Research Article

1,3-Dipolar Cycloaddition Reactions and Nitrones : An Overview

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Abstract

1,3-Dipolar Cycloadditions, sometimes called Huisgen Cycloadditions, after the name of the outstanding German chemist who contributed to the initial systematic study of these reactions, describes a class of reactions in which a 1,3-dipolar species reacts with a dipolarophile leading to 5-membered heterocycles. Examples of dipolarophiles are alkenes and alkynes and molecules that possess related heteroatom functional groups (such as carbonyls and nitriles).This article outlines the type and scope of the reaction with the special emphasis of cycloadditions of nitrones. Qualitative explanations on the basis of MO theory of the mechanism and selectivities are briefly discussed.

Keywords: 1,3-DC, nitrones, dipolarophiles, cycloadducts, FMO

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Introduction

A 1,3-dipolar species is a three atom four π-electron system with a central hetero atom, which is isoelectronic with allyl anion. The two terminal atoms can be carbon or heteroatomic, usually oxygen, nitrogen or sulphur. Dipolar species can be divided into two categories depending on whether the central atom is sp^2- or sp-hybridised; this implies that the species can be bent or linear respectively [1].1,3-dipolar species readily undergo cycloadditions to double bonds and triple bonds to furnish five-membered rings. 2 π-electrons of the dipolarophile and 4 π-electrons of the 1,3-dipolar species participate in a concerted pericyclic cycloaddition – suprafacial on both components. The reaction is therefore a ($_{\pi}2_s+_{\pi}4_s$) cycloaddition similar to the Diels-Alder reaction. Some authors still use "(2+3) cycloaddition", which counts the number of involved atoms but does not follow IUPAC recommendations which indicates number of participating electrons and the stereochemical modes. IUPAC recommends the use of "(2+3)" for the number of involved atoms instead.

Nitrones and nitrile oxides are important dipolar species which have been used in 1,3-dipolar cycloadditions (1,3-DC) to constitute 5-membered isoxazole ring systems Nitrones or azomethine N-oxides have the following characteristic functional group [2]. The name 'nitrone' is obtained from the contraction of the name 'nitrogen ketone' **(Figure 1)** [2].

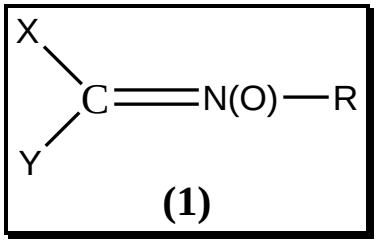


Figure 1 Representation of Nitrone as Nitrogen Ketone

These are formulated as 1,3-dipolar species, in which 4π electrons are delocalised over three atoms. In valence bond terms the structure of the nitrone functional group can be represented by the following canonical forms:

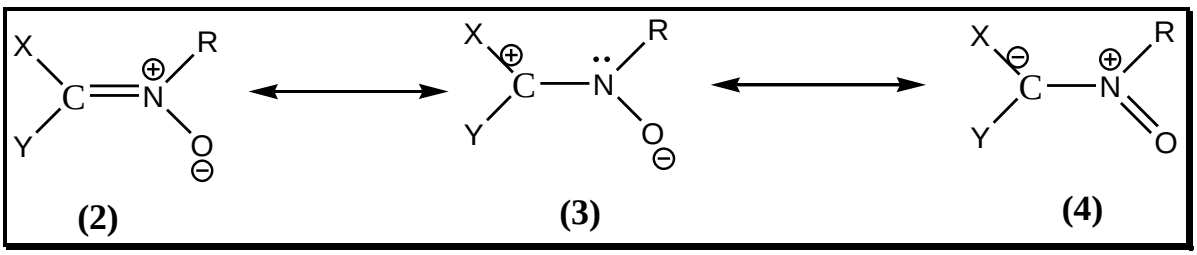


Figure 2 Different canonical forms of nitrones

Structures (**2**) and (**3**) are the most important contributing forms, with the contribution from (**4**) being negligible. **(Figure 2)** The positive charge is delocalised between the nitrogen and the α-carbon as represented resulting in a 1,3-dipolar structure. It has become customery to represent nitrones by structure (**2**).

The molecular orbital description [3] of the structure of nitrones involves a 4π-delocalised system, resembling that of the allyl anion. However, unlike the allyl anion, the nitrone group is highly polarised; this is reflected in the magnitude of the orbital co-efficients. Normally in the HOMO, the orbital co-efficient on oxygen is larger than on the carbon. In the LUMO, however, the orbital co-efficient is larger on carbon **(Figure 3)**, which is the electron-deficient centre and susceptible to nucleophilic attack.

Figure 3 Size of orbital coefficients in HOMO and LUMO of nitrones

The extent of electron delocalisation is influenced by the substitution on the carbon as well as on nitrogen; hence, these have a marked influence upon the reactivity of the nitrone functionality. MO calculations were carried out by the parent molecule (**5**) and its eight isomers, showing that formamide (**6**) is far more stable than the other isomers **(Figure 4)** [4]. However the calculated dipole moment of 4.99D was quite far from the experimental value of 3.37-3.47D. Subsequent *CNDO/2* and *INDO* calculations give results closer to the experimental value [5]. *CNDO/2* was also used to calculate the α- π-electron density of *C*-phenyl-*N*-methyl nitrone (**7**) [5].

Figure 4 Isomers : nitrone and formamide

Structures of nitrones

Nitrones are capable of *cis, trans*-isomerism. The predominance of a particular form depends on the relative size of the substituents and their polar character. In some instances the *E*- and *Z*-isomers have been separated and configurations assigned [6-9].

Most acyclic aldonitrones usually exist entirely as the Z-isomers (**7**). It has been found that in derivatives of (**7**) with highly substituted aryl groups, it was possible to isolate the stable E-isomer **(Figure 5)** [10].

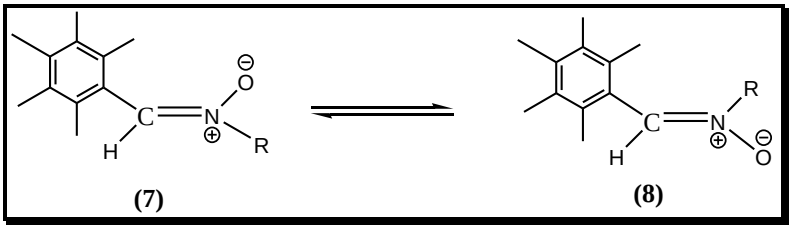


Figure 5 E/Z isomerism of nitrones

Structural investigations of Nitrones : X-Ray Crystallographic studies

Structures of some nitrones have been determined by X-ray crystallography. Folting, Lipscomb and Jerslev determined the structures of *C*-(4-chlorophenyl)-*N*-methyl nitrone (**9**) [11]. X-ray analysis confirmed the *trans*-disposition of the aryl and methyl groups in the *N*-methyl nitrone (**9**), and hence its ***Z***-configuration. The N-O bond length in (**9**) was 1.284 Å, considerably shorter than the N-O distance in isomeric syn oxime (1.480 Å) indicating the partial double bond character of this bond in nitrone. Moreover the C=N distance of 1.309 Å in the nitrones is longer

than the corresponding bond in the O-methyloxime 1.260 Å; this indicates a diminution of double bond character **(Figure 6)**. The corresponding data for *α,α,N*-triphenyl nitrone (**10**) are indicated in the formula [12].

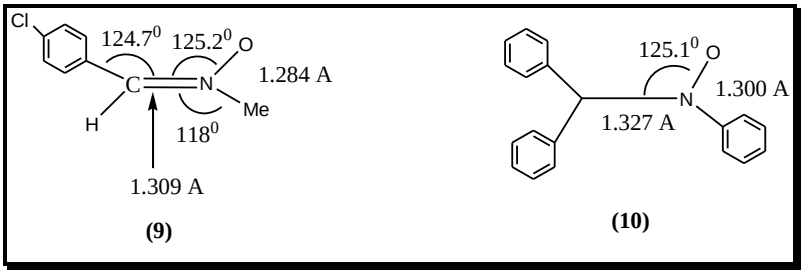


Figure 6 Structural data of two different nitrones

The nitrones and nitrile oxides can be regarded as masked 1,3-difunctionalised compounds and can be utilised as templates in various synthetic schemes.

The isoxazolidines are thus accessible from simple starting material; *viz.* olefins, aldehydes, ketones, nitro compounds and acetylenes from the dipolarophile side; and substituted hydroxylamines from the dipolar side. These isoxazolidines are fairly stable, allow considerable regiochemical and stereochemical control during cycloaddition, and can be functionalised to a certain extent.

Mechanistic considerations of 1,3-dipolar cycloaddition reactions: MO Interactions

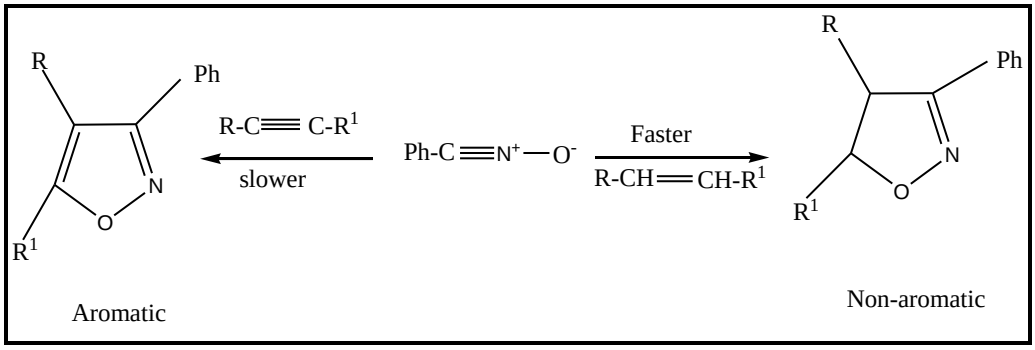
There are several common characteristic features of 1,3-dipolar cycloadditions (1,3-DC) irrespective of the structures of the reactants[13].

A great deal of attention has been devoted to the problem of timing of formation of the two bonds. Does this follow a pericyclic pathway with simultaneous formation of the new σ-bonds, or are the bonds formed successively with the intervention of a diradical or even a dipolar intermediate?

Earlier calculations on the formation of transition state (TS) led to ambiguous results depending on the theoretical method chosen [3, 14]. Earlier *ab initio* calculations favoured a symmetrical (or close to symmetrical) and early transition state formation, whereas parametricised MINDO calculations resulted in the prediction of a highly unsymmetrical and late transition state of zwitterionic and biradical character [3, 13]. In recent years the use of more sophisticated programmes such as B3LYP calculations based on the Density Functional Theory (DFT) give strong support for the concerted mechanism for the synchronised bond formation. In other words, the 1,3-dipolar cycloadditions are (π^4s+π^2s) pericyclic processes in general. Experimental data accumulated so far overwhelmingly support the concerted mechanism.

Some of these are summarised below:

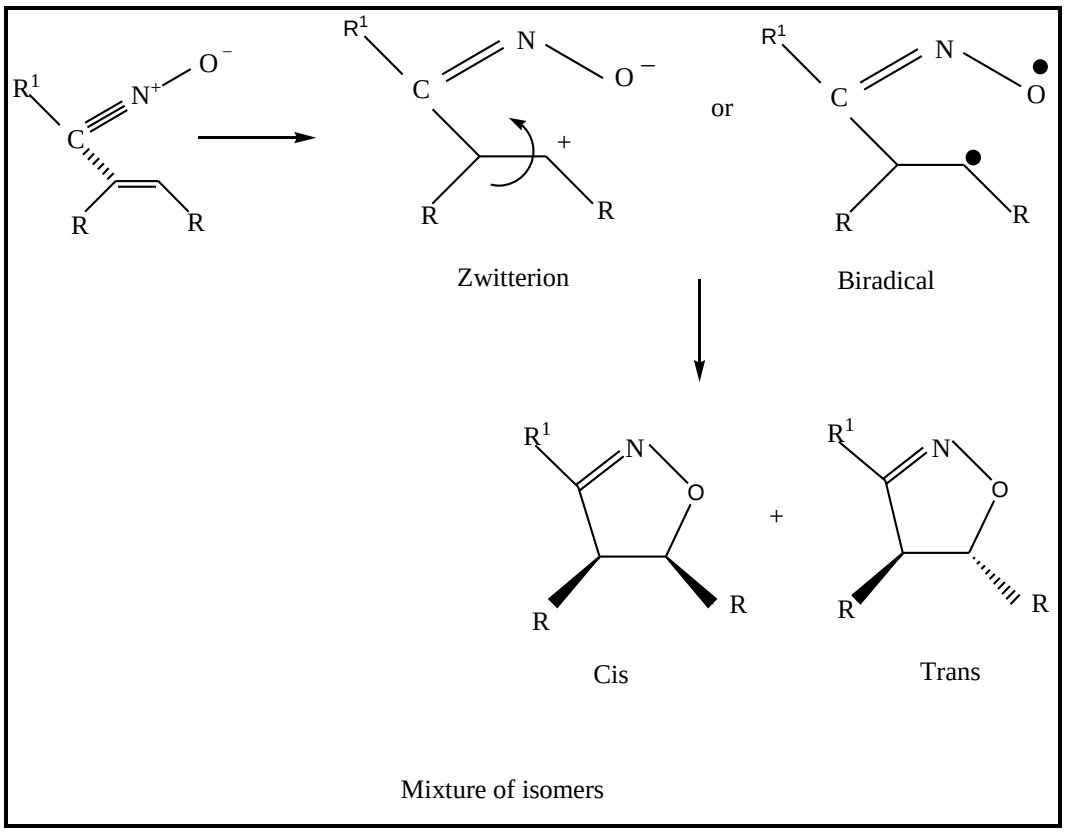
1. Second order rate constants for the cycloadditions of the benzonitrile oxides to various acetylenes have been found to be always smaller than those for the corresponding ethylenes (**Scheme 1**). Consequently the reactions with acetylenes which give aromatic isoxazoles, do not profit from gain in aromaticity and transition state is therefore located early on the reaction path [15].



Scheme 1

2. Solvent polarity effects on reaction rate are usually small, indicating the absence of zwitterionic intermediates in the TS. The solvation energy of the reactants is thus similar to that of TS.

3. The large negative entropy of activation[16(a-f)] (ΔS* about - 30eu) reveals a highly ordered TS resembling that of the Diels-Alder reaction. The activation enthalpies are comparatively modest (ΔH* about 15 Kcal mol^{-1}). All these data favour an early TS and synchronised formation of bonds.
4. Preservation of the steric relationships of the reactants in the product formed is a crieterion for synchronised bond formation. If stepwise formation of bonds occurs, *i.e.* formation of zwitterionic or biradical intermediates, there is probability of bond rotation and consequent loss of stereoselectivity. In the latter case presumably to some extent would give rise to stereoisomeric cycloadducts, unless the rotation is slow (rotation barrier is high) in comparison to the rate of cyclisation (**Scheme 2**).



Scheme 2

Careful analysis of the reaction products by chromatographic and NMR techniques have demonstrated the very high stereoselectivity of most 1,3-DC reactions [1-3,14-16].

The calculated rotation barriers for the hypothetical biradical intermediates would have to be 4 to 6 Kcal mol^{-1} for rotation to be slower than cycloadditions. These are considerably higher than the actual barrier to rotation of simple primary, secondary and tertiary alkyl radicals which vary between 0-1.2 Kcal mol^{-1}. Since the actual rotation barriers for the radicals are so low, there can actually be no cyclisation barrier and scrambling of relative stereochemistry will occur if diradical intermediates were actually involved. These considerations offer compelling evidence for the concerted pathway in which the formation of both bonds occurs in a concerted manner [3].

The FMO interactions of the reactants oriented in two parallel planes is schematically shown (**Figure 7**), for 1,3-dipolar species of both types. Lobe-signs (phases) are shown only, not the relative size of coefficients.

1,3-Dipolar Cycloaddition Reactions - Theoretical Considerations

The regio- and stereoselectivity of the cycloaddition process can be correctly predicted by considering frontier orbital interactions [17, 18]. Sustmann [18(a,b)] (1971) analysed these in detail for 1,3-Dipolar Cycloadditions which he classified into three types, *viz.*

I. **Type I:** The dipole HOMO-dipolarophile LUMO interaction is the predominant one. This is observed when electron-donating or conjugating substituents are present on the dipole and electron-withdrawing or conjugating substituents are present on the dipolarophile.
II. **Type II:** Both pairs of FMO interactions are of comparable importance.

III. **Type III:** The dipole LUMO-dipolarophile HOMO interaction predominates. This is observed when electron-donating or conjugating substituents are present on the dipolarophiles and electron-withdrawing or conjugating substituents on the dipole (reverse electron demand to Type I).

These are schematically shown in **Figure 8**.

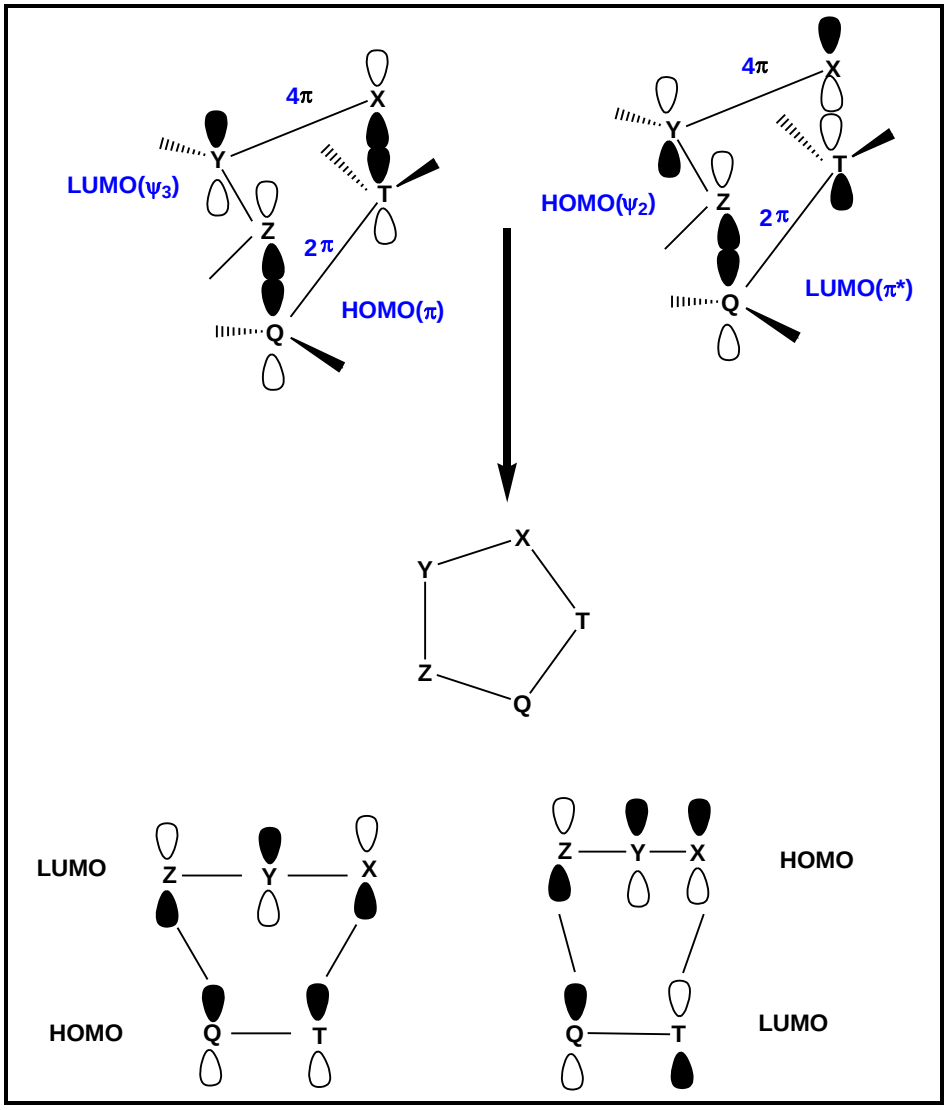


Figure 7 Molecular orbital interactions in 1,3-dipolar cycloadditions

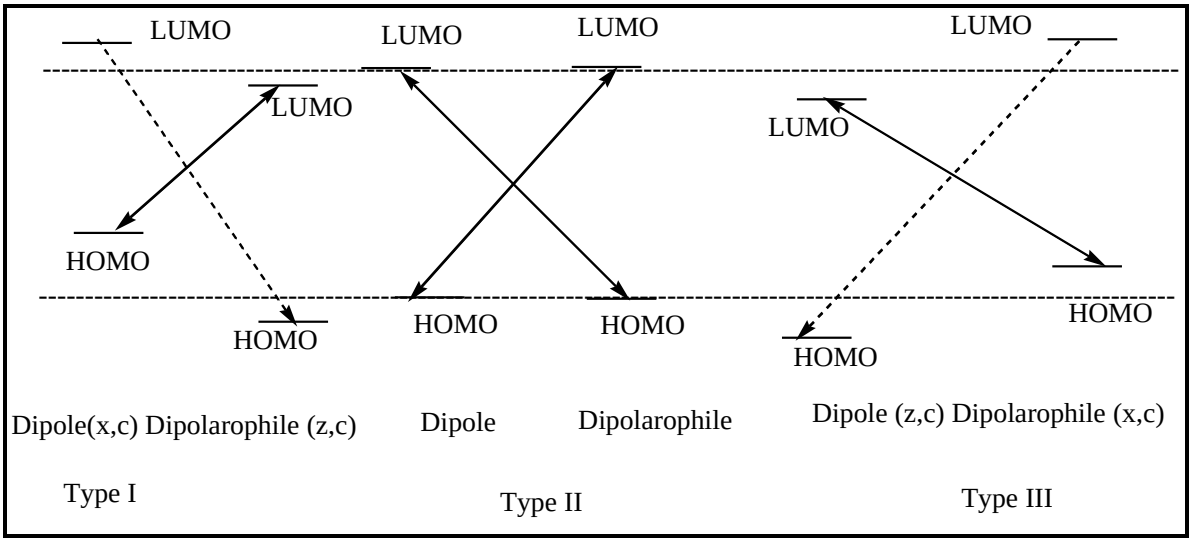


Figure 8 Schematic representation of HOMO-LUMO interactions and energy gaps in above three cases

The usual convention for denoting substituents is used.
X: represents electron-donating (+R) groups with a lone-pair: –OMe, -NR_2, -SR.
Z represents electron-withdrawing groups: –NO_2, -COR,-CO_2R, -SO_2R.
C represents groups which extend the conjugation: –CH=CH-, -Ph.

The size and energies of frontier orbitals of alkenes are affected by substituents in the following manner [17a,b] (schematically shown in **Figure 9**):

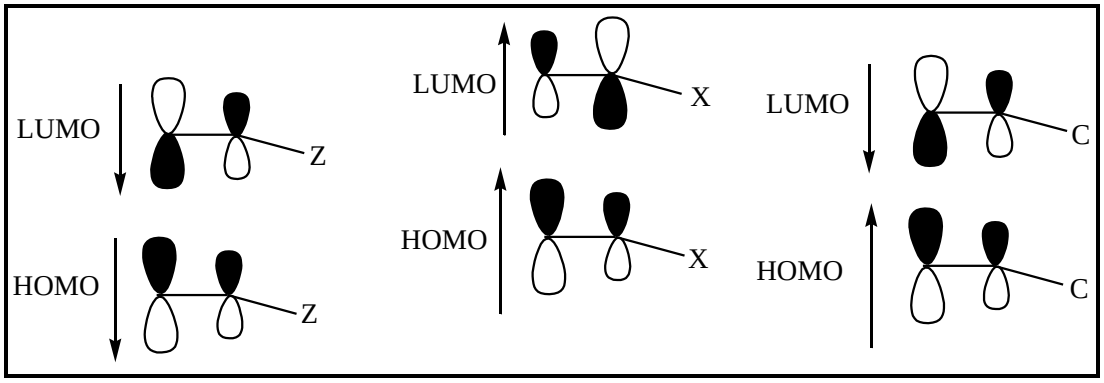


Figure 9 Size and energies of frontier orbitals of alkenes affected by substituents

1. Electron withdrawing groups decrease the energies of the HOMO and LUMO, the latter more than the former. In both HOMO and LUMO the unsubstituted end has the larger orbital coefficient.
2. Electron donating groups increase the energies of the HOMO and LUMO, the former more than the latter. The unsubstituted end in the HOMO has the larger coefficient than the substituted end. The relative magnitudes of the coefficients are reversed in the LUMO.
3. In conjugated alkenes the HOMO energy is raised and LUMO energy is lowered. The coefficient at the unsubstituted end is larger in both HOMO and LUMO.

Depending on the relative position of energies of the interacting frontier orbitals, the 1,3-dipolar reaction can either be controlled by the dipole HOMO–dipolarophile LUMO interaction (Type I) or by the dipole LUMO-dipolarophile HOMO interaction (Type III) or by both (Type II). In the first case the energy gap between the dipole HOMO and dipolarphile LUMO is the smallest, *i.e* the denominator in Eq.1 becomes smaller and consequently ΔE becomes larger.

$$\Delta E_{covalent} = 2(C_d^{HO} C_a^{LU} \Delta\beta_{ad} + C_{d'}^{HO} C_{a'}^{LU} \Delta\beta_{a'd'})^2 / E_D^{HO} - E_A^{LU} + 2 (C_d^{LU} C_a^{HO} \Delta\beta_{ad} + C_{d'}^{LU} C_{a'}^{HO} \Delta\beta_{a'd'})^2 / E_A^{HO} - E_D^{LU} \quad (1)$$

In Type III, the energy gap between the dipole LUMO and dipolarophile HOMO is smaller. A reaction with a dipolarophile carrying an electron-donating group will thus preferably be dipole-LUMO controlled. Conversely when the dipolarophile carries electron withdrawing groups, the dipole HOMO-control asserts itself. In both cases the HOMO-LUMO gap is reduced compared to the uncatalysed reactions and explains why electron donating and electron withdrawing substituents can accelerate a 1,3-dipolar reaction. Many nitrones and nitrile oxides are electron deficient species with a low lying LUMO. Thus the 1,3-DCs involving these species are of Sustmann Type III, where the dipole LUMO-dipolarophile HOMO is the predominant Frontier MO interactions. Qualitatively in the dipole LUMO the coefficient on carbon is larger than on oxygen. In monosubstituted dipolarophiles, the coefficient on carbon to which the substituent is attached, is smaller irrespective of the nature of the substituent (**Figure 9**).

The orbital size represents the magnitude of the coefficients. The stabilisation is more effective in approach A than in approach B (**Figure 10**) because this alignment makes the numerator in equation…1 larger. Thus the predominant interaction would lead regioselectivity to a 5-substituted isoxazolidines with most monosubstituted olefins as substrates.

With very strong electron-withdrawing substituent, such as nitro-, sulphone or sulphoxide, the dipolarophile becomes electron-deficient with a low lying LUMO. Thus the reaction changes over to Sustmann I type, where the dipole HOMO-dipolarophile LUMO becomes the predominant interaction. Pairing the larger coefficients on both the reactants leads to the 4-substituted isoxazolidine (**Figure 11**).

Intermediate situations where both pairs of interactions are about equally important (Sustmann Type II) leads to a loss of regioselectivity.

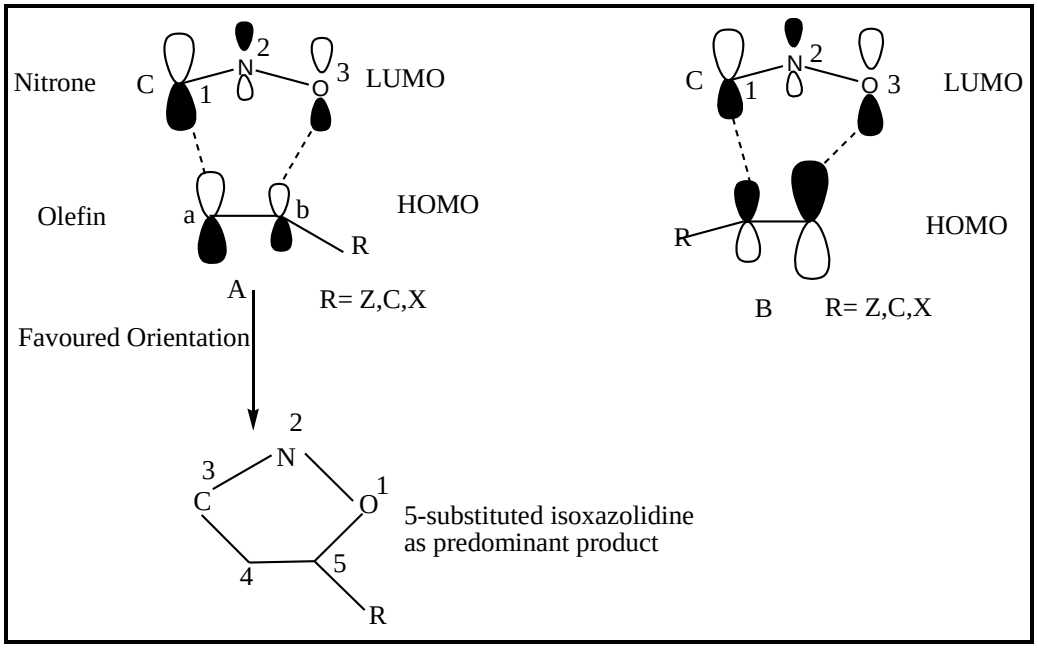


Figure 10 Schematic representation of the orbital interaction between the LUMO of a 1,3-dipole and the HOMO-dipolarophile, a-b

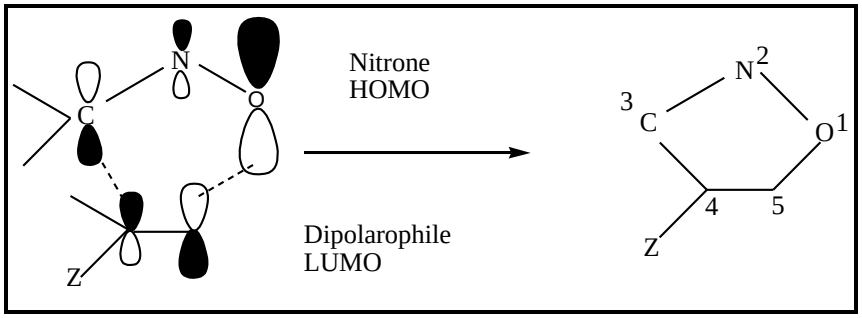


Figure 11 Schematic representation of the orbital interaction between the HOMO of a 1,3-dipole and the LUMO-dipolarophile, a-b

Figure 12 explains the outcome of the reactions between benzonitrile oxide and electron rich vinyl ethyl ether and the reaction between benzonitrile oxide and electron-deficient methyl acrylate, both giving the same substitution pattern in the product. Both cycloadditions are dipole-LUMO controlled and the magnitudes of the orbital coefficients align the alkene so that the carbon atom carrying the substituent approaches the oxygen atom of the nitrile oxide. The energy separation for the dipole-HOMO controlled reaction is larger, but provided that it contributes, the vinyl ether will still give the 5-substituted derivatives because the LUMO coefficient at the unsubstituted end is smaller. For methyl acrylate the situation is opposite in the dipole HOMO controlled reaction, which will give the 4-substituted derivative.

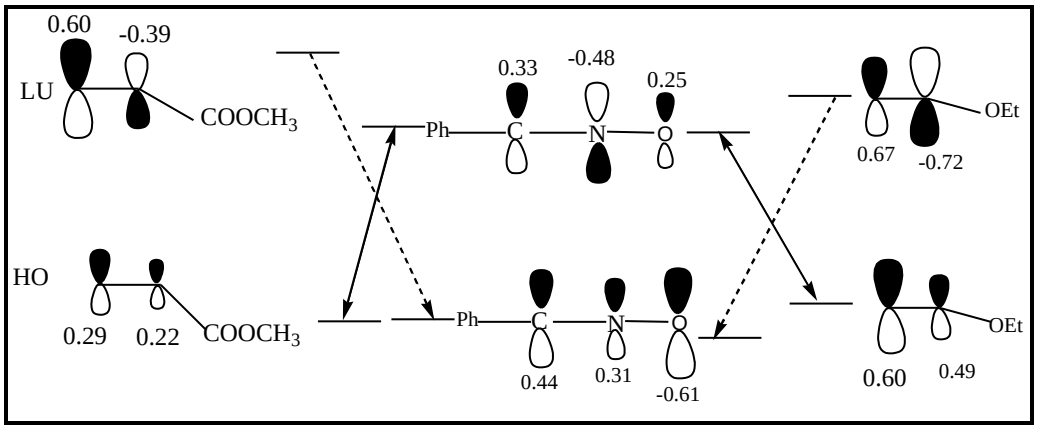


Figure 12 Regioselective alignment of vinyl ethyl ether and methyl acrylate to benzonitrile oxide

It is anticipated that electron donating groups on the nirile oxide or nitrone and very strong electron withdrawing groups on the dipolarophile should increase the 4:5 substitution ratio. The reaction of diethyl methylmalonate [19], trimethyl ethylene tricarboxylate [20], with *C,N*-diphenyl nitrone give exclusively 4,4-disubstituted isoxazolidine and the effect is also observable in the reaction of a *C*-alkoxynitrone with methyl propionate [21].

The corresponding acetylenic derivatives have generally higher ionisation potentials than the alkenes, and hence lower-lying HOMOs. This is reflected in more Sustmann Type II like behavior, and hence a higher 4:5 substitution ratio for the dipolar addition.

When steric requirements dictate the formation of a 5-substituted cyclisation product, it is possible for orbital control to be bypassed.

The factors controlling *exo-endo* ratio are more complex. Electronic and steric effects, dipolar interactions, and secondary orbital interactions all play their part.

Conclusions

The following general conclusion can therefore be drawn from the extensive experimental work:

- The 1,3-dipolar cycloaddition is a concerted cis-addition suprafacial on both compounds, *i.e.* it is a ($\pi^4s+\pi^2s$) pericyclic process.

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