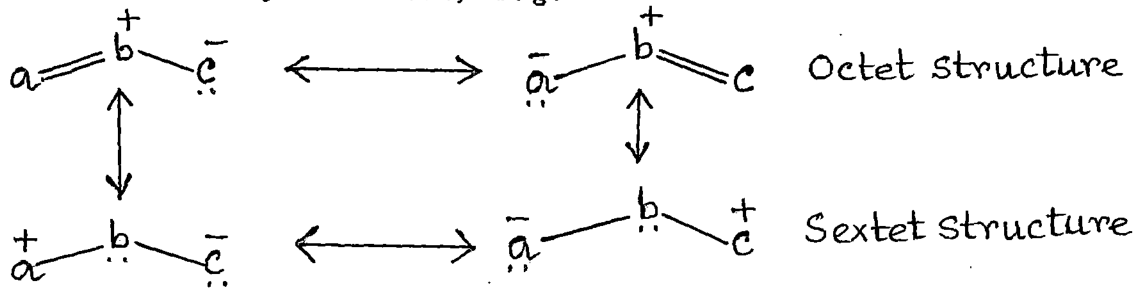
THEORETICAL APPROACH

1.General :

The " 1,3 dipole ", $\overset{+}{a} - b - \overset{-}{c}$, 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 unshaired pair of electrons and which undergoes 1,3 dipolar 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 stabilized by internal octet stabilization.

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

(1) Propagyl - Allenyl 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.

$\overset{+}{a} = b - \overset{-}{c}$ <--------------> $a \equiv \overset{+}{b} - \overset{-}{c}$

(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.

$\overset{+}{a} - b - \overset{-}{c}$ <-------------> $a = \overset{+}{b} - \overset{-}{c}$

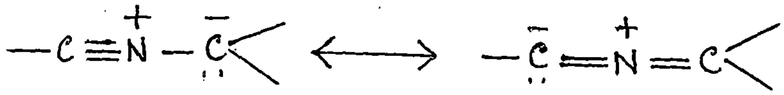
1,3 - Dipoles can be classified between two types viz, with double bond and without double bond and are represented in the **Table-I** .

In this 1,3 Dipoles the central atom is never a carbon atom. If the central atom be a carbon function then internal octet stabilization 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.

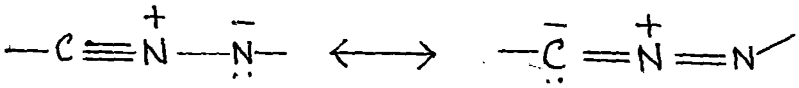
Table I

Classification of 1,3 Dipoles consisting of carbon, nitrogen and oxygen centres :

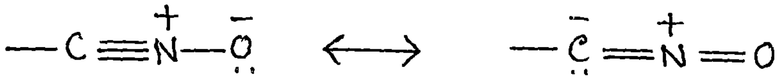
[A] Propagyl - Allenyl Type :



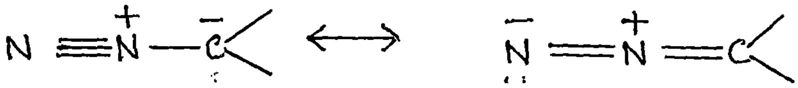
Nitrile Ylides.



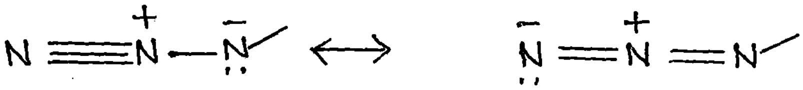
Nitrile Imines.



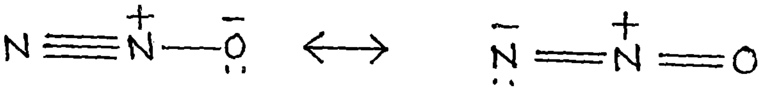
Nitrile Oxides.



Diazo alkanes

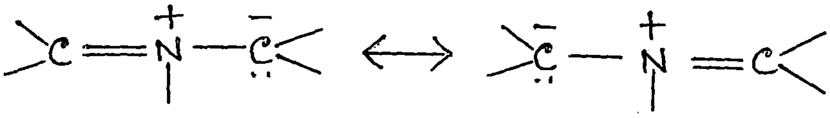


Azides.

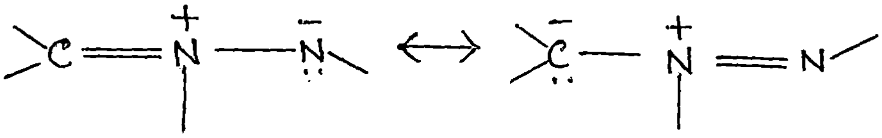


Nitrous Oxide.

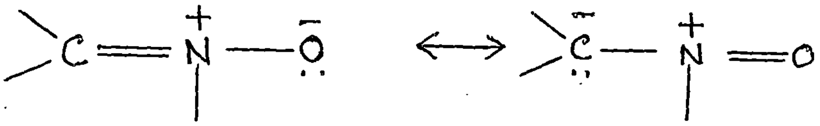
[B] Allyl Type :



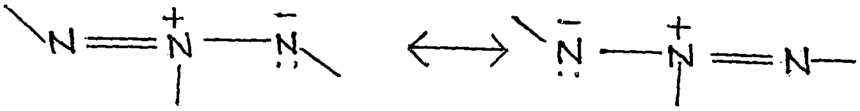
Azomethine Ylides.



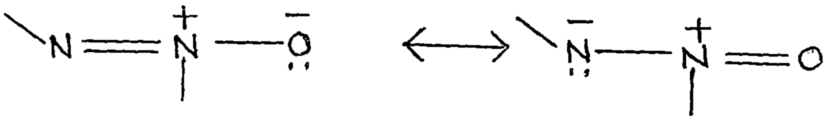
Azomethine Imines.



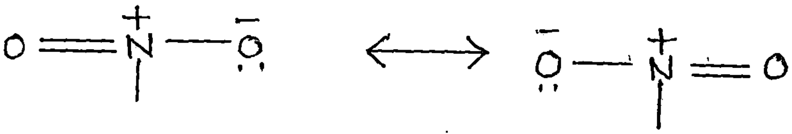
Nitrones.



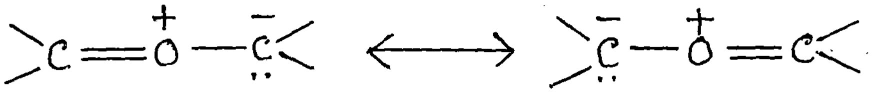
Azimines.



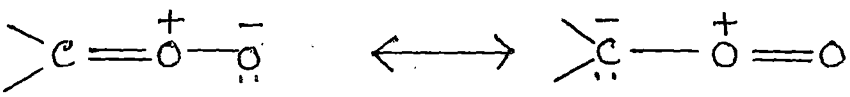
Azoxy Compounds.



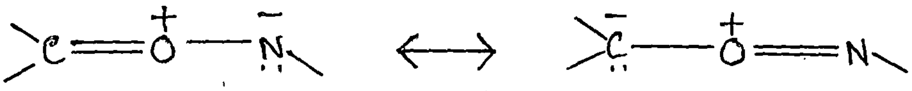
Nitro Compounds.



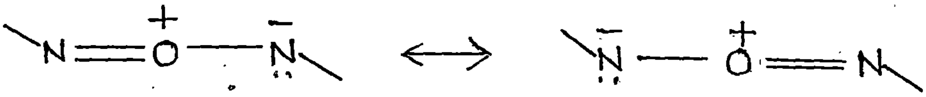
Carbonyl Ylides.



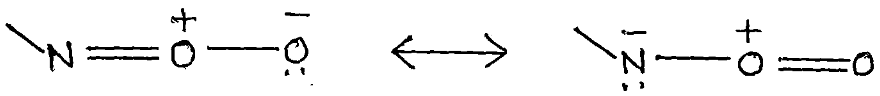
Carbonyl Oxides.



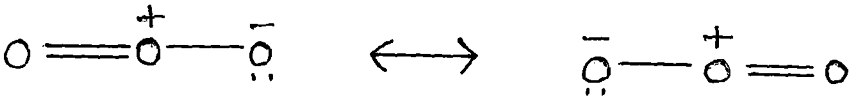
Carbonyl Imines.



Nitrosoimines.

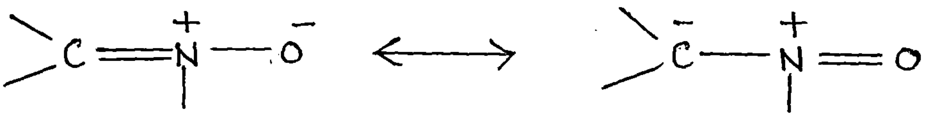


Nitrosoxides.

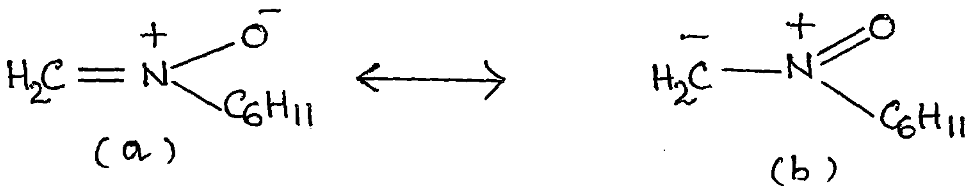


Ozone.

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



In order to verify the energies associated with the two canonical forms, N- cyclohexyl methylene - nitrone was taken as an ideal example (2). Approximate qualitative information of the non - uniform distribution of electronic charge of the nitrone could be obtained by applying the HMO method. The canonical forms of the nitrone are :



In 1971, Sustmann classified 1,3 dipoles into 3 main types (23). This classification was based on perturbation treatments of cycloaddition reactivity described earlier by Fukui (29), Salem (30), and Herndon (31) and also described generally by several authors (32).

According to this theory, the intermolecular interactions that occur in the transition state of a cycloaddition are divided into destabilizing closed shell- replusions, stabilizing or destabilizing coulombic interactions and stabilizing charge - transfer interactions. The charge transfer stabilization arises from the overlaps of filled orbitals on one molecule with vacant orbitals on the other.

Sustmann showed the reactivity trends expected for various relative energies of the frontier orbitals (23) starting from the case where both 1,3 dipole and dipolarophile have similar frontier orbital energies (Fig. F)

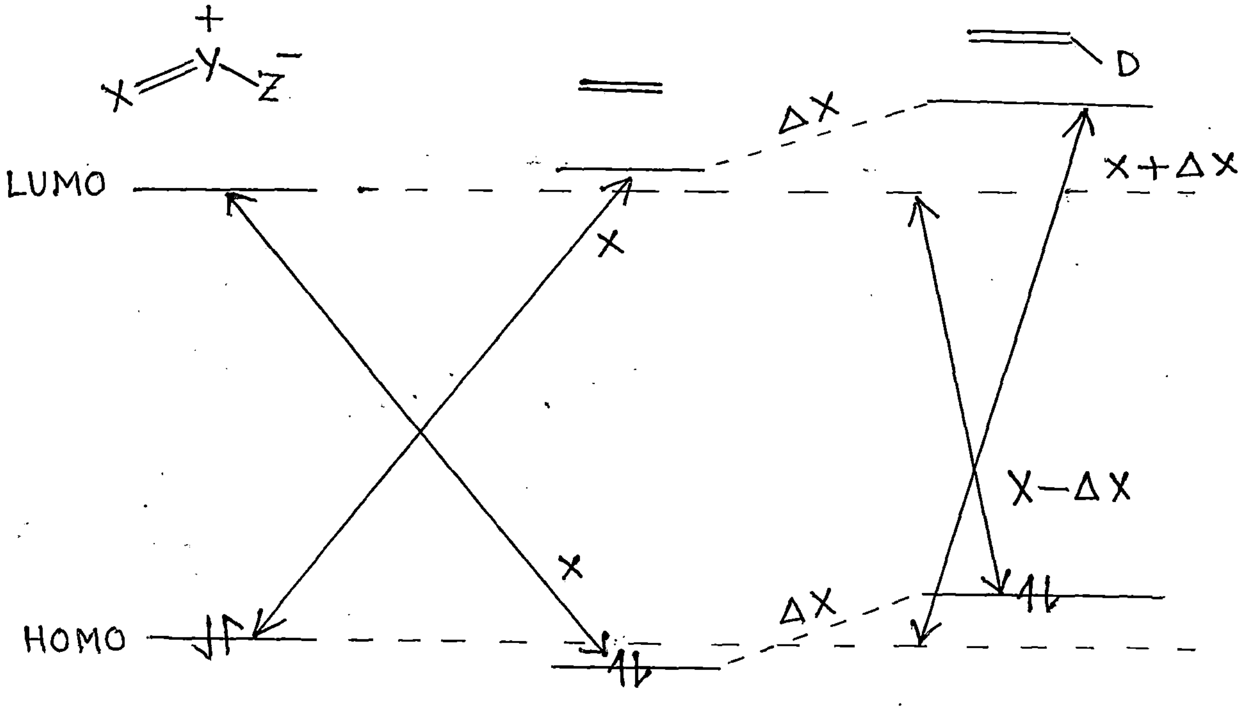


Fig. F.

Pattern of frontier molecular orbitals for a type II (ambiphilic) 1,3 dipole demonstrating the sustmann approximation.

Our one of the nitrones i.e. N- cyclohexyl 5- hydroxy - nitrone (245) belongs to type II i.e. ambiphilic in nature and the nature of frontier molecular orbitals are same as shown in the Fig. F.

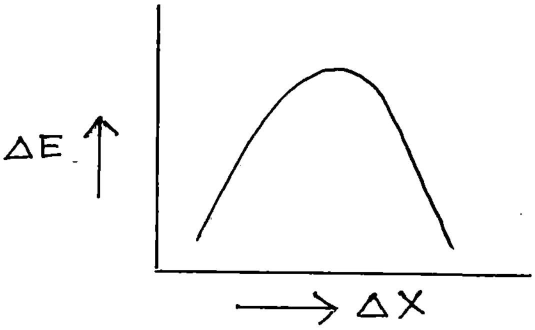
Sustmann made the following approximations in order to facilitate the analysis of interactions between the HOMO of the dipole and the LUMO of the dipolaro phile. For ambiphillic 1,3 dipole, both frontier energy gaps are assumed to be equal with a value X with these assumptions, the stabilization becomes,

$$\Delta E_{\text{frontier}} \cong \frac{1}{X} + \frac{1}{X}$$

When the dipolaro phile is substituted, the HOMO and LUMO of this species are assumed to change by an equal amount, ΔX. This decreases one frontier orbital gap to $X - \Delta X$, and increases the other to $X + \Delta X$, as indicated for a donar - substituted alkene in Fig. F. The new Stabilization energy is :

$$\Delta E'_{frontier} \cong \frac{1}{X-\Delta X} + \frac{1}{X+\Delta X}$$

The term $\frac{1}{X-\Delta X}$ increases faster than $\frac{1}{X+\Delta X}$ decreases and if ΔE is plotted versus ΔX , a parabola results.



Type I dipoles are those that have relatively high lying HOMO'S and LUMO'S . An increase in the narrowest frontier molecular orbital gap will decelerate the reaction. This is termed as HOMO controlled or neocleophilic 1,3 dipoles.

Finally a type III , LUMO - controlled or electrophilic 1,3 dipole is one with low - lying frontier molecular orbitals. Electron donars on the dipolaro- phile accelerate reaction, whereas acceptors slow the reaction. These are indicated schematically in Fig. G.

Type of 1,3 - Dipole.

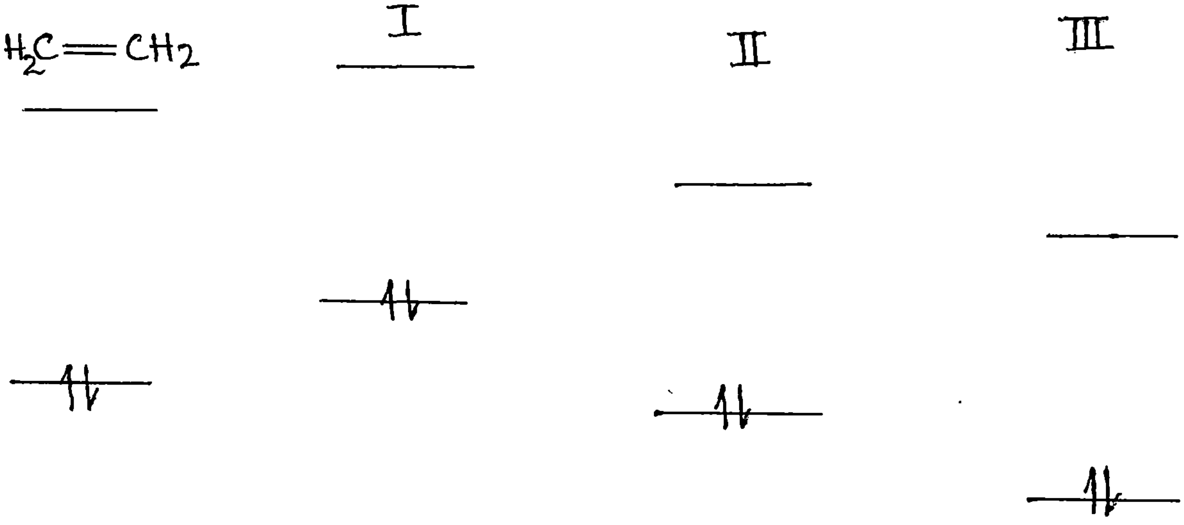


Fig G.

Types I,II,III, dipoles are also known as HOMO, HOMO - LUMO and LUMO controlled 1,3 dipoles or nucleophilic, ambiphilic and electrophilic 1,3 dipoles.

Our second nitrone, N- cyclohexyl chloro nitrone belongs to the type III i.e. LUMO controlled 1,3 dipoles or electrophilic 1,3 dipoles. In these type of nitrones the frontier molecular orbitals are placed low lying compared to the type I & II in the energy level diagram as shown in Fig. G.

Effect of Substituents on the dipolarophiles

According to Sustmann (22), electron attracting substituents on the dipolaro philes will lower both the Ψ_A and Ψ_B in energy Fig. I. Therefore the interaction leading to Ψ_2 will become stronger, resulting in a stabilization of the transition state. Although Ψ_B and Φ_A will now interact less strongly this effect will be smaller owing to the higher difference in orbital energy already present in the molecule. As a result, the LUMO - ethylene - HOMO - allyl anion interaction will exist. Experimentally an increase in reactivity due to electron attracting substituents for most 1,3 dipolar cycloadditions, for instance with nitrile imines (33), azides (9) and sydnones (34).

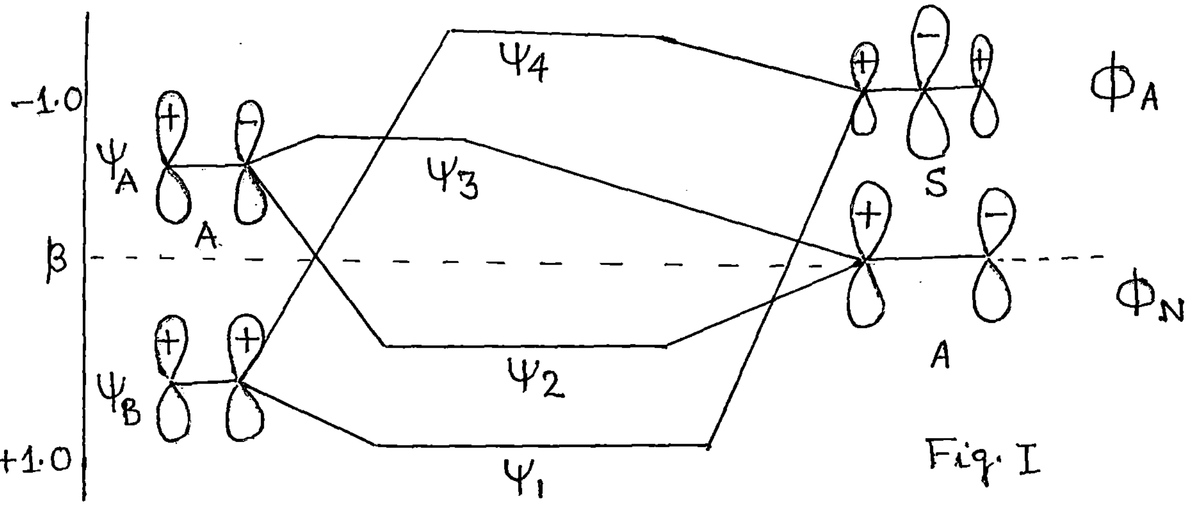


Fig. I

On the other hand electron relaeasing substituents on the dipolaro phile will raise the energy of Ψ_B and Ψ_A . As a consequence Ψ_A and Φ_B will show smaller and Ψ_B and Φ_A stronger interaction.

Approximate HMO calculation of the structure (a)

The secular determinant could be set up using the suggested parameter values (3) for hetero atoms for use with simple LCAO treatment, viz, $h_{N^+} = 2$; $h_{O^-} = 2$; $K_{C-N} = 1.1$; $K_{N-O} = 0.7$ etc.

$$\begin{vmatrix} \alpha_0 - \epsilon & \beta_{12} & \beta_{13} \\ \beta_{21} & \alpha_0 - h_N + \beta_0 - \epsilon & \beta_{23} \\ \beta_{31} & \beta_{32} & \alpha_0 + h_0 - \beta_0 - \epsilon \end{vmatrix} = 0$$

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

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

The secular polynomial of the system was :

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

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

Therefore the energy levels are :

$$\epsilon_1 = \alpha_0 + 0\cdot5175\,\beta_0$$
$$\epsilon_2 = \alpha_0 - 1\cdot58775\,\beta_0$$
$$\epsilon_3 = \alpha_0 - 2\cdot9297\,\beta_0$$

And the total π - energy of the system [a] was $E_\pi = 4\alpha_0 + 5\cdot03495\beta_0$

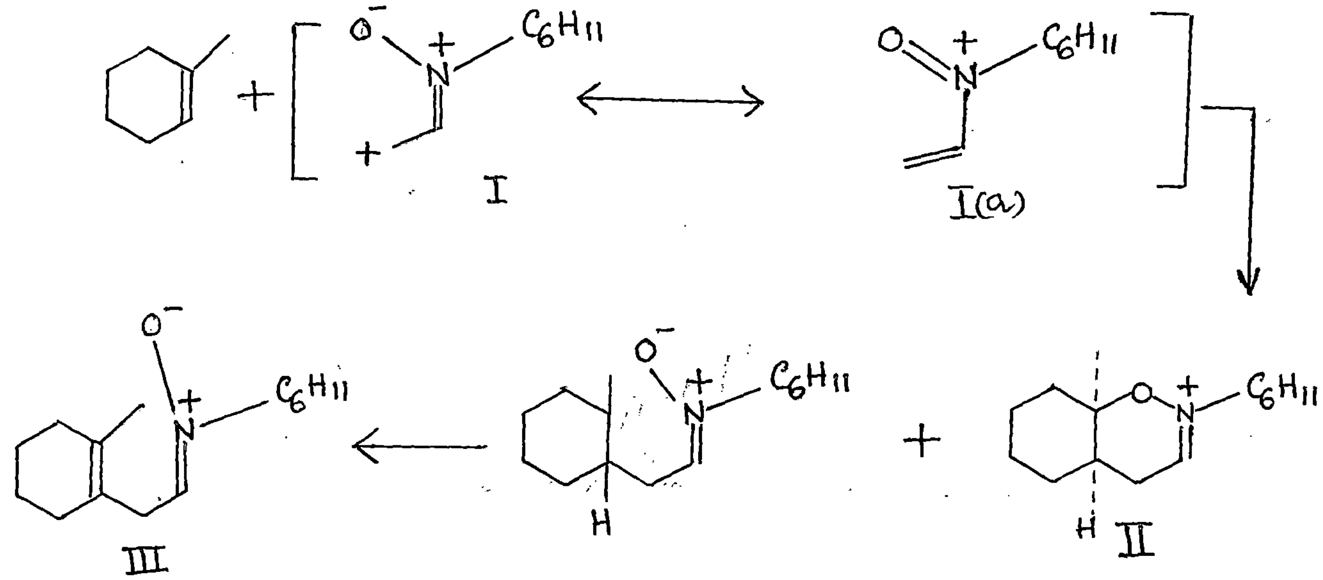
Similar treatment on the system [b] gave the following values.

$$\epsilon_1 = \alpha_0 + 3\cdot035\,\beta_0$$
$$\epsilon_2 = \alpha_0 - 0\cdot3304\,\beta_0$$
$$\epsilon_3 = \alpha_0 - 1\cdot295\,\beta_0.$$

The total π - energy of the system [b] was $E_\pi = 4\alpha_0 + 4.6604\beta_0$

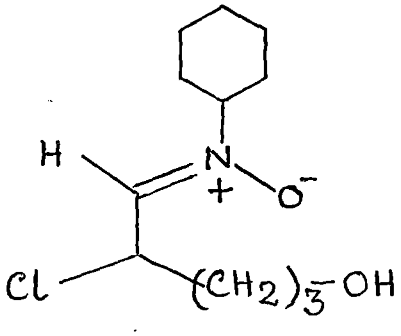
From the calculated result, it is evident that the canonical form [a] is more stable and favourable on energy ground and this is also in agreement with the existing principle.

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



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 MO'S are filled and the antibonding MO'S are vacant and acts as a diene component in the hetero Diels - Alder reaction with olefins (4π + 2π - cycloaddition).

In order to verify the stability of such type of nitrones, N - cyclohexyl chloro - nitrone (IV) was taken as example for approximate HMO calculation.



(IV)

The Secular determinant for nitrone (IV) could be studied in two ways, viz. C & D :

(C) :

$$\begin{vmatrix} \alpha_0+2\beta_0-\epsilon & \beta_{12} & \beta_{13} & \beta_{14} \\ \beta_{21} & \alpha_0-\epsilon & \beta_{23} & \beta_{24} \\ \beta_{31} & \beta_{32} & \alpha_0+2\beta_0-\epsilon & \beta_{34} \\ \beta_{41} & \beta_{42} & \beta_{43} & \alpha_0+2\beta_0-\epsilon \end{vmatrix} = 0$$

$$\begin{vmatrix} x+2 & 0.4 & 0 & 0 \\ 0.4 & x & 1.1 & 0 \\ 0 & 1.1 & x+2 & 0.69 \\ 0 & 0 & 0.69 & x+2 \end{vmatrix} = 0$$

Thus solving X = 0.578 ; -1.5607 ; -2.9436 ; -2.0656 .

The energy levels were :

$$\epsilon_1 = \alpha_0 - 0.578\,\beta_0$$
$$\epsilon_2 = \alpha_0 + 1.5607\,\beta_0$$
$$\epsilon_3 = \alpha_0 + 2.9436\,\beta_0$$
$$\epsilon_4 = \alpha_0 + 2.0656\,\beta_0$$

The total π energy of the system was = $4\alpha_0 + 7.1479\,\beta_0$

(D) :
$$\begin{vmatrix} \alpha_0+2\beta_0-\epsilon & \beta_{12} & \beta_{13} & \beta_{14} & \beta_{15} \\ \beta_{21} & \alpha_0-\epsilon & \beta_{23} & \beta_{24} & \beta_{25} \\ \beta_{31} & \beta_{32} & \alpha_0+2\beta_0-\epsilon & \beta_{34} & \beta_{35} \\ \beta_{41} & \beta_{42} & \beta_{43} & \alpha_0+2\beta_0-\epsilon & \beta_{45} \\ \beta_{51} & \beta_{52} & \beta_{53} & \beta_{54} & \alpha_0+2\beta_0-\epsilon \end{vmatrix} = 0$$

$$\begin{vmatrix} x+2 & 0.4 & 0 & 0 & 0 \\ 0.4 & x & 0.9 & 0 & 0 \\ 0 & 0.9 & x & 1.1 & 0 \\ 0 & 0 & 1.1 & x+2 & 0.69 \\ 0 & 0 & 0 & 0.69 & x+2 \end{vmatrix} = 0$$

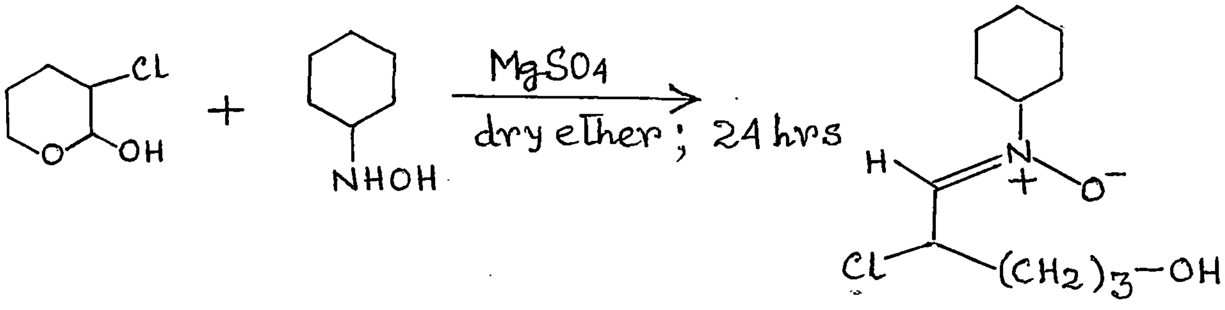
Solving ; X = 1.129; X = =1.20; X = -.555; X = -2.954;
X = - 2.4195 .

The energy levels were :
$\epsilon_1 = \alpha_0 - 1.129\beta_0$
$\epsilon_2 = \alpha_0 + 1.20\beta_0$
$\epsilon_3 = \alpha_0 + 0.555\beta_0$
$\epsilon_4 = \alpha_0 + 2.954\beta_0$
$\epsilon_5 = \alpha_0 + 2.4195\beta_0$

Total π - energy of the system was = $5\alpha_0 + 8.2575\beta_0$.

Considering the calculated energy levels associated with nitrone (IV) it was expected to be unstable.

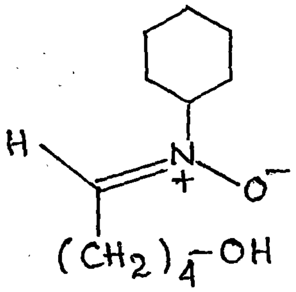
Keeping in mind the nitrone was synthesised from chlorohydrin (240)and N-cyclohexyl hydroxyl amine and was quickly chromatographed with Al_2O_3 . Nitrone was highly hygroscopic in nature.



The above assusmption could also be rationalised on the basis on the Fukui's Frontier Orbital Theory. The Sustman classification of 1,3 dipoles (details discussed in this chapter already) strictly holds only for the parent species, could be adapted qualitatively to substituted 1,3 dipole as well. Electron donar gr in 1,3 dipole shifts the 1,3 dipolar character towards the type - I i.e. HOMO controlled or nucleophilic 1,3 dipole. Where as an electron acceptor shift the behavior towards type-III i.e. electrophilic character.

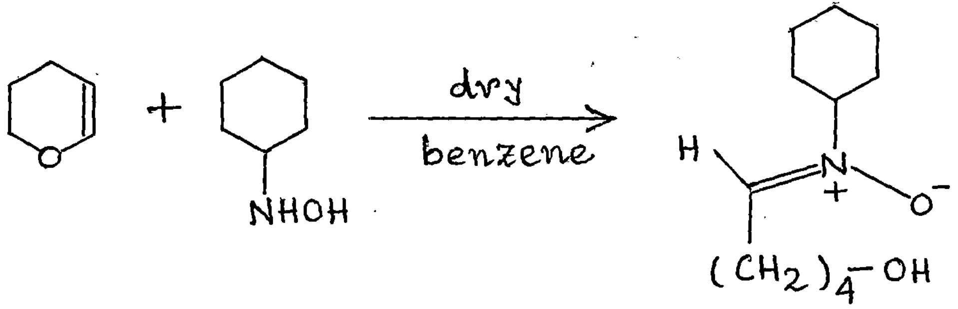
N - cyclohexyl chloro nitrone has a chlorine group at the β position of the nitrone which has a strong electron with drawing nature. Therefore, this nitrone should be electrophilic in character. In general nitrones are HOMO - LUMO controlled 1,3 dipoles skewing towards LUMO - controlled side. The high reactivity of N - cyclohexyl chloro nitrone could also be explained on the basis of Perturbation Theory (6), where in the HOMO level of a parent nitrone is raised in energy by the introduction of an chlorine group on the β - carbon atom and the corresponding LUMO level of the nitrone is stabilized. Thus the stabilization of the dipole LUMO level, thereby providing relative stabilization to the transition state for the cycloaddition and consequently increasing the rate of reaction.

On the other hand, N- cyclohexyl 5- hydroxy nitrone (V) do not have any withdrawl or electron donar group and therefore this nitrone is more or less neutral in character.



(V)

Keeping in mind N- cyclohexyl 5-hydroxy nitrone (245) was synthesised directly by refluxing Dihydropyran and N - cyclohexyl hydroxyl amine in dry benzene for 24 hours.



2. 1,3 Dipolar Cycloaddition

Houk et al (18) pointed out that mechanistic investigations have shown that cycloadditions of 1,3 dipole to alkenes are stereo specifically 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 regio selectivity phenomenon, have been considered totally compatible only with a concerted five centre mechanism. Orbital symmetry consideration have provided permissive, though not obligatory, theoretical evidence for the concerted mechanism and the observation of ($4\pi s + 6\pi s$) cycloaddition but not ($4\pi s + 4\pi s$) cycloaddition of 1,3 dipoles to triene has provided further evidence for the concerted mechanism (19,20). But the experimentally observed regio selectivity 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 Table - III. In each fig. (-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 MO'S 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 donar. The conjugated alkene (Table - III) raise HOMO'S and lower LUMO'S as compared to ethylene. Frontier MO'S of some 1,3 dipoles (Table IV) show relatively small gap in their HOMO - LUMO levels and therefore their reactivity are quite high. Hauk et al. further proposed that bending of either terminus can reverse these generalisations (21).

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 rule (17). And the allowed process can be of three types as proposed by Sustman (Fig. - C) (22,23). The type - I involves dominent interaction between HOMO (dipole) and LUMO (dipolarophile). Type - III involves LUMO (dipole)-HOMO (dipolarophile) .

Table - II

The frontier MO'S of electron rich alkenes.

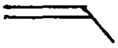
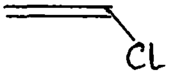
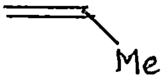
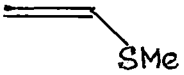
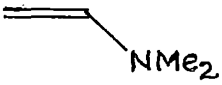
						
LUMO	·71,−·71 +1·5	·67,−·54 ~+5	·67,−·65 +1·8	·66−·72 +2·0	·63,−·48 −1·0	·62,−·69 2·5
HOMO	·71,·71 −10·52	·44,·30 −10·15	·67,·56 −9·88	·61,·39 −9·05	·34,·17 −8·45	·50,·20 −8·0

Table - III

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

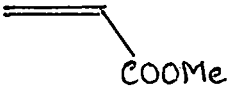
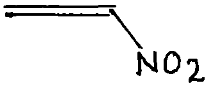
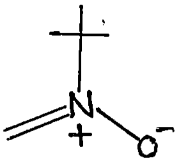
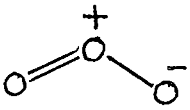
					
LUMO	·69,−·47 ~0·0	·66,−·54 ~0·0	·54,−·32 ~−0·7	·56,−·42 1·0	·48,−·35 +0·8
HOMO	·43,·33 −10·72	·60,·49 −10·92	·62,·60 ~−11·4	·57,·41 −9·03	·49,·32 −8·48

Table - IV

The frontier MO'S of 1,3 dipoles :

	$N\equiv\overset{+}{N}-\overset{-}{C}H_2$	$H-C\equiv\overset{+}{N}-\overset{-}{O}$		
LUMO	·50,−·70,−·51 ~+·2	·68,−·67,−·30 ~0	·58,−·67,·41 −·5	·53,−·67,·53 −2
HOMO	·61,−·13,·78 −8·99	·56,·21,−·80 −10·5	·69,·15,−·70 −8·64	·71,0,·71 −13·02

But in type-II both the LUMO (dipole) - HOMO (dipolarophile) and the HOMO (dipole) - LUMO (dipolarophile) are important in determining reactivity and regio-chemistry.

Type - I dipoles are those having high lying HOMO'S and LUMO'S and referred as HOMO controlled or nucleophilic 1,3 dipoles. Type III are having low lying FMO'S and referred as LUMO controlled or electrophilic dipoles. The type-II, 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.

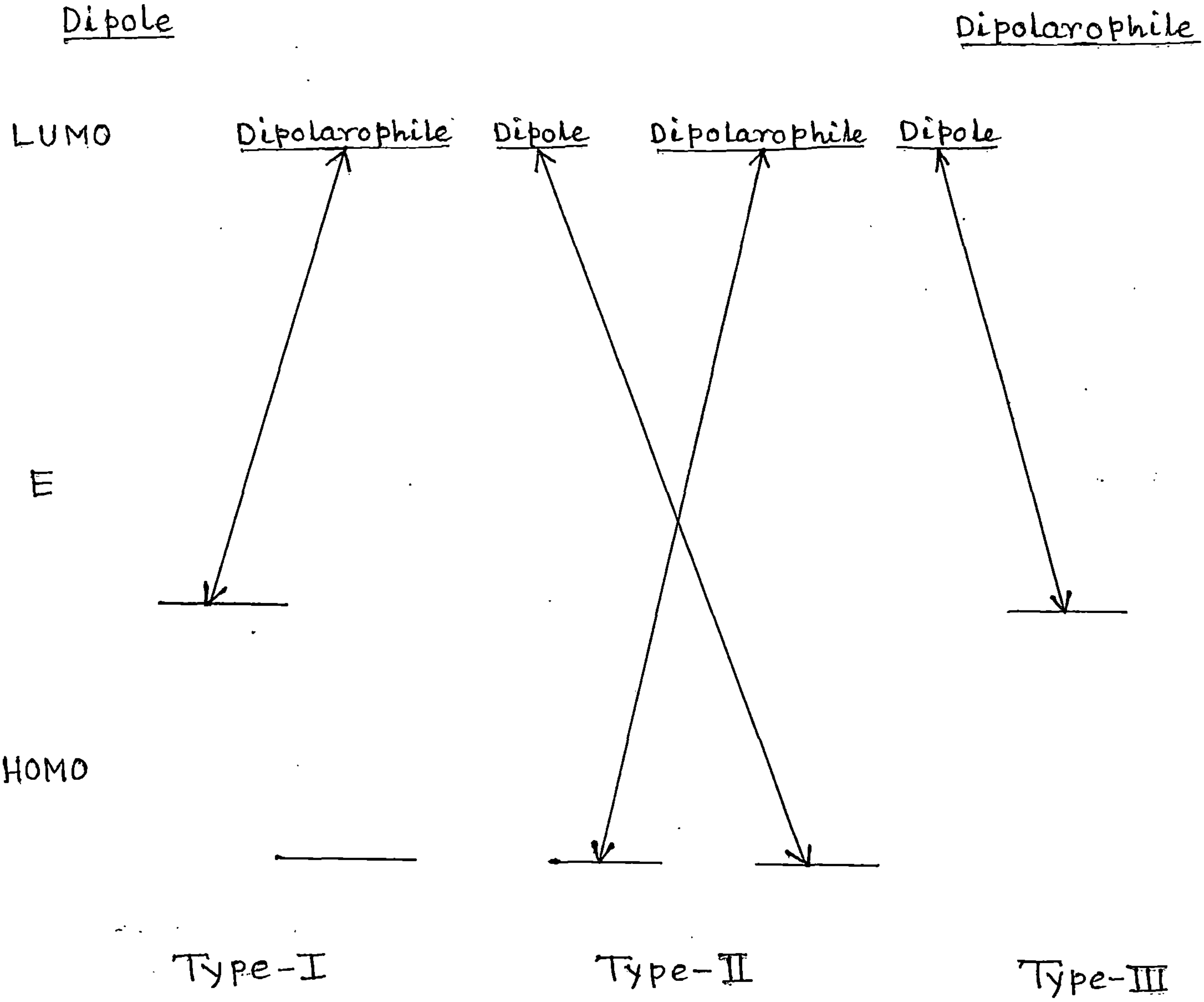


Fig-C.

The nitrile ylides, diazoalkanes 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.

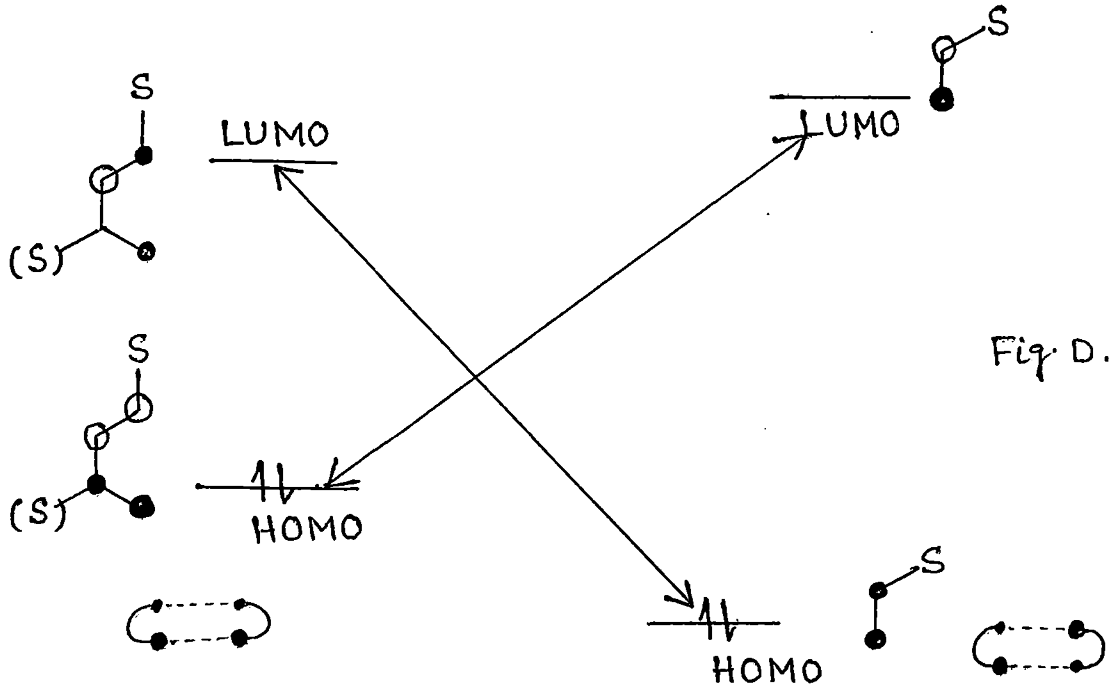


Fig. D.

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

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

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

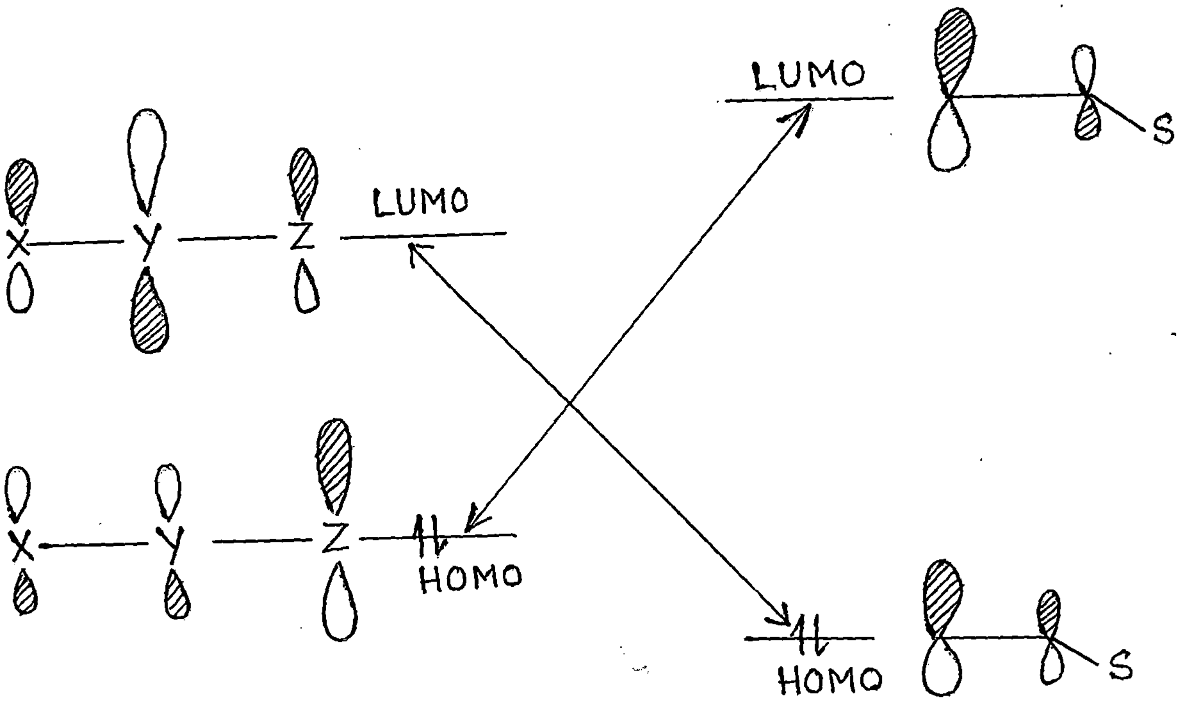


Fig. E

The HOMO'S of the 1,3 dipolar system generally have the larger terminal co-efficient on the group 'Z', while the LUMO'S have the larger co efficient at the opposite terminus 'X'. The HOMO'S and LUMO'S 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 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 oxides and nitrones react to give mainly the 5 - substituted adduct with weakly electron deficient alkenes such as acrylonitrile and acrylates. The HOMO'S and LUMO'S of these electron deficient alkenes both interact fairly strongly with the LUMO'S and HOMO'S of the nitrile oxides of 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 regio selectivity. 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 dipolaro philies are less reactive than expected on the basis of their IP'S (28). Since alkynes have larger HOMO - LUMO gap than the analogues 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 regio chemistry 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 such 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.