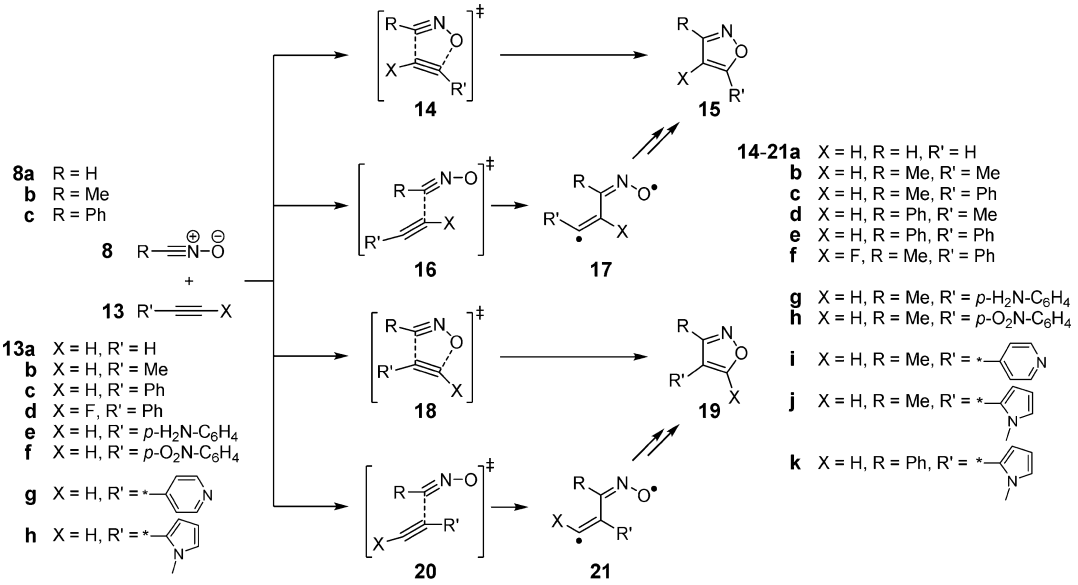
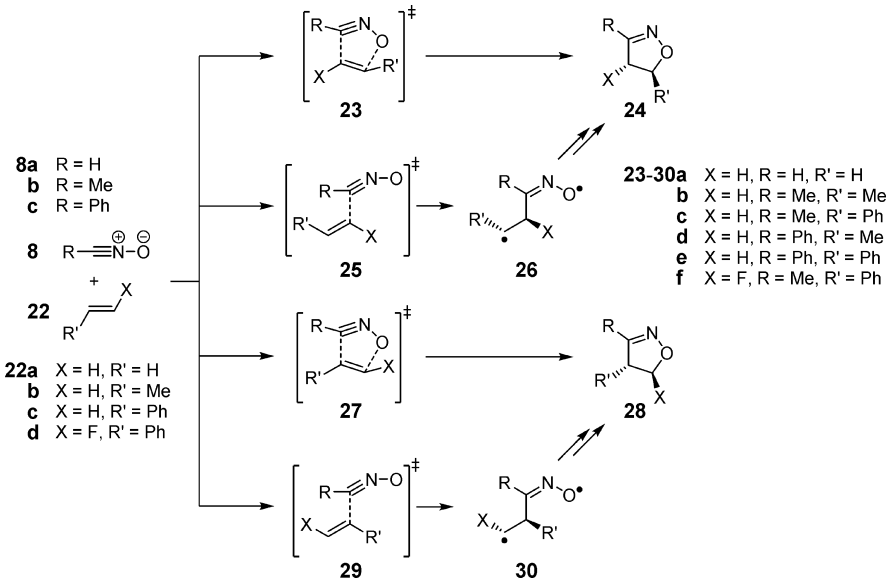
Scheme 4. 1,3-Dipolar Cycloaddition of Nitriles Oxides 8 with Acetylenes 13 to Isoxazoles 15 and 19



Scheme 5. 1,3-Dipolar Cycloaddition of Nitrile Oxides 8 with Ethylenes 22 to Isoxazolines 24 and 28



mechanisms: On the one hand is a concerted 1,3-dipolar cycloaddition process, where the C−N triple bond of one nitrile oxide acts as dipolarophile while the other nitrile oxide acts as 1,3-dipole (Scheme 3).[12] On the other hand, a stepwise mechanism via the formation of the diradical **12** is possible.[13] Density functional theory calculations at the UB3LYP/6-31G* level of the dimerization reactions of acetonitrile oxide and *para*-chlorobenzonitrile oxide showed that these processes proceed stepwise involving *anti*-diradical intermediates.[14] These results suggest that nitrile oxides are also prone to form *anti*-diradical intermediates with alkenes and alkynes during 1,3-dipolar cycloaddition reactions.

To investigate the substituent dependence on the reaction path, the cycloadditions of nitrile oxides **8** with the alkynes **13** and alkenes **22** were studied (Schemes 4 and 5). As nitrile oxides, acetonitrile oxide (**8b**) and benzonitrile oxide (**8c**) were mainly used. In almost all cases (except **13d**), only single-substituted alkynes were examined. The substituents R′ were in addition to the methyl group (**13b**) mainly aromatic units (**13c−h**) differing in their electronic properties (electron-rich units as **13e** and **13h** as well as electron-deficient aromatics such as **13f** and **13g**). For the alkenes, only the methyl (**22b**) and the phenyl group (**22c,d**) were used as substituent R′. In the case of the reaction of the alkyne **13**, all four possible transition states (**14**, **16**, **18**, and **20**), the two diradical intermediates **17** and **21**, as well as the products **15** and **19** were calculated (Scheme 4). For the sake of simplicity, we assumed that the stereochemical information at the alkene **22d** (X = F, R′ = Ph) is maintained during the cycloaddition (Scheme 5). Again, the regioselectivity was taken into account because both isoxazolines **24** and **28** can be formed.

The stationary points of the 1,3-cycloaddition reactions were optimized using the double hybrid method B2PLYPD by Grimme[15] in conjunction with the 6-31G*[16] basis set. Subsequently frequency calculations by means of B2PLYPD/6-31G* were carried out to verify the nature of the stationary

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Table 1. Energies (ΔE in kcal/mol) of the Transition States (14, 16, 18, and 20), Intermediate States (17 and 21), and Products (15 and 19) Relative to the Corresponding Starting Materials (8 and 13)

	R	X	R′	ΔE^a B2PLYPD	ΔE^b B2PLYPD	ΔE^c CCSD(T)	ΔE^d UB3LYP
14a	H	H	H	9.8	12.3	13.1	15.4
15a	H	H	H	−84.7	−75.3	−79.5	−75.4
16a	H	H	H	14.4	17.4	18.8	20.3
17a	H	H	H	0.6	6.6	−107.6	2.2
14b	Me	H	Me	9.9	12.1	12.2	17.4
15b	Me	H	Me	−82.9	−74.8	−80.6	−71.4
16b	Me	H	Me	12.7	15.3	16.0	20.5
17b	Me	H	Me	3.1	7.8	−54.8	6.3
18b	Me	H	Me	12.0	14.2	14.1	20.7
19b	Me	H	Me	−80.0	−71.8	−77.7	−67.8
20b	Me	H	Me	17.7	20.6	20.9	24.5
21b	Me	H	Me	7.0	12.0	11.1	14.5
14c	Me	H	Ph	9.4	11.5	11.5	18.0
15c	Me	H	Ph	−83.2	−74.8	−80.1	−70.8
16c	Me	H	Ph	8.7	10.6	11.8	16.6
17c	Me	H	Ph	−3.7	0.5	−48.0	0.4
18c	Me	H	Ph	10.3	12.1	11.0	20.5
19c	Me	H	Ph	−80.1	−72.4	−78.8	−66.3
20c	Me	H	Ph	18.9	21.0	20.2	27.8
21c	Me	H	Ph	8.6	12.8	11.9	18.4
14d	Ph	H	Me	8.9	11.2	11.0	18.0
15d	Ph	H	Me	−82.3	−74.2	−80.3	−69.8
16d	Ph	H	Me	11.9	14.6	14.8	22.5
17d	Ph	H	Me	3.9	8.2	−55.7	10.0
18d	Ph	H	Me	11.3	13.4	12.2	21.7
19d	Ph	H	Me	−78.9	−71.0	−77.6	−64.8
20d	Ph	H	Me	18.0	20.7	20.0	25.8
21d	Ph	H	Me	8.7	13.3	11.1	18.3
14e	Ph	H	Ph	8.4	10.7	10.3	18.7
15e	Ph	H	Ph	−82.7	−74.4	−80.2	−69.2
16e	Ph	H	Ph	8.0	10.0	10.4	19.3
17e	Ph	H	Ph	−1.6	1.7	−39.6	5.1
18e	Ph	H	Ph	9.2	10.8	8.7	23.0
19e	Ph	H	Ph	−79.4	−72.2	−80.2	−63.2
20e	Ph	H	Ph	18.5	20.4	19.0	29.1
21e	Ph	H	Ph	8.9	12.7	10.2	20.7
14f	Me	F	Ph	8.9	11.3	11.8	18.4
15f	Me	F	Ph	−93.1	−84.8	−89.8	−80.2
16f	Me	F	Ph	6.2	8.1	10.0	−1.7
17f	Me	F	Ph	−14.2	−10.5	−9.5	−7.5
18f	Me	F	Ph	9.2	10.8	10.0	18.9
19f	Me	F	Ph	−94.1	−86.5	−93.0	−79.6
20f	Me	F	Ph	13.6	15.6	14.5	23.0
21f	Me	F	Ph	−4.2	0.9	−6.7	5.7
14g	Me	H	*p*-H_2N−C_6H_4	9.4	11.6	11.6	17.9
15g	Me	H	*p*-H_2N−C_6H_4	−83.5	−75.1	−80.4	−71.1
16g	Me	H	*p*-H_2N−C_6H_4	8.1	10.0	11.1	15.5
17g	Me	H	*p*-H_2N−C_6H_4	−3.5	0.7	−38.2	−0.5
18g	Me	H	*p*-H_2N−C_6H_4	10.8	12.6	11.4	21.4
19g	Me	H	*p*-H_2N−C_6H_4	−79.7	−72.0	−78.6	−65.7
20g	Me	H	*p*-H_2N−C_6H_4	18.8	20.9	19.9	27.7
21g	Me	H	*p*-H_2N−C_6H_4	8.9	13.1	11.8	18.7
14h	Me	H	*p*-O_2N−C_6H_4	8.3	10.4	10.6	16.9
15h	Me	H	*p*-O_2N−C_6H_4	−83.0	−74.8	−80.0	−70.7
16h	Me	H	*p*-O_2N−C_6H_4	8.6	10.5	12.4	16.6
17h	Me	H	*p*-O_2N−C_6H_4	−6.0	−1.8	−49.1	−1.2
18h	Me	H	*p*-O_2N−C_6H_4	9.7	11.5	10.7	19.7
19h	Me	H	*p*-O_2N−C_6H_4	−80.2	−72.6	−78.9	−66.6
20h	Me	H	*p*-O_2N−C_6H_4	18.5	20.4	19.6	27.3
21h	Me	H	*p*-O_2N−C_6H_4	7.9	12.1	11.4	17.8

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Table 1. continued

	R	X	R′	ΔE^a B2PLYPD	ΔE^b B2PLYPD	ΔE^c CCSD(T)	ΔE^d UB3LYP
14i	Me	H	C_5H_4N	8.8	10.9	11.0	17.4
15i	Me	H	C_5H_4N	−83.1	−74.8	−80.1	−70.9
16i	Me	H	C_5H_4N	8.9	10.8	12.4	16.9
17i	Me	H	C_5H_4N	−4.8	−0.6	−51.2	0.2
18i	Me	H	C_5H_4N	9.6	11.4	10.5	19.5
19i	Me	H	C_5H_4N	−80.5	−72.9	−79.1	−66.9
20i	Me	H	C_5H_4N	8.1	12.3	11.7	17.8
21i	Me	H	C_5H_4N	18.6	20.7	20.0	27.4
14j	Me	H	C_5H_6N	9.4	11.7	12.1	18.3
15j	Me	H	C_5H_6N	−81.2	−72.9	−78.1	−68.5
16j	Me	H	C_5H_6N	7.5	9.6	10.8	15.1
17j	Me	H	C_5H_6N	−4.8	−0.1	−2.7	−2.9
18j	Me	H	C_5H_6N	10.4	12.1	10.7	22.3
19j	Me	H	C_5H_6N	−78.9	−71.0	−77.4	−64.5
20j	Me	H	C_5H_6N	19.1	21.2	20.0	28.9
21j	Me	H	C_5H_6N	9.3	13.2	11.6	20.0
14k	Ph	H	C_5H_6N	8.1	10.6	10.6	18.8
15k	Ph	H	C_5H_6N	−80.9	−72.7	−78.6	−66.8
16k	Ph	H	C_5H_6N	3.8	6.2	6.2	19.1
17k	Ph	H	C_5H_6N	−6.2	−1.3	−2.3	1.1
18k	Ph	H	C_5H_6N	10.1	11.9	9.8	23.2
19k	Ph	H	C_5H_6N	−77.5	−70.0	−78.2	−60.9
20k	Ph	H	C_5H_6N	17.5	19.5	18.5	28.6
21k	Ph	H	C_5H_6N	9.9	13.7	10.3	21.0

[a]B2PLYPD/6-31G*. [b]B2PLYPD/def2-TZVP//B2PLYPD/6-31G*. [c]CCSD(T)/def2-TZVP//B2PLYPD/6-31G*. [d]UB3LYP/def2-TZVP//B2PLYPD/6-31G*.

point. It turned out that all transition states have exactly one imaginary frequency, whereas all other stationary points have none. Furthermore, the energy of the stationary points was calculated using B2PLYPD and CCSD(T)[17] in conjunction with the def2-TZVP[18] basis set. These methods were chosen as the obtained values with these approximations show a very high consistency with experimental data[9a,10a,19] for the activation barriers of the formation of diradicals.[9c,10a,20] Furthermore, the energies of the B2PLYPD/6-31G* optimized structures were calculated by means of UB3LYP.[21] Here again, the def2-TZVP basis set was employed. For these open-shell calculations, the spin projection procedure proposed by Yamaguchi and Houk was applied.[8g,22] This procedure removes triplet contamination of the singlet wave function and the artificial lowering of the energy of the species due to a single determinante wave function. The calculated data are shown in Tables 1 and 2 as well as in Figures 1 and 2.

Considering the values of B2PLYPD/def2-TZVP and CCSD(T)/def2-TZVP calculations, it is obvious that the energies of the transition states (**14**, **16**, **18**, **20**, **23**, **25**, and **27**) match very well. The differences between these two methods are on average <1 kcal/mol and a maximum of 2 kcal/mol. On the other hand, very strong deviations are found for the energy values of the diradical intermediates (e.g., **17** and **21**). This aspect will be discussed later in this section; here the focus is put on the transition states. The energies of the transition states and the intermediates from calculations by UB3LYP/def2-TZVP//B2PLYPD/6-31G* are always higher than the data obtained by B2PLYPD/def2-TZVP//B2PLYPD/6-31G*. The inclusion of dispersion and an MP2-like feature in B2PLYPD may be the source of this disagreement.

Comparing the regioselectivity of the reactions of the B2PLYPD/def2-TZVP calculations, one can see that the isoxazoles **15** and isoxazolines **24**, respectively, should be preferably formed in all cases. This is consistent with the experimental data.[23] Thus, the mechanisms that lead to the isoxazoles **19** and isoxazolines **28**, respectively, can be left aside for a final evaluation of the mechanism. Nevertheless, it is interesting to look at the comparison between concerted and stepwise mechanism. It turns out that in all cases the concerted mechanism for the formation of isoxazoles **19** and isoxazolines **28** is much more favorable than the stepwise one. The calculated differences using B2PLYPD/def2-TZVP are about 5−11 kcal/mol.

A completely different picture emerges by looking at the mechanism for the formation of isoxazoles **15** from the nitrile oxides **8** and acetylenes **13**. Which of the competing transition states (**14** or **16**) is more favorable strongly depends on the substituents. As a rule of thumb, one can say that the concerted mechanism is then effective when the acetylene contains an alkyl group (**13b**). If the acetylene contains an aryl group, the stepwise diradical mechanism is equivalent to or even better than the concerted mechanism (Table 1 and Figure 1). The latter applies, if the aryl group is electron-rich (**13e** and **13h**) or the acetylene contains an electronegative group such as fluorine (**13d**). The substituent R in the nitrile oxide does not matter, which can be seen by a comparison of the formation of isoxazoles **15c** and **15e**. One explanation for this change of reaction mechanisms can be easily found by looking at Figure 1: The energy of the transition states **14** via concerted step is only slightly dependent on the substituents. The variation amounts to only 2−3 kcal/mol. In contrast to that, the energy of the *anti*-diradical transition states **16** is very strongly influenced by the substituents. If there is an electron-withdrawing substituent attached at the reaction center (like F) or an aryl substituent bound to the radical centers, which is

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Table 2. Energies (ΔE in kcal/mol) of the Transition States (23, 25, 27, and 29), Intermediate States (26 and 30), and Products (24 and 28) Relative to the Corresponding Starting Materials (8 and 22)

	R	X	R′	ΔE^a B2PLYPD	ΔE^b B2PLYPD	ΔE^c CCSD(T)	ΔE^d UB3LYP
23a	H	H	H	8.0	10.4	11.7	14.4
24a	H	H	H	−46.5	−39.4	−45.8	−37.5
25a	H	H	H	17.5	19.8	19.4	16.6
26a	H	H	H	15.2	18.3	0.1	10.4
23b	Me	H	Me	8.0	9.9	10.3	16.4
24b	Me	H	Me	−47.4	−41.5	−49.2	−35.5
25b	Me	H	Me	16.0	17.9	17.4	19.7
26b	Me	H	Me	13.9	16.7	2.6	13.1
27b	Me	H	Me	9.9	11.8	12.3	19.3
28b	Me	H	Me	−44.2	−38.7	−46.4	−32.4
29b	Me	H	Me	18.6	20.2	18.9	22.8
30b	Me	H	Me	17.1	19.4	8.2	18.1
23c	Me	H	Ph	6.8	8.1	8.0	16.1
24c	Me	H	Ph	−44.4	−39.0	−48.3	−31.6
25c	Me	H	Ph	9.1	11.1	11.7	18.6
26c	Me	H	Ph	3.8	6.9	−12.8	5.6
27c	Me	H	Ph	7.2	8.5	7.3	18.5
28c	Me	H	Ph	−43.8	−38.6	−47.9	−29.9
29c	Me	H	Ph	18.9	20.2	15.6	23.7
30c	Me	H	Ph	18.7	20.2	11.0	22.0
23d	Ph	H	Me	6.5	8.8	9.7	16.7
24d	Ph	H	Me	−48.0	−41.9	−49.4	−35.0
25d	Ph	H	Me	14.9	17.3	16.5	21.1
26d	Ph	H	Me	13.5	16.5	6.1	14.8
27d	Ph	H	Me	8.2	10.5	11.0	20.0
28d	Ph	H	Me	−45.1	−39.4	−47.2	−31.2
29d	Ph	H	Me	18.6	20.7	18.1	24.7
30d	Ph	H	Me	17.6	20.1	6.1	20.7
23e	Ph	H	Ph	5.2	6.8		16.5
24e	Ph	H	Ph	−44.9	−39.3		−30.8
25e	Ph	H	Ph	7.7	10.6		20.3
26e	Ph	H	Ph	3.3	6.9		7.4
27e	Ph	H	Ph	6.1	7.2		20.7
28e	Ph	H	Ph	−44.5	−39.2		−28.2
29e	Ph	H	Ph	*e*	*e*	*e*	*e*
30e	Ph	H	Ph	*e*	*e*	*e*	*e*
23f	Me	F	Ph	8.9	10.5	10.6	19.0
24f	Me	F	Ph	−43.7	−38.9	−47.7	−31.2
25f	Me	F	Ph	10.0	12.7	13.7	19.6
26f	Me	F	Ph	5.3	8.7	−9.4	7.4
27f	Me	F	Ph	6.8	8.6	7.7	18.4
28f	Me	F	Ph	−52.6	−47.4	−56.8	−38.1
29f	Me	F	Ph	17.3	19.0	16.9	24.0
30f	Me	F	Ph	15.9	18.5	8.3	19.8

[a]B2PLYPD/6-31G*. [b]B2PLYPD/def2-TZVP//B2PLYPD/6-31G*. [c]CCSD(T)/def2-TZVP//B2PLYPD/6-31G*. [d]UB3LYP/def2-TZVP//B2PLYPD/6-31G*. [e]No stationary point found.

responsible for a conjugative stabilization, the stepwise mechanism is facilitated. The energy variation for the *anti*-diradical amounts to more than 12 kcal/mol. While it can be assumed that a cycloaddition of methyl nitrile oxide (**8b**) and methyl acetylene (**13b**) toward isoxazole **15b** proceeds in a concerted way, the cycloaddition of benzonitrile oxide (**1c**) to the electron-rich 2-ethynyl-1-methylpyrrole (**13h**) probably passes through a stepwise mechanism. The cycloaddition of nitrile oxides to phenyl acetylene (**13c**) or electron-deficient aromatics (like **13f** and **13g**) could run through both mechanisms in terms of energy.

A different picture is obtained for the 1,3-dipolar cycloaddition of nitrile oxides **8** with ethylenes **22** to isoxazolines **24**. Here again, the energies of the transition states **23** are independent of the substituents R′ and are found in a relatively narrow range (about 3.5 kcal/mol for B2PLYPD/def2-TZVP calculations), while the energies of the transition states **25** with an *anti*-diradical character show a range of about 9 kcal/mol (Table 2 and Figure 2). Yet in contrast to the previously discussed cycloaddition of acetylenes, none of the examined cases showed that the *anti*-diradical mechanism is more favorable than the concerted one. While the barrier heights of the concerted cycloaddition of a given 1,3-dipole with ethylenes

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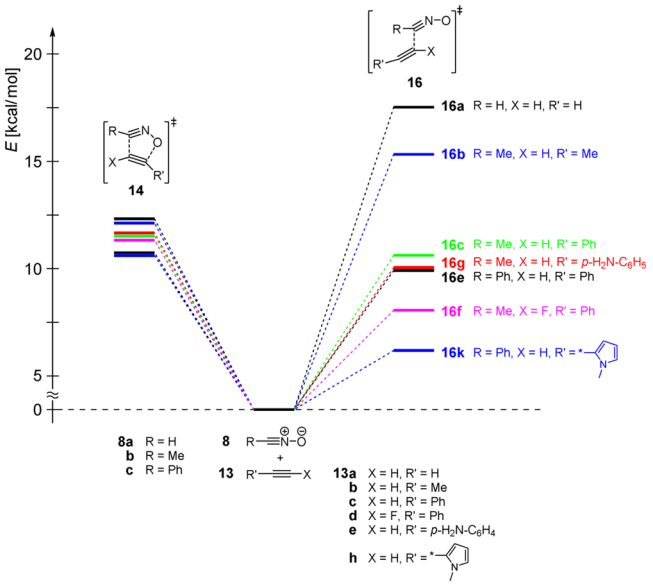

Figure 1. Comparison of the transition energy for the concerted (**14**) and stepwise addition (**16**) of nitriles oxides **8** to acetylenes **13** calculated using B2PLYPD/def2-TZVP//B2PLYPD/6-31G*.

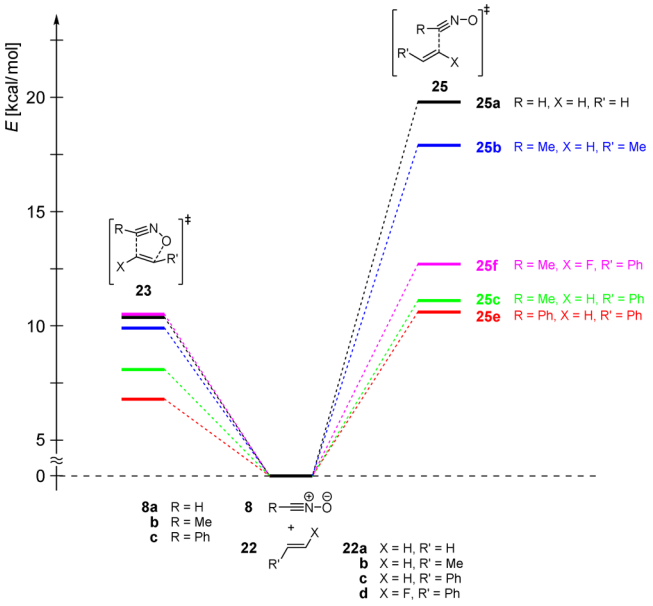

Figure 2. Comparison of the transition energy for the concerted (**23**) and stepwise addition (**25**) of nitriles oxides **8** with ethylenes **22** calculated using B2PLYPD/def2-TZVP//B2PLYPD/6-31G*.

and acetylenes are very similar,[8g] the energy of the diradical transition states **25** is a few kcal/mol higher than that of the corresponding transition states **16**. The lower energy of the transition states **16** and diradicals **17** relative to the corresponding transition states **25** and diradicals **26** can be easily explained by the fact that in the case of **16** and **17** there is an additional stabilization due to the interaction of π orbitals, which are perpendicular to the reacting orbitals. This stabilizing interaction can only occur when both reacting species (alkyne **13** and nitrile oxides **8**) contain a triple bond. In the case of **25** and **26**, which are formed from alkene **22** and nitrile oxide **8**, this conjugative stabilizing effect is not present. Furthermore, the possibility of π delocalization for the O-centered radical center in diradical **17** with the N═C−C═C system could lead to zwitterionic electron structure or to carbenes: Such zwitterionic electron structures and carbenes have been observed in diradicals formed in cycloaromatization reactions,[24] and the formation of dicarbenes has been predicted for the dimerization of acetylenes showing NH_2 and OH groups.[9c]

The π conjugation is also responsible for the fact that the formation energy of 1,3-butadiene-1,4-diyl from acetylene amounts to 37.7 kcal/mol (B2PLYPD/def2-TZVP), while butane-1,4-diyl is not a minimum on the potential surface using this method, but it departs into two ethylene units. Butane-1,4-diyl with a constrained C2−C3 length of 1.54 Å is 53.5 kcal/mol (B2PLYPD/def2-TZVP) higher in energy than two ethylene units. This difference clearly shows the stabilizing effect of additional π orbitals being perpendicular to the reacting orbitals.

For a more detailed study of the diradical character of the stationary states, which lead to the isoxazoles **15**, we also optimized the geometry of the transition states **31** of selected substituents using B2PLYPD/6-31G* (Scheme 6). Additionally, single point calculations were performed on the geometrically optimized structures using B2PLYPD, CCSD(T), (12/10)CASSCF,[25] and (12/10)CASPT2[26] approximations. The def2-TZVP basis set was employed (Table 3). While B2PLYPD and CCSD(T) are based on a single reference configuration, the methods CASSCF and CASPT2 are able to describe nondynamic correlation effects. This is important for species with high diradical character. Furthermore, the CASPT2 approximation considers dynamic correlation effects.

For the determination of the diradical character of the stationary points, the CASSCF wave function can be used. The occupation numbers of the frontier orbitals n_1 and n_2 allow the determination of the diradical character (Figure 3 and Table 3).[27] In a perfect diradical, both frontier orbitals would be equally populated. An alternative analysis of the radical character of the stationary points is computing the total number of effectively unpaired electrons N_U,[28] which provides a measure for the splitting of an electron pair into different spatial regions. Because of the nonlinear formula of N_U, only the truly open-shell contributions of the radical centers contribute to the total number of effectively unpaired electrons.[28] In Table 3, the occupation numbers of the frontier orbitals (n_1 and n_2) and the total number of effectively unpaired electrons (N_U) of the transition states **14**, **16**, and **31**, intermediate states **17**, and products **15** are listed.

A comparison of the transition states for the concerted (**14**) and the *anti*-diradical mechanism (**16**) shows that in both states the frontier orbitals n_2 have only a small occupation number, which is equivalent to a low diradical character for **14** and **16**. Furthermore, the sum of unpaired electrons for **14** and **16** is lower than 0.4. The values for **14c** and **16c** are actually almost identical. Because of these low values, the usage of one-determinant methods such as B2PLYPD or CCSD(T) is absolutely justified for the calculation of the activation heights of these two mechanisms.

As mentioned above, the intermediates **17** could in principle be diradicals, carbenes, or zwitterionic intermediates. The analysis of the wave functions shows that they all prefer the diradical state (Table 3). The donor character of only one oxygen is obviously too low to stabilize a singlet carbene,[9c] and probably the Coulombic penalty for separating charges disfavors the formation of zwitterionic species.[24] The occupation numbers of n_2 for the intermediates **17** and the transition states **31** amount to 0.6−0.7 electrons. This is still far

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Scheme 6. Concerted and Stepwise Mechanisms of the 1,3-Dipolar Cycloaddition of Nitrile Oxides 8 with Acetylenes 13 to Isoxazoles 15

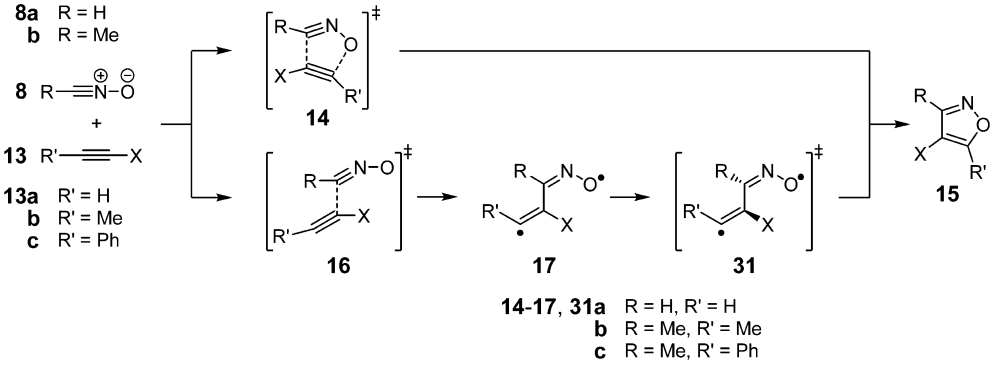

Table 3. Occupation Numbers of the Frontier Orbitals (n_1 and n_2), the Total Number of Effectively Unpaired Electrons (N_U), and the Energies (ΔE in kcal/mol) of the Transition States (14, 16, and 31), Intermediate States (17), and Products (15) Relative to the Corresponding Starting Materials (8 and 13)[a]

	R	R′	ΔE[b] B2PLYPD	ΔE[c] CCSD(T)	ΔE[d] CASSCF	ΔE[e] CASPT2	n_1	n_2	N_U
14a	H	H	12.3	13.1	30.0	10.3	1.88	0.15	0.25
16a	H	H	17.4	18.8	34.1	13.7	1.82	0.21	0.39
17a	H	H	6.6	−107.6	28.2	−1.2	1.31	0.72	1.87
31a	H	H	19.8	11.7	35.4	7.3	1.41	0.62	1.57
15a	H	H	−75.2	−79.5	−71.7	−79.0	1.93	0.09	0.08
14b	Me	Me	12.1	12.2	28.4	9.6	1.89	0.13	0.23
16b	Me	Me	15.3	16.0	35.7	11.5	1.84	0.18	0.31
17b	Me	Me	7.8	−54.8	33.2	−2.3	1.40	0.63	1.64
31b	Me	Me	19.2	7.6	38.4	5.8	1.41	0.62	1.56
15b	Me	Me	−74.8	−80.6	−70.6	−79.8	1.94	0.08	0.07
14c	Me	Ph	11.5	11.5	33.4	7.3	1.91	0.12	0.20
16c	Me	Ph	10.6	11.8	36.2	6.9	1.90	0.12	0.21
17c	Me	Ph	0.5	−48.0	33.7	−7.1	1.30	0.70	1.78
31c	Me	Ph	13.7	−3.5	32.3	2.8	1.37	0.66	1.68
15c	Me	Ph	−74.8	−80.1	−58.1	−81.1	1.90	0.11	0.17

[a]The occupation numbers and N_U are taken from (12,10)CASSCF/def2-TZVP calculations. [b]B2PLYPD/def2-TZVP//B2PLYPD/6-31G*. [c]CCSD(T)/def2-TZVP//B2PLYPD/6-31G*. [d](12,10)CASSCF/def2-TZVP//B2PLYPD/6-31G*. [e]CASPT2/def2-TZVP//B2PLYPD/6-31G*.

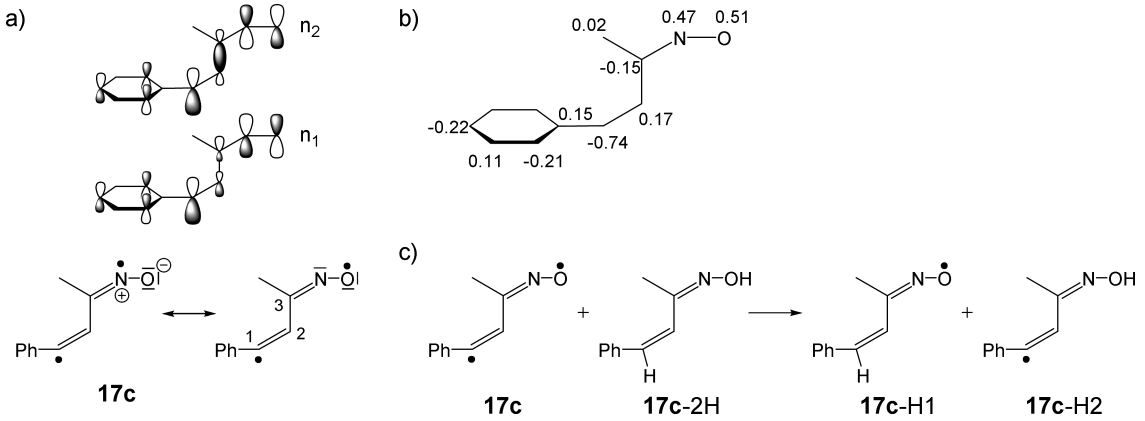

Figure 3. (a) Schematic representation of the linear combinations of the frontier orbitals (n_1 and n_2) of the intermediate state **17c**. (b) Mulliken atomic spin densities of **17c** taken from UB3LYP calculation. (c) Isodesmic equation for the evaluation of the diradical stabilization energy in **17c**.

from a perfect diradical, in which a uniform distribution is found. One reason for this can be seen by looking at the two frontier orbitals n_1 and n_2 of **17c** (Figure 3a). The largest coefficient can be found at the carbon atom C1, the oxygen atom, and the nitrogen atom. Thus, the diradical **17c** can be represented by two resonance formulas, which are shown in Figure 3a. Please note that the aromatic unit in **17c** is rotated in such a way that the π orbitals of the phenyl group interact with the nonbonding orbitals of the radical center and not with the π orbitals of the C═C−C═NO unit. Because the nitrogen atom represents a radical center (Figure 3b), a through-bond interaction[29] between the orbital located at the nitrogen and

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Scheme 7. 1,3-Dipolar Cycloaddition of the Dipoles 32 to Phenylacetylene (13c)

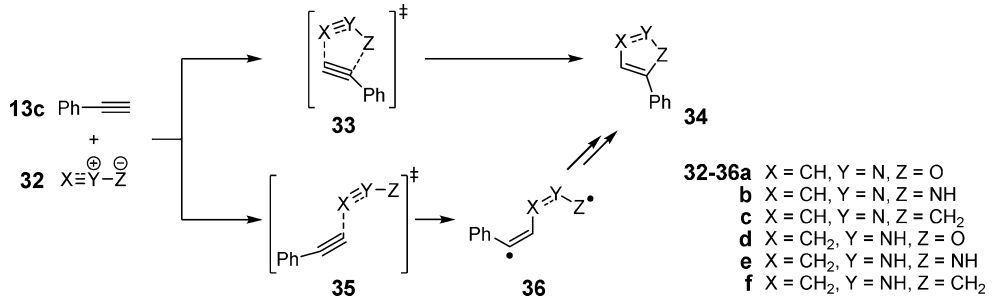

Table 4. Energies (ΔE in kcal/mol) of the Transition States (33 and 35), Intermediate States (36), and Products (34) Relative to the Corresponding Starting Materials (13c and 32)

	X	Y	Z	ΔE^a B2PLYPD	ΔE^b B2PLYPD	ΔE^c CCSD(T)	ΔE^d UB3LYP
33a	CH	N	O	9.6	12.0	12.5	17.0
34a	CH	N	O	−84.5	−75.8	−79.8	−73.5
35a	CH	N	O	9.7	11.8	13.7	14.7
36a	CH	N	O	−4.2	0.4	−68.0	−2.8
33b	CH	N	NH	5.0	6.4	6.9	12.6
34b	CH	N	NH	−108.7	−101.8	−104.1	−97.3
35b	CH	N	NH	6.7	8.3	10.3	10.9
36b	CH	N	NH	−9.2	−4.7	−8.7	−7.8
33c	CH	N	CH_2	5.2	6.2	6.3	13.1
34c	CH	N	CH_2	−97.2	−89.3	−92.4	−81.9
35c	CH	N	CH_2	4.6	6.5	8.4	9.8
36c	CH	N	CH_2	−14.9	−10.6	−11.1	−9.3
33d	CH_2	NH	O	8.8	11.5	12.1	16.8
34d	CH_2	NH	O	−53.9	−45.6	−49.9	−40.9
35d	CH_2	NH	O	10.8	13.2	15.5	14.7
36d	CH_2	NH	O	6.1	9.7	7.1	3.9
33e	CH_2	NH	NH	3.5	5.5	6.2	12.0
34e	CH_2	NH	NH	−68.9	−62.4	−66.6	−56.9
35e	CH_2	NH	NH	8.5	10.3	12.5	13.7
36e	CH_2	NH	NH	1.7	4.5	5.0	0.4
33f	CH_2	NH	CH_2	−1.5	−0.3	0.0	6.6
34f	CH_2	NH	CH_2	−88.0	−79.2	−84.1	−71.1
35f	CH_2	NH	CH_2	3.0	5.2	6.5	9.6
36f	CH_2	NH	CH_2	*e*	*e*	*e*	*e*

[a]B2PLYPD/6-31G*. [b]B2PLYPD/def2-TZVP//B2PLYPD/6-31G*. [c]CCSD(T)/def2-TZVP//B2PLYPD/6-31G*. [d]UB3LYP/def2-TZVP//B2PLYPD/6-31G*. [e]No stationary point found.

the orbital at the radical carbon atom can occur. This interaction leads to the raising of n_2, which represents the bonding linear combination of the orbitals of the radical centers. This kind of interaction also stabilizes the cyclic 1,4-diradical (*p*-benzyne) intermediate by 3−5 kcal/mol[30] and has been implicated in other processes.[31] To evaluate the magnitude of this interaction, we used the isodesmic reaction shown in Figure 3c. The thus calculated (B2PLYPD/def2-TZVP//B2PLYPD/6-31G*) diradical stabilization energy of **17c** amounts to 10.5 kcal/mol.

The sum of unpaired electrons (N_U) is, with a value of 1.6−1.9 electrons, very large in the case of the intermediates **17** and the transition states **31**. At such high values, the use of one-determinant methods such as B2PLYPD and CCSD(T) should be considered critically. As a method of choice, the CASPT2 approximation has to be used, because it takes the dynamic and nondynamic correlation into account. A comparison of the energy of the intermediates **17** and the transition states **31** shows that the energies from the CASSCF calculations are too high because no dynamic correlation was taken into account. The values of the B2PLYPD method are up to 13 kcal/mol too high, which is due to the aforementioned fact that it cannot describe properly the nondynamic correlation effects. The same applies to the CCSD(T) values, which are more than 100 kcal/mol too low. Such strong differences between the CCSD(T) and the CASPT2 values (>18 kcal/mol) were already found in the calculation of a diradical, which is formed from 1,3-diacetylene in the 1,2′-dimerization.[10b] This is probably a systematic error due to the usage of the one-determinant method CCSD(T) for a species with high diradical character.

The CASPT2 values of the transition states **14** and **16** show the same behavior as the above-discussed B2PLYPD data. In the case of acetylene and methylacetylene, the concerted mechanism is preferred; in the case of phenylacetylene, the stepwise diradical runs favorable. The transition states **31** are always lower in energy as compared to the transition states **16**. Thus, the rate-limiting step is the addition; the rotation around the newly formed single bond proceeds rapidly.

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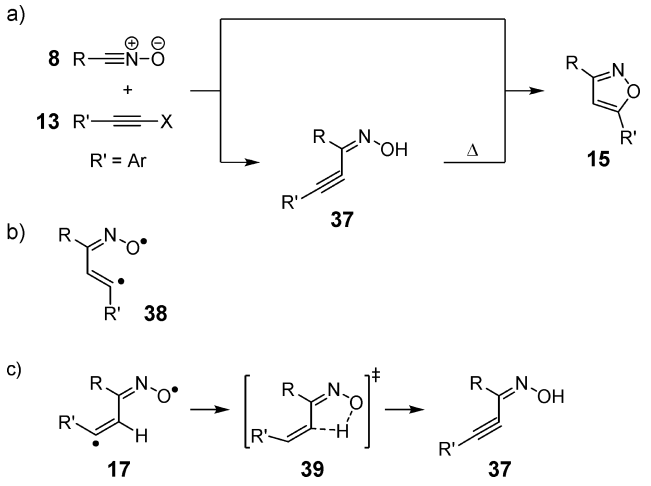
Scheme 8. (a) Reaction of Nitrile Oxides 8 with Arylacetylenes 13 to Isoxazoles 15 and α-Acetylenic Oximes 37; (b) the *syn*-Diradical 38 Was Proposed as Intermediate for the Reaction to the α-Acetylenic Oximes 37; and (c) Hydrogen Transfer from the *anti*-Diradical 17 to the α-Acetylenic Oximes 37



b. Model Study on the Cycloaddition of 1,3-Dipoles with Phenylacetylene. As shown in the previous chapter, the 1,3-cycloaddition proceeds partially or completely in a two-step *anti*-diradical mechanism if an aryl group is attached to the sp atom of the alkyne. We wanted to investigate whether the diradical mechanism takes also place in the cycloaddition of other 1,3-dipoles. Therefore, we have calculated the stepwise and the concerted mechanism of phenylacetylene to the 1,3-dipoles **32** (Scheme 7). The optimization of the stationary points was again performed by B2PLYPD/6-31G*. Afterward, the energies of these optimized structures were computed with B2PLYPD, CCSD(T), and UB3LYP in conjunction with the def2-TZVP basis set. The obtained data are listed in Table 4.

It turns out that only in the case of the fulminic acid (HC≡NO) and the formonitrile ylides (HC≡NCH$_2$) the transition states **33** and **35** have similar energies and thus could drive the reaction through both mechanisms. Depending on the method used, either **33** or **35** is energetically preferred, but the difference is always low. In all other cases, the concerted mechanism is always favored as compared to the stepwise. Interestingly, the azomethine betaines (H$_2$C═NZ) favor the concerted mechanism more strongly than the corresponding nitrilium betaines (HC≡NZ). This can be explained analogous to the effect of alkenes versus alkynes during the cycloaddition with nitrile oxides. The nitrilium betaines (HC≡NZ), which have a CN triple bond, show an additional stabilization of the transition states **35** due to the interaction of π orbitals of the nitrilium betaines, which are perpendicular to the reacting orbitals, with the corresponding π orbitals of the phenylacetylene. The azomethine betaines (H$_2$C═NZ) lack this stabilizing conjugative effect in the transition states **35**, so that **33** is always energetically more favorable.

c. Experimental Hints for Diradical Formation in 1,3-Cycloadditions of Nitrile Oxides to Arylacetylenes. The performed calculations show that during the 1,3-cycloaddition of nitrile oxides and nitrile ylides with acetylenes, which have an aryl group bonded at the sp carbon, the stepwise mechanism is also possible. Two questions that immediately arise are: Do experimental results support this assumption, and is there already evidence for the *anti*-diradical mechanisms that has been overlooked or misinterpreted? The experimental data favor the concerted mechanism especially when steoreochemistry is considered as stereochemical information is always retained at the dipolarophiles.[7a] These findings do not contradict the above-mentioned results, which clearly predict a preference for the concerted reaction path for alkenes. In the case of alkynes, because there is no stereochemical information that is maintained during the reaction, there is no way to determine the mechanism of alkynes in an analogous manner. The mechanism for alkynes has always been based on the results for the alkenes. Yet as shown above, this assumption is no longer valid.

When searching for an experimental confirmation of the above statements, one must therefore look for features that only occur during the reaction with arylacetylenes. For this, there are in fact some examples. Thus, one finds in the reaction of aliphatic and aromatic nitrile oxides (**8**) with arylacetylenes (**13**, R′ = aryl) that, in addition to the formation of the isoxazoles **15**, also the corresponding α-acetylenic oximes **37** are formed (Scheme 8a).[32] The isolated oximes **37** can subsequently be transformed into the corresponding isoxazoles **15** by heating.[32a] Because of a series of kinetic investigations,[33] it was vigorously debated whether the α-acetylenic oximes **37** were formed via the *syn*-diradical **38**[34] (Scheme 8b) or through another intermediate, which may represent a zwitterion.[23] One of the objections to the postulated *syn*-diradical **38** was the fact that the rate of formation of **37** increases with the electron density at the aromatic R′.[23]

These experimental results can easily be interpreted using the above-mentioned calculations as follows: The α-acetylenic oximes **37** are formed starting from the *anti*-diradicals **17** by a hydrogen transfer from the carbon to the oxygen atom via the transition states **39** (Scheme 8c). According to CASPT2/def2-TZVP//B2PLYPD/6-31G* calculations, the energy of the transition state **39c** (R = Me, R′ = Ph) amounts to only 4.7 kcal/mol relative to the *anti*-diradical **17c**. In sum, the observed isoxazoles **15** can be formed both by a concerted one-step mechanism as well as via the *anti*-diradicals **17**. The fact that this phenomenon is only observed for arylacetylenes and that electron-rich aromatic compounds increase the rate of formation of **37** confirm the calculations predicting a favorable formation of *anti*-diradicals under these conditions.

■ CONCLUSION

We were able to show that the energetically preferred reaction path for 1,3-dipolar cycloadditions is not always a concerted one-step mechanism. In some cases, a two-step mechanism, which proceeds via an *anti*-diradical, is equal in energy or even energetically preferred. Conditions for a stabilization of the *anti*-diradical are, on the one hand, the presence of a triple bond in the 1,3-dipole as well as in the dipolarophile. On the other hand, the dipolarophile is required to have an aryl group as a substituent stabilizing the resulting *anti*-diradical. The more electron-rich these aromatic units are, the stronger the *anti*-diradical transition state is stabilized relative to the concerted state. A proof of the existence of *anti*-diradical intermediates is the formation of α-acetylenic oximes, which were already described in the literature. Their formation is only observed if the above conditions are met and their origin can be explained by a hydrogen transfer starting from the *anti*-diradical.

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COMPUTATIONAL DETAILS

All calculations were performed by using the program packages Gaussian 09[35] and MOLPRO.[36] The geometrical parameters of the stationary points were optimized by means of B2PLYPD[15] in conjunction with the 6-31G*[16] basis set. For all stationary points, no symmetry restriction was applied. Frequency calculations were carried out at each of the structures to verify the nature of the stationary point. It turned out that all transition states have exactly one imaginary frequency, whereas all other stationary points have none. The energies of the stationary points were calculated using UB3LYP,[21] B2PLYPD, CCSD(T),[17] (12/10)CASSCF,[25] and (12/10)CASPT2/6-31G*.[26] The def2-TZVP[18] basis sets were employed.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02230.

Cartesian coordinates and absolute energies for all calculated compounds, and complete refs 35 and 36 (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

This work is dedicated to Professor Frank-Gerrit Klärner on the occasion of his 75th birthday.

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