5.5 MECHANISM OF CYCLOADDITION REACTIONS

5.5.1 2 + 2 Cycloadditions

$\pi^2s+\pi^2s$ are photochemical processes is supported by experiment and are highly useful in the synthesis of natural products which are highly strained molecules. Examples are :

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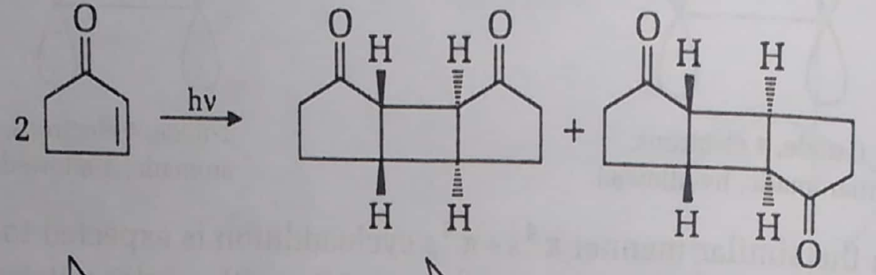
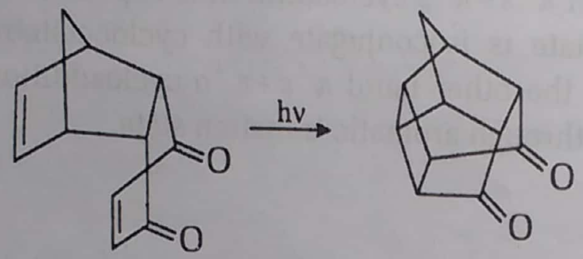


(b)



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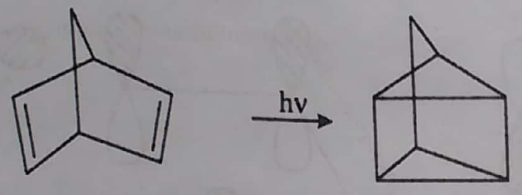


Several questions are to be answered while considering mechanistic aspects of cycloaddition reactions. For example :

(i) What is the impact of multiplicity of excited state on the reaction?
(ii) If triplet excited state undergoes concerted cycloaddition?
(iii) If triplet excited state leads to triplet biradicals.

Let us consider photocycloaddition of *trans*-stilbene to the olefins. During this cycloaddition S_1 state of *trans*-stilbene attacks olefin, whereas, T_1 state results in *cis-trans*-isomerization without involving addition to olefines. Stereochemical identity of *trans*-stilbene is maintained during the course of this reactions.

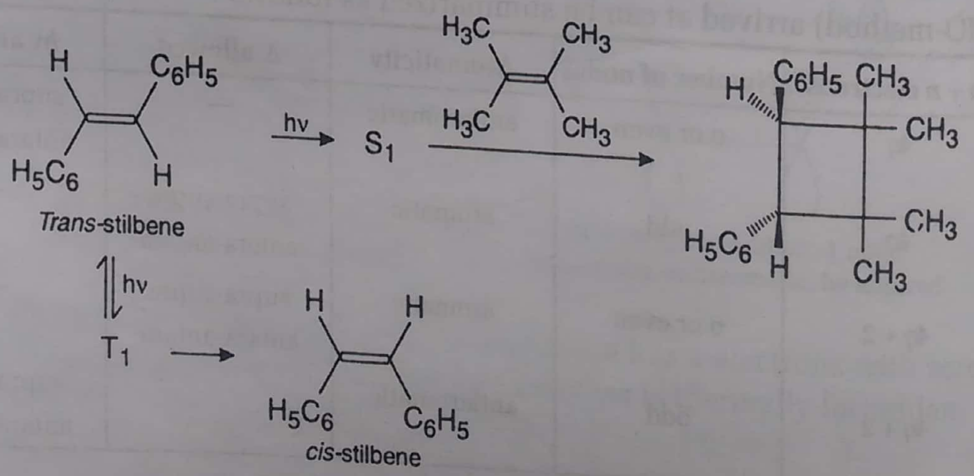
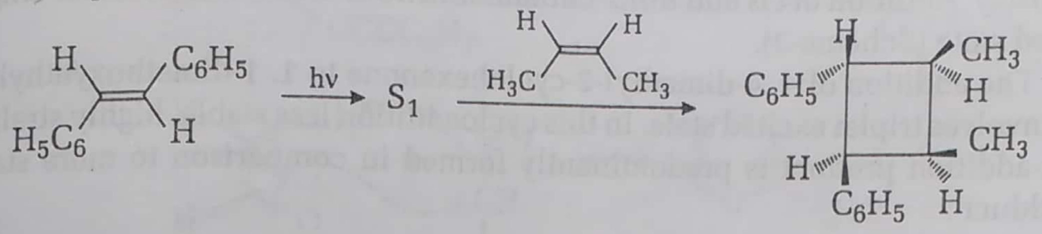
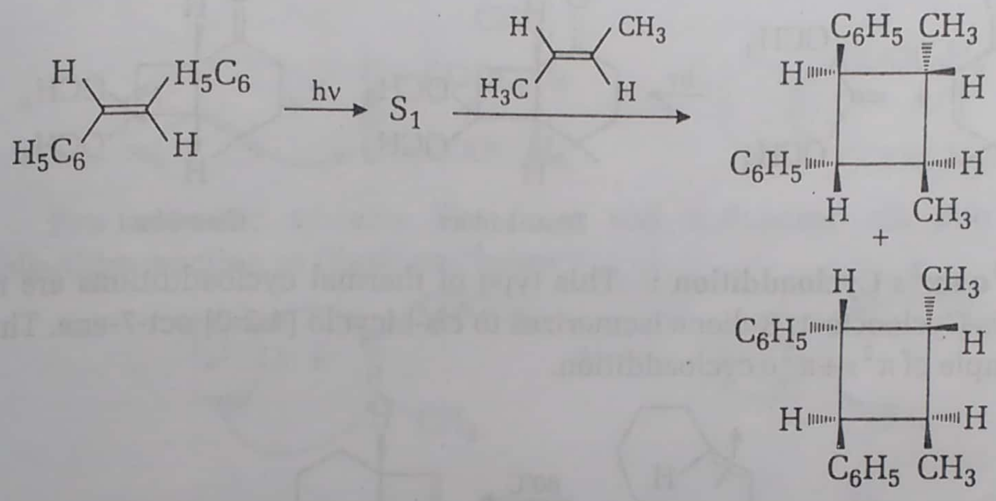


Fig. 5.16. Cycloaddition of stilbene to olefin.

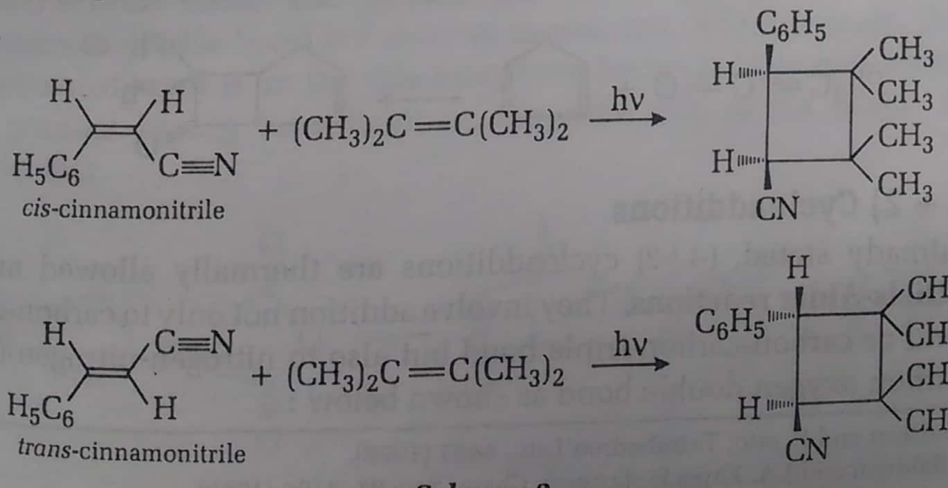
On the other hand, photocycloaddition of *trans*-stilbene to *cis* and *trans* 2-butene result in conservation of stereochemistry of both stilbene as well as olefin. Thus, it may be concluded that addition of S_1 of *trans*-stilbene to olefin is concerted process :





Quenching of emission of light from an excited state is helpful in the study of mechanism, specially in the identification of reactive singlet state. Irradiation of *trans*-stilbene alongwith tetramethyl ethylene results in 1 : 1 adduct with the quantum efficiency (ϕ) of ·54 at room temperature. Photocycloaddition of *trans*-stilbene to tetramethylethylene when sensitized with thioxanthone, only *trans* to *cis* isomerization is observed which indicates but does not prove low-lying singlet excited state of *trans*-stilbene adds to tetramethylethylene. *trans*-Stilbene emits light from singlet state, *i.e.*, it fluoresces. Addition of tetramethylethylene to S_1 state of *trans*-stilbene should quench the fluorescence. Quenching follows the **Stern-Volmer equation.**

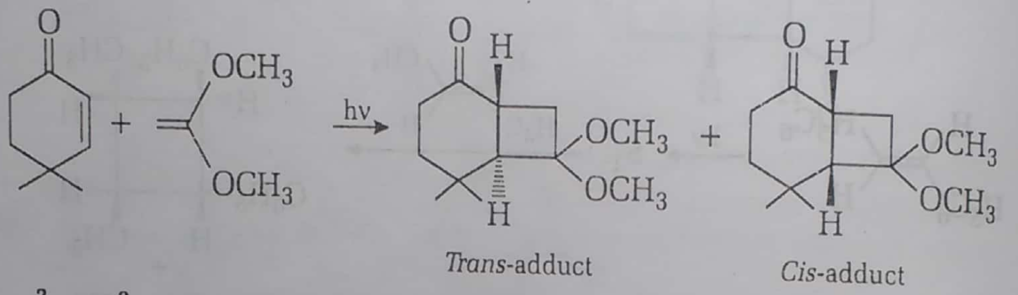
It is important to note that much higher concentrations of quencher are required to quench the excited state (singlet) than for quenching the triplet



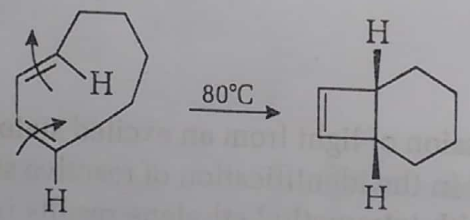
Scheme-3

excited state in 4, 4-dimethyl-2-cyclohexenone. Quenching of *trans*-stilbene fluorescence by tetramethylethylene is a consequence of exciplex formation. *cis* and *trans*-cinnamonitrile adds to tetramethylethylene with retention of stereochemistry. Addition of *cis* and *trans*-cinnamonitrile to olefin also involves singlet excited state (Scheme-3).

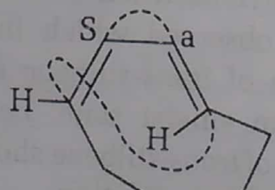
The addition of 4, 4-dimethyl-2-cyclohexenone to 1, 1-dimethoxyethylene also involves triplet excited state. In this cycloaddition less stable, highly strained *trans*-addition product is predominantly formed in comparison to more stable *cis*-adduct :



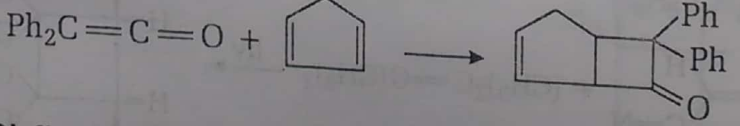
$\pi^2a+\pi^2s$ Cycloaddition : This type of thermal cycloadditions are rare. *trans*, *cis*-Cycloocta-1, 3-diene isomerizes to *cis*-bicyclo [4.2.0] oct-7-ene. This is an example of $\pi^2s+\pi^2a$ cycloaddition.



This addition is **antarafacial** on *trans*-double bond and **suprafacial** on *cis*-double bond.



Thermal addition of ketene to olefin is **antara** on ketene and **supra** on olefin. Here $\pi^2a+\pi^2s$ cycloaddition is preferred over $\pi^2s+\pi^2s$ cycloaddition.*



5.5.2 (4 + 2) Cycloadditions

As already stated, (4+2) cycloadditions are thermally allowed and are known as **Diels-Alder reactions.** They involve addition not only to carbon-carbon double bond or carbon-carbon triple bond but also to nitrogen-nitrogen double bond or carbon oxygen double bond as shown below :

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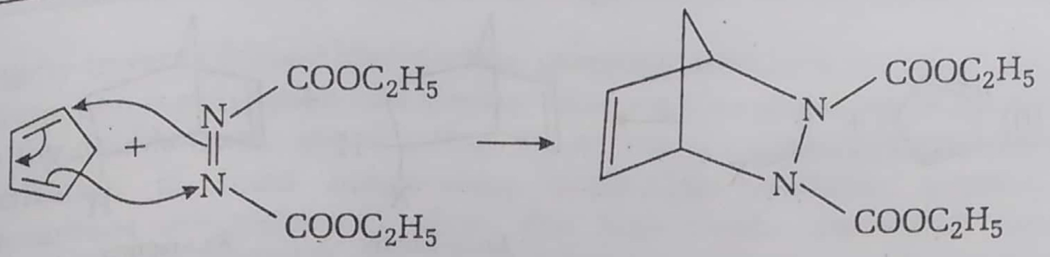
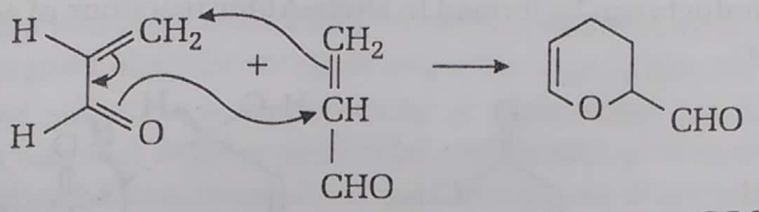
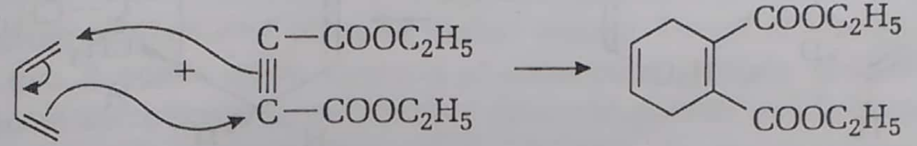
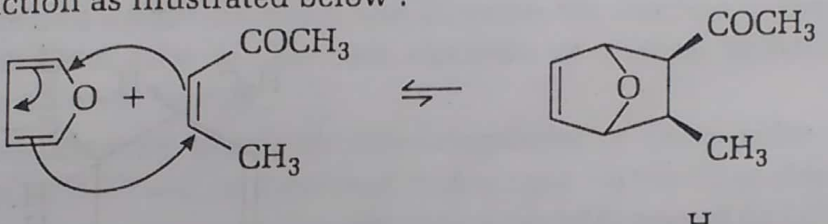
* (a) R. Huisgen and P. otto, Tetrahedron Lett., 4491 (1968).
(b) J.E. Baldwin and J.A. Kapecki, J. Amer. Chem. Soc; 91, 3106 (1969).

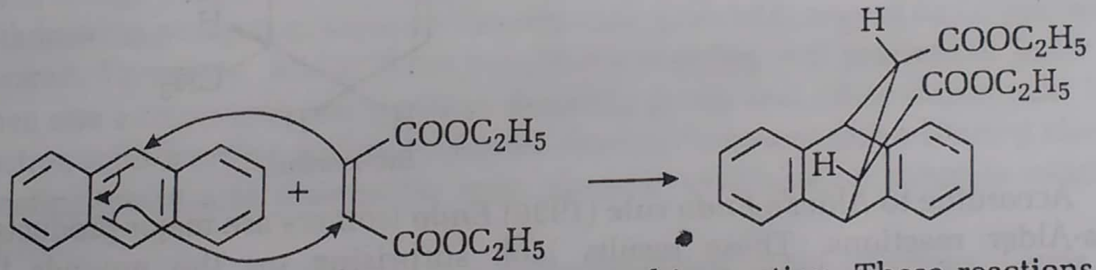






Few aromatic systems like furan and anthracene etc also undergo Diels-Alder reaction as illustrated below :

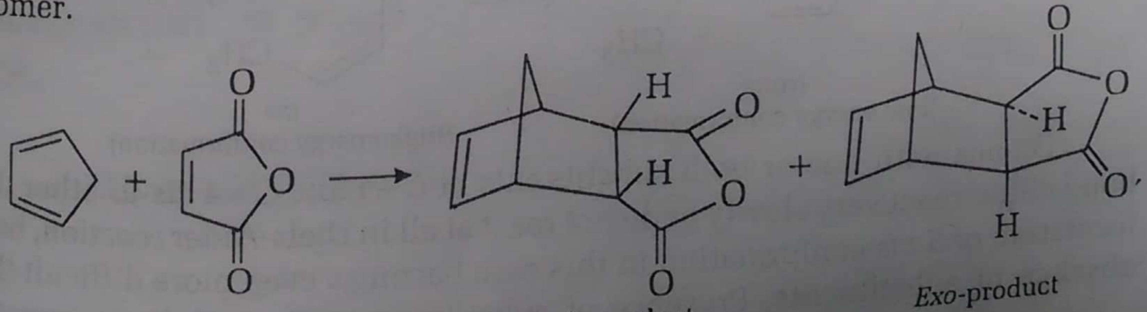




Benzene and naphthalene do not give this reaction. These reactions are highly stereospecific and geometries are maintained through out the course of reaction. As a result of these reactions six-membered ring is formed.

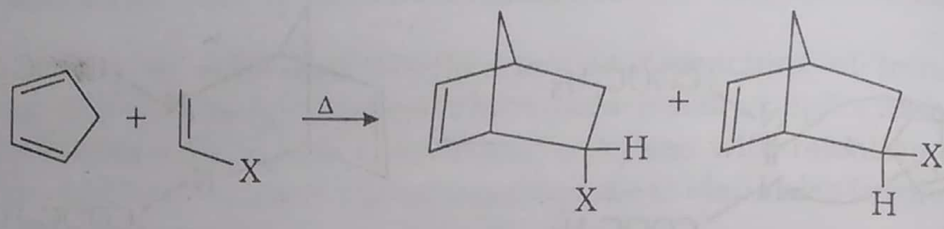
***Endo-Exo* Stereochemistry :** Sometimes Diels-Alder reactions give two types of products, viz, *endo* and *exo* isomers. The product in which substituent on dienophile are *cis* to double bond formed in diene after Diels-Alder reaction is known as *endo*-isomer and the other product in which substituent on dienophile are *trans*-to double bond is known as *exo*-isomer. Alteranatively, the product in which substituent is on the side away from bridge is known as *endo*-isomer and the product having substituent on the same side of the bridge is known as *exo*-isomer.

(i)



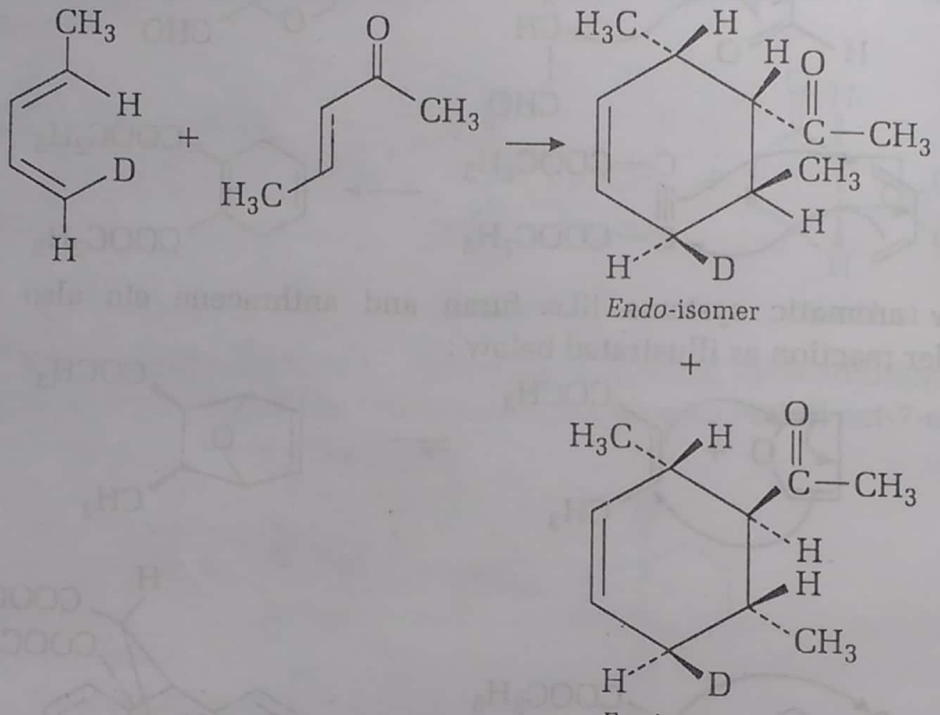
Endo-product *Exo*-product

(ii)



Endo-isomer *Exo*-isomer

Endo-exo products can be formed in **Diels-Alder** reactions of acyclic dienes also. For example :

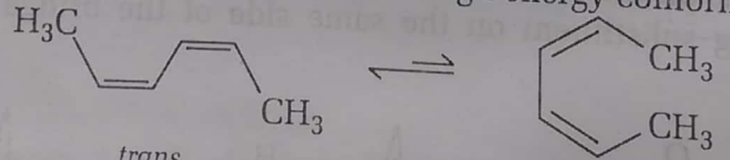


Endo-isomer

Exo-isomer

According to Alder's ***Endo* rule** (1930) *Endo* isomers are major products in Diels-Alder reactions. These results look surprising on the grounds that *Endo*-isomers are less stable for steric reasons. But, *Endo-rule* can be rationalized on the basis of **frontier orbital theory**. *Endo*-transition state is stablized by **secondary interactions** in comparison to *exo*-isomers in which secondary interactions are absent. This facts makes *endo*-isomers more stable, *i.e.*, why they are major-products in Diels-Alder reactions.

Reactivities in Diels-Alder Reactions : Rates of Diels-Alder reactions are affected by steric as well as electronic factors. For Diels-Alder reaction to proceed dienes must have double bonds on the same side of central-single bond, *i.e.* there must be *cis*-conformation; because this is high energy conformation.



trans
(low energy conformation)

cis
(high energy conformation)

Dienes with one or both substituents at $C-1$ anc $C-4$ *cis*-to other double bond either react very slowly or do not react at all in Diels-Alder reaction, because formation of *S-cis* conformation in this case becomes even more difficult than in absence of substituents. Presence of substituent at $C-2$ of diene increase its reactivity towards Diels-Alder reaction as energy difference in favour of *S-trans* conformation is reduced in this manner. Most reactive dienes are those in which both the double-bonds are in a ring. For example, cyclopentadiene undergoes dimerization at room temperature. Diels-Alder reactions between two hydrocarbons are extremely slow. For high yields, dienophile must be substituted with powerful electron withdrawing group like carbonyl group or carboxyl group which is rationalized by the fact that reactions occur easily if one is substituted good electron acceptor and other is good electron donor.

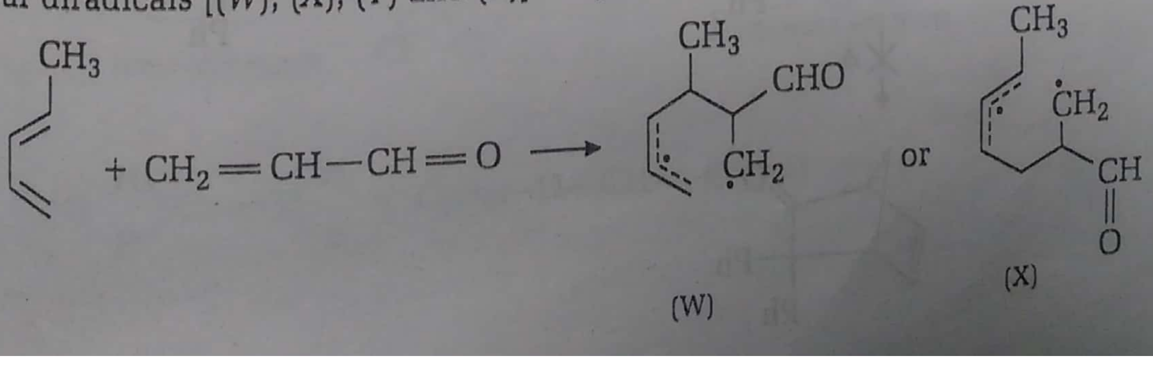
Effect of substituent on reactivity of Diels-Alder reactions may also be visualized in terms of frontier molecular orbital theory. Interaction of these two orbitals result in the formation of two new orbitals one of lower energy than either of interacting orbitals and other of higher energy. Extent of energy difference between two depends upon energies of interacting orbitals. If HOMO of one component is much lower than LUMO of other component; newly formed HOMO will be much lower in energy than original HOMO. On the other hand, if energy difference between two interacting orbitals is low, the energy difference between original orbitals and transition states will increase; the reaction in that condition will proceed at faster rate. In this case electrons of original HOMO will go to transition state of lower energy.

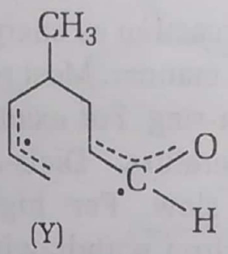
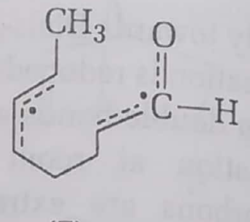
If electron-donating group on one component of Diels-Alder reaction is there, energy of HOMO will be increased in that case; on the other side if electron withdrawing group is present on the other component energy of its LUMO will be lowered. Therefore, under these conditions reaction will proceed at faster rate when one component has electron donating group and other component bears electron withdrawing group. However, reaction between diene bearing electron donating group and dienophile with electron withdrawing group is relatively easier.

Lewis acids (strong) act as catalyst for Diels-Alder reactions. Lewis acid usually forms complex with **dieneophile** which lowers energy of its LUMO. This way activation energy of reaction is decreased, hence, reaction proceeds at faster rate.

Regioselectivity in Diels-Alder Reaction : Regioselectivity during Diels-Alder reaction is based upon the rule that **major product from Diels-Alder reaction will arise from transition state that resemble the most stable of the possible diradical intermediates that might be formed in the reaction.** An example is discussed below :

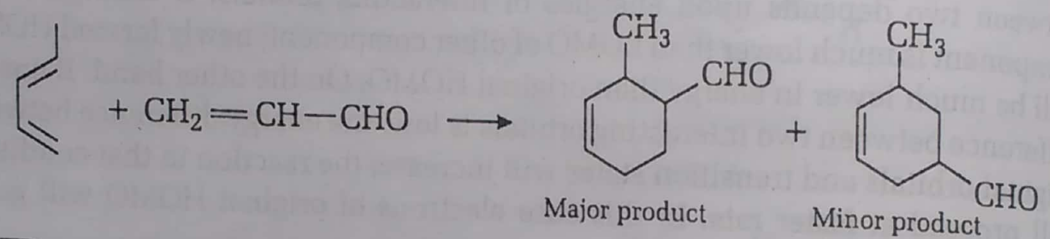
In the Diels-Alder reaction between 1, 3-pentadiene and acrolein following four diradicals [(*W*), (*X*), (*Y*) and (*Z*)] are possible :



or  or 

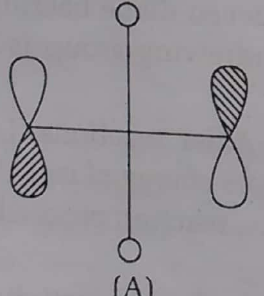
(Y) (Z)

In (*W*), (*X*), (*Y*) and (*Z*), (*Z*) is most stable diradical which can be written as hybrid of two secondary radical resonance forms. (*Y*) contains pentadiene as a hybrid of one secondary radical resonance form and one primary radical form. In (*W*) and (*X*) there is only resonance stablization. Thus, in this reaction major product will be from (*Z*) and minor product from (*Y*). Major regioisomer in Diels-Alder reaction can be predicted on the basis of **diradical like transition state rule.**

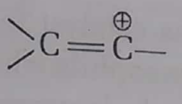


5.6 2 + 2 THERMAL CYCLOADDITION OF KETENES

$2s+2a$ thermal cycloadditions are symmetry allowed. But this stereochemical mode of cycloaddition can be expected only when two double bonds are disposed **orthogonally** to each other (*i.e.*, they are perpendicular to each other) as given in figure *A* below :

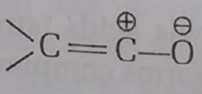


(A)



$$>C=\overset{\oplus}{C}-$$

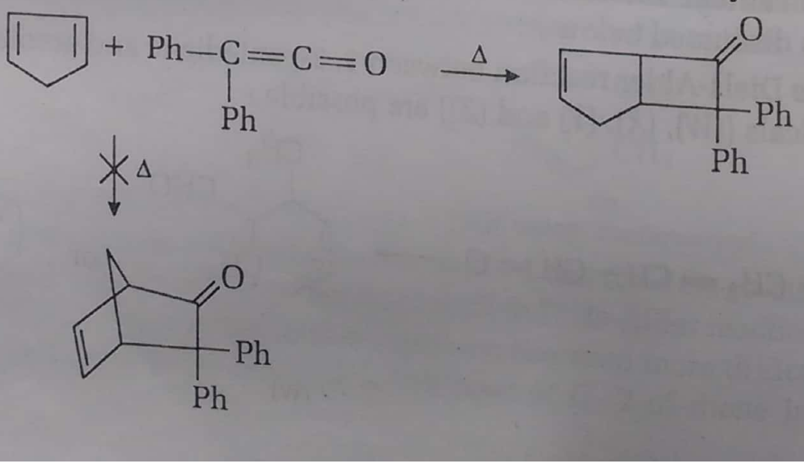
(B)



$$>C=\overset{\oplus}{C}-\overset{\ominus}{O}$$

(C)

This type of orientation is rarely feasible. Vinyl cation (*B*) or Ketene (*C*) add to ethylene readily under thermal conditions to give cyclobutanes; even cyclopentadiene in which 1, 4-addition is expected add this way.



Frontier molecular orbital (FMO) treatment of these reactions indicates that bond formation between $C-1$ and $C-1$ of ketene and olefin is due to interaction of HOMO of alkene and LUMO of Ketene. At the same time bond formation between $C-2$ of olefin and $C-2$ of ketene is by the coupling of HOMO of ketene and LUMO of alkene as shown below :

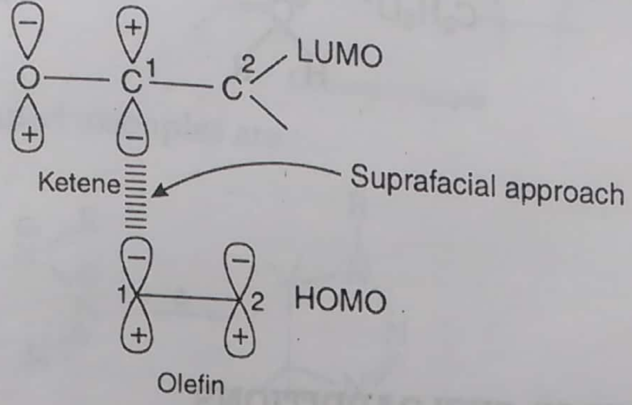


Fig. 5.17. Bond formation between C_1 of olefin and C_1 of ketene.

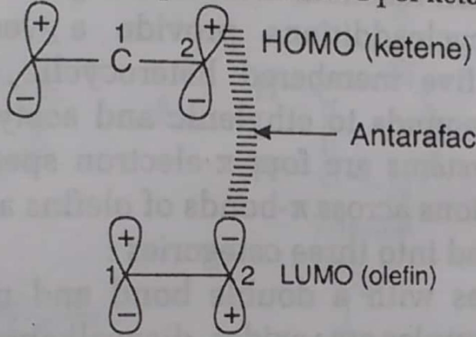
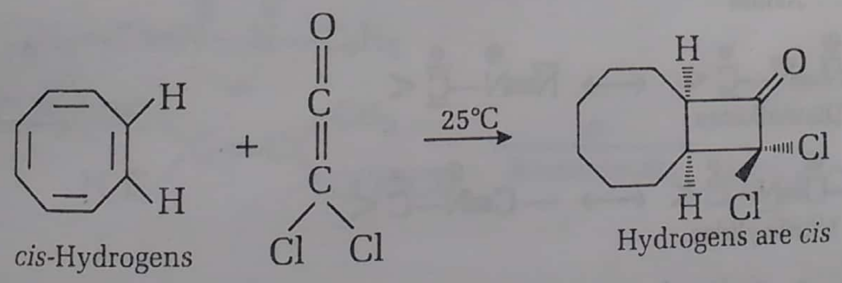


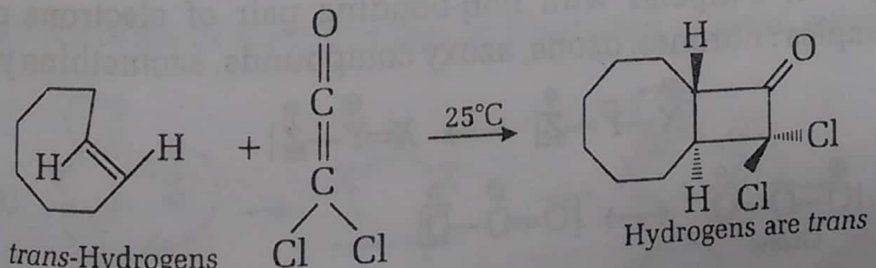
Fig. 5.18. Bond formation between C_2 of ketene and C_2 of olefin.

This addition is *syn*. Geometry of reactants is conserved in the products. For example :

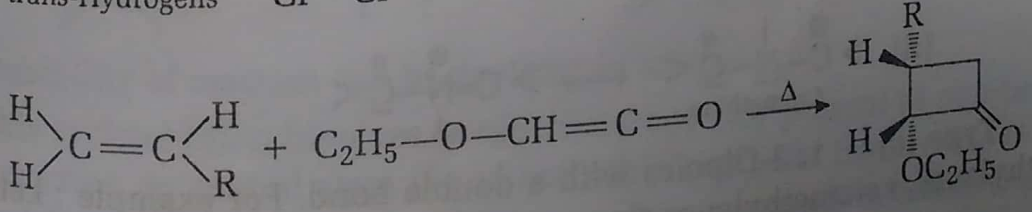
(a)



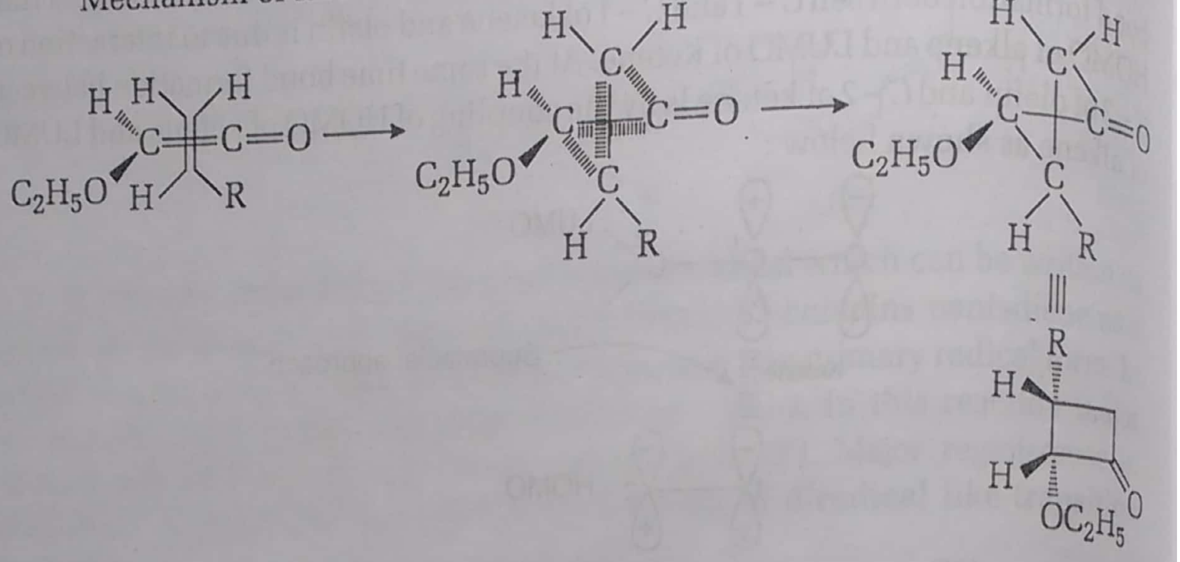
(b)



(c)



Mechanism of last reaction is :



5.7 1, 3-DIPOLAR CYCLOADDITIONS

1, 3-Dipolar cycloaddition reactions were investigated by Huisgen and his co-workers. 1, 3-Dipolar cycloadditions provide a versatile method for stereospecific synthesis of five membered heterocyclic compounds by the addition of 1 3-dipolar compounds to ethylenic and acetylenic double bonds (dipolarfiles). 1, 3-dipolar systems are four π-electron species which undergo $\pi_s^4 + \pi_s^2$ concerted cycloadditions across π-bonds of olefins and acetylenes.

1, 3-Dipoles are classified into three categories :

Type (a) : 1, 3-Dipoles with a double bond and non-bonding pair of electrons on central atom. Examples are : azides, diazoalkanes, nitrile ylides etc.

$$\overset{\oplus}{X}=Y-\overset{\ominus}{\underline{Z}} \longleftrightarrow \overset{\oplus}{X\equiv Y}-\overset{\ominus}{\underline{Z}} \text{ /(a 1, 3-dipolar species)}$$

(i) $|\overset{\oplus}{\underline{N}}=\overline{N}-\overset{\ominus}{\underline{\overline{N}}}- \longleftrightarrow \overline{N}\equiv\overset{\oplus}{N}-\overset{\ominus}{\underline{\overline{N}}}-$
Azides

(ii) $|\overset{\oplus}{\overline{N}}=\overline{N}-\overset{\ominus}{\underline{C}}< \longleftrightarrow \overline{N}\equiv\overset{\oplus}{N}-\overset{\ominus}{\underline{C}}<$
Diazoalkanes

(iii) $-\overset{\oplus}{C}=\underline{N}-\overset{\ominus}{C}< \longleftrightarrow -C\equiv\overset{\oplus}{N}-\overset{\ominus}{C}<$
Nitrile ylides

Type (b) : 1, 3-dipoles with non-bonding pair of electrons on central atoms. For examples : nitrones, ozone, azoxy compounds, azomethine ylides etc.

$$\overset{\oplus}{X}-\overline{Y}-\overset{\ominus}{\underline{Z}}| \longleftrightarrow X=\overset{\oplus}{Y}-\overset{\ominus}{\underline{Z}}|$$

(i) $|\overset{\oplus}{\underline{O}}-\overline{O}-\overset{\ominus}{\underline{\overline{O}}}| \longleftrightarrow |\overline{O}=\overset{\oplus}{O}-\overset{\ominus}{\underline{\overline{O}}}|$
Ozone

(ii) $>\overset{\oplus}{C}-\overset{|}{\underline{N}}-\overset{\ominus}{\underline{C}}< \longleftrightarrow >C=\underset{|}{\overset{\oplus}{N}}-\overset{\ominus}{\underline{C}}<$
Azomethine

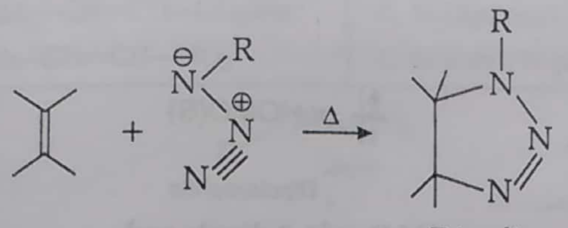
Type (c) : 1, 3-Dipoles with a double bond. For example : ketonitrenes, methylenes, ketomethylenes etc.

Some examples of 1, 3-dipolar cycloadditions are :

General example

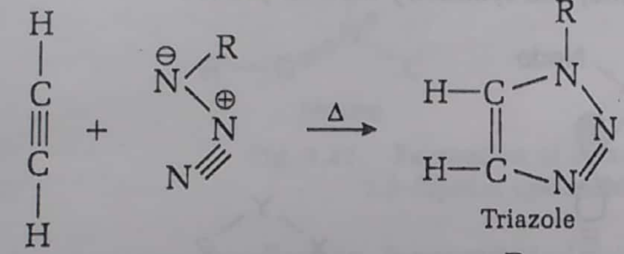
Few specified examples are :

(1)



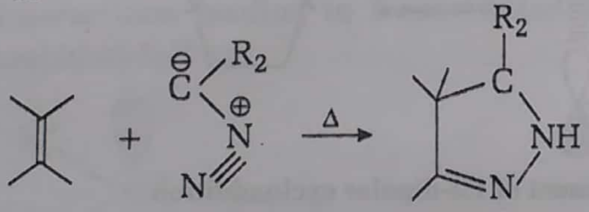
Triazoline

(2)



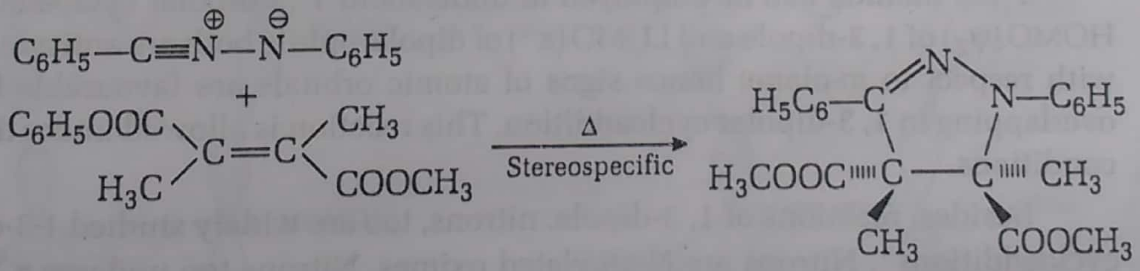
Triazole

(3)



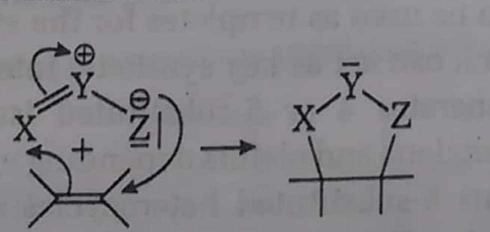
Pyrazoline

(4)

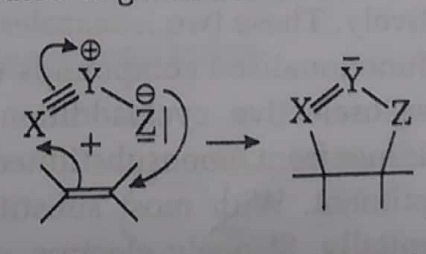


Mechanisms of reactions can be illustrated as given below :

(a)



(b)



Feasibility of reaction can be depicted as follows :

This cycloaddition involves 6π-electrons, one pair present as non-bonding pair of electron on central atom (let *y*) and other two pairs involved in σ-bonds C—X and C—Z. During this cycloaddition *m*-plane symmetry is conserved.

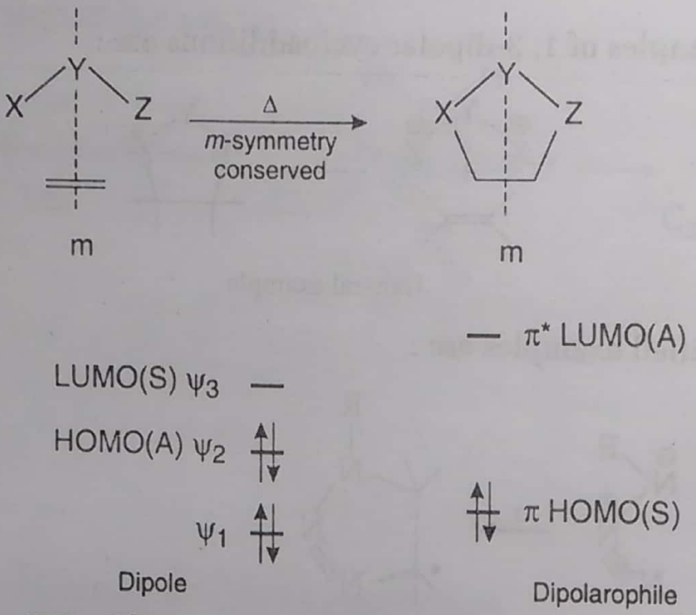


Fig. 5.19. Electronic occupancy of M.Os of 1,3-dipole and alkene (dipolarophile) and symmetry w.r.t. *m*-plane .

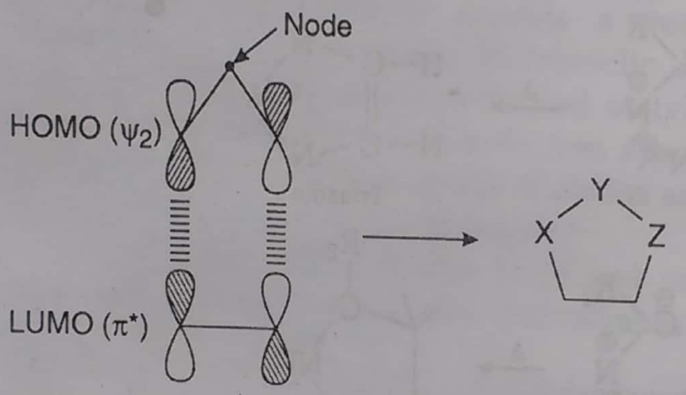


Fig. 5.20. FMO treatment of 1,3-dipolar cycloaddition.

FMO method can be employed to understand 1 ,3-dipolar cycloadditions. HOMO (ψ_2) of 1, 3-dipole and LUMO (π^*) of dipolarophile both are antisymmetric with respect to *m*-plane; hence signs of atomic orbitals are favourable for the overlapping in 1, 3-dipolar cycloaddition. This reaction is allowed under thermal conditions.

Besides, reactions of 1, 3-dipole, nitrons, too are widely studied 1 3-dipolar cycloadditions*. Nitrons are N-alkylated oximes. Nitrons too undergo $\pi^4 s+\pi^2 s$ cycloadditions to olefins and acetylenes to yield isoxazolidines and isoxazolines respectively. These two isoxazoles can be used as templetes for the synthesis of 1, 3-difunctionalised compounds which can act as key synthetic intermediates. This regioselective cycloaddition generates 4 or 5-substituted isoxazolines/ oxazolidines from monosubstituted acetylene and olefins depending upon nature of substituent. With most substituents 5-substituted heterocycles are formed preferentially. Strongly electron withdrawing groups on dipolarophile change the selectivity in the favour of 4-substituted heterocycle. Beside this selectivity is also affected by electronic and steric demands which are very delicately balanced as is clear by **Table 1.**

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* A. Banerji, J. Indian Chem. Soc; 77, 637 (2000).

Table 1 : Regioselectivity in Nitrone Cycloadditions

Olefins	Nitrones	Ratio of 5 : 4 substitution
$Ph—CH=CH_2$	C, N-Diphenyl	~100 : 0
$CH_3O_2C—CH=CH_2$	C, N-Diphenyl	100 : 0
$AcO—CH=CH_2$	C, N-Diphenyl	~100 : 0
$PhSO_2—CH=CH_2$	C-phenyl, N-methyl	32 : 68
$CH_3O_2C—C\equiv CH$	C-phenyl, N-methyl	42 : 58
(E) $CH_3—CH=CH—CO_2Me$	C, N-Diphenyl	~0 : 100
(E) $Ph—CH=CH—NO_2$	C-Benzoyl, N-phenyl	~0 : 100

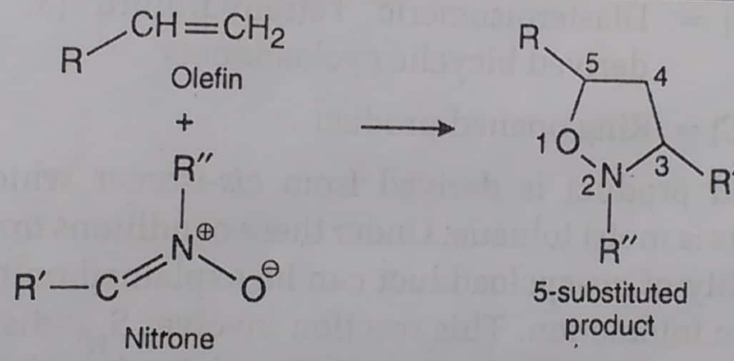
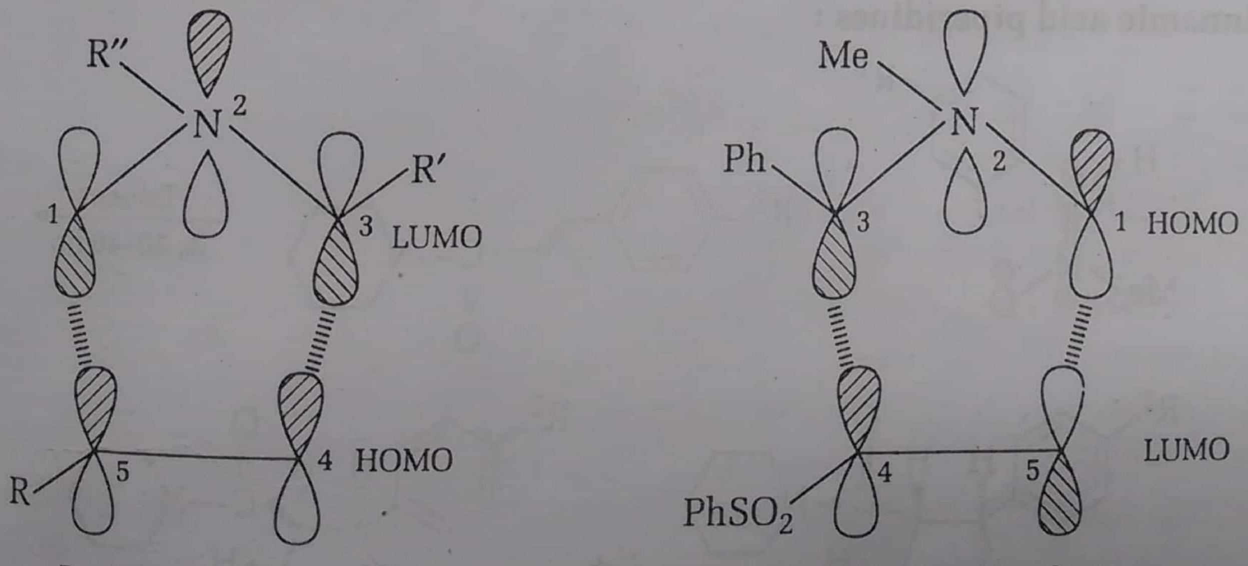


Fig. 5.21. Formation of isoxazolidine form 1,3-dipolar cycloaddition.

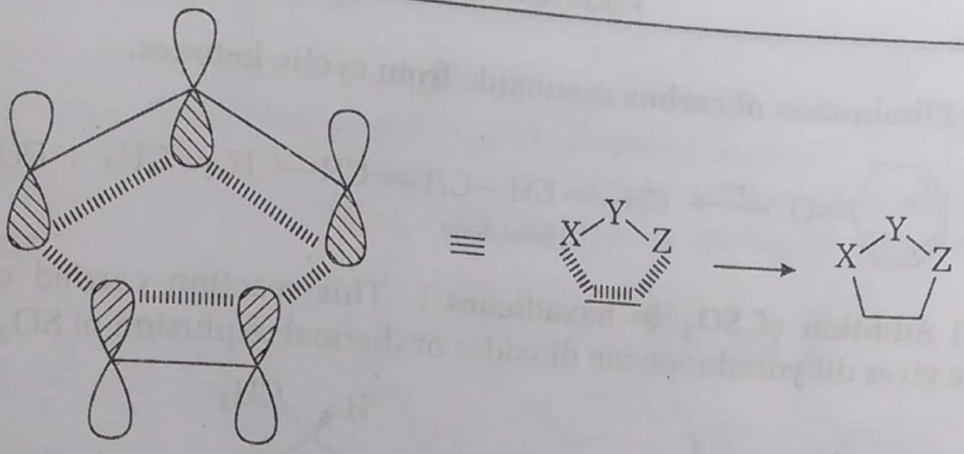
Interactions leading to 5-substituted and 4-substituted products can be represented as follows :



5-substituted product

4-substituted product

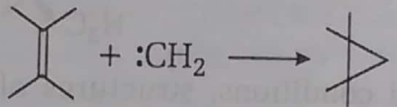
PMO-treatment of 1, 3-dipolar cycloaddition : The transition state for concerted 1, 3-dipolar cycloaddition has six electrons without any node; it is aromatic. Hence, reaction is thermally allowed.



T.S. : 0 node, 6 electrons, aromatic, thermally allowed

5.8 CHELETROPIC REACTIONS

Cheletropic reactions are special type of concerted cycloadditions or cycloreversions in which two bonds are formed on or fissioned from same atom. For example, reaction of a singlet carbene with olefin.



These reactions can be considered in terms of HOMO-LUMO interactions of reactants. Carbenes can approach alkenes in two ways :

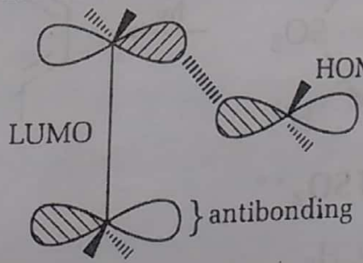
(i) linearly (ii) Non-linearly.

There are two π-molecular orbitals in carbene :

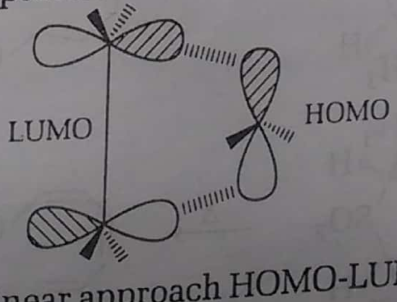
(i) HOMO containing both the electrons

(ii) LUMO which is vacant.

(i) Linear approach : In linear approach of carbene, plane of two substituents is perpendicular to C—C bond of olefin.



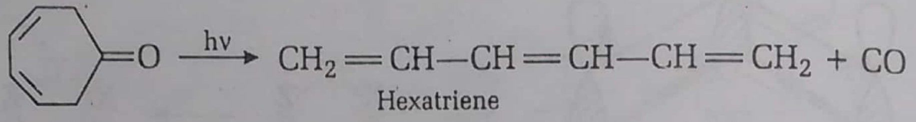
(ii) Non-linear approach : In non-linear approach, plane of bonds of two substituents on carbene is parallel to C—C bond of olefin.



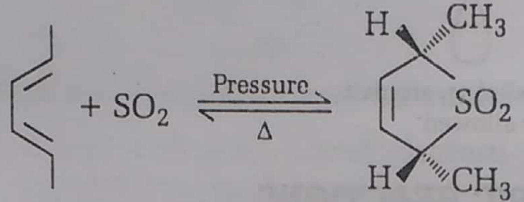
It is clear that is non-linear approach HOMO-LUMO interaction approach is suprafacial and bonding. In this approach electrons reorganise themself into a new bond. However, whether approach is linear or non-linear is not proved.

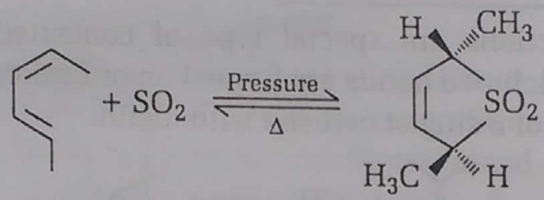
Few examples of cheletropic rearrangement are discussed below :

(1) Elimination of carbon monoxide from cyclic ketones.

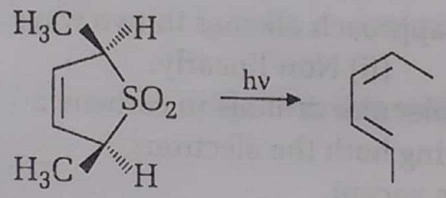


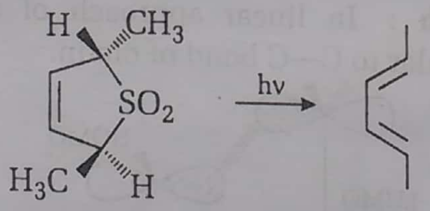
(2) Addition of SO_2 to hexadienes : This reaction carried out under pressure gives dihydrothiophene dioxides or thermal explusion of SO_2.*



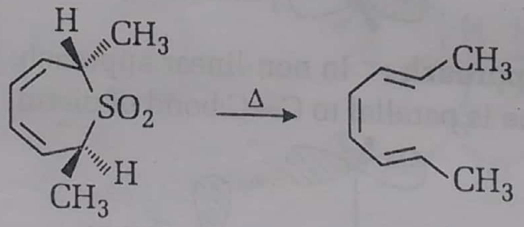


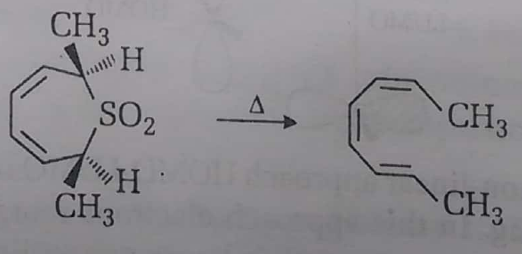
Under photochemical conditions, structures of products are opposite to that under thermal conditions.





2. Thermal expulsion of SO_2**





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* W.L. Mock, J.A.CS **88**, 2857 (1966).

** W.L. Mock, J-A-C.S., **91**, 5682 (1969); **92**, 3807 (1970).

Interaction of HOMO and LUMO applied to $4q\pi$ and $(4q+2)\pi$ systems during addition and expulsions of SO_2 are discussed below :

(i) $4q\pi$-system : Linear approach of SO_2 to $4q\pi$ system is suprafacial to olefinic system and is bonding. This reaction is thermally allowed through disrotation.

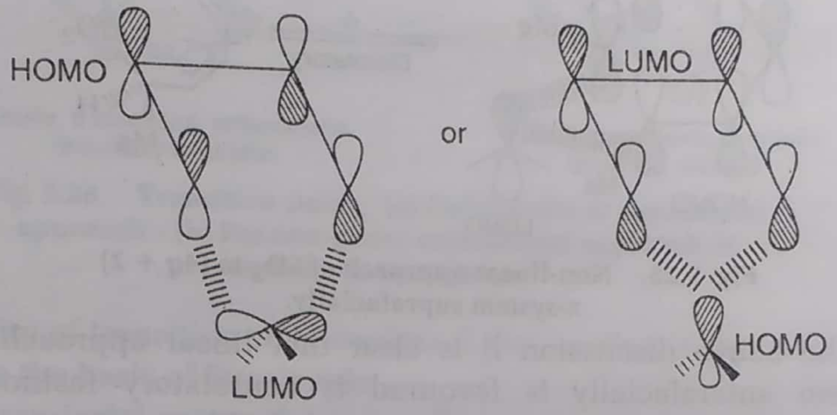


Fig. 5.22. **Linear approach of SO_2 suprafacial to $4q\pi$-system.**

On the other hand non-linear approach of SO_2 antarafacial to $4q\pi$ system is too symmetry allowed. Reaction involving ring closure as well as expulsion of SO_2 proceeds through conrotation.

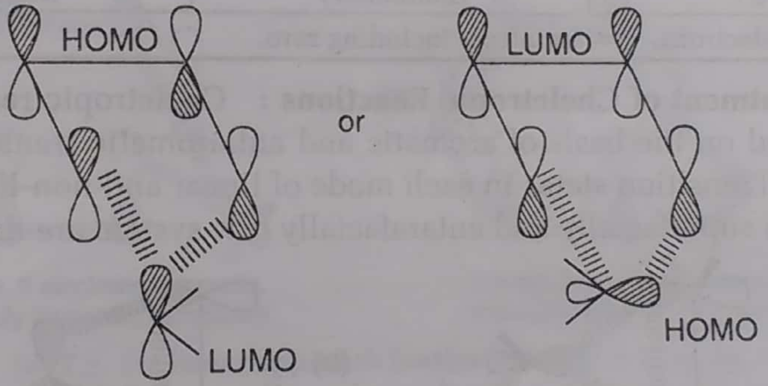


Fig. 5.23. **Non-linear approach of SO_2 antarafacial to $4q\pi$-system.**

Because suprafacial approach is bond-forming, hence reagent approaches $4q\pi$-system linearly.

(ii) $(4q+2)\pi$-system : Approach of SO_2 antarafacially to $(4q+2)\pi$-system in linear manner can be explained by considering HOMO-LUMO of these two systems. However, ring closure in this manner is not experimentally proved. HOMO-LUMO interactions in this manner take place under thermal condition and are bonding interactions. Besides, conrotatory mode of ring-closure is followed.

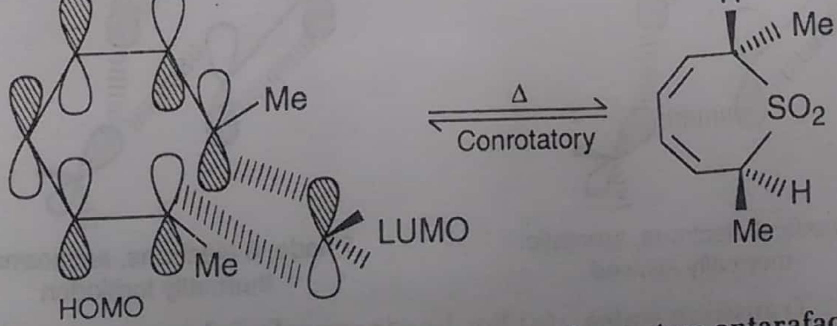


Fig. 5.24. **Linear approach of SO_2 to $(4q + 2)\pi$-system antarafacially.**

However, non-linear approach of SO_2 to $(4q+2)\pi$-system takes place suprafacially. This is also symmetry allowed and follows disrotatory mode of ring-closure.

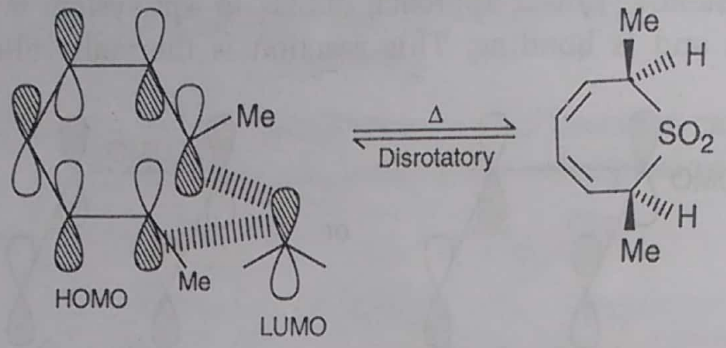


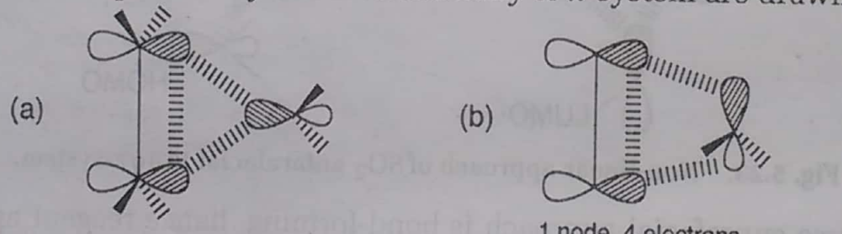
Fig. 5.25. Non-linear approach of SO_2 to $(4q+2)$ π-system suprafacially.

From the above discussion it is clear that linear approach of SO_2 to $(4q+2)\pi$-system antarafacially is favoured is conrotatory fashion, whereas non-linear approach antaraficially is symmetry-forbidden.

Table : Selection Rules for thermal cheletropic Reactions

m	Linear Approch	Non-linear Approach
4*q*	Disrotatory	Conrotatory
4*q* + 2	Conrotatory	Disrotatory
m = Number of electrons, *q* = an integer including zero.		

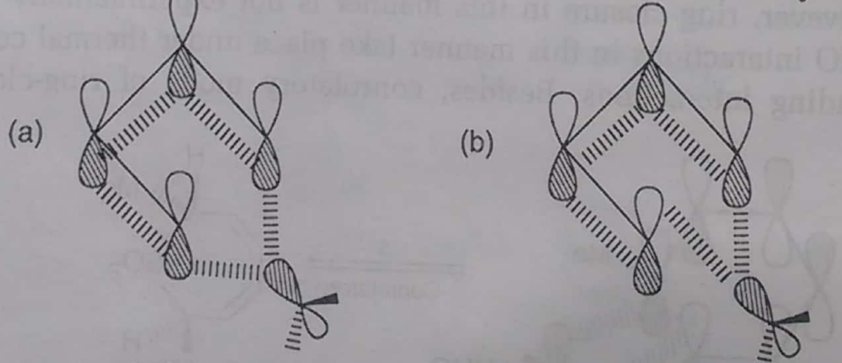
PMO-treatment of Cheletropic Reactions : Cheletropic reactions can be easily explained on the basis of aromatic and antiaromatic transition states by PMO-method. Transition states in each mode of linear and non-linear approach of carbene both suprafacially and antarafacially to π-system are drawn below :



0 node, 4 electrons
antiaromatic, Δ-forbidden

1 node, 4 electrons,
aromatic, thermally allowed

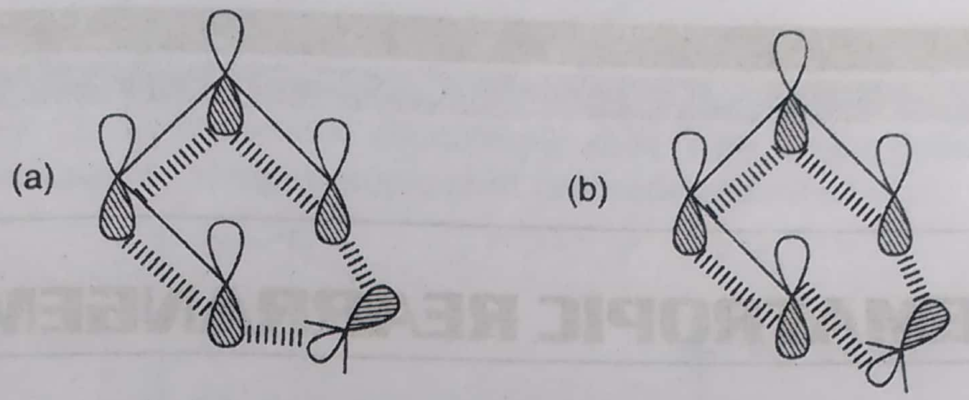
Fig. 5.26. **Transition states (a) For linear suprafacial approach (b) Non-linear suprafacial approach of carbene to a $(4q+2)$ π-olefinic system.**



0 node, 6 electrons, aromatic,
thermally allowed

1 node, 6 electrons, antiaromatic,
thermally forbidden

Fig. 5.27. **Transition states (a) For linear suprafacial approach (b) For linear antarafacial approach of carbene to $4q$ π-system.**



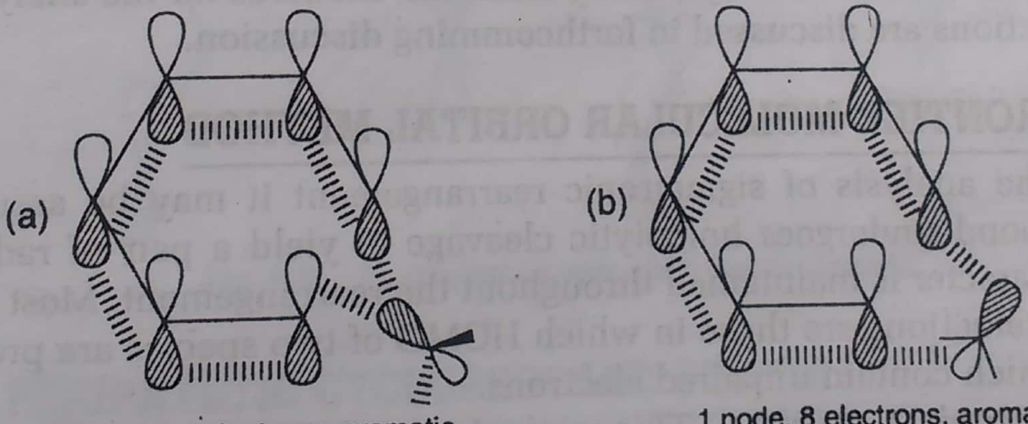
1 node, 6 electrons, antiaromatic, thermally forbidden

0 node, 6 electrons, aromatic, thermally allowed

Fig. 5.28. Transition states (a) For non-linear suprafacial approach (b) For non-linear antarafacial approach of carbene to $4q$ π-system.

Aromaticity of transition state decides if the reaction is thermally allowed or forbidden on the basis of Evan's rule.

Linear-antarafacial approach (*a*) as well as non-linear-suprafacial approach (*b*) in figure given below for the addition of SO_2 to triene, $[4q+2]\pi$ system, both are thermally favourable.



1 node, 8 electrons, aromatic, thermally favoured, disrotatory

1 node, 8 electrons, aromatic, thermally allowed conrotatory

Fig. 5.29. (a) T.S. for linear approach (antarafacial) of SO_2 to $(4q + 2)$ π-system. (b) T.S. for non-linear (suprafacial) approach of SO_2 to $(4q + 2)$ π-system.

Conversly linear-suprafacial as well as non-linear-antarafacial approaches both involve antiaromatic transition states with eight electrons and 0 nodes. Hence, both reactions are thermally disallowed. However, there is no way to prove if approach of SO_2 is linear or non-linear.