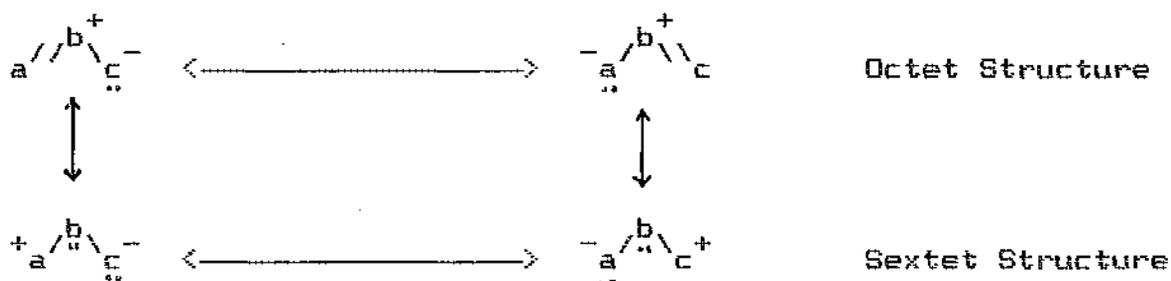


CHAPTER-I (THEORETICAL APPROACH)

1. GENERAL :

The "1,3-Dipole", $a-b-c$, may be defined such that atom "a" possesses an electron sextet, i.e., an incomplete valence shell combined with a formal positive charge, and that atom "c", the negatively charged centre, has an unshared pair of electrons and which undergoes 1,3-cycloaddition to a multiple bond system, the "dipolarophile"¹.

Since compounds with six electrons in the outer shell of an atom are usually not stable, the $a-b-c$ system is actually one canonical form of a resonance hybrid, for which at least one other structure may be drawn, e.g.,



1,3-Dipoles can be further stabilised by internal octet stabilisation.

1,3-Dipolar compounds can be divided into two main types:

(1). Propagyl-Allyl Type: Those in which the dipolar canonical form has a double bond on the sextet atom and the other canonical form a triple bond on that atom:



(2). Allyl Type: Those in which the dipolar canonical form has a single bond on the sextet atom and the other form a double bond:



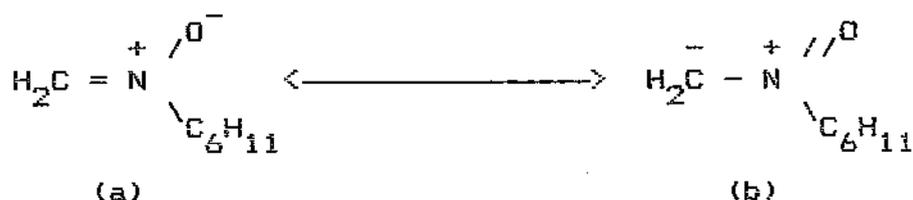
1,3-Dipoles can be classified among two types, viz., with double bond and without double bond and represented in the Table-I.

In this 1,3-dipoles the central atom is never a carbon atom. If the central atom be a carbon function then internal octet stabilisation is prevented by lack of an available free electron pair. Such system are therefore extremely reactive and short lived. Example of this type are the unsaturated carbenes and azenes.

In allyl type of 1,3-dipole, if one restricts the atom a, b and c to carbon, nitrogen and oxygen, results Nitron:



In order to verify the energies associated with the two canonical forms, N-cyclohexyl methylene nitron was taken as an ideal example². Approximate qualitative information of the non-uniform distribution of electronic charge of the nitron could be obtained by applying the HMO method. The canonical forms of the nitron are:



Approximate HMO calculation of the structure (a):

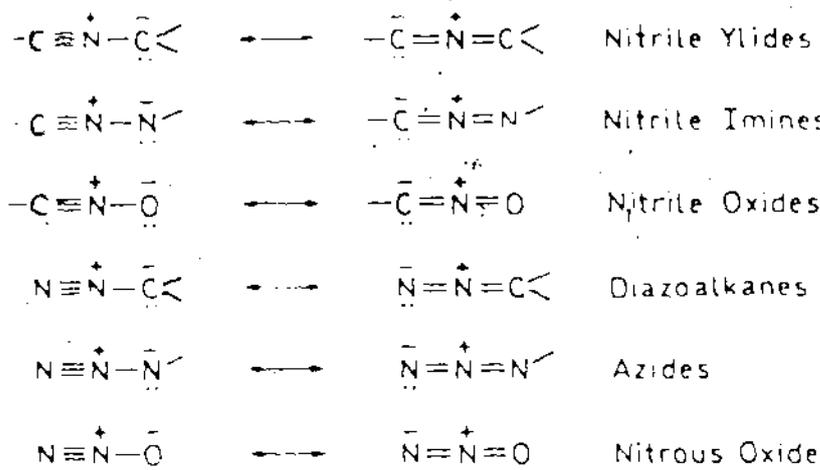
The secular determinant could be set up using the suggested parameter values³ for heteroatoms for use with simple LCAO treatment, viz., $h_{\text{N}^+}=2$; $h_{\text{O}^-}=2$; $K_{\text{C-N}}=1.1$; $K_{\text{N-O}}=0.7$; ect.

$$\begin{vmatrix} \alpha_0 - \epsilon & \beta_{12} & \beta_{13} \\ \beta_{21} & \alpha_0 - h_{\text{N}^+} + \beta_0 - \epsilon & \beta_{23} \\ \beta_{31} & \beta_{32} & \alpha_0 + h_{\text{O}^-} - \beta_0 - \epsilon \end{vmatrix} = 0$$

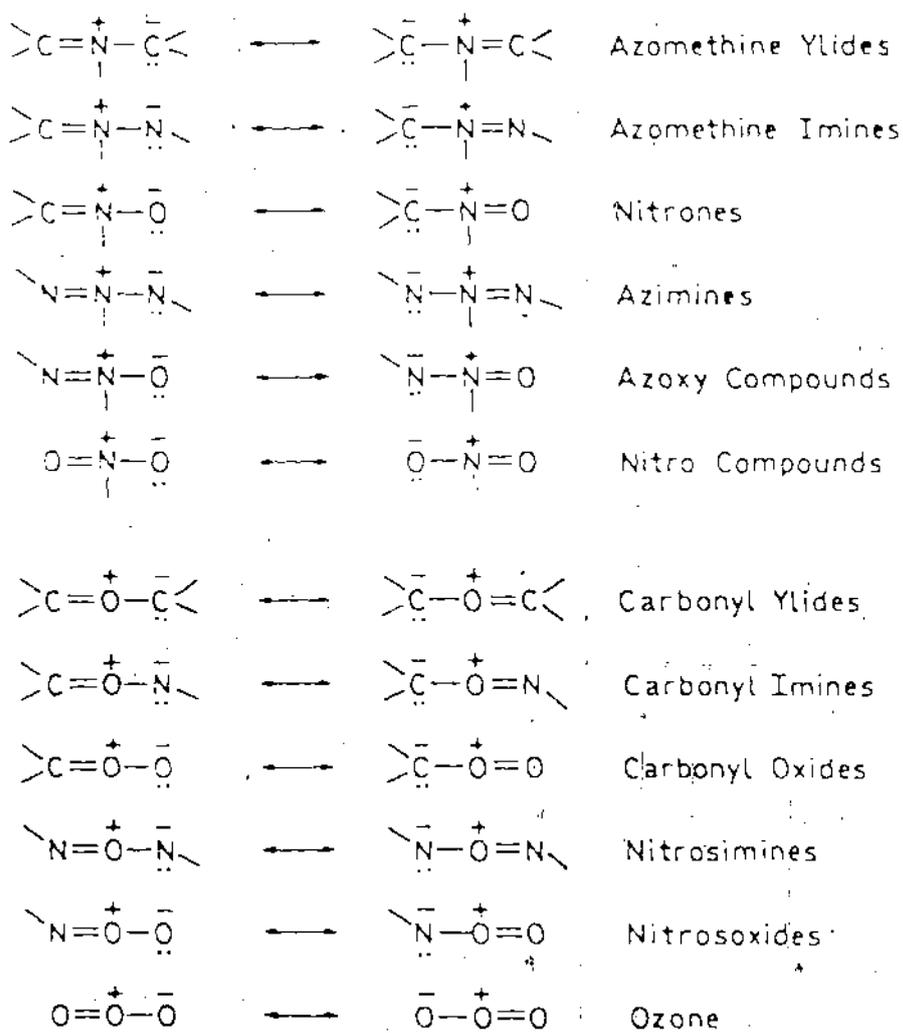
Putting the above values and $X = \alpha_0 - \epsilon / \beta_0$,

Table 1
 Classification of 1,3-Dipoles Consisting of
 Carbon, Nitrogen, and Oxygen Centers

A. Propargyl-Allenyl Type



B. Allyl Type



$$\begin{vmatrix} X & 1.1 & 0 \\ 1.1 & X + 2 & 0.7 \\ 0 & 0.7 & X + 2 \end{vmatrix} = 0$$

or, $X^3 + 4X^2 + 2.3X - 2.4 = 0$

i.e., $X = 0.5175, -1.58775$ and -2.9297 .

Therefore,

$$\begin{aligned} \epsilon_1 &= \alpha_0 + 2.9297\beta_0 \\ \epsilon_2 &= \alpha_0 + 1.58775\beta_0 \\ \epsilon_3 &= \alpha_0 - 0.5175\beta_0 \end{aligned}$$

And the total Π -energy of the system (a) was $4\alpha_0 + 9.0349\beta_0$.

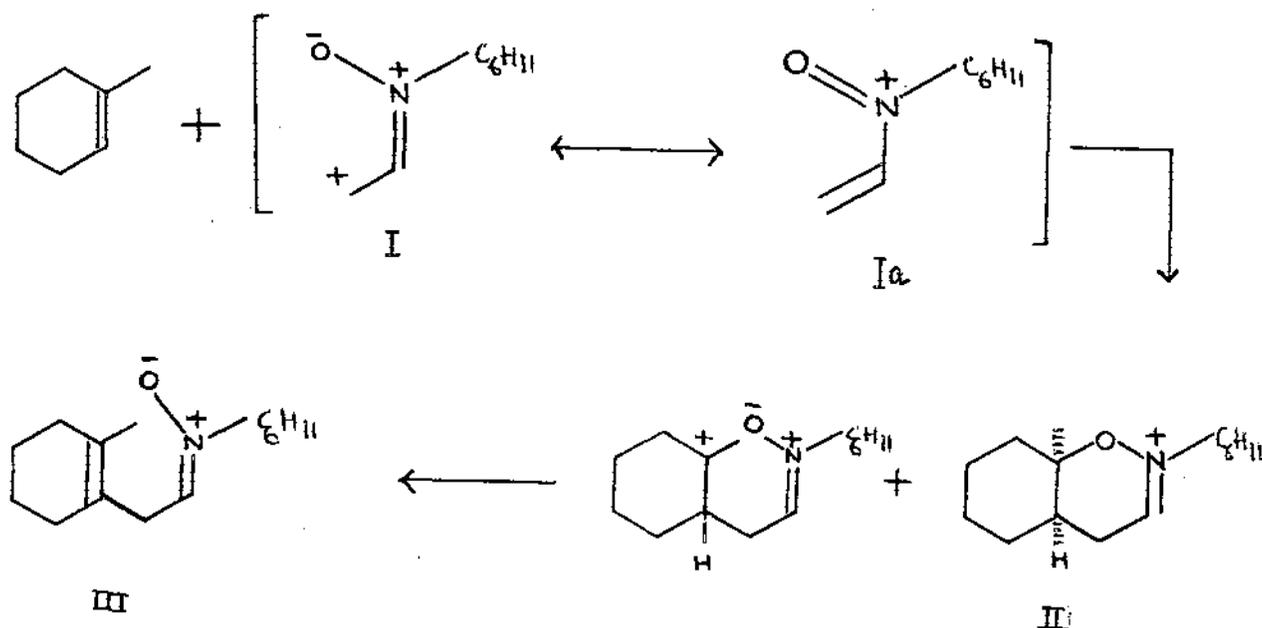
Similar treatment on the system (b) gave the following values:

$$\begin{aligned} \epsilon_1 &= \alpha_0 + 3.035\beta_0 \\ \epsilon_2 &= \alpha_0 - 0.3304\beta_0 \\ \epsilon_3 &= \alpha_0 - 1.295\beta_0 \end{aligned}$$

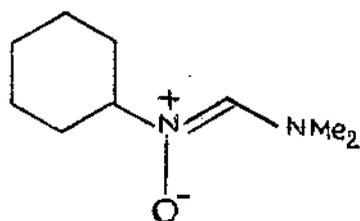
And the total Π -energy of the system (b) was $4\alpha_0 + 5.4092\beta_0$.

From the calculated result, it is evident that the canonical form (a) is more favourable on energy ground and this is also in agreement with the existing principle.

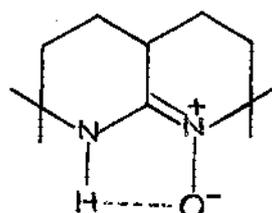
Eschenmoser et.al.⁴ has shown that, a cation, and only a cation can be formed α - to the nitrono group. The reaction between unsymmetrically substituted olefins and vinyl nitrosonium cation ($I \rightleftharpoons Ia$) produces not only cycloadduct but also a substitution product (III)⁵.



It was therefore, very striking on the light of these observations that α -Amino Nitronium could be prepared as stable compounds (IV and V)⁶.



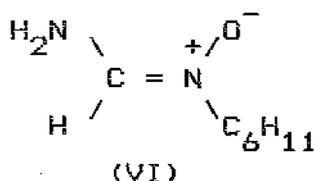
(IV)



(V)

On the basis of qualitative Molecular Orbital (MO) theory, the formation of vinyl nitrosonium ion is quite logical, it is butadiene-like 4-centered-4-electron- π -system having both bonding MOs are filled up and the antibonding MOs are vacant and acts as a diene component in the hetero Diels-Alder reaction with olefins ($4\pi + 2\pi$ -cycloaddition). But α -amino nitrones are 4-centered-6-electrons- π -system in which the lower lying antibonding orbital is also filled up resulting the system to be comparatively unstable. But the system is not so, has been demonstrated by the synthesis of α -amino nitrones (IV and V)⁶.

In order to verify the stability of such type of nitrones, α -amino-N-cyclohexyl nitronium (VI) was taken as example for approximate HMO calculation.



(VI)

The secular determinant for α -amino-N-cyclohexyl nitronium was as follows:

$$\begin{vmatrix} \alpha_0 + h_N \beta_0^- \epsilon & \beta_{12} & \beta_{13} & \beta_{14} \\ \beta_{21} & \alpha_0^- \epsilon & \beta_{23} & \beta_{24} \\ \beta_{31} & \beta_{32} & \alpha_0 + h_N + \beta_0^- \epsilon & \beta_{34} \\ \beta_{41} & \beta_{42} & \beta_{43} & \alpha_0 + h_O \beta_0^- \epsilon \end{vmatrix} = 0$$

By putting, $X = \alpha_0 - \epsilon / \beta_0$,

$$\begin{vmatrix} X + 1.5 & 0.8 & 0 & 0 \\ 0.8 & X & 1.1 & 0 \\ 0 & 1.1 & X + 2 & 0.7 \\ 0 & 0 & 0.7 & X + 2 \end{vmatrix} = 0$$

Thus solving, $X = -2.96$; -1.97 ; -1.32 and 0.75 .

The energy levels were :

$$\epsilon_1 = \alpha_0 + 2.96\beta_0$$

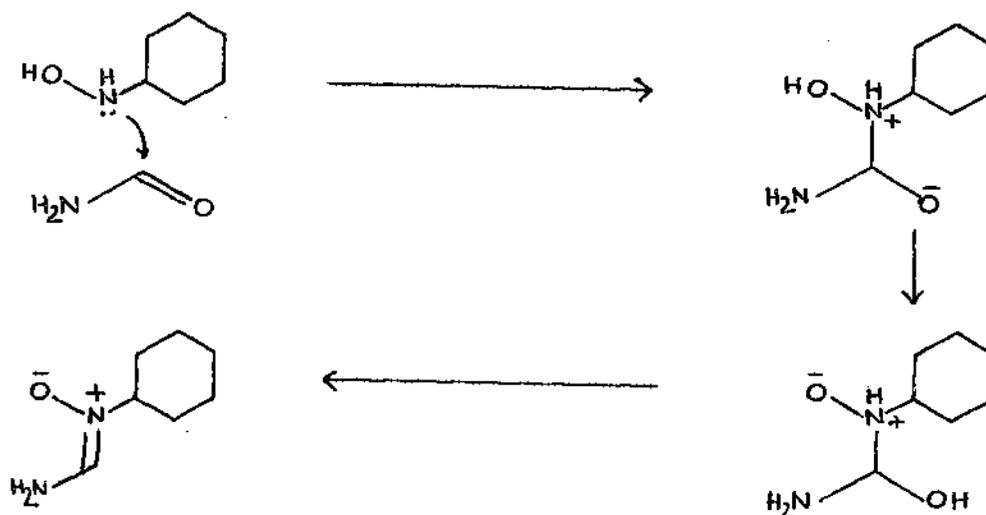
$$\epsilon_2 = \alpha_0 + 1.97\beta_0$$

$$\epsilon_3 = \alpha_0 + 1.32\beta_0$$

$$\epsilon_4 = \alpha_0 - 0.75\beta_0$$

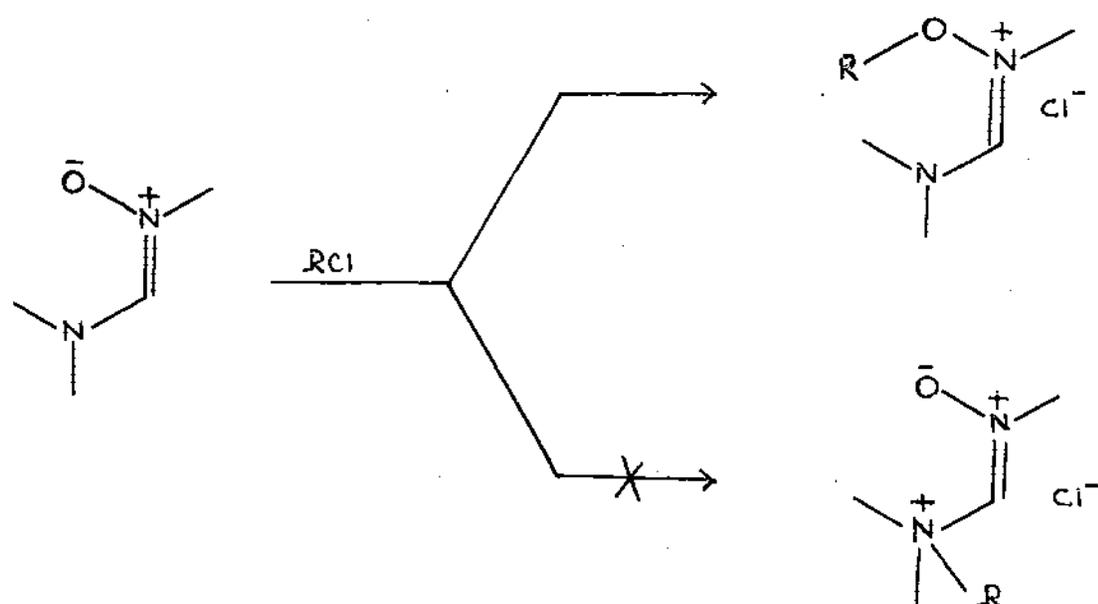
The total Π -energy was $6\alpha_0 + 12.5\beta_0$.

Considering the calculated energy levels associated with both the nitrones, viz., N-cyclohexyl methylene nitron and α -amino-N-cyclohexyl nitron (VI), it was also evident that the latter one was not so unstable. Keeping the above observations in mind, finally the α -Amino-N-Cyclohexyl Nitron was synthesised directly from the simplest of the amide, formamide, and N-cyclohexyl hydroxylamine. The choice of formamide rested on the fact that it not only has sufficient carbonyl functionality but also could function as a good solvent when used in excess. A plausible mechanism of the possible formation of the nitron is given bellow:



The most important step in the formation of the nitron (VI) was the dehydration process, so the efficient execution of the preparative method needed the use of dehydrating agent. Anhydrous Magnesium sulphate was chosen for this purpose.

From the above discussion one thing was apparent that the α -amino nitron should be very reactive due to the presence of a filled up antibonding MO, and indeed should act as a powerful nucleophile. There are two electron rich centers, one at the oxy-anion and the other at the α -nitrogen. But the density of the electrons being more at the oxy-anion end (three electron pairs) and steric hindrance is minimum, this end should preferably act as a powerful nucleophilic centre in S_N2 reactions. Simple nitrones are not known to act as nucleophile in this fashion.



The above assumption could also be rationalised on the basis of Fukui's Frontier Orbital Theory. The Sustman Classification Of 1,3-dipoles (details discussed in Chapter-I/2) strictly holds only for the parent species, could be adapted qualitatively to substituted 1,3-dipole as well. Electron donor group in 1,3-dipole shifts the 1,3-dipolar character towards the Type-1, i.e., HOMO controlled or nucleophilic 1,3-dipole. Whereas an electron acceptor shifts the behavior towards Type-3, i.e., electrophilic character.

α -Amino-N-cyclohexyl nitron (VI) has an amino group at C-terminus which is a strong electron donor. Therefore, this nitron should be nucleophilic in character. In general, nitrons are HOMO-LUMO controlled 1,3-dipoles skewing towards LUMO-controlled side, and do not react as nucleophiles.

The high reactivity of α -amino nitron could also be explained on the basis of Perturbation Theory⁷ wherein the HOMO level of a parent (unsubstituted) nitron is raised in energy by the introduction of an amino group on the α -carbon atom and the corresponding LUMO level of the nitron is stabilised. Thus the stabilisation of the dipole LUMO level should increase the interaction with the dipolarophile HOMO level, thereby providing relative stabilisation to the transition state for the cycloaddition and consequently increasing the rate of reaction.

2. 1,3-DIPOLAR CYCLOADDITION (MECHANISTIC APPROACH) :

According to Huisgen et.al., a cycloaddition of type 3+2 \rightarrow 5 leading to an uncharged 5-membered ring cannot possibly occur with octet stabilised reactants which have no formal charges. Combination of a 1,3-dipole with a multiple bond system d=e, termed the dipolarophile, is referred to as a 1,3-dipolar cycloaddition^{1,8}.



1,3-Dipolar cycloadditions are concerted reactions, i.e., both the σ -bonds are formed simultaneously and the reaction profile passes through a maxima^{1,9}. Such type of single step reactions sometimes referred to as no mechanism reactions. A 1,3-dipole is always an ambivalent compound, which either displays electrophilic or nucleophilic activity in position 1 and 3. The mesomerism of the octet and sextet resonance structures of the 1,3-dipole results in charge compensation and charge exchange, respectively which makes it impossible to identify unequivocally an

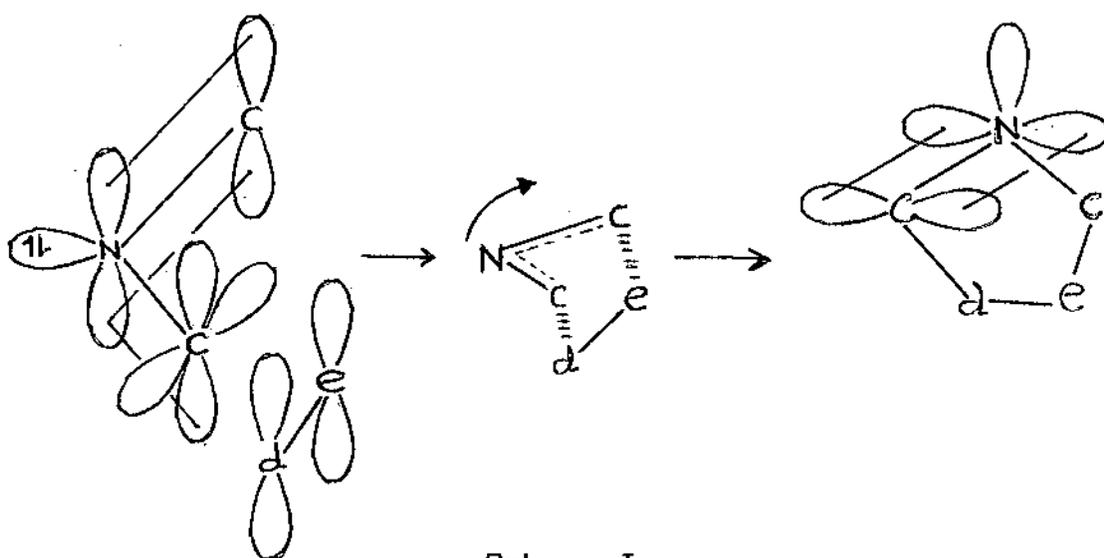
electrophilic and nucleophilic centers. In other words, the question whether the cyclic electron shifts in Fig-A takes place clockwise or anti-clockwise is meaningless. Furthermore, though both the σ -bonds are formed simultaneously there is no reason to consider that the bonds at transition state be formed to the same extent.



Fig-A

The evidence in favour of the concerted process¹ in 1,3-dipolar cycloaddition came from their independence of solvent polarity^{10,11}, the negative entropies of activation¹² and the stereospecificity and regioselectivity⁸.

Taking nitrile as a model system Huisgen described the cycloaddition according to the Scheme-I



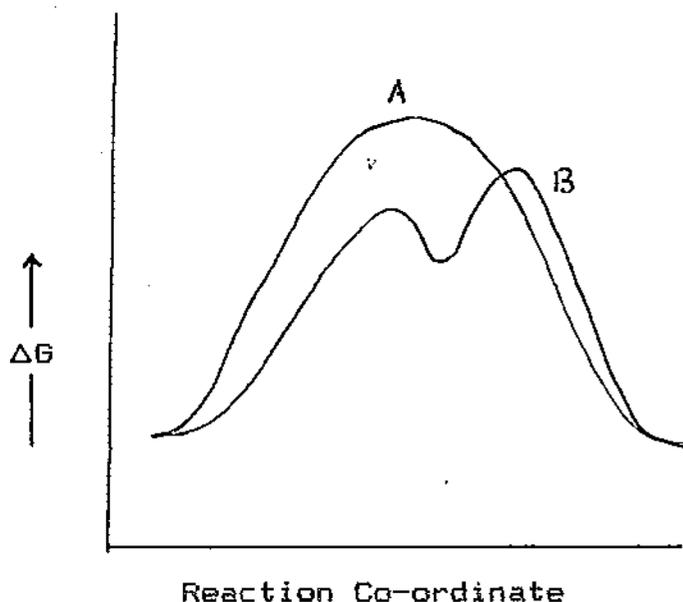
Scheme-I

1,3-Dipoles "without a double bond" are already bent in the ground stable state, but the 1,3-dipoles "with a double bond" i.e., propargyl-allenyl type, the linear bond system a-b-c must necessarily bend in order to place centres "a" and "c" in contact with the Π -bond system of the dipolarophile. Calculation¹³ shows that the resonance energy of the allyl anion is not disturbed by bending. The gradual transformation of p-orbitals into sp^2 or sp^3 orbitals of the new σ -bonds is accompanied by an interesting change of configuration. The nitrogen moves upwards until it reaches the plane of the remaining four centers in the adduct. In the course of this continuous transition, the orbital of the lone pair at nitrogen attains P-character; the σ -bond of the product originates from this pair of electrons. For 1,3-dipoles "without a double bond", the nitrogen at the transition state needs not to be shifted to the plane of the remaining four atoms and rather will shift in such a way that the product conformation at ground state can be achieved.

R.A.Firestone^{14,15,16} observed some discrepancies in the mechanism proposed by Huisgen et.al. and suggested an alternative two-step mechanism for the 1,3-dipolar cycloadditions (Scheme-II).

Firestone considered three principal canonical forms of a typical 1,3-dipole (A,B and C in Scheme-II). These are all octet structures which have the same number of bonding electrons. All other forms such as sextet structures, have fewer bonding electrons and are therefore, discounted. Form "C" is drawn according to Linnett's method and is quantum-mechanically equivalent to "A" and "B". Since the dipole moment of most 1,3-dipoles are small compared to the theoretical values for full charge separation, Firestone stressed that the expression "C" may usually be accepted as the principal representation of the 1,3-dipole.

He considered all the modes of addition of the dipole and the dipolarophile and selected two possible regioisomeric products 3 and 4 respectively. Diradical 5 and 6 expected to be less important because they do not utilize the radical-stabilizing power of the substituent "X". For any individual 1,3-dipole, a preference for either 1 or 2 is expected, and this preference



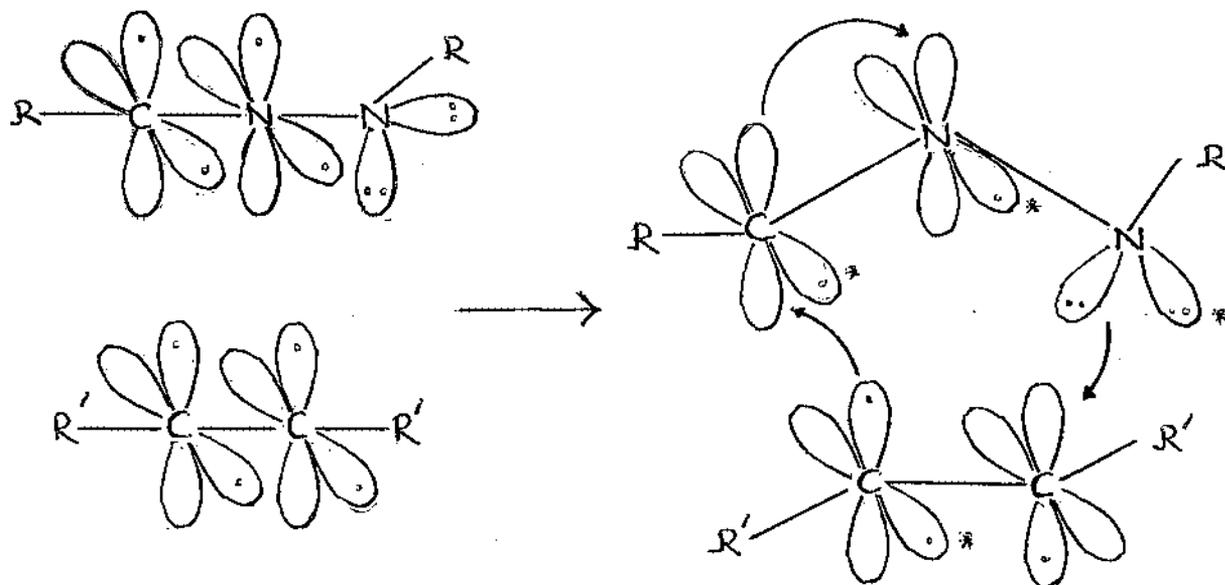
A-Reaction profile for concerted reaction.
 B-Reaction profile for two-step reaction.

Fig-B

Firestone thought that when the dipolarophile bears a substituent with appreciable conjugation energy, which is lost in the transition state in concerted process and this would retard the reaction relative to one with unsubstituted dipolarophile. But the fact is that all substituents in the dipolarophile strongly accelerate 1,3-dipolar cycloadditions.

Furthermore, a number of 1,3-dipoles react with acetylenes to produce aromatic system directly e.g., nitrile imine, nitrile oxide and azides. In a concerted reaction, a portion of this aromatic stabilisation should exist in the transition state on this basis. Firestone formulated a planar transition state as Scheme-III.

Although the observed fact of low activation energy for the 1,3-dipolar cycloaddition seems to contradict two step process, Firestone explained on the basis of bond energy calculations that actually the energy differences for the two processes is very low. He tried to rationalize all other general characteristics of these type of reactions.



The orbitals marked with asterisks constitute developing aromatic π -cloud.

Scheme-III

But Huisgen strongly refuted¹⁷ the above diradical mechanism. He argued that the greatest obstacle for the assumption of a diradical intermediate is the stereospecificity observed in the cycloadditions of the 1,3-dipole with *cis*- and *trans* dipolarophiles; energy calculations of diradical intermediate are not adequate and planar transition state as proposed by Firestone is not in accord with the Woodward-Hoffman Rules²¹. Lots of other discrepancies had also been pointed out by Huisgen in the Firestone model of 1,3-dipolar cycloadditions and he ultimately concluded that all mechanistic criteria underline the superiority of the concerted mechanism over the diradical hypothesis.

Houk et.al., pointed out that mechanistic investigations have shown that cycloadditions of 1,3-dipole to alkenes are stereospecifically suprafacial; solvent polarity has little effect on reaction rates, and small activation enthalpies and large negative entropies are generally found. These facts, along with

reactivity and regioselectivity phenomenon, have been considered totally compatible only with a concerted five-center mechanism. Orbital symmetry consideration have provided permissive, though not obligatory, theoretical evidence for the concerted mechanism and the observation of $[\pi^4s + \pi^6s]$ cycloaddition but not $[\pi^4s + \pi^4s]$ cycloadditions of 1,3-dipoles to triene has provided further evidence for the concerted mechanism^{18,19}. But the experimentally observed regioselectivity of most 1,3-dipolar cycloadditions has been the most difficult phenomenon to explain. Houk et.al. solved this vexing problem with the use of generalised frontier orbitals of 1,3-dipoles and dipolarophiles within the frame work of qualitative Perturbation Molecular Orbital Theory.

Qualitative orbital energies and co-efficients are of great importance here. For this purpose frontier orbitals of representative alkenes are shown in Table-II and III. In each figure, (-)ve of the ionisation potential (IP) of alkene is given under the horizontal line for the HOMO (Highest Occupied Molecular Orbital) and the (-)ve of the electron affinity is given under LUMO (Lowest Unoccupied Molecular Orbital) level. The units are electron volt (eV). The AO (Atomic Orbital) co-efficients for the frontier MOs are also given. For the electron rich alkenes (Table-II), the trend of decreasing HOMO co-efficients as the IP decreases results from the greater admixture of substituent orbitals with the ethylene π -orbitals as the group becomes a better donor. The conjugated alkenes (Table-III) raise HOMOs and lower LUMOs as compared to ethylene. Frontier MOs of some 1,3-dipoles (Table-IV) show relatively small gap in their HOMO-LUMO levels and therefore their reactivity are quite high. Houk et.al. further proposed that bending of either terminus can reverse these generalisations²⁰.

Now whether an 1,3-dipolar cycloaddition to be allowed or forbidden may be judged according to the symmetry properties of the HOMO and LUMO orbitals of the dienes and dipolarophiles as proposed in Woodward-Hoffman rule²¹. And the allowed process can be of three types as proposed by Sustman^{22,23} (Fig-C). the Type-1 involves dominant interaction between HOMO(dipole) and LUMO (dipolarophile). Type-3 involves LUMO(dipole)-HOMO(dipolarophile).

TABLE - II

The frontier MO's of electron-rich alkenes.

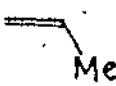
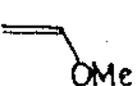
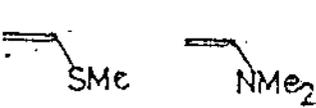
					
LUMO	$\frac{71, -71}{+1.5}$	$\frac{67, -54}{\sim +5}$	$\frac{67, -65}{+1.8}$	$\frac{66, -72}{+2.0}$	$\frac{62, -69}{2.5}$
HOMO	$\frac{71, -71}{-10.52}$	$\frac{44, -30}{-10.15}$	$\frac{67, -56}{-9.88}$	$\frac{61, -39}{-9.05}$	$\frac{34, -17}{-8.45}$

TABLE - III

The frontier MO's of electron-deficient and conjugated alkenes.

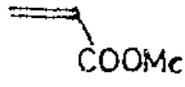
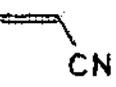
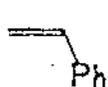
					
LUMO	$\frac{69, -47}{\sim 0.0}$	$\frac{66, -54}{\sim 0.0}$	$\frac{54, -32}{\sim -0.7}$	$\frac{56, -42}{1.0}$	$\frac{48, -35}{+0.8}$
HOMO	$\frac{43, -33}{-10.72}$	$\frac{60, -49}{-10.92}$	$\frac{62, -60}{\sim -11.4}$	$\frac{57, -41}{-9.03}$	$\frac{49, -32}{-8.48}$

TABLE - IV

The frontier MO's of 1,3-dipoles.

$\text{N} \equiv \overset{+}{\text{N}} - \overset{-}{\text{C}}\text{H}_2$	$\text{H} - \text{C} \equiv \overset{+}{\text{N}} - \overset{-}{\text{O}}$	$\begin{array}{c} + \\ \\ \text{N} - \text{O}^- \\ \\ + \end{array}$	$\begin{array}{c} + \\ \\ \text{O} = \text{O} - \text{O}^- \\ \\ + \end{array}$
$\frac{50, -70, -51}{\sim +2}$	$\frac{68, -67, -30}{\sim 0}$	$\frac{58, -67, 41}{-5}$	$\frac{53, -67, 53}{-2}$
$\frac{61, -13, -78}{-8.99}$	$\frac{56, -21, -80}{-10.5}$	$\frac{69, -15, -70}{-8.64}$	$\frac{71, 0, -71}{-13.02}$

But in type-2, both the LUMO(dipole)-HOMO(dipolarophile) and the HOMO(dipole)-LUMO(dipolarophile) are important in determining reactivity and regiochemistry.

Type-1 dipoles are those having high lying HOMOs and LUMOs and referred as HOMO controlled or nucleophilic 1,3-dipoles. Type-3 are having low lying FMOs and referred as LUMO controlled or electrophilic dipoles. The type-2 1,3-dipoles are referred as HOMO-LUMO controlled dipoles.

Houk et.al.²⁴ have treated all common 1,3-dipoles, according to this simple model and have shown that the prediction nicely explains the experimental results.

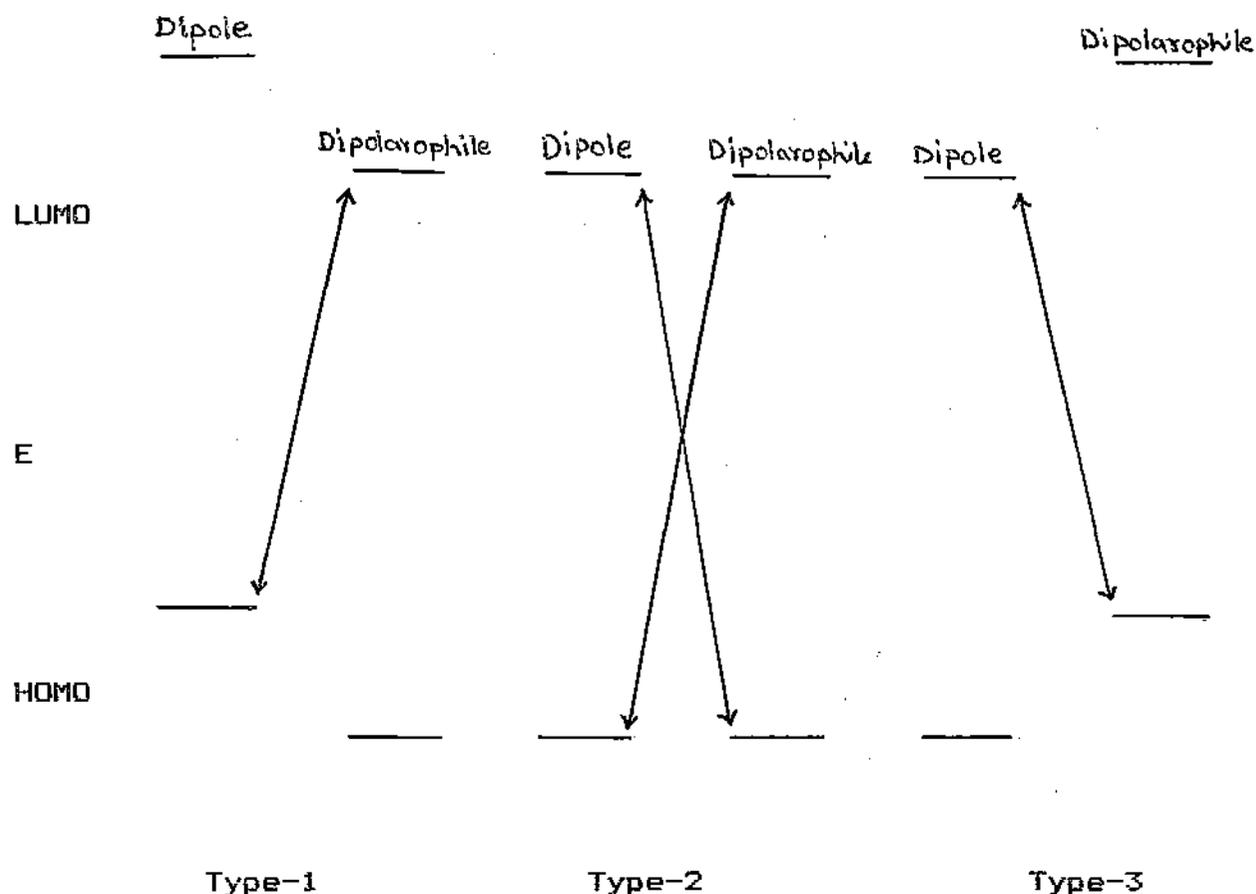
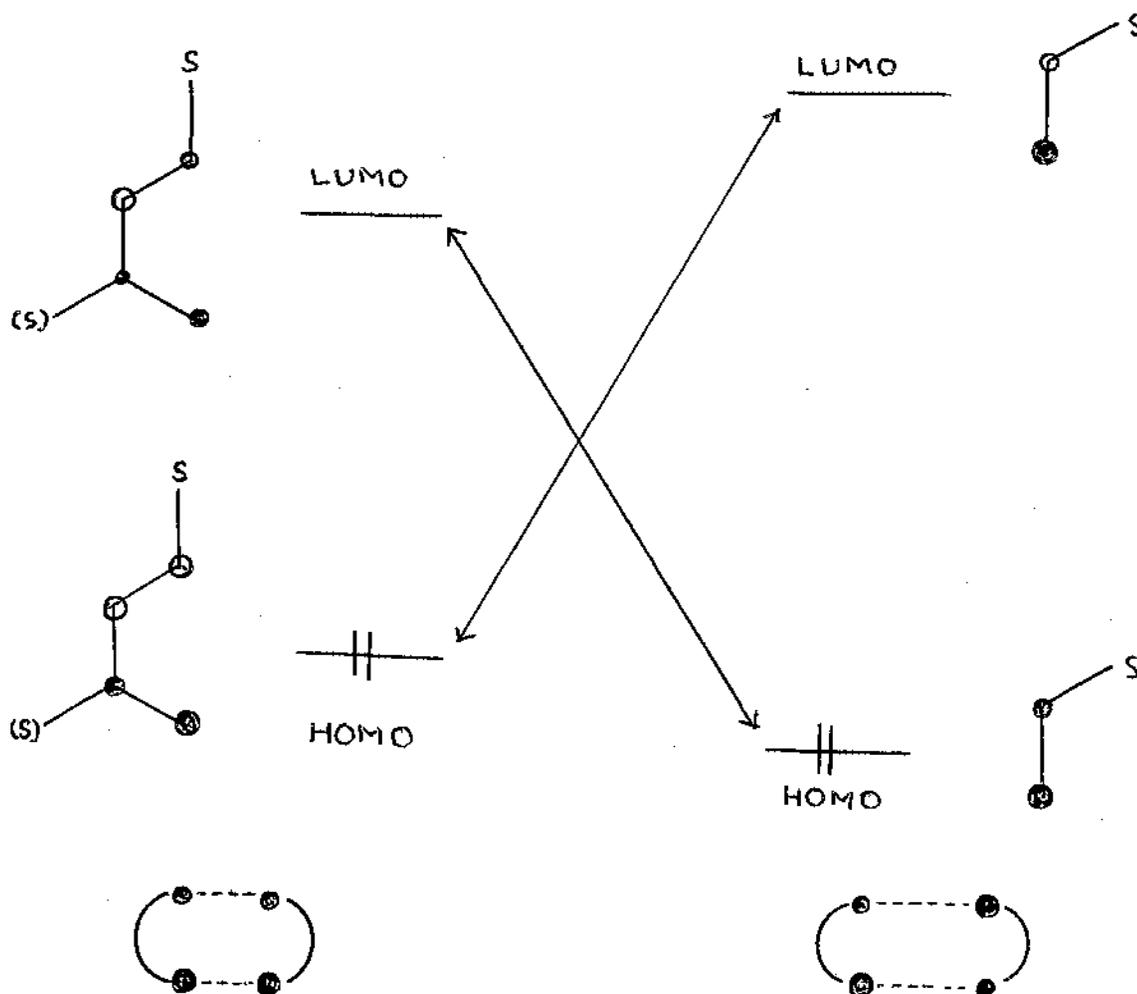


Fig-C

The nitrile ylides, diazoalkenes and azomethine ylides are HOMO controlled 1,3-dipoles, reacting fastest with alkenes having one or more electron withdrawing substituents. The nitrile imines, azides and azomethine imines are HOMO-LUMO controlled dipoles react rapidly with both electrone rich and electron deficient dipolarophiles. The nitrile oxides and nitrones are also HOMO-LUMO controlled dipoles but these species are skewed toward the LUMO controlled side. Finally, species with several electronegative atoms are LUMO controlled, 1,3-dipoles e.g., nitrous oxide, ozone.



$\Delta E \propto L^2 + S^2$ is better than $\Delta E \propto 2LS$; L and S are larger and smaller co-efficient at the concerning C-atom respectively.

Fig-D

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Nicety of Houk's model lies specially in its general applicability in the problem of regioselection. Fig-D summerizes the frontier MOs of monosubstituted alkenes and 1- and 2-substituted dienes. In the case of a donor or conjugatively substituted diene, the acceptor substituent at the 1-position of a diene or alkene will enlarge the co-efficient at the most remote position in the LUMO. In the case of donor diene and acceptor alkene, the diene HOMO - dienophile LUMO interaction will be the largest when the transition state involves bond formation leading to the "ortho" or (Z) adduct This is because the stabilisation energy will be larger when the larger terminal co-efficients and the smaller terminal co-efficient of the two interacting orbitals overlap, which gives a larger net overlap, and thus larger transition state stabilisation, than if a large co-efficient on one orbital interacts with a small on the second at both bond forming centers.

Calculation on all of the common parent and a number of substituted 1,3-dipoles have lead to the generalisation about the frontier orbitals of 1,3-dipoles (Fig-E).

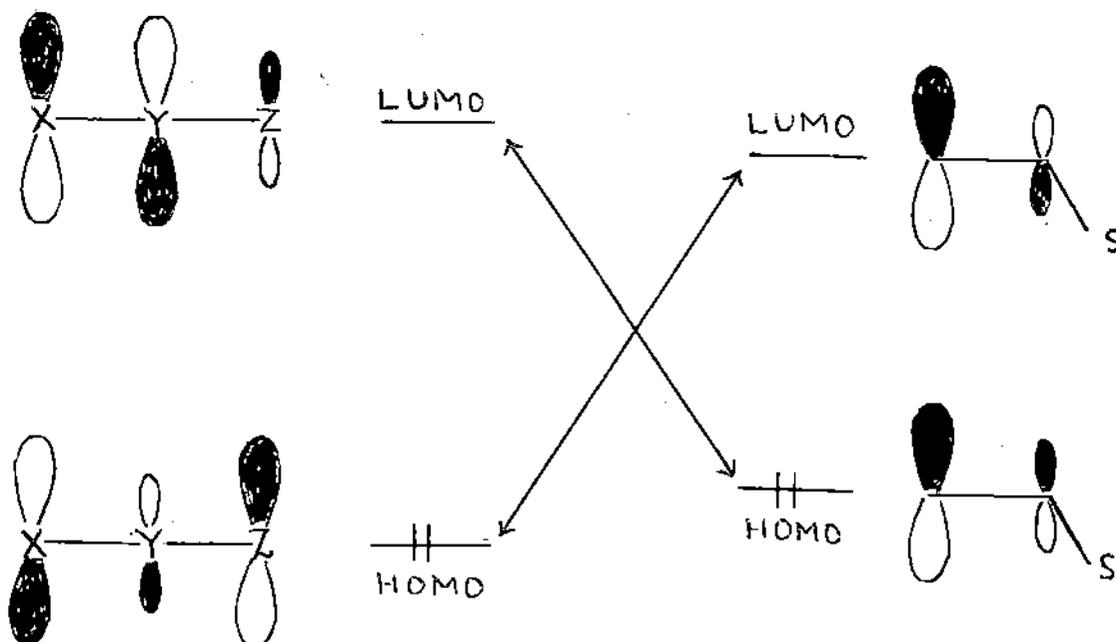


Fig-E

The HOMOs of the 1,3-dipolar system generally have the larger terminal co-efficient on the group "Z", while the LUMOs have the larger co-efficient at the opposite terminus, "X". The HOMOs and LUMOs of the 1,3-dipoles are qualitatively similar to those of an allyl anion but are distorted in unsymmetrical systems. The greater differences in terminal co-efficients occur when the two termini differ greatly in electronegativity.

The interaction of the dipole LUMO with dipolarophile HOMO favours the formation of the product with the substituent on carbon adjacent to "Z", while the opposite frontier orbital interaction favours the opposite regioisomer.

Nitrile oxide and nitrones react to give mainly the 5-substituted adduct with weakly electron deficient alkenes such as acrylonitrile and acrylate. The HOMOs and LUMOs of these electron deficient alkenes both interact fairly strongly with the LUMOs and HOMOs of the nitrile oxides or nitrones, so that orientation is influenced by both the interactions. The experimental results show that the dipole LUMO - dipolarophile HOMO interaction has more influence on regioselectivity. Houk et.al. has studied a number of such reactions with different nitrones^{25,26,27} and has shown that all of them are in accordance to the predicted results.

From the plots of rates versus IP of dipolarophiles, Huisgen observed that acetylenic dipolarophiles are less reactive than expected on the basis of their IP's²⁸. Since alkynes have larger HOMO-LUMO gap than the analogous alkenes, one would expect that in reactions where interaction with the alkyne LUMO is of most important, the alkyne will be less reactive than expected. The actual fact is that though the reactivity of nitrones with both electron deficient alkenes and alkynes are determined by the HOMO dipole - LUMO dipolarophile interaction, the regiochemistry in the former case is still controlled by the LUMO(dipole) - HOMO(dipolarophile) interaction. Therefore, in the case of alkyne, the dipole HOMO - dipolarophile LUMO interaction becomes so much more important than the dipolarophile HOMO - dipole LUMO interaction, that the former completely dominates the reaction and leads to the formation of only the 4-substituted adducts.