Cycloaddition of Benzonitrile Oxide to Acetonitrile, Propyne and Propene – A Comparative Theoretical Study of the Reaction Mechanism and Regioselectivity

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Quantum chemical calculations (MP2/6-31G* and B3LYP/6-31G*) were used to compare the reactivity, regioselectivity and orbital involvement of the reaction of benzonitrile oxide with the dipolarophiles acetonitrile, propyne and propene. All reactions are thermodynamically favoured. The product stability decreases in an order propyne > acetonitrile > propene, and reflects the degree of aromatic stabilisation of the product. The activation barriers depend strongly on the computational method used and decrease in the expected order of increasing reactivity (acetonitrile > propyne > propene) in the MP2 calculations, but are similar to each other when B3LYP is applied. The regiochemistry is correctly predicted for all reactions and the experimentally observed regioisomer is both thermodynamically and kinetically favoured. The transition state geometries indicate that, in some of the reactions, the benzonitrile oxide does not interact through its frontier orbitals, as traditionally assumed. Instead, the FMO±2 are involved in the reaction, indicating that the classical FMO concept should be applied with care as it might lead to wrong conclusions.

Introduction

Five-membered heterocycles can be synthesised in a convenient and atom-economic way through [2+3] cycloaddition of appropriate dipolar reagents with dipolarophiles containing a carbon–carbon or carbon–hetero multiple bond.[1] Thus, isoxazoles and isoxazolines can be prepared by cycloaddition of nitrile oxides to alkynes or alkenes.[2] This method is fairly general and complements classical condensation methods because of its higher functional group compatibility and the use of milder reaction conditions. Cycloadditions of nitrile oxides with C≡N bonds, in contrast, are still rare in the literature and much restricted to aromatic or electron-deficient nitriles.[3] Therefore, classical condensation reactions, as for example the Tiemann condensation of amidoximes with acid chlorides or anhydrides, are still widespread in the synthesis of 1,2,4-oxadiazoles.[4]

The limited application range of the C≡N bond in cycloadditions is also illustrated in the reaction of nitriles with nitrones. This reaction is equally restricted to electron-deficient nitriles,[5] but becomes much broader in scope and occurs under far milder conditions if the nitrile is coordinated to an appropriate metal centre.[6] In our previous computational study, we found that the reaction is indeed a concerted pericyclic reaction. However, its thermodynamic driving force is generally low and its activation barrier is high. Electron-withdrawing substituents or the presence of a Lewis acid facilitate the reaction by reducing the activation barrier and by stabilising the product.[7]

In the framework of our research project on the extension of the chemistry of nitriles and the development of new methods for the synthesis of heterocycles, we now became interested in comparing the behaviour of nitriles as dipolarophiles in the cycloaddition with nitrile oxides with the corresponding reaction of alkenes and alkynes, for which more experimental and theoretical material exists. Our computational study aims to analyse in how much the mechanisms of these reactions are related, or whether there is a principal difference between reactive dienophiles such as alkynes or alkenes, and unreactive ones like nitriles. We also expect to understand the reactivity scale of the dipolarophiles chosen, and the regioselectivities of the individual reactions. Information on the orbital interactions involved in the reaction will give additional insight into the reaction mechanism and show up possibilities how to influence these reactions.

Computational Details

Calculations were performed with the programme packages GAMESS(US)[8] and GAUSSIAN98.[9] For visualis-

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ation of the results MOLDEN[10] and MOLEKEL[11] were used. Molecular geometries were fully optimised on MP2 and B3LYP levels of theory, using the standard basis set 6-31G* [12] for all atoms. The harmonic vibrational frequencies of stationary points were computed in order to characterise them as local minima (no imaginary frequency found) or transition states (only one imaginary frequency exists). Reaction pathways were traced from the transition states towards both directions along the imaginary mode of vibration using the algorithm developed by Gonzáles and Schlegel.[13] All transition states were found to correctly connect the reactants and products.

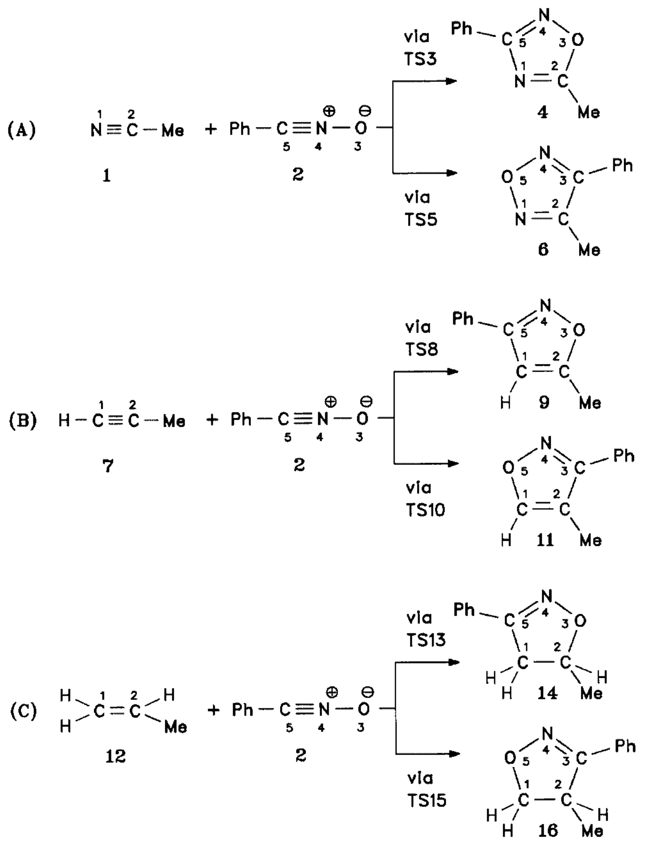
Results and Discussion

For the present study, acetonitrile, propyne and propene were chosen as dipolarophiles because of the different nature of their dipolarophilic centre. At the same time, other parameters such as steric bulk and electronic influence of the substituents were retained as constant as possible. Benzonitrile oxide was selected to keep close to the type of nitrile oxides most frequently used in organic synthesis.

Thermodynamic Considerations

Full geometry optimisations were performed on MP2/6-31G* and B3LYP/6-31G* levels of theory for benzonitrile oxide (**2**), the dipolarophiles acetonitrile (**1**), propyne (**7**) and propene (**12**), and the corresponding regioisomeric cycloaddition products **4** and **6**, **9** and **11**, **14** and **16**, whose structures are shown in Scheme 1.

The relative energies given in Table 1 show that the formation of all products is thermodynamically favourable. The values provided by MP2 and B3LYP calculations show similar trends, both with respect to chemo- and regioselectivity of the reaction. However, the relative energy values obtained with the DFT method are slightly higher. The reaction of benzonitrile oxide with propyne is most exothermic, followed by the reaction with acetonitrile. This is plausible because the products of both reactions are aromatic, and the reaction energy, in a first approximation, is thus a sum of the change in bond energy and the resonance energy. In the reaction with propene, considerably less energy is released because the products **14** and **16** are not aromatic. Their relative energy therefore reflects the change in bond energy only. From the difference in the relative energy of **14** vs. **9** or **16** vs. **11**, the resonance energy of isoxazoles roughly estimates to 34−36 kcal/mol, independent whether MP2 or B3LYP results are used. In the same way, the relative energies of the products of reaction of acetonitrile with a nitrone[7] or nitrile oxide can be compared to estimate the resonance energy of the 1,2,4-oxadiazole to approximate 35.6−37 kcal/mol. Both values are in the same range as the experimental value of benzene (36 kcal/mol),[14] although the heterocycles are expected to be less resonance-stabilised than benzene.



Scheme 1. Reactions studied

Table 1. Relative energies [kcal/mol] and dipole moments [Debye] for the reactions of benzonitrile oxide (**2**) with acetonitrile (**1**), propyne (**7**) and propene (**12**); relative energy of dipolarophile + dipole = 0 kcal/mol

Reaction	MP2/6-31G*					B3LYP/6-31G*			
	Reactant	Transition state		Product		Transition state		Product	
	μ	E	μ	E	μ	E	μ	E	μ
1 + **2** → **4**	2.0	+12.4	1.8	−50.1	1.9	+14.6	1.2	−48.1	1.6
1 + **2** → **I5**	8.9	+13.0	7.4	+12.9	7.1	+28.3	6.5	–	–
I5 → **6**	7.1	+13.6	6.5	−23.2	5.0	–	–	−18.1	4.3
7 + **2** → **9**	4.9	+6.4	3.4	−82.1	3.9	+14.9	2.7	−74.7	2.9
7 + **2** → **11**	5.8	+8.3	4.5	−79.1	4.4	+18.5	4.0	−69.7	3.1
12 + **2** → **14**	5.0	+4.5	3.3	−47.7	3.8	+14.1	2.7	−38.6	3.2
12 + **2** → **16**	5.4	+5.0	3.7	−45.1	4.6	+17.1	3.2	−34.5	3.3

Alkynes are known to be weaker dipolarophiles than alkenes in the cycloaddition with nitrile oxides.[15] With monoalkyl-substituted alkynes or alkenes, the reactions are regioselective to produce 3,5-disubstituted isoxazoles or isoxazolines.[16] Nitriles are less reactive than alkenes or alkynes and produce 3,5-disubstituted oxadiazoles exclusively, no formation of the regioisomeric 3,4-substituted 1,2,5-oxadiazole was ever observed experimentally. The calculated relative energies of the products thus do not reflect the experimentally observed reactivity scale, indicating that the reactions are not thermodynamically controlled. However, in all cases, the experimentally observed product is lower in energy than the corresponding regioisomer, thermodynamic control of the reactions would therefore leave the regioselectivities unchanged.

Kinetic Aspects

The transition states for all reactions shown in Scheme 1 were located. Their MP2-geometries are presented in Figures 1 and 2, characteristic bond lengths are given in Table 2. The hypothetical reaction of acetonitrile to produce the experimentally not observed 1,2,5-oxadiazole **6** was found to occur through a two-step reaction when MP2 was used, whereas all other reactions are concerted and involve rather symmetric transition states.

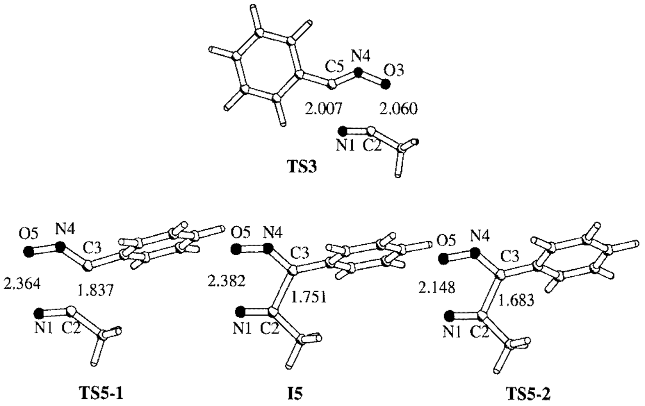


Figure 1. Transition states and intermediate in the reaction of benzonitrile oxide with acetonitrile

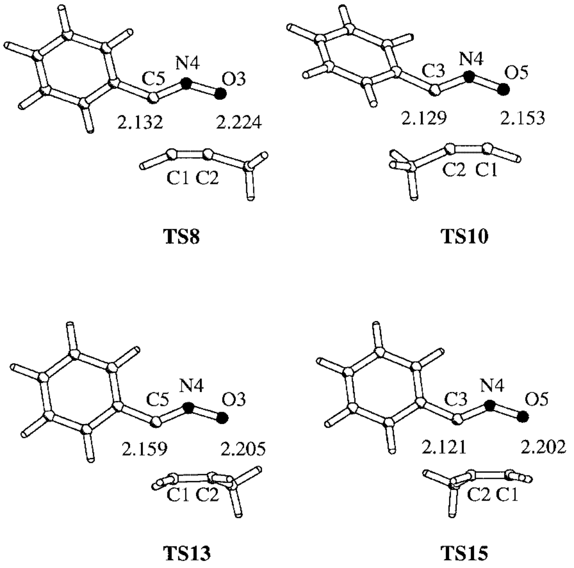


Figure 2. Transition states in the reaction of benzonitrile oxide with propyne and propene

The relative energies of the transition states depend strongly on the computational method used. With MP2, the activation barriers are lowest for the reaction with propene and highest for the reaction with acetonitrile. The experimental reactivity scale is thus correctly reproduced, suggesting that the reactions are kinetically controlled. In all cases, the transition state leading to the experimentally observed regioisomer is lower in energy, indicating that also the regiochemistry is correctly predicted under kinetic control of the reaction. In contrast to the good performance of MP2, B3LYP gives poor results for the relative energies of transition states. Although the regioselectivity for each individual dipolarophile is correctly reproduced, the chemoselectivity cannot be predicted with B3LYP since all transition states have similar relative energies (14.1−14.9 kcal/mol).

Overall, the cycloadditions of benzonitrile oxide to acetonitrile or propyne both lead to aromatic products of high stability, however, the transition states of these reactions appear not to benefit from any aromatic stabilisation. This

Table 2. Selected bond lengths [Å] and angles [°] for transition states **TS3**, **TS5-1**, **TS5-2**, **TS8**, **TS10**, **TS13**, **TS15** and intermediate **I5**

	TS3	**TS5-1**	**I5**	**TS5-2**	**TS8**	**TS10**	**TS13**	**TS15**
1−2	1.208	1.222	1.229	1.229	1.246	1.247	1.378	1.382
2−3	2.060	1.837	1.751	1.683	2.224	2.153	2.205	2.202
3−4	1.252	1.263	1.265	1.268	1.225	1.229	1.231	1.232
4−5	1.229	1.213	1.209	1.216	1.243	1.247	1.247	1.251
5−1	2.007	2.364	2.382	2.148	2.132	2.129	2.159	2.121
1−2−3	107.26	114.57	116.47	116.10	101.00	103.55	100.58	94.03
2−3−4	94.48	103.03	104.72	104.33	96.01	98.09	98.40	97.42
3−4−5	135.25	138.17	137.67	130.39	138.91	136.90	138.29	137.12
4−5−1	99.33	88.76	87.49	93.92	96.70	96.48	98.35	97.55
5−1−2	103.69	95.42	93.61	95.25	107.37	104.96	104.03	102.70
1−2−Me	151.23	140.04	136.54	134.11	162.37	155.20	122.14	121.06
N−C−Ph	141.02	129.55	127.23	126.99	133.60	132.16	132.24	131.40

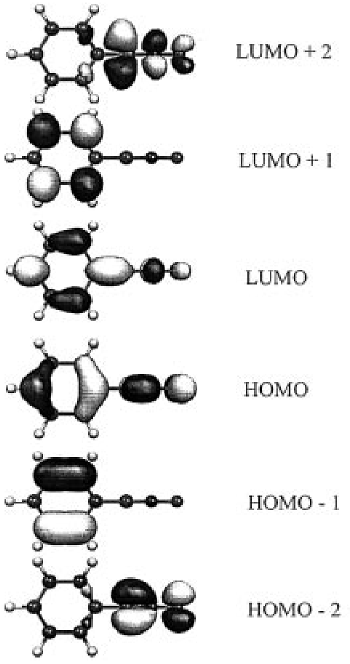


Figure 3. Relevant orbitals of benzonitrile oxide

suggests that the stabilising effect of aromaticity builds up late, when the reaction has passed the transition state already. With this, the cycloadditions of nitriles or alkynes are mechanistically very similar to each other. On the other hand, they differ from reported aromaticity-driven Diels−Alder reactions of quinodimethanes. These reactions were described as both kinetically and thermodynamically more favourable than corresponding reactions leading to a non-aromatic product, and the authors interpreted their results with an early build-up of aromaticity on the reaction coordinate leading to an aromatic stabilisation of the transition state.[17,18]

Orbital Involvement

Frontier orbital considerations are frequently used in organic chemistry to explain experimentally observed reactivities and selectivities of cycloaddition reactions. This approach is comparatively safe as long as double bond systems are involved in the reaction. However, care must be taken with triple bonds because the orbitals building up the two orthogonal π-bonds are often energetically not degenerate, as shown for benzonitrile oxide in Figure 3. The HOMO/LUMO pair is orthogonal to the plane of the phenyl ring and delocalised over both the CNO moiety and the aromatic ring. The next lower occupied orbital (HOMO−1) and the next higher unoccupied orbital (LUMO+1) are restricted to the aromatic ring. The HOMO−2/LUMO+2 orbital pair is located at the nitrile oxide CNO atoms only and in plane with the aromatic ring. Both HOMO/LUMO or HOMO−2/LUMO+2 are potentially suited in terms of their symmetry to interact with a dipolarophile, and only analysis of the transition state geometry of a reaction can reveal which orbital pair is relevant for the bond formation. This is occasionally overlooked, as, for example, in a recent computational study of the reaction of phenylazide with alkenes where FMO interaction is discussed in the text, although the depicted transition state shows that the attack of the reagent occurs from a direction orthogonal to the one expected for an FMO interaction.[19]

The reactions analysed in the present study allow for a closer look at such effects and the parameters influencing the orbital interaction. The reaction of benzonitrile oxide with acetonitrile to give product **4** involves a transition state **TS3** in which the phenyl group is in plane with the heterocycle being formed in the reaction (see Figure 1). This implies that the reaction does not involve the frontier orbitals (HOMO/LUMO) but the HOMO−2/LUMO+2 orbital pair (see Figure 3). The CNO unit thus remains in conjugation with the π-system of the phenyl substituent in the course of the reaction, and the associated resonance stabilisation seems to compensate for the use of an energetically less favourable orbital. Surprisingly, the situation is totally different in the formation of the other regioisomer **6**. This reaction occurs via transition states **TS5-1**, **TS5-2** and an intermediate **I5** in which the phenyl group of the nitrile oxide is oriented perpendicularly to the newly forming heterocycle (Figure 1). This clearly indicates an interaction of the dipolarophile with the FMOs of the benzonitrile oxide. In the course of the reaction the conjugation of the phenyl substituent to the newly forming heterocycle is lost, but on the other hand, steric interaction of the phenyl group with the methyl substituent of the nitrile is reduced.

The cycloaddition of benzonitrile oxide to propyne shows similar trends. Also here, the experimentally observed regioisomer is formed through interaction of the nonconjugated HOMO−2/LUMO+2 orbitals rather than the FMOs, in order to retain the conjugation of the phenyl group to the newly forming heterocycle. The effect is less clear in this reaction because the phenyl group in **TS8** interacts with the hydrogen atom of the alkyne, leading to a tilt of the phenyl ring of 30° from the plane of the heterocycle (see Figure 2). In **TS10** yielding the less favourable isomer, the phenyl ring is rotated by approximately 60° to allow for involvement of the FMOs in the reaction, with loss of conjugation and avoidance of steric interaction with the methyl group at the alkyne.

Transition states **TS13** and **TS15** of the reaction with propene clearly show the phenyl group in-plane with the heterocycle being formed. Both reactions thus involve the FMO±2 orbitals in the formation of the regioisomeric products. Since the substituents of the alkene are not in-plane with the forming heterocycle, hardly any steric interaction with the phenyl group of the nitrile oxide emerges. Keeping in mind that the products of this reaction are not aromatic, it is the more surprising that conjugation of the phenyl substituent to a single neighbouring π-bond is sufficient to favour an FMO±2 involvement over an FMO one.

Overall, one can say that benzonitrile oxide preferentially involves the less delocalised orbital in the cycloadditions studied in this work, in order to conserve the delocalisation energy of the system as far as possible. Only if steric interactions of the substituents disfavour the approach of the reagent to the less delocalised orbital, the more conjugated one gets involved in the reaction. Traditional FMO considerations only look at electronic effects influencing the energies and coefficients of the frontier orbitals of the reactants. However, if substituents are compared which are electronically similar but sterically much different, the reactions can involve interaction of different orbitals and the FMO concept then is likely to fail. Such effects might have contributed to the difficulties to explain unexpected regioselectivities in dipolar cycloadditions of methyl propiolate with benzonitrile oxides and the sterically more hindered 2,4,6-trimethylbenzonitrile oxide.[20] For the latter case, the transition states of the reactions were calculated.[21] From their geometries, it can be seen that FMO interaction is relevant for the formation of both isomers. Unfortunately, the reaction with benzonitrile oxide was not calculated for comparison but the results of our work suggest a different orbital involvement in this case.

Reaction Mechanism

The transition state geometry indicates which orbital pair is relevant for the bond formation, but it does not allow for any conclusions about whether the occupied or unoccupied orbital is involved. For this purpose, orbital coefficients are used to determine nucleophilic and electrophilic centres of the reactants, then the intrinsic reaction pathway is calculated to determine whether the reactants have more nucleophilic or electrophilic character. For benzonitrile oxide, both LUMO and LUMO+2 show a high orbital coefficient at the carbon atom of the nitrile oxide, indicating that this carbon atom is electrophilic. The HOMO and HOMO−2, in contrast, has its highest orbital coefficient at the oxygen atom which thus is the most nucleophilic atom. Both propene and propyne show quite similar orbital coefficients at both carbon atoms. However, acetonitrile is clearly electrophilic at the carbon atom and nucleophilic at the nitrogen.

The IRCs (see Figures 4 and 5, and S1−S4 in the Supporting Information; for Supporting Information see also the footnote on the first page of this article) demonstrate that the mechanism of all three reactions is highly similar in being concerted but somewhat non-synchronous. The nitrile oxide's carbon atom attacks a bit earlier and the formation of the bond to the oxygen is slightly delayed. This suggests for all three dipolarophiles a control of the reaction by interaction of an unoccupied orbital of the dipole and an occupied one of the dipolarophile. For the reaction of alkyl-substituted alkynes and alkenes, this was observed previously.[22] However, it is known that for sufficiently electron-deficient alkynes both occupied and unoccupied orbitals are lowered in energy, and therefore, the interaction of an occupied orbital of the dipole and an unoccupied one of the dipolarophile can then dominate.[21] Nitriles appear to react according to exactly the same mechanism. Also here, experimental results indicate a change in orbital involvement when electron-deficient nitriles are used. The reaction of nitriles with nitrile oxides can therefore be classified as a Sustmann type II cycloaddition.

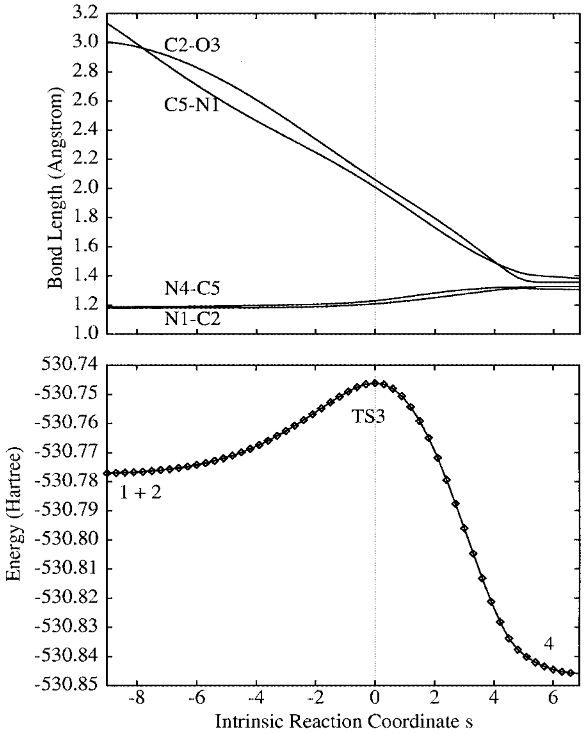


Figure 4. Intrinsic reaction coordinate [amu$^{1/2}$ Bohr] for the reaction **1** + **2** → **4**

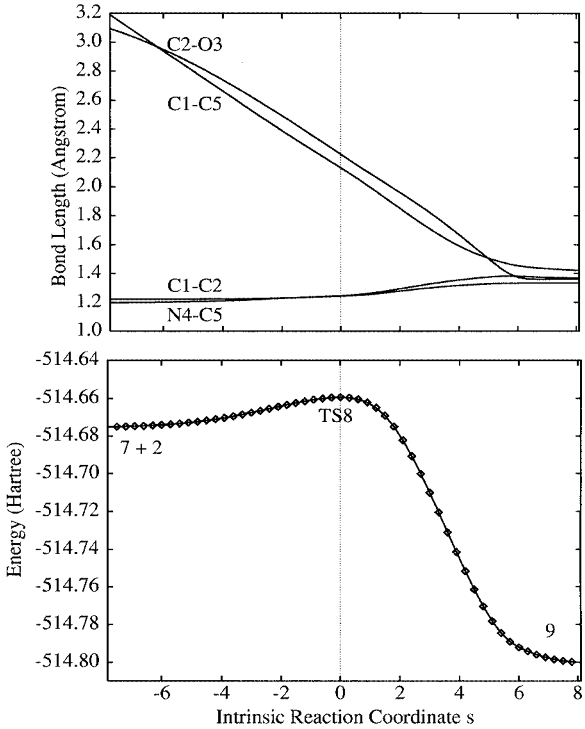


Figure 5. Intrinsic reaction coordinate [amu$^{1/2}$ Bohr] for the reaction **7** + **2** → **9**

With this, the reaction of nitriles with nitrile oxides differs mechanistically from the corresponding reaction of nitriles with nitrones. In the later case, the C−O bond forms a bit earlier than the C−N bond, and both substituent influence and quantum mechanical calculations [7] suggested that this reaction is dominated by an interaction of the LUMO of the nitrile with the HOMO of the nitrone.

Comparison of the dipole moments of starting materials and transition states (see Table 1.) can be used as a first approximation to estimate solvent effects. A different approach is based on analysis of local charges building up or cancelling in the course of the reaction. For this, the sum over the absolute value of the Mulliken or NBO charges of all atoms were calculated as a measure of the charge separation in the molecule (Table 3).

Table 3. Sum over absolute values of the NBO and Mulliken charges

Compound	ΣMulliken charge	ΣNBO charge
1 + **2**	5.026539	5.63614
TS3	5.463198	5.95362
4	5.851444	6.25188
1 + **2**	5.026539	5.63614
TS5-1	4.501536	4.92697
I5	4.478003	4.86438
TS5-2	4.419437	4.73546
6	4.193858	4.45129
7 + **2**	4.979376	5.37026
TS8	4.745572	5.16149
9	4.903295	5.66533
7 + **2**	4.979376	5.37026
TS10	4.473674	5.04998
11	4.452062	5.1273
12 + **2**	5.087757	5.99066
TS13	5.092861	5.92613
14	5.027608	5.86215
12 + **2**	5.087757	5.99066
TS15	4.978732	5.81308
16	4.799075	5.54455

The transition states of the reactions of benzonitrile oxide with propyne or propene (**TS8**, **TS10**, **TS13** and **TS15**) possess smaller dipole moments and bear less local charge than the starting materials. The same holds true for the reaction with acetonitrile through **TS5-1**, **I5** and **TS5-2** to give the regioisomer **6**. In all these cases, one would expect the transition states to be less stabilised by a polar solvent than the starting materials, leading to a slight increase of the activation barrier and reduced reactivity in polar solvents. Cycloaddition to the nitrile to give product **4** via transition state **TS3** occurs practically without change of the dipole moment, but the charge separation is increasing. The solvent dependence in this case is not predictable with simple means but requires more detailed calculations which are currently in progress.

Conclusions

Quantum mechanical calculations allow for a comparison of the reactivity of benzonitrile oxide with propene and propyne and confirm that formation of both possible regioisomers occurs through a concerted cycloaddition, with almost synchronous bond formation, the C−C bond being only slightly advanced. This indicates that interaction of an unoccupied orbital of the nitrile oxide with an occupied one of the dipolarophile is involved. Reaction with an alkyne is more exothermic since an aromatic product is formed, but reaction with alkenes occurs through a lower activation barrier and is thus kinetically preferred. The experimentally observed higher reactivity of alkenes can therefore be ascribed to kinetic control of the reaction. The regiochemistry of both reactions is correctly reproduced under both thermodynamic and kinetic control.

Acetonitrile reacts with benzonitrile oxide through an analogous concerted mechanism to give the 1,2,4-oxadiazole **4** exclusively. Also this reaction is dominated by interaction of an unoccupied orbital of the nitrile oxide and an occupied one of the nitrile. The activation barrier is considerably higher and the thermodynamic driving force is lower than for alkynes.

The transition state geometries reveal that benzonitrile oxide generally tends not to involve its FMOs in the reaction but rather the orthogonal FMO±2 orbitals. These orbitals are energetically less favourable, but on the other hand, their involvement in the bond formation does not cause any loss of conjugation of the CNO unit with the phenyl substituent. Only if steric interactions prevent interaction with the FMO±2, the reaction occurs under involvement of the FMOs and on expenses of the resonance energy that is lost by interrupting the conjugation of the phenyl group with the CNO moiety. Such a change of orbital interaction can complicate the application of the FMO concept to assess reactivities and selectivities of cycloadditions.

Overall, the results of our study allow for the following predictions: (a) Since the cycloaddition of benzonitrile oxide to nitriles was found to involve interaction of the occupied orbitals at the nitrile with unoccupied ones at the nitrile oxide, electron donation into the C≡N bond, for example, by suitable substitution or by coordination to an electron-rich metal centre, should promote the reaction. (b) Equally, Lewis acid coordination or electron-withdrawing substituents at the nitrile oxide are expected to promote the reaction. (c) In contrast to this, electron-withdrawing substituents on the nitrile are known to promote the reaction with nitrile oxides, supposedly by changing the mechanism towards an interaction of occupied orbitals at the nitrile oxide with unoccupied ones at the nitrile, according to a Sustmann type II mechanism. Thus, coordination of the nitrile to a Lewis acid is expected to exhibit a similar effect, equally resulting in an increased reaction rate. Further quantum chemical calculations and experimental work to verify these hypotheses are ongoing in our group.

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