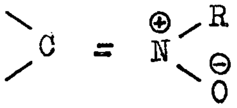
CHAPTER - I

Review of the Chemistry of nitrones

The term nitrone was coined from nitrogen ketone (azomethine oxide), in order to keep its resemblance to the carbonyl group in its several reactions[1].



The nitrones were known since 1887. The nomenclature employed by chemical abstract is as follows:

α,N diphenyl nitrone

α-phenyl-α- (p-tolyl)-N-methylnitrone.

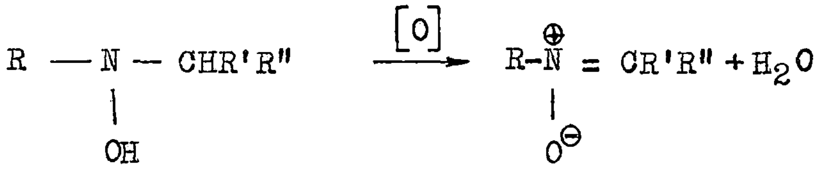
The cyclic nitrones are named according to the parent heterocyclic structure, e.g., 2,4 dimethyl-Δ^1-pyrolidine N-oxides, Δ^1-tetrahydropyridine N-oxide etc. Of late nitrones have also been named as C-cyclopropyl N-methyl nitrone, C,C-dicyclopropyl-N-methylnitrone etc.

Nitrones may exibit geometric isomerism because of the double bond in the nitrone moity. The existence of geometric isomerism was first demonstrated in 1918 for α-phenyl-α-(p-tolyl)-N-methyl nitrone[2]. The configuration of the isomers were established by dipole moment studies[1]. It has, also been established that aldonitrones exist in stable <u>trans</u> forms and this has been confirmed by uv, nmr and ir data[3]. The only example of the existence of both the geometric isomers in an aldonitrone is known for α-phenyl-N-t-butylnitrone[4]. Therefore in such cases where geometric isomerisms are possible E/Z system of nomenclature may be introduced.

1.1 Syntheses of nitrones:

The chemistry of nitrones along with their syntheses were reviewed in 1938[1] and 1964[5]. The general methods of their syntheses are briefly discussed here.

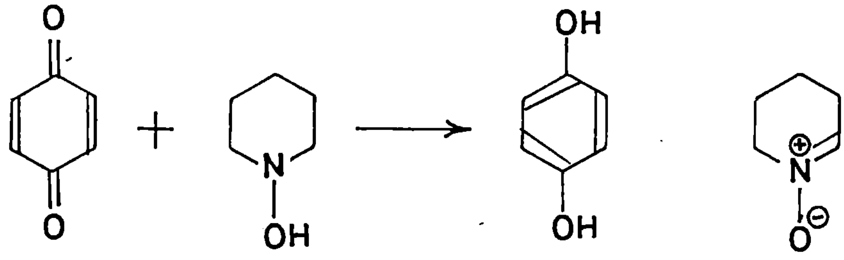
(A) By the method of oxidation of N,N-disubstituted hydroxylamines:



$$R-\underset{OH}{\underset{|}{N}}-CHR'R'' \xrightarrow{[O]} R-\underset{O^{\ominus}}{\underset{|}{\overset{\oplus}{N}}}=CR'R''+H_2O$$

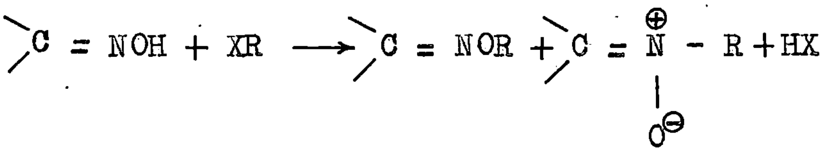
Both cyclic and acylic nitrones were prepared in this method and varied number of oxidizing agents were used, e.g. molecular oxygen[6,7,8,9,10], yellow mercuric oxide[11,3,12,13,14], "active" lead oxide[15], potassium ferricyanide[16,7,13,11] potassium permanganate[18], t-butyl hydroperoxide[19] and hydrogen peroxide[17,18].

Some other oxydative methods are also known e.g. diamminosilver nitrate was used as the reagent for the preparation of α-styryl α-benzyl-N-phenylnitrone from the corresponding hydroxylamine[7] and the formation of nitrone "salt" was reported from the reaction between p-benzoquinone and 1-hydroxy piperidine[20].



B. From oximes:

Alkylation of oximes afford nitrones along with oxime ethers. These methods were reviewed[1].

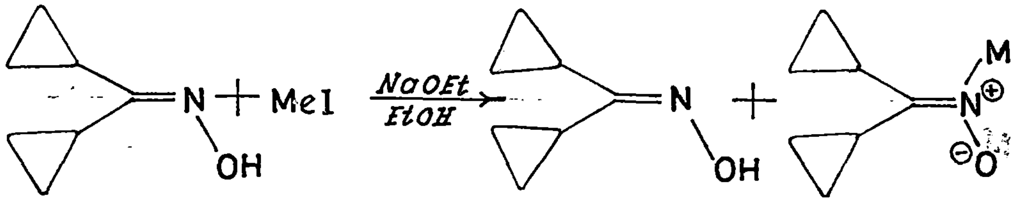


$$>C=NOH+XR\longrightarrow\ >C=NOR+\ >C=\underset{|\atop O^{\ominus}}{\overset{\oplus}{N}}-R+HX$$

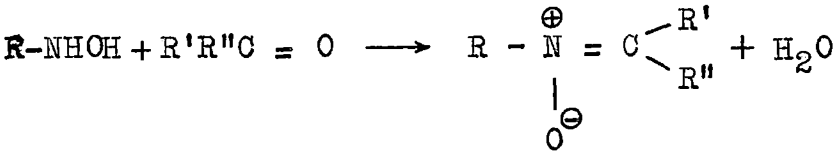
Lithium, sodium, potassium or trimethylammonium oxime salts did not show a significant difference in the product ratio of oxime ether to nitrone. Electron-withdrawing groups in p, p'-disubstituted benzephenone oxime salts markedly promoted the formation of nitrones, while electron donating groups favoured oxime ether formation. A pronounced steric effect was observed by comparing the reactions between benzophenone oxime sodium salt with methyl bromide or benzyl bromide, the small size of the alkylating reagent favouring nitrone formation and the larger size, oxime ether formation.

Heptanal oxime when treated with benzyl chloride in a solution of ethanol and sodium ethoxide yielded 77% of α-hexyl-N-benzylnitrone[21]. Dimethyl sulfate was employed in the alkylation of various ketoximes[22,23].

Recently C, C-dicyclopropyl-N-methylnitrone has been synthesized by this method[24].



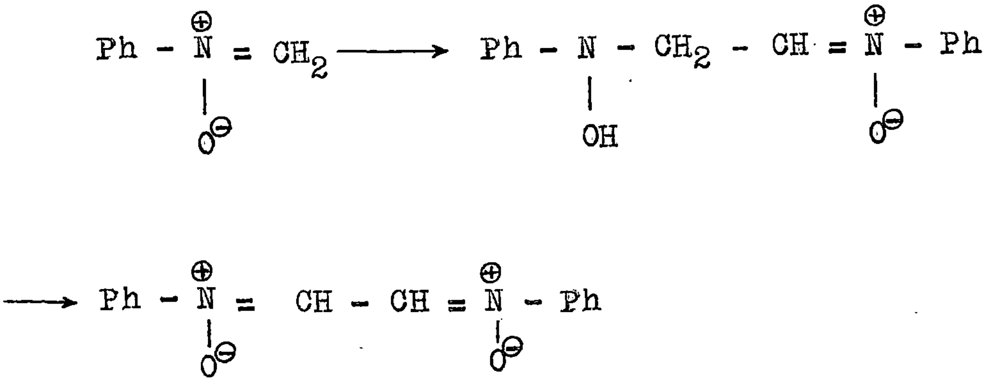
C. From N-substituted hydroxylamines



$$R\text{-}NHOH + R'R''C = O \longrightarrow R - \overset{\oplus}{N}(\underset{O^{\ominus}}{|}) = C\begin{matrix} R' \\ R'' \end{matrix} + H_2O$$

This reaction proceeds smoothly and in high yields when R is an allyl or aryl group and if R' and R" are of small size. When R' and R" are bulky groups the reaction does not proceed to any extent[25].

This method is treated as one of the best methods for the preparation of aldonitrones. N-phenylhydroxylamine has been treated with a variety of aldehydes and ketones. With n-butyraldehyde 80% yield of α-propyl-N-phenyl nitrone was obtained[16]. With benzaldehyde a 90% yield of the nitrone[26,27], with O-, m-, or p-nitrobenzaldehyde good yields[28], with p-N, N-dimethylaninobenzaldehyde a 79% yield[29] and good yields with other substituted benzaldehydes[30] were also reported. N-phenyl hydroxylamine and formaldehyde appear to form N-phenylnitrone which in situ undergoes an intermolecular 1,3 addition following by the loss of hydrogen and the formation of a dinitrone[7].



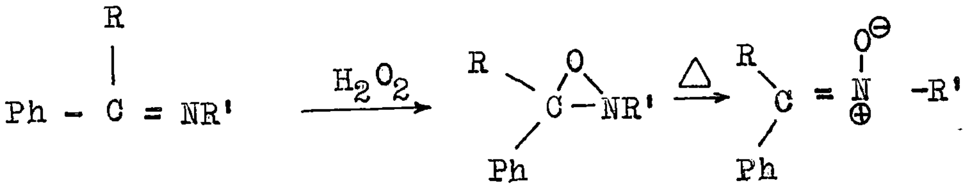
$$\mathrm{Ph-\overset{\oplus}{\underset{O^{\ominus}}{N}}=CH_2} \longrightarrow \mathrm{Ph-\underset{OH}{N}-CH_2-CH=\overset{\oplus}{\underset{O^{\ominus}}{N}}-Ph}$$

$$\longrightarrow \mathrm{Ph-\overset{\oplus}{\underset{O^{\ominus}}{N}}=CH-CH=\overset{\oplus}{\underset{O^{\ominus}}{N}}-Ph}$$

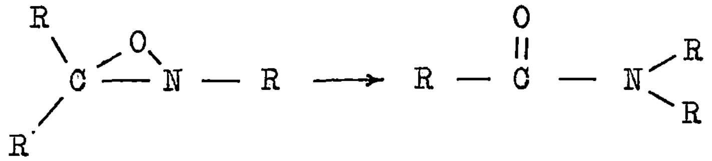
A similar 2:1 product was observed in the reaction between N-phenylhydroxylamine and α-bromocrotanaldehyde[7]. A number of sensitive nitrones have been prepared by this method and have been trapped in situ[31,32]. The bisulfite addition compounds of aldehyde and ketones may be used instead of the aldehydes or ketones[33]. Five-membered cyclic nitrones have been prepared in yields ranging from 50-80% by reductive cyclization of γ-nitro ketones[34,35,36] or γ-nitronitriles by employing zinc dust and aqueous ammonium chloride.

D. From oxaxiranes

The thermal rearrangement of 3-phenyl oxirane derivatives to the corresponding nitrones has been reported by various workers[38,4,39,40] in yields ranging from 50-100%



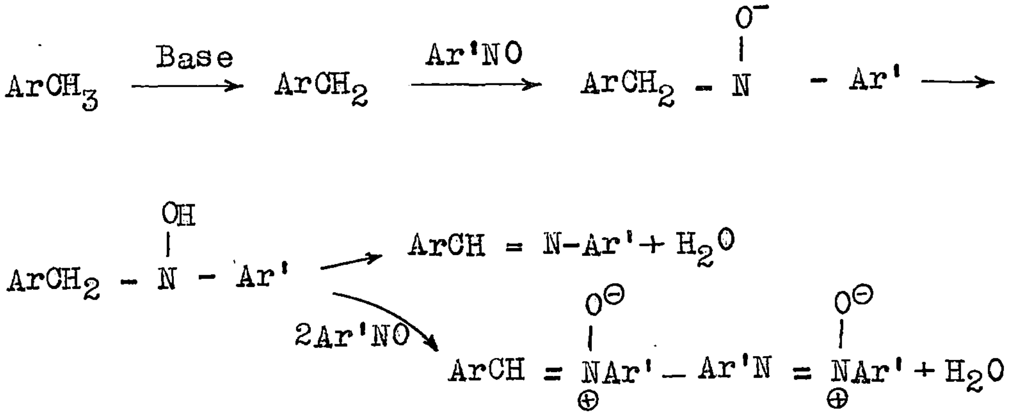
Thermal isomerizations of oxiranes other than 3-phenyl oxiranes did not lead to nitrones but to various rearranged products, mainly amides.



This method is not a general method for the preparation of nitrones since the oxaziranes are prepared either by the photochemical isomerization of nitrones or by the reaction between imines and hydrogen peroxide and moreover some other rearranged products are frequently encountered.

E. <u>From aromatic nitroso compounds</u>:

Aromatic nitroso compounds react with a variety of compounds to produce nitrones. 2,4,6-trinitrotoluence or 9-methylacridine, containing a sufficiently active methyl group react with aromatic nitroso compounds, the products often are a mixture of anils and nitrones[42,43,44,45]. The reaction is normally catalyzed by small amounts of base such as pyridine, piperidine, and sodium carbonate. The following sequence of steps has been proposed for the reaction.



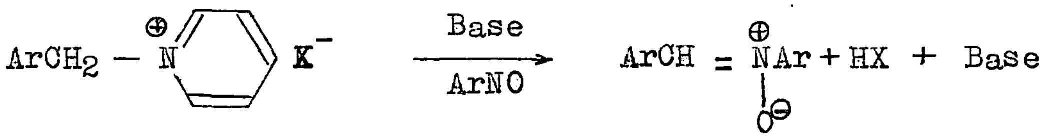
$$ArCH_3 \xrightarrow{Base} ArCH_2 \xrightarrow{Ar'NO} ArCH_2 - \overset{O^-}{N} - Ar' \longrightarrow$$

$$ArCH_2 - \overset{OH}{N} - Ar' \longrightarrow ArCH = N\text{-}Ar' + H_2O$$

$$\xrightarrow{2Ar'NO} ArCH = \underset{\oplus}{\overset{O^{\ominus}}{N}}Ar' - Ar'N = \underset{\oplus}{\overset{O^{\ominus}}{N}}Ar' + H_2O$$

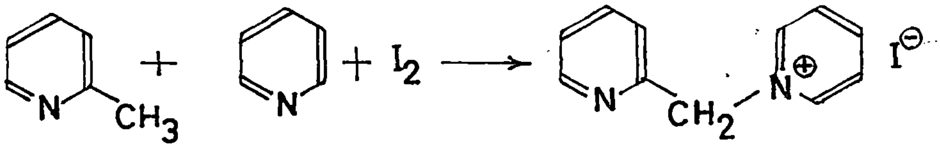
Such type of reactions are also known with lepidine N-oxide[48], quinaldine N-oxide[48,49] and 2- and 4-picoline[42,43].

The nitrones uncontaminated with the anils may be prepared by Kroehnke reaction (reviewed[50,53] by Kroehnke in 1953 and in 1963). In Kroehnke reaction aromatic nitroso-compounds, in presence of base reacts with pyridinium salts to give nitrones.



Quinolinium or isoquinolinium salts have been employed occasionally.

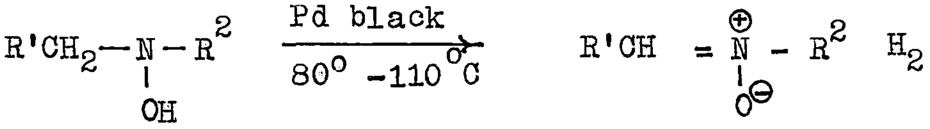
The pyridinium salts may be prepared by reaction between a compound containing active methylene group with pyridine and iodine[51,52]. This is known as King reaction.



The King reaction is specially helpful for preparing pyridinium salts of methyl-substituted heterocyclic aromatic compounds, α-methyl ketones[53] etc.

Aromatic nitroso compounds react with benzyl derivatives such as benzyl chloride[54,55] etc and fluorene[56] and similar[9] compounds[57,58,59] in presence of some suitable base to give nitrone.

Lots of other compounds like diazo compounds, sulfur ylides, Alkenes and Alkynes can react with aromatic nitroso compounds to produce nitrones[5]. Some other miscellaneous methods for the preparation of nitrones has also been reviewed[5]. Recently it has been reported that the palladium catalyzed reaction of N, N-disubstituted and N-substituted hydroxylamines give the corresponding nitrones and azoxy compounds highly efficiently. The former reactions are performed in the presence of alkenes to give the cycloadducts[60]



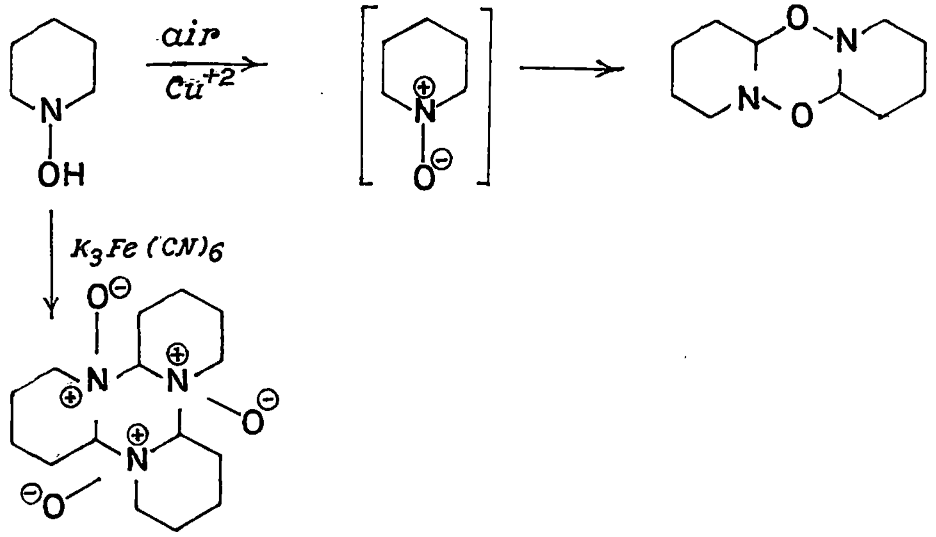
$$R'CH_2-\underset{\displaystyle OH}{\underset{|}{N}}-R^2 \xrightarrow[80^o\ -110^oC]{\text{Pd black}} R'CH=\overset{\oplus}{\underset{\displaystyle O^{\ominus}}{\underset{|}{N}}}-R^2\quad H_2$$

1.2 Reactions of nitrone

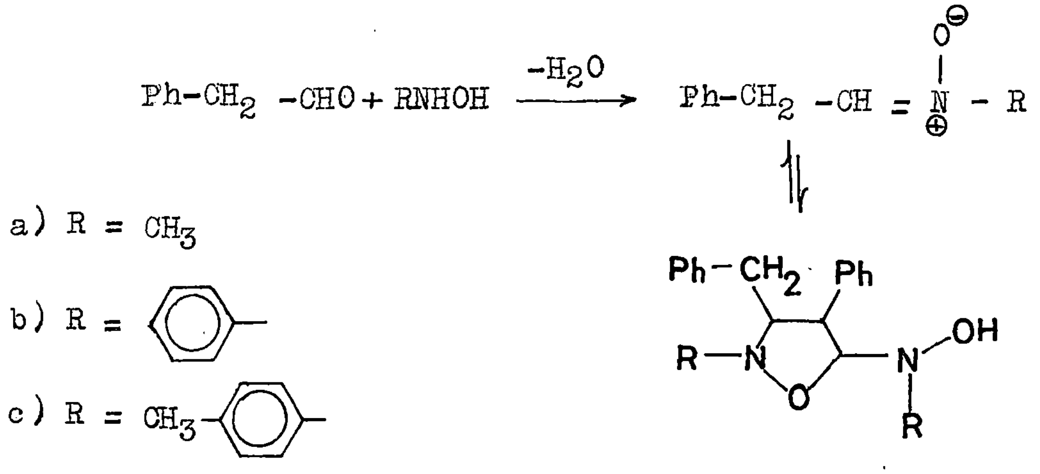
The major reactions of nitrones are their cycloadditions with a wide variety of multiple bonds. Due to the vastness of these reactions they are discussed in a separate section of this chapter; here a brief review of other reactions of nitrones are summarized. The reactions of nitrones known prior to 1964 are reviewed by Jan Hamer and Anthony Macaluso[5].

Dimerization:

Nitrones are sometimes very susceptible to dimerisation e.g. N-hydroxypiperidine did not give the expected cyclic nitrone; only the dimer[10] or trimer[11] was isolated. The corresponding five-



membered cyclic nitrones were found to be monomeric[8]. For aliphatic nitrones dimerization appeared to occur very readily. Acetone and N-phenylhydroxylamine, for instance, yielded an aldol-type dimer[34]; n-butyraldehyde and N-phenylhydroxylamine yielded a dimer of the same type. Dimerization with a loss of hydrogen molecule for a methylene nitrone is also reported[7]. For aliphatic nitrones following type of cyclodimerization has been reported[132] recently and in some cases the dimers shown to be the major products.

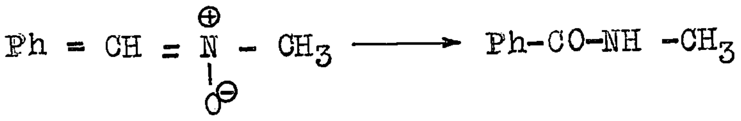


Other reactions:

Nitrones behave like carbonyl compounds in wide variety of reactions. They may undergo aldol type of condensations[61,62,87], additions to Grignard reagents[7,63,64,3,8,65] and hydrogen cyanide[8,66,67,68,69,70]. Other types of miscellaneous additions are also known[7,8,9].

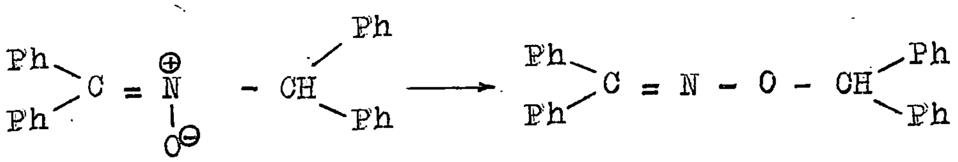
Rearrangements:

Aldonitrones rearrange to isomeric amides by treatment of variety of reagents[23,71-77,68]



$$\mathrm{Ph = CH = \underset{O^{\ominus}}{\overset{\oplus}{N}} - CH_3 \longrightarrow Ph{-}CO{-}NH\ {-}CH_3}$$

In some cases under heat[78,14] or on being catalysed by acids[79,80,81,92] nitrones may rearrange to O-ethers.

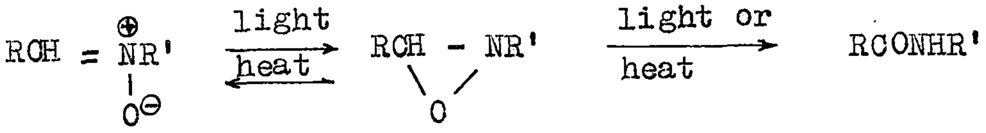


Ketonitrones in presence of base may rearrange to aldonitrones[78,82, 83] and such type of rearrangement are also observed during synthesis of some nitrones[79,83]. This type of rearrangements are known as Behrend Rearrangement.

Some other transformations of nitrones:

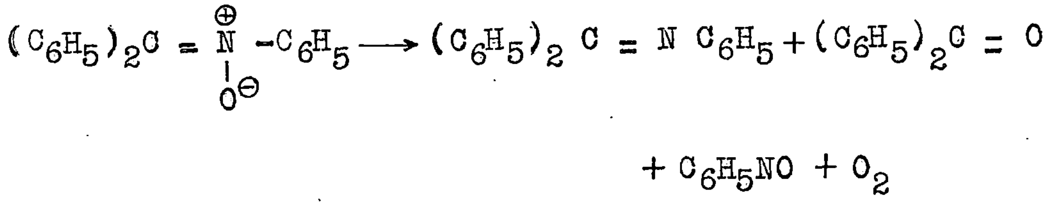
Irradiation of nitrones was found to lead to the isomeric oxaziranes, which were further found to rearrange thermally to the nitrones or photochemically to amides[84,26,40]. On pyrolysis nitrones were found split into anil, with traces of nitrosobenzene and benzophenone[85,86,87].

Photolysis



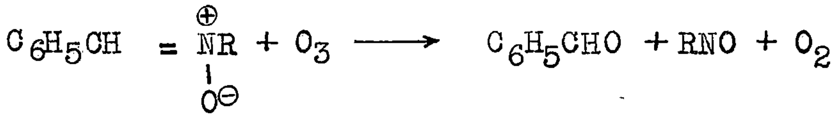
$$RCH=\overset{\oplus}{N}R'(O^{\ominus}) \underset{heat}{\overset{light}{\rightleftharpoons}} RCH\!-\!NR'(\text{-O-}) \xrightarrow[heat]{light\ or} RCONHR'$$

Pyrolysis



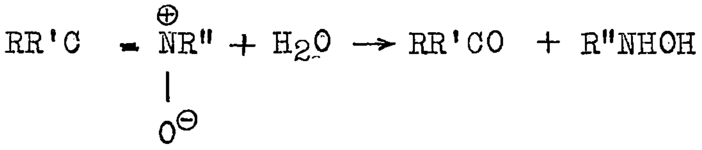
$$(C_6H_5)_2C=\overset{\oplus}{N}(O^{\ominus})-C_6H_5 \longrightarrow (C_6H_5)_2C=N\,C_6H_5+(C_6H_5)_2C=O + C_6H_5NO + O_2$$

Ozonolysis of nitrones is very rapid. Formation of green or blue colour indicates nitroso compounds as intermediates and the second mole or ozone oxidize the nitroso compounds to the nitro compound[88,87].



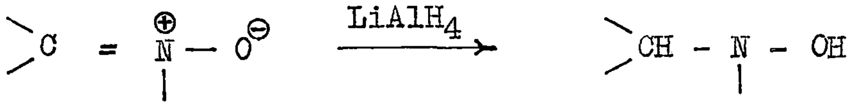
$$C_6H_5CH=\overset{\oplus}{N}R(O^{\ominus}) + O_3 \longrightarrow C_6H_5CHO + RNO + O_2$$

Nitrones generally hydrolyze readily, forming an aldehyde or a ketone[80,50] and an N-substituted hydroxylamine. Arylnitrones are far less susceptible to hydrolysis than alkyl nitrones.



$$RR'C=\overset{\oplus}{N}R''(O^{\ominus}) + H_2O \rightarrow RR'CO + R''NHOH$$

Nitrones upon treatment with either lithium aluminium hydride or sodium borohydride yielded the corresponding hydroxylamines, generally in high yields[89,90,71,3,4].



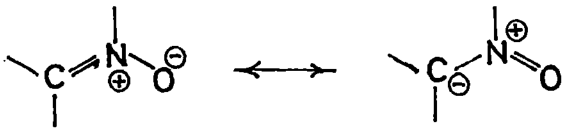
$$>C=\overset{\oplus}{N}(-)-O^{\ominus} \xrightarrow{LiAlH_4} >CH-N(-)-OH$$

Treatment of α-hexyl-N-benzylnitrone with sodium and alcohol yielded N-heptyl-N-benzylamine[21].

Dexoygenation of nitrones has been accomplished by zinc, tin or iron dust, phosphines, sulfur dioxide, sulfur and catalytic hydrogenation[8,34,36,87].

1.3 Cycloaddition reactions of nitrones:

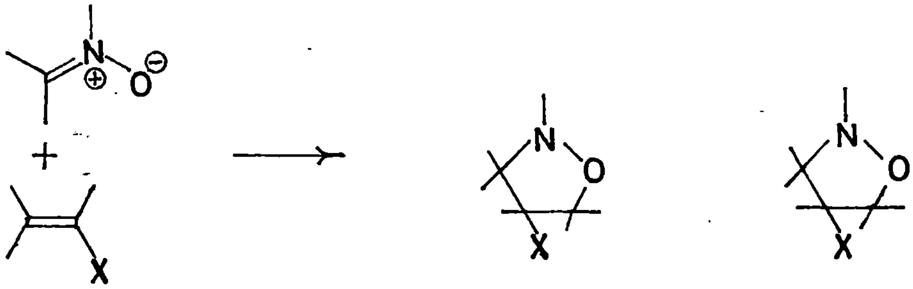
Nitrones readily undergo 1,3-dipolar cycloaddition reactions with a wide variety of multiple bonds. The nitrone additions are comprehensively reviewed in 1964[5] and 1975[91]. Nitrones are a system of three atoms, over which are distributed four π-electrons as in the allyl anion system. The term "1,3-dipole" arose because in valence-bond theory such compounds can only be described in terms of dipolar resonance contributors.



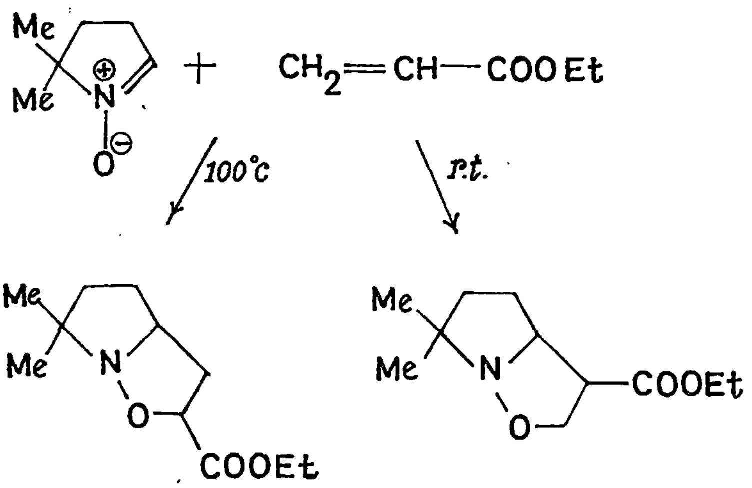
And dipolarophiles are the substrates having at least two π-electrons and can undergo cycloadditions with the 1,3-dipoles.

The mechanistic view point will be summarized in the next section of the chapter; only the findings dealing with the cycloadditions are reviewed here.

Addition of a nitrone to a carbon-carbon double bond gives rise to an 1,2-isoxazolidine, which is usually quite stable.



Unconjugated alkenes appear to react considerably slower than conjugated unsaturated systems, as a result of which sometimes very drastic conditions are needed with the former. On the other hand, with electron-deficient dipolarophiles nitrones react smoothly. In the addition of an unsymmetrical dipolarophile to nitrone, two orientations are possible. The direction of nitrone addition can be reversible and therefore subject to both thermodynamic and kinetic control[93]. For instance, the addition of ethyl acrylate to 5,5 dimethyl - Δ^1 - pyrroline N-oxide at room temperature yields 100% of one structural isomer but at 100°C 98% yield of the other structural isomer is obtained.



Consequently, regioselectivity applies to addition under conditions of kinetic control. Both steric and electronic factors are important[94] and in general the more hindered end of the dipolarophile adds to the nitrone oxygen atom to give 5-substituted product. However, this generalization does not hold good in all cases. The reversal of regiosection has been observed with the nitrones of very low ionization potential[96] or with the very electron deficient dipolarophiles[95]. In such cases preponderance of the 4-substituted isoxazolidines are observed. Table I illustrates how the regioselection changes with different dipolarophiles and with nitrones of different types. Other reported cycloadditions are given in the Tables - II, III & IV.

Only 5-substituted isoxazolidine adducts are formed in nitrone additions to 1,1 disubstituted alkenes. Most additions of

TABLE--I

Ratio of 5-substituted:4-substituted adducts from nitrone cycloadditions of electron-deficient dipolarophiles.

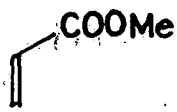
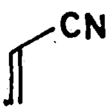
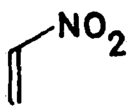
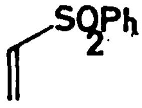
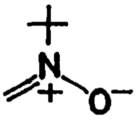
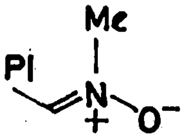
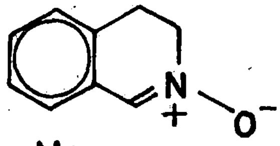
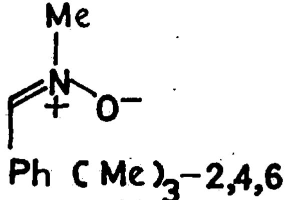
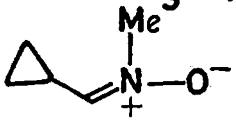
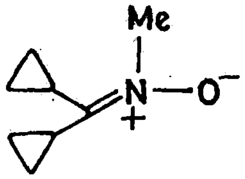
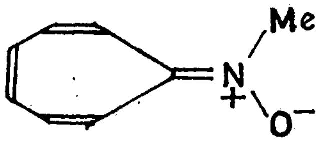
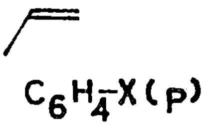
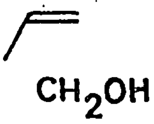
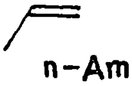
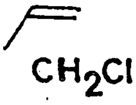
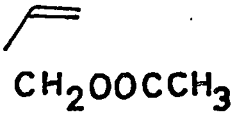
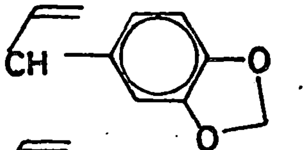
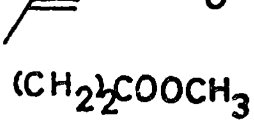
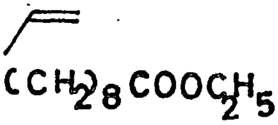
Dipolarophiles:						
Nitrones:						
	100:0	100:0	100:0	70:30	70:30	50:50
	100:0	100:0	0:100	32:68	42:58	0:100
	100:0	20:80	-	-	0:100	0:100
	50:50	15:85	0:100	0:100	0:100	0:100
	80:20	66.6:33.3	-	37:63	20:80	-
	50:50	25:75	-	0:100	0:100	-
	-	-	-	0:100	-	-

TABLE - II

Monosubstituted alkene dipolarophiles in nitrone cycloadditions

Dipolarophiles	Yield(%) of adducts	References
	57 - 100	95,101,102,97,104, 99,98,100.
	64 - 93	93,98.
	75 - 100	93,99.
	93	93.
	65 - 93	97,98.
	76	93.
	97	93.
	98	93.
	67	93.
	100	105,99.
	12	106.
	50	106.

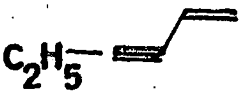
Dipolarophiles	Yield(%) of adducts	References
	50	106.
	61 - 100	95,93,107,108,99,35, 109,110,98.
	34 -100	93,95,107,97,109,110, 98,111,112,113,114.
	75 - 79	104,109,114.

TABLE - III

1,1-disubstituted alkene dipolarophiles in nitrone cycloadditions.

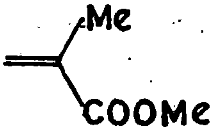
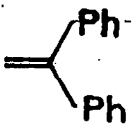
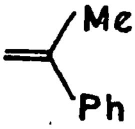
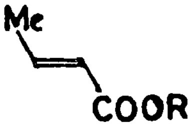
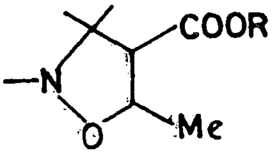
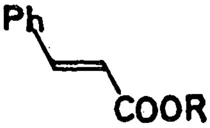
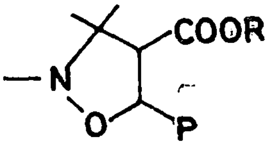
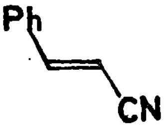
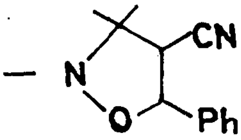
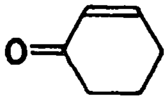
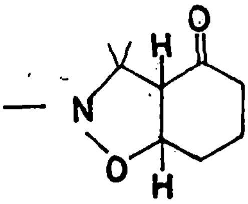
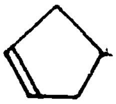
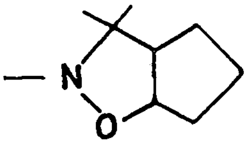
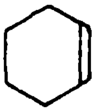
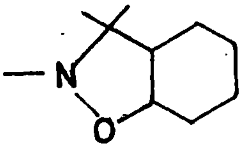
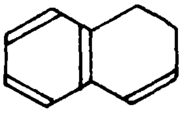
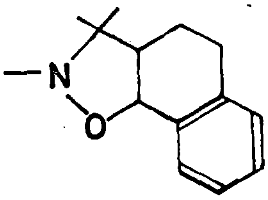
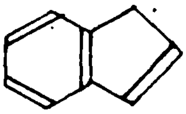
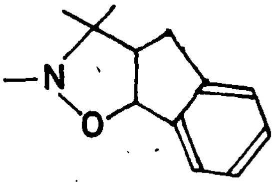
Dipolarophiles	Yield(%) of adducts.	References
	90 - 100	93,45.
	65 - 86	105
	70 - 85	105

TABLE - IV

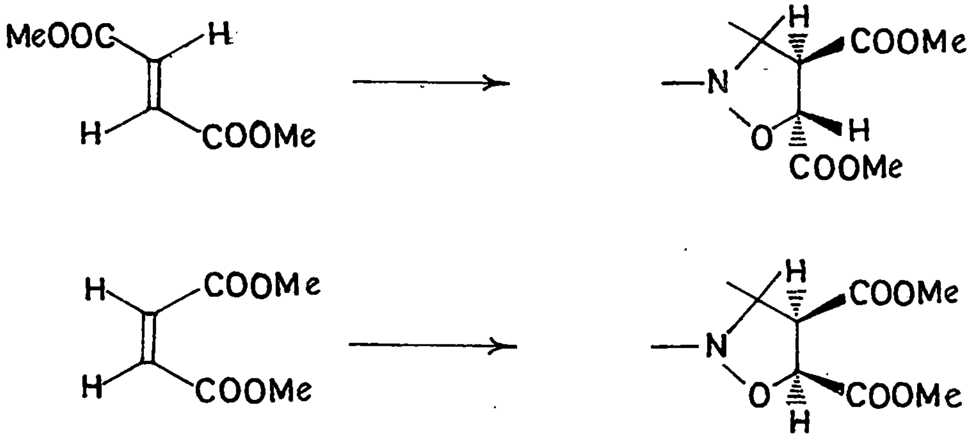
Unsymmetrical 1,2-Disubstituted Alkene Dipolarophiles in Nitrone Cycloadditions.

Dipolarophiles	Adducts	Yields (%)	Ref.
		63 -96	93, 98, 99, 100, 115.
		70 - 100	93, 115, 116.
		50 - 78	116.
		-	115.
		-	117.
		-	117.
		97	117.
		70 - 92	105.

trisubstituted alkenes to nitrone yield 4,5,5-trisubstituted isoxazolidines, but in one reaction of a hindered enamine a 4,4,5-trisubstituted isoxazolidine is produced[118]. Cycloadditions of tetrasubstituted alkenes to nitrones are not common and regioselectivity factors are similar to those discussed for unsymmetrical 1,2 disubstituted alkenes.

1.4 Stereochemistry of Addition:

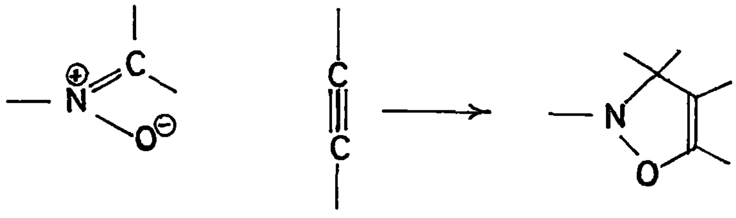
Studies of addition of dimethyl maleate and dimethyl fumarate to a variety of nitrones[119,120] have established stereospecific cis additions by the production of mutually uncontaminated, diastereomeric adducts.



This general principle has been confirmed in many other cases of cycloadditions[93,116,119]. Cis-trans isomerisms of dipolarophile substituents with respect to the nitrone α-substituents has been noted in many cases and is caused by the fact that the nitrone can approach the dipolarophile from two different sides. Isomer ratios ranging from 50:50 to 100:0 have been observed. There is good evidence[121] that the more favoured transition state is the one in which the dipole of the reactants are opposed and that an increase in dipole moments increases the stereospecificity and vice versa.

1.5 Addition to alkynes:

Acetylenic compounds react smoothly with the nitrones to give 4-isoxazolines (2,3-dihydro-1,2-oxazoles, I). But very seldom the adduct (I) has been isolated. In major cases some rearranged products are found. The instability of the isoxazoline system is most plausibly responsible for the rearrangement[151]. Depending on the nature of substituents a number of different rearranged products may be formed as shown in Scheme I that the products



(I)

SCHEME - I

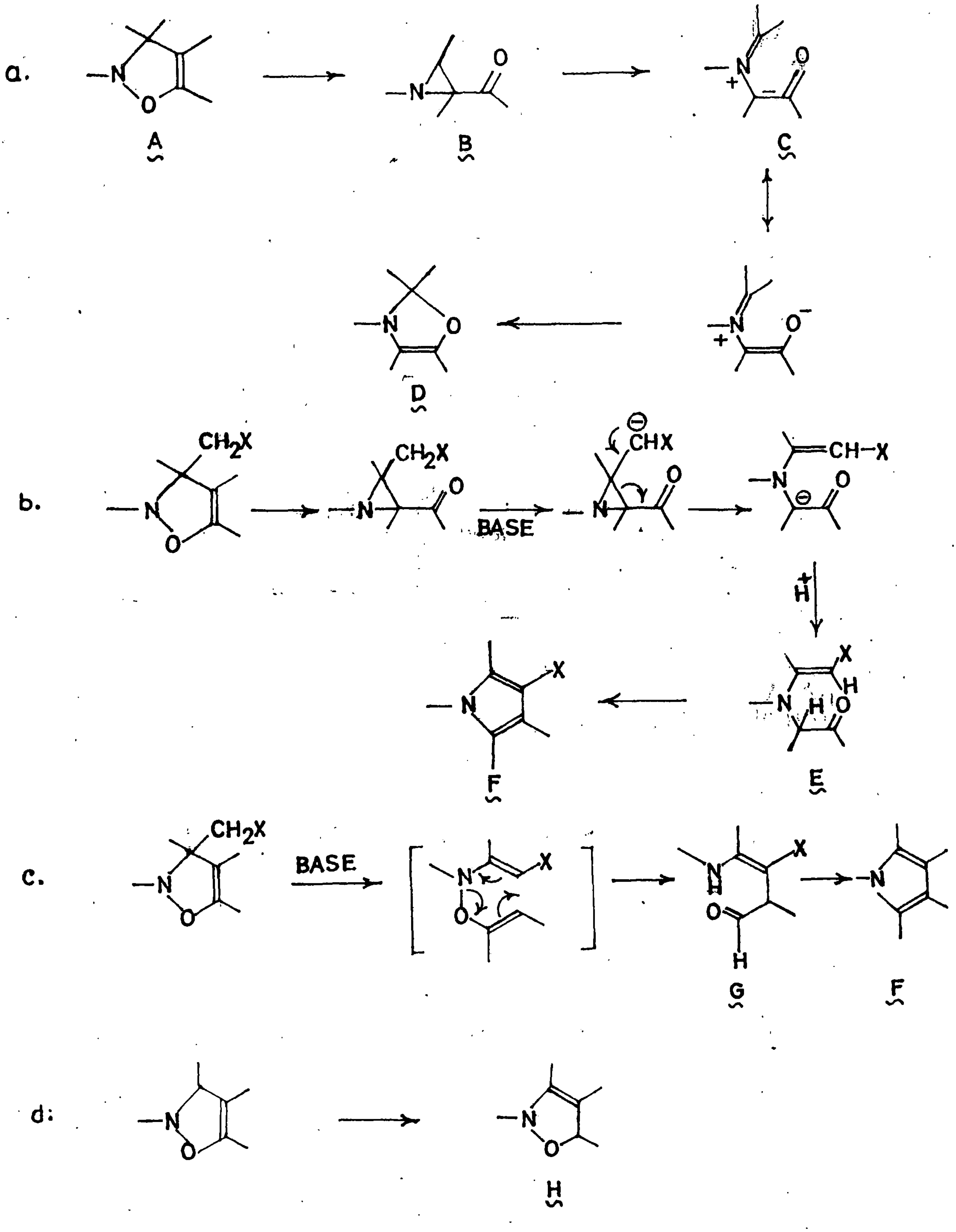
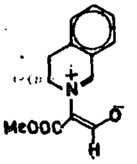
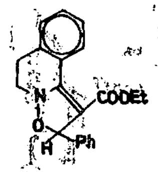
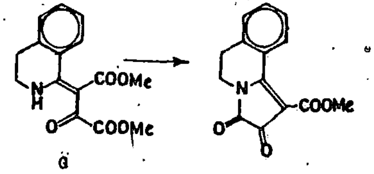
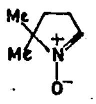
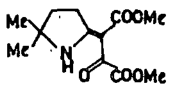
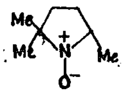
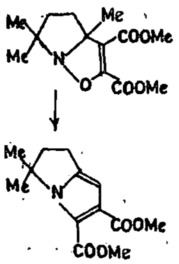
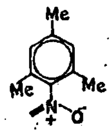
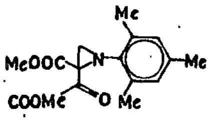
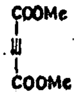
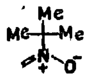
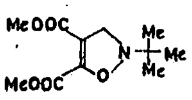
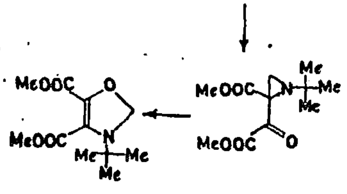


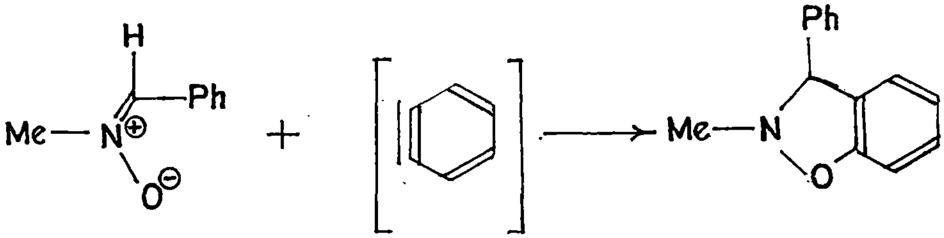
TABLE - V

DIPOLAROPHILES	DIPOLES	ADDUCTS	TYPE	REF.
	3,4-dihydro isoquinoline N-oxide.		C	122, 123.
	" "		B	122, 123.
	 G			122, 123.
			G	129.
			A F	129.
			B	130.
		  D	A B	130.
Alkynes	1,2-dimethyl benzimidazole N-oxide, Isoquinoline N-oxide, Phenathridine N-oxide.		C	124, 125, 126. 127. 127, 128.

isolated in different cases are summarized in the Table - V.

Relatively stable 4-isoxazoline adducts (I) have also been prepared from 2-phenylisatogen[123] and from single nitrones using phenylacetylenes[131], diphenylacetylenes, cyanoacetylenes[95] and ynamines[132].

Benzyne forms stable adducts with simple nitrones[123], but those derived from heteroaromatic N-oxides cannot be detected and are postulated to undergo rearrangement to phenolic derivatives[124,133].

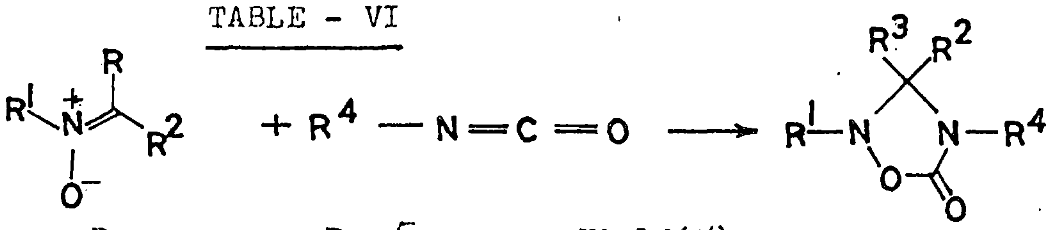


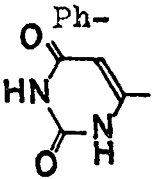
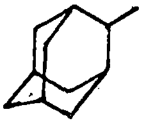
Allenes and ketenes also give different products which arise presumably from rearrangements of the initial adducts[37,135,136,137].

Additions to carbon nitrogen bonds:

Nitrone addition to - C≡N bond is not hitherto reported[91]. But isocyanates add spontaneously with a wide variety of nitrones to afford stable products as reported in Table - VI.

TABLE - VI



R'	R_2	R_3	Yield(%)	Ref.
Ph-CH$_2$-	Ph-	H-	-	138, 139, 140.
Ph-	Ph-	H-	71 - 100	141, 142, 143.
Me-	Ph-	H-	56 - 100	141, 142, 143.
Ph-	Ph-CH CH-	H-	89	7.
Ph-	Ph-	Ph-	92	87.
Ph-		H-	62	99.
Alkyl, Aryl.	H-	H-	98	101, 102, 140, 145.
	Aryl	H-	81 - 83	147.
	Alkyl	H-	47 - 91	148.

Similar cycloaddition reactions with isothiocyanates, carbodiimides and Aziridinium and Azetidinium salts are also reported and reviewed[91]. Other examples of nitrones additions to carbon-sulphur, carbon-phosphorus and nitrogen-phosphorus multiple bonds are also reviewed in the same paper.

1.6 1,3-Dipolar cycloadditions - Review from mechanistic point of view

According to Huisgen et al who were the first to recognize fully the general concept and scope of 1,3-dipolar cycloadditions, a cycloaddition of the type 3 + 2 → 5 leading to an uncharged 5-membered ring cannot possibly occur with octet stabilized reactants which have no formal charges. Rather, a 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 center, has an unshared electron pair. Combination of such a 1,3-dipole with a multiple bond system d = e, termed the dipolarophile, is referred to as a 1,3-dipolar cycloaddition[149,150].

1,3-dipoles can be further stabilized by internal octet stabilization.

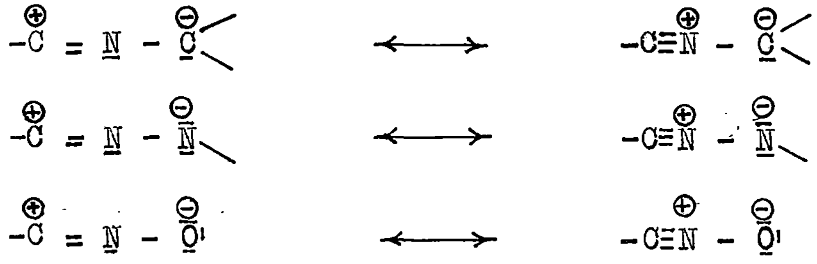
1,3-dipoles can be classified among two types viz. with double bonds and without double bonds and are presented in the table - VII.

Table- VII

1,3-Diples with a double bond.

Propargyl - Allenyl Type

Nitrilium betaines:

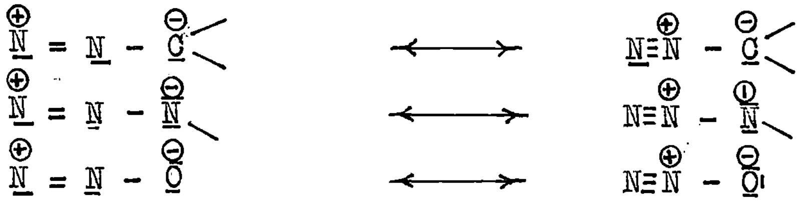


Nitrile ylides

Nitrile imines

Nitrile oxide

Diazonium betaines:



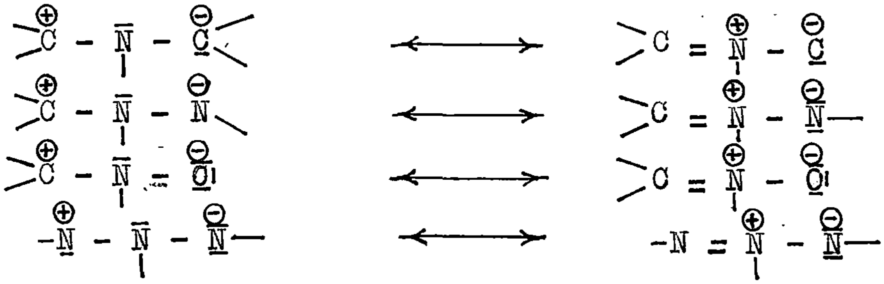
Diazo alkanes

Azides

Nitrous oxide

1,3 Dipoles without a double bond (Allyl type)

Nitrogen as central atom

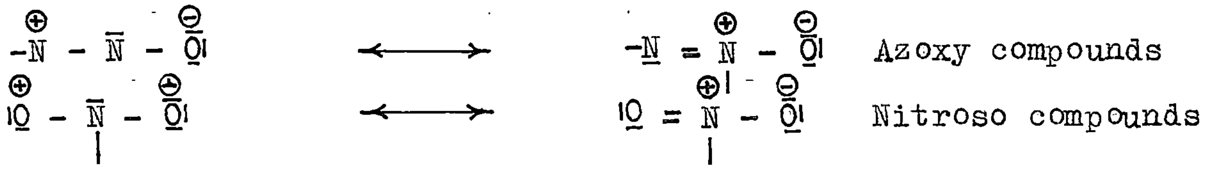


Azomethine ylides

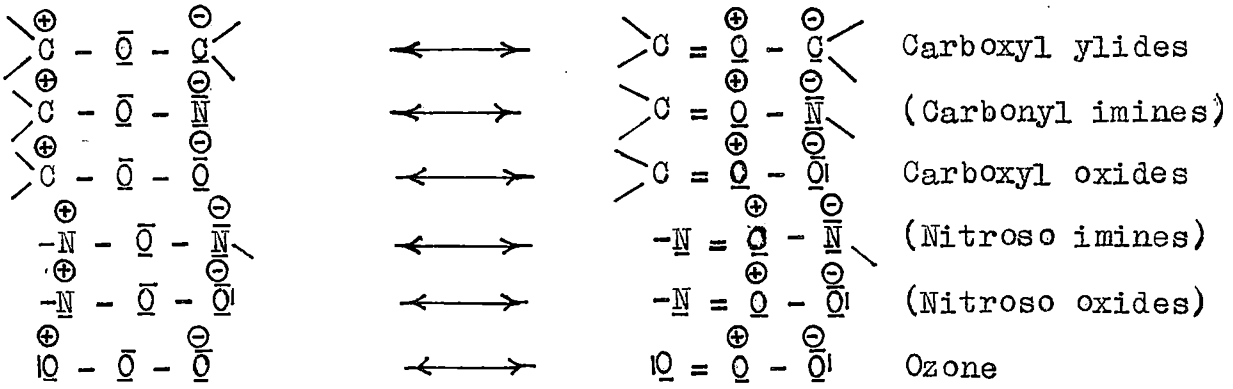
Azomethine imines

Nitrones

(Azimines)



Oxygen as central atom



The sextet and octet formula of the 1,3-dipoles are represented respectively in the left and right side of the double arrows.

In these 1,3-dipoles the central atom is never a carbon atom. If the center 'b' of the 1,3 dipole a-b-c is a carbon function then the internal octet stabilization is prevented by lack of an available free electron pair. Such systems are therefore extremely reactive and short-lived. Examples of this type are the unsaturated carbenes and azenes.

1,3-dipolar cycloadditions are concerted reactions i.e. both the σ-bonds are formed simultaneously and the reaction profile passes through a maxima[94]. Such types of single-step reactions are sometimes referred as "no-mechanism reactions". A

1,3-dipole is always an ambivalent compound, which either displays electrophilic and nucleophilic activity in positions 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 shift in Fig. A takes place clockwise or anticlock-wise 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.

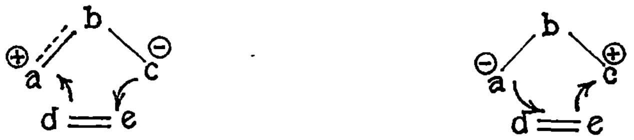
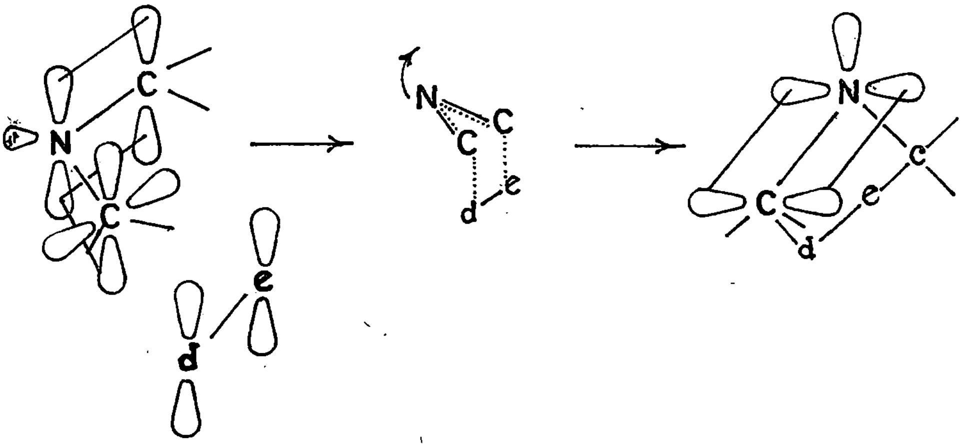


Fig- A

The evidences in favour of the concerted process[156] in 1, 3-dipolar cycloaddition come from their independence of solvent polarity[153,154] the negative entropies of activation[152], and the stereospecificity and regioselectivity[155].

Taking nitrile ylides as a model system Huisgen described the cycloaddition according to the scheme - II.

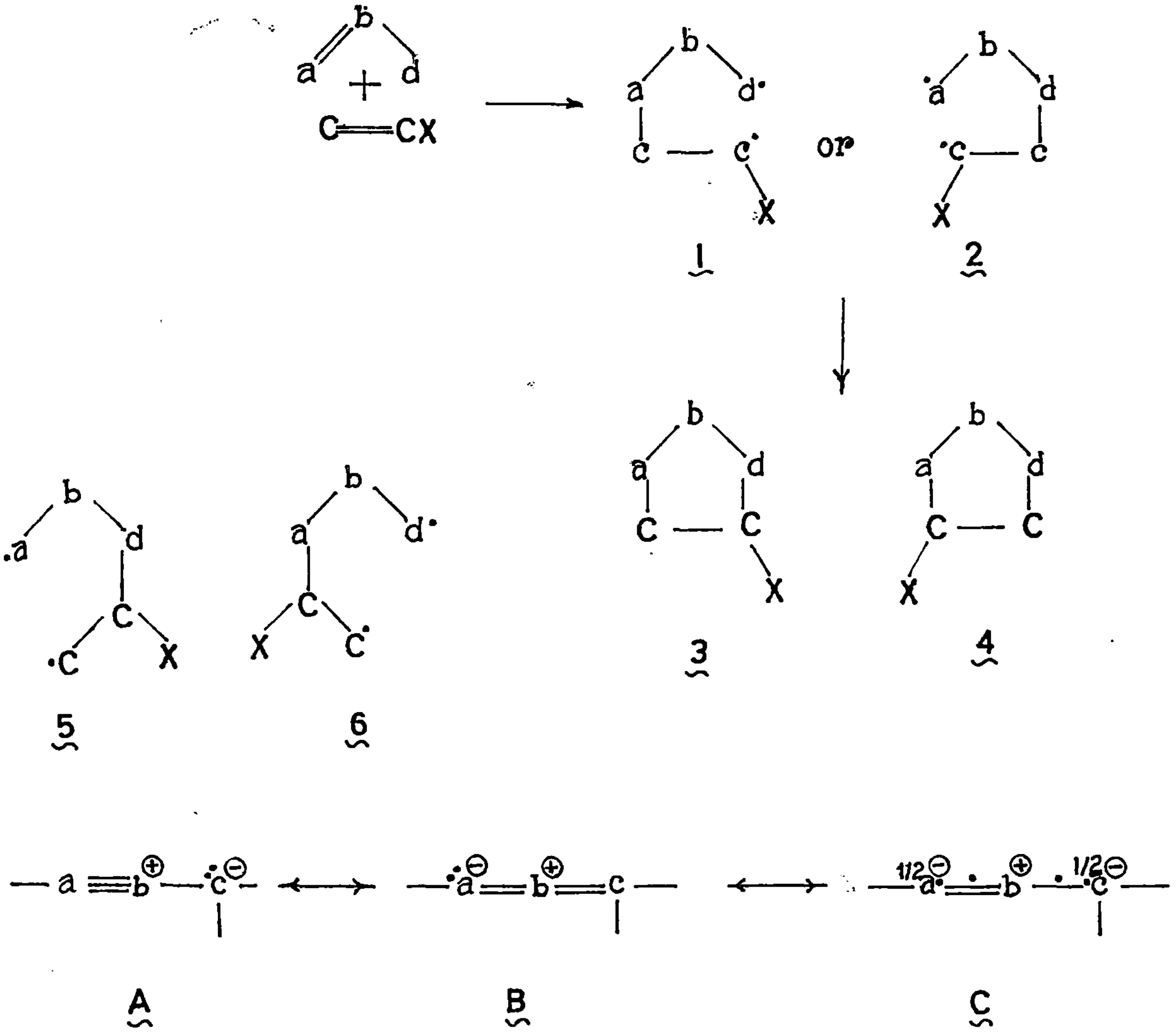
Scheme - II



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 types, 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. Calculations[159] show that the resonance energy of the "allyl anion" is not disturbed by the 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 transitions, the orbital of the lone pair at nitrogen attains p-character; the π-bond of the product originates from this pair of electrons. For 1,3 dipoles "without a double bond" the nitrogen atom at the transition state needs not 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[160,161,162] has observed some discrepancies in the mechanism proposed by Huisgen et al and proposed an alternative two-step mechanism for the 1,3 dipolar cycloadditions (Scheme - III).

Scheme - III

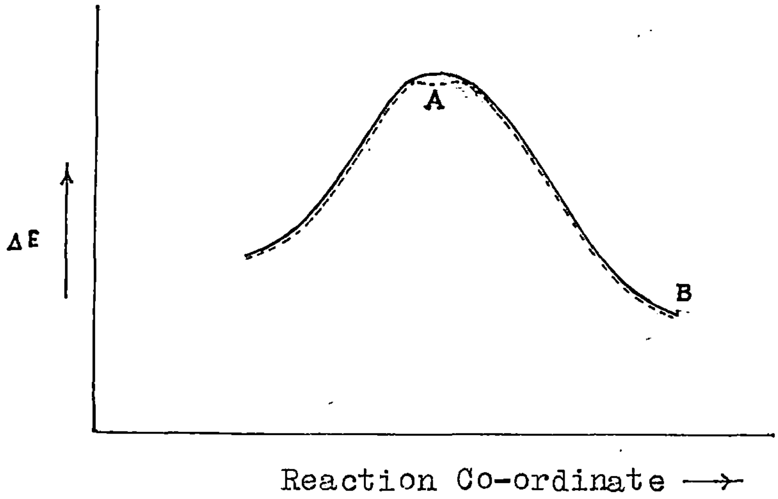


Firestone has considered three principal cannonical forms of a typical 1,3 dipole (A, B and C in Scheme III). These are all octet structures which have the same number of bonding electrons. All other forms, such as sextet structures, have fewer bonding electrons and are therefore discounted. Form C is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

He also considered all the modes of addition of the dipole and dipolarophile and selected two possible regioisomeric products '3' and '4' respectively. Diradicals '5' and '6' are thought 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 should be the same whether the substituent 'X' in the dipolarophile is electron-attracting or electron-releasing and expectedly this preference will govern the regioselection of the additions.

For the two step process the first step is the rate determining step and the activation energies for both advance and retrograde motion along the reaction co-ordinate (Fig. C) from the intermediate is very small, smaller in fact than that for rotation around a single bond.

Fig. C



B - Reaction profile for concerted reaction

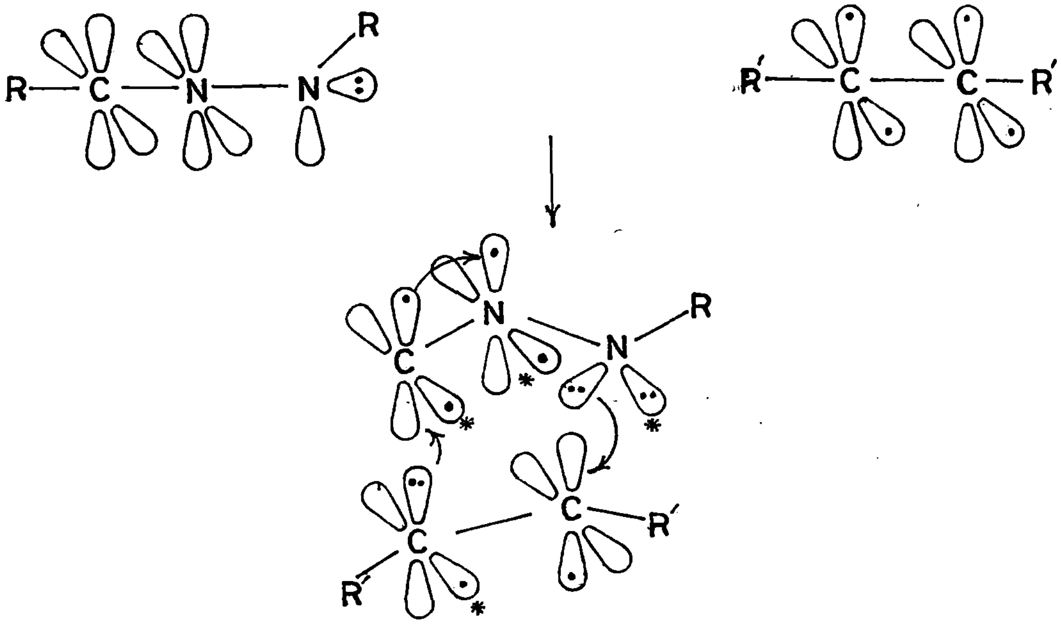
A - Reaction profile for the two-stepped process

Firestone thinks 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.

Further, a number of 1,3-dipoles react with acetylenes to produce aromatic systems directly e.g. nitrile imine nitrile oxides and azides. In a concerted reaction, a portion of this aromatic stabilization should exist in the transition state on this basis.

Firestone formulated a planner transition state as <u>Scheme - IV</u>.

Scheme - IV



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

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

But Huisgen strongly refuted[155,162] 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 intermediates are not adequate and planner transition state as proposed by Firestone is not in accord with the Woodward-Hoffmann rules. Lots of other discrepancies had also been pointed out by Huisgen in the Firestone's 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*[164] pointed out that mechanistic investigations have shown that cycloadditions of 1,3 dipoles to alkenes are stereospecifically suprafacial; solvent polarity has little effect on reaction rates, and small activation enthalpies and large negative activation 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 considerations have provided permissive, though not obligatory, theoretical evidence for the concerted mechanism, and the observation of $[{}_{\pi}4_s + {}_{\pi}6_s]$ but not $[{}_{\pi}4_s + {}_{\pi}4_s]$ cycloadditions of 1,3 dipoles to trienes has provided further evidence for the concerted mechanism[165]. 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 framework of qualitative perturbation molecular orbital theory.

Qualitative orbital energies and coefficients are of great importance here. For this purpose frontier orbitals of representative alkenes are shown in Table - VIII and IX. In each figure, the -ve of the ionization potential of the alkene is given under the horizontal line for the HOMO, (highest occupied molecular orbital) and the -ve of the electron affinity is given under the LUMO (lowest unoccupied molecular orbital) level. The units are ev. The AO (atomic orbital) coefficients for the frontier MO's are also given. For the electron-rich alkenes (Table - VIII), the trend of decreasing HOMO coefficients as the IP decreases results from greater admixture of substituent orbitals with the ethylene π-orbital as the group becomes a greater donor. The conjugated alkenes (Table - IX) raise HOMO's and lower LUMO's as compared to ethylene. The frontier MO's of some 1,3-dipoles (Table - X) show relatively small gap in their HOMO - LUMO level and therefore their reactivities are quite high. Houk et al further proposed that bending of either terminus can reverse these generalization[166].

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 diene and the dipolarophiles as proposed in Woodward-Hoffmann rule. And the allowed processes can

TABLE - VIII.

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

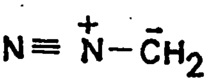
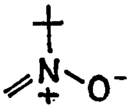
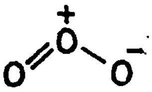
TABLE - IX.

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

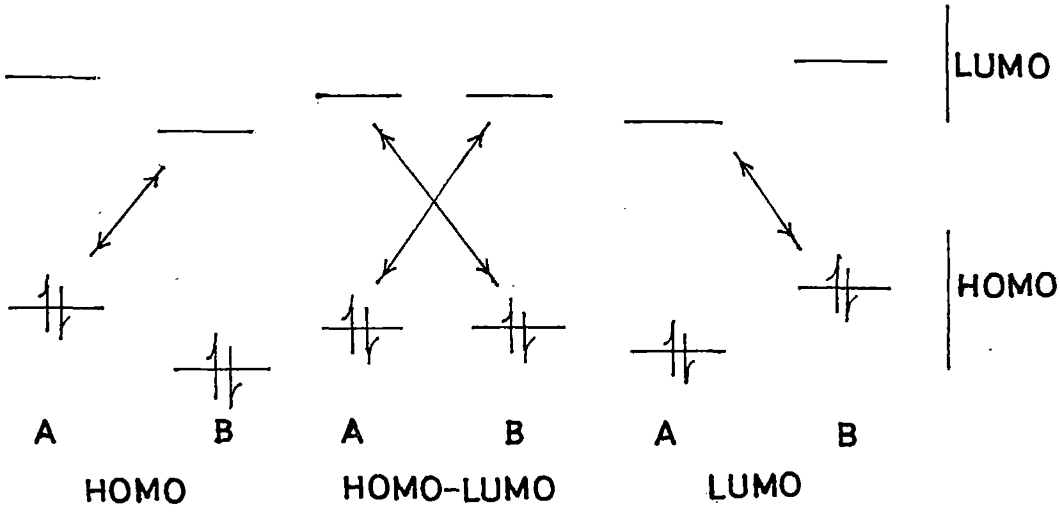
TABLE - X.

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

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

be of three types (Fig. D) as proposed by Sustmann[167,168].

Fig. D

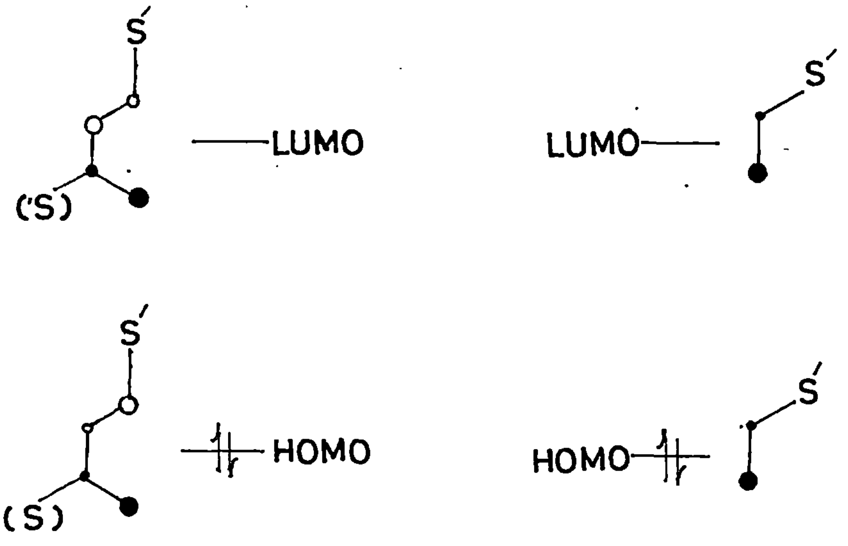


Houk et al[169] have treated all common 1,3-dipoles according to this simple model and have shown that the predictions nicely explain the experimental results.

The nitrile ylides ($R\text{-}C\equiv\overset{+}{N}-\overset{-}{C}R_2$), diazoalkanes ($R_2\overset{-}{C}-\overset{+}{N}\equiv N$), and azomethine ylides ($R_2C=\overset{+}{N}(R)-\overset{-}{C}R_2$) are HOMO-controlled 1,3-dipoles, reacting fastest with alkenes having one or more electron withdrawing substituents. The nitrile imines ($RC\equiv\overset{+}{N}-\overset{-}{N}R$), azides ($R\overset{-}{N}-\overset{+}{N}\equiv N$), and azomethine imines ($R_2C=\overset{+}{N}(R)-\overset{-}{N}R$) are HOMO-LUMO controlled reagents, reacting rapidly with both electronrich and electron-deficient dipolarophiles. The nitrile oxides ($R\text{-}C\equiv\overset{+}{N}-\overset{-}{O}$) and nitrones are also HOMO-LUMO-controlled 1,3-dipoles, but these species are skewed toward the LUMO controlled side. Finally, species with several electronegative atoms are LUMO-controlled e.g. nitrous oxide, zone etc.

Nicety of Houk's model lies specially in its general applicability in the problem of regioselection. Fig. E summarizes the frontier MO's of monosubstituted alkenes and 1 and 2 substituted dienes. In the case of a donor or conjugatively substituted diene and acceptor substituent at the 1-position of a diene or alkene will enlarge the remote coefficient in the HOMO, while an acceptor group at the 1-position of a diene or on an alkene will enlarge the coefficient 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 (Z-regioselectivity is said to have occurred for a cycloaddition reaction when the termini of larger Cahn Ingold-Prelong priorities will unite together in the product). This is because the stabilization energy will be larger when the larger terminal coefficients of the two interacting orbitals overlap, which gives a larger net overlap and thus larger transition state stabilization than if a large coefficient on one orbital interacts with a small coefficient on the second at both bond-forming centers.

Fig. E



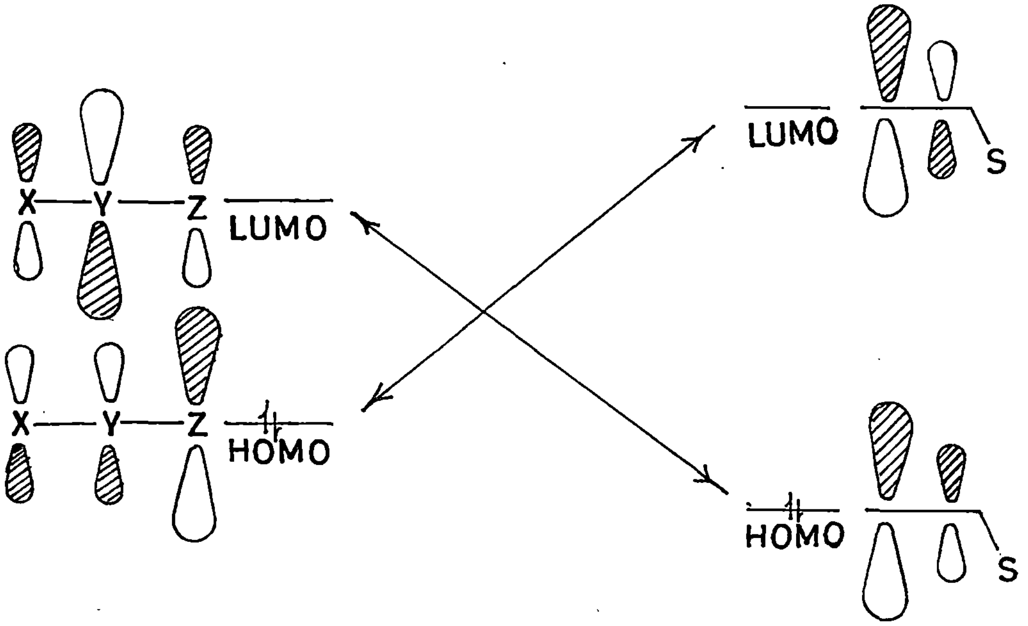
$\Delta E \propto L^2 + S^2$ is better than $\Delta E \propto 2\ LS$

L - larger coefficients at the concerning C-atoms

S = smaller coefficients " " " "

Calculations on all of the common parent and a number of substituted 1,3-dipoles have led to the generalizations about the frontier orbitals of 1,3-dipoles (Fig. F). The HOMO's of the 1,3-dipolar systems generally have the larger terminal coefficient 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 greatest differences in terminal coefficients occur when the two termini differ greatly in electronegativity.

Fig. F



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

Nitrile oxide and nitrones react to give mainly the S-substituted products with weakly electron-deficient alkenes such as acrylonitrile and acrylate. The HOMO's and LUMO's of these weakly electron-deficient alkenes both interact fairly strongly with the LUMO's of the nitrile oxides or nitrones, so that orientation is influenced by both interactions. The experimental results show that the dipole-LUMO-dipolarophile-HOMO interactions are of more influence on regioselectivity. Houk et al has studied a number of such reactions with different nitrones[24,95,96] and has shown that all of them are in accordance to the predicted results.