KRISHNAVENI DEGREE & PG COLLEGE

Under affiliated by

ACHARYA NAGARJUNA UNIVERSITY (ANU)

2nd YEAR M.Sc

IV Semester

Paper-II: Organic Synthesis & Reaction Mechanisms-II

(R22OC42)

Department of Chemistry

Krishnaveni Degree & PG College

Narasaraopet – 522601

ACHARYA NAGARJUNA UNIVERSITY
DEPARTMENT OF CHEMISTRY

M.Sc. ORGANIC CHEMISTRY :: SEMESTER–IV

PAPER–II: ORGANIC SYNTHESIS & REACTION MECHANISMS-II (R22OC42)

(For the students admitted from the A.Y. 2022-2023 onwards)

Max. Marks: 100 (Internal-30M & External-70M)

SYLLABUS

Learning Objectives:

- ✓ To learn about the basics of C-C single and double bond formations and Diels-Aider reactions.
- ✓ To learn terminology and develop skills in writing retro-synthetic routes for target molecules with one and two functional groups.
- ✓ To learn different approaches in photochemical and pericyclic reactions.
- ✓ To learn terminology and selectivity in asymmetric synthesis and also apply the approaches in organic synthetic reactions.
- ✓ To learn the Nucleophilic additions to chiral carbonyl compounds and Felkin-Anhmodel.

UNIT-I ✓ 12H

Formation of C-C Single & Double Bonds and Diels–Aider & Related Reactions:
Formation of C-C single bonds–enamines and related reactions.
Formation of C-C double bonds–Corey-winter olefination, Peterson olefination, Julia olefination, McMurry coupling, witting reaction of Phosphorus ylides–stereoselective synthesis of tri and tetra- substituted alkenes.
Diels–Aider and related reactions – diene-dienophile, intramolecular Diels –Alder reactions, Stereochemistry and mechanism Retro Diels – Alder reaction –1, 3-dipolar reactions.

UNIT-II ✓ 12H

Synthetic Strategies or Retro Synthetic Analysis: Terminology- Target Molecule(TM), synthon, synthetic equivalent, functional group interconversion (FGI), and representation of disconnection of bonds. Linear and convergent synthesis. One group and two group disconnections in simple molecules- Alcohols, Olefins, aryl ketones, α,β-Unsaturated compounds – 1,3 dicarbonyl compounds. synthesis involving chemoselectivity, regioselectivity, reversal of polarity and cyclizations.

UNIT-III ✓ 12H

Photochemistry: Photochemistry of olefins–conjugated olefins–Aromatic compounds–isomerisation–additions. Photochemistry of carbonyl compounds–Norrish type I and II reactions–Paterno–Buchi Reaction. Photo reduction, Photochemical rearrangements–Photo Fries rearrangement, Di-π-methane rearrangement.

UNIT-IV✓ **12H**

Pericyclic Reactions: Definition, classification, MO theory, Electronic configuration in ground and first excited states of aliphatic conjugated polyene system (upto 4 double bonds).

Electrocyclic Reactions: Mechanism, stereochemistry, PMO, FMO, correlation diagram, Woodward Hoffman rules. **Cycloaddition Reactions:** FMO and correlation diagram methods-(2+2) and (4+2) cycloaddition reactions, stereochemistry. Woodward Hoffman rules.

Sigmatropic Rearrangement: classification, Mechanism by FMO method, Woodward Hoffman rules. Cope, claisen and Aza-cope rearrangements.

UNIT-V **12H**

Asymmetric Synthesis-II: Substrate Controlled Asymmetric Synthesis: Nucleophilic additions to chiral carbonyl compounds. 1, 2- asymmetric induction, Cram's rule, and Felkin-Anhmodel. i) Chiral auxiliary controlled asymmetric synthesis: [-Alkylation of chiral Enolates, aza enolates, 1,4-Asymmetric induction and Prelog's rule. Use of chiral auxiliaries in DielsAlder and Aldol reactions. ii) Chiral reagent controlled asymmetric synthesis: Asymmetric reductions using BINAL-H.; Asymmetric Hydroboration using $(IPC)_2$ BH and IPCBH$_2$.

Reference Books:

1) Some Modern methods of synthesis By Caruthers (Cambridge)
2) Organic synthesis by Robert & Ireland (Printce Hall of India)
3) Designing Organic Synthesis B staurt Warron, John Wiley & Sons
4) "Pericyclic reactions a mechanistic study" S.M. Mukheji
5) Synthetic approaches in Organic Chemistry " R.K. Bansal Narosa Publications
6) Advances in Organic Chemistry – Reaction mechanism and structure" by J. March (Mc Graw Hill).
7) 'Organic Photo chemistry and Pericyclic reactions' M.G. Arora Anmol Publications Pvt. Ltd.
8) Fundamentals of photochemistry by K.K. Rohatgi–Mukharjee Now Age international publishers.
9) Photochemistry by C W S Wells.
10) Organic Photochemistry by Turro.
11) Molecular Photo chemistry by Gilbert & Baggo.
12) Organic Photo chemistry by D Coyle.
13) Asymmetric synthesis by Nogradi.
14) Asymmetric organic reactions, J. D. Morrison and H. S. Moscher.
15) Principles of Asymmetric synthesis, R. E. Gawley and J. Aube, 2nd Ed., Elsevier, 2012.

Learning Outcomes:

- ✓ Students understand the basics of C-C single and double bond formations and Diels–Aider reactions.
- ✓ Students learnt the terminology and develop skills in writing retro-synthetic routes for target molecules with one and two functional groups.
- ✓ Students learnt different approaches in photochemical and pericyclic reactions
- ✓ Students are able to understand the terminology and able to know selectivity in asymmetric synthesis and also able to apply the approaches in organic synthetic reactions.
- ✓ Students understand the Nucleophilic additions to chiral carbonyl compounds and Felkin-Anhmodel.

Prof. M. SUBBARAO
M.Sc., M.Phil., Ph.D.,
Chairman, BOS in Chemistry (PG)
Acharya Nagarjuna University
N.Nagar, Guntur-522 510. A.P. India.

Paper-II: Organic Synthesis & Reaction Mechanisms-II

UNIT - I

V.R.S. & Y.R.N. College, CHIRALA

M.Sc (Final) Organic Chemistry - Semester-IV

Paper-II, Organic Synthesis & Mechanisms-II

UNIT-I

Formation of Carbon-Carbon single Bonds

Many of the most useful procedures for the formation of Carbon-Carbon single bonds in organic synthesis involve Carbanions. They include reactions which proceed by attack of the carbanion on a carbonyl or conjugated carbonyl group, as in the Grignard reaction, the aldol and claisen ester condensations and Michael reaction, and reactions which involve nucleophilic displacement at a saturated carbon atom, as in the alkylation of ketones and the coupling reactions of some organometallic compounds. Other reactions employed in the formation of carbon-carbon bonds involve carbonium ions and pericyclic processes and recently free-radical reactions have been finding useful application.

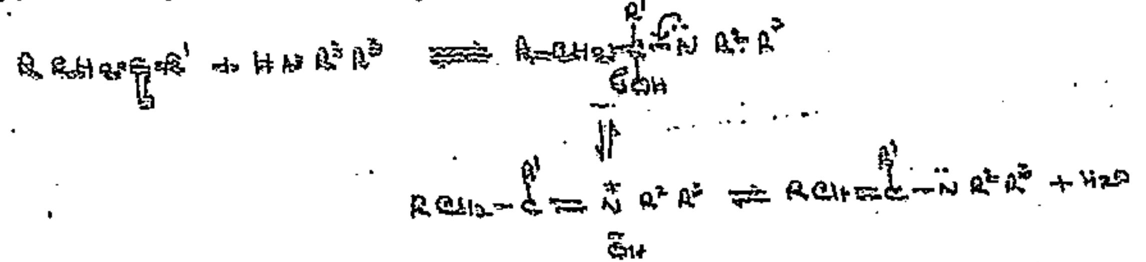
1. The enamine and related reactions

Enamines are α, β- unsaturated amines and their reaction provides a valuable method for the selective alkylation and acylation of aldehydes and ketones.

Preparation of enamines

Enamines are obtained by reaction of an aldehyde or ketone with a secondary amine in the presence of a dehydrating agent such as potassium carbonate or, better, by heating in benzene solution in the presence of a catalytic amount of toluene-p-sulphonic acid, with azeotropic removal of the water formed. The amines found most generally useful in forming enamines are pyrrolidine, , morpholine, , and piperidine, , in descending order of reactivity.

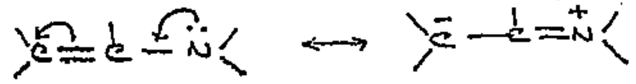
All the steps of the reaction are reversible and enamines are readily hydrolysed by water to form the carbonyl compound. All reactions of enamines must therefore be conducted under anhydrous conditions, but once reaction has been effected the the modified carbonyl compound is easily liberated from the product by addition of dilute acid to the reaction mixture.



$$RCH_2COR^1 + HNR^2R^3 \rightleftharpoons RCH_2\overset{R^1}{\underset{OH}{C}}-NR^2R^3$$

$$\rightleftharpoons RCH_2-\overset{R^1}{C}=\overset{+}{N}R^2R^3\ \overset{-}{O}H \rightleftharpoons RCH=\overset{R^1}{C}-\ddot{N}R^2R^3 + H_2O$$

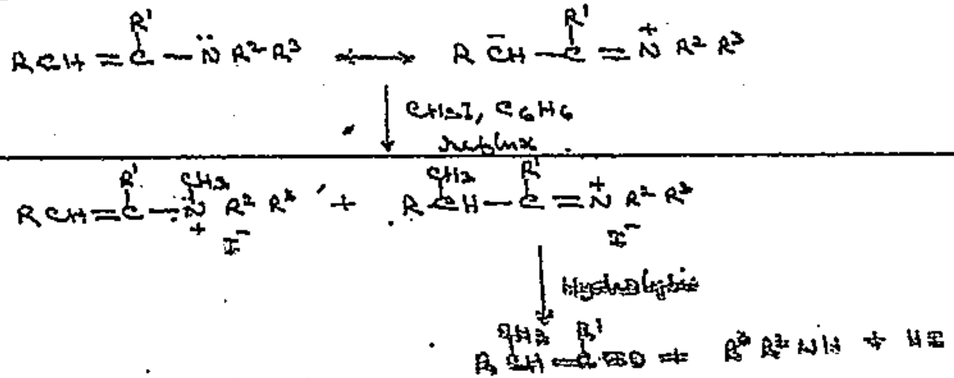
The usefulness of enamines in synthesis is due to the fact that there is some negative charge on the β-carbon atom (ie the α-carbon atom of the original carbonyl compound) which can therefore act as a nucleophile in reactions with alkyl and acyl halides and with electrophilic alkenes.



$$>C=C-\ddot{N}< \longleftrightarrow >\bar{C}-C=\overset{+}{N}<$$

Synthetic Applications

1. Alkylation of enamines. Reaction with alkyl halides, for example, leads irreversibly to C-alkylated and N-alkylated products. Subsequent hydrolysis of the C-alkylated iminium salt gives the alkylated ketone; the N-alkylated product is usually water soluble and is unaffected by the hydrolysis.



$$RCH=\overset{R^1}{C}-\ddot{N}R^2R^3 \longleftrightarrow R\bar{C}H-\overset{R^1}{C}=\overset{+}{N}R^2R^3$$

$$\Big\downarrow\ CH_3I,\ C_6H_6,\ \text{reflux}$$

$$RCH=\overset{R^1}{C}-\overset{CH_3}{\underset{+}{N}}R^2R^3\ I^- + R\overset{CH_3}{C}H-\overset{R^1}{C}=\overset{+}{N}R^2R^3\ I^-$$

$$\Big\downarrow\ \text{Hydrolysis}$$

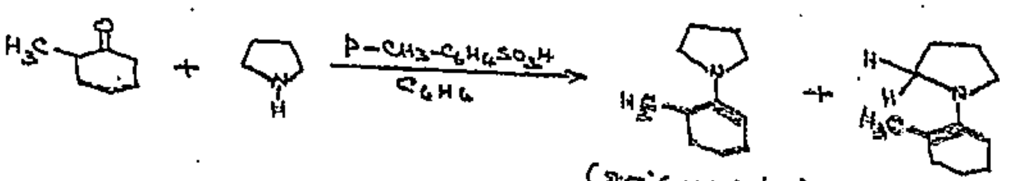
$$R\overset{CH_3}{C}H-\overset{R^1}{C}=O + R^2R^3NH + HI$$

Enamine alkylation has a number of advantages over direct base-catalysed alkylation of aldehydes and ketones.

Since no base or other catalyst is required, there is less tendency for wasteful self-condensation reactions of the carbonyl compound, and even aldehydes can be alkylated and acylated in good yield.

Another valuable feature of the enamine reaction is that it is regio-selective. In alkylation of an unsymmetrical ketone the product of reaction at the less substituted α-carbon atom is formed in larger amount, in contrast to direct base-catalysed alkylation of unsymmetrical ketones which usually gives a mixture of products.

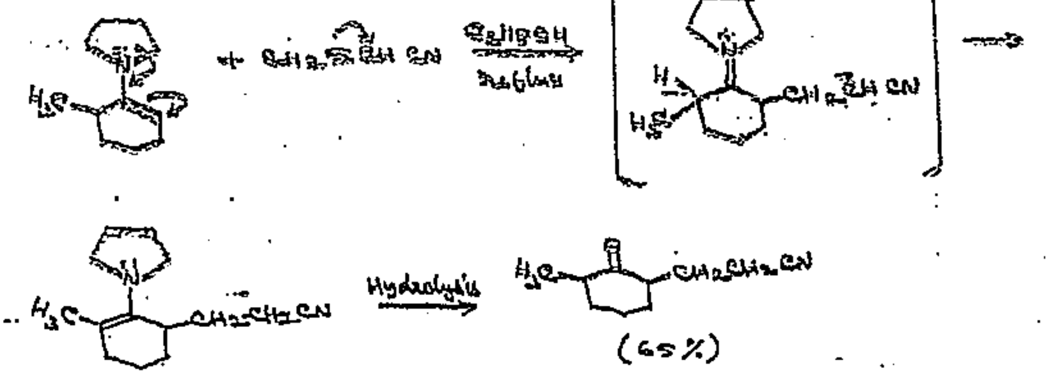
For example, reaction of the pyrrolidine enamine of 2-methylcyclohexanone with methyl iodide gives 2,6-dimethylcyclohexanone almost exclusively. This selectivity derives from the fact that the enamine from an unsymmetrical ketone consists mainly of the more reactive isomer in which the double bond is directed towards the less substituted carbon. In the more substituted enamine there is decreased interaction between the nitrogen lone pair and the π-system of the double bond because of steric interference between the α-substituent (CH_3 in the example) and the α-methylene group of the amine.

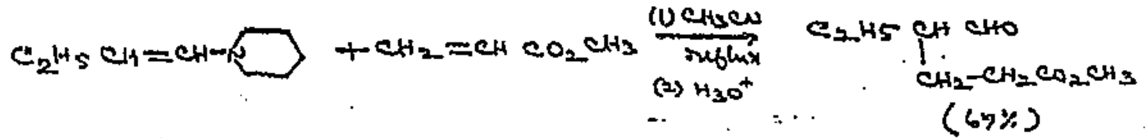


(85% of mixture) (15% of mixture)

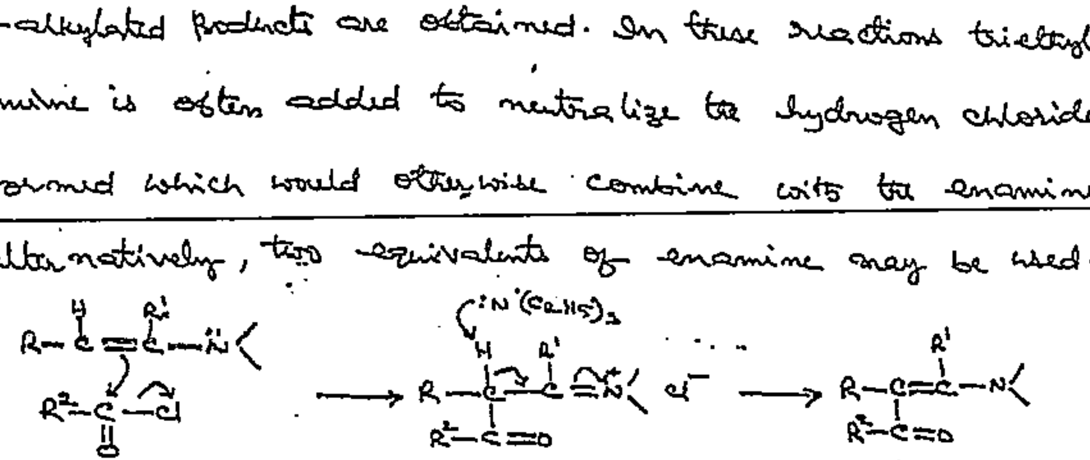
Alkylation of enamines with alkyl halides generally proceeds in only poor yield because the main reaction is N-alkylation rather than C-alkylation. Good yields of alkylated products are obtained using reactive halides such as benzyl or allyl halides, and it is believed that in these cases there is migration of the substituent group from nitrogen to carbon.

2. Reaction with electrophilic alkenes. Alkylation of enamines can also be effected with electrophilic alkenes, such as α,β-unsaturated ketones, esters or nitriles to give high yields of monoalkylated carbonyl compounds, and the sequence provides a useful alternative to base-catalysed Michael addition. In these reactions N-alkylation is reversible and good yields of C-alkylated products are usually obtained. Reaction again takes place at the less substituted α-carbon.





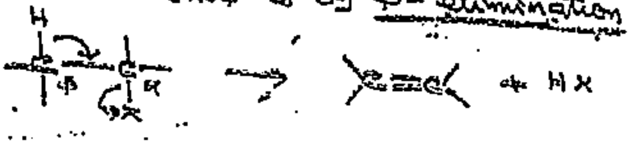
3. Acylation of enamines. Enamines also react readily with acid chlorides or anhydrides to give products which, on hydrolysis, afford β-diketones or β-keto-esters. Reaction at the nitrogen atom is again reversible, and good yields of C-alkylated products are obtained. In these reactions triethyl amine is often added to neutralize the hydrogen chloride formed which would otherwise combine with the enamine; alternatively, two equivalents of enamine may be used.



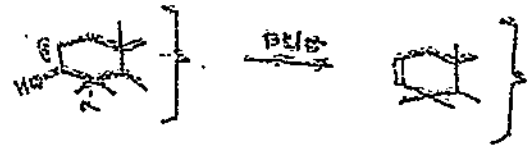
2. Formation of carbon-carbon double bonds

1. By β-Elimination Reactions

One of the most commonly used methods for forming carbon-carbon double bonds is by β-elimination reactions of the type –

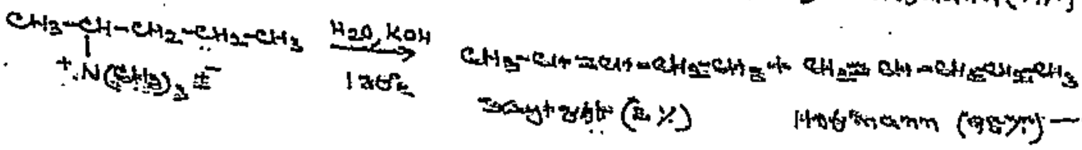


where $X = \ddot{O}H$, OCOR, halogen, OSO_2Ar, SR_2^+, NR_3^+ etc. Included among these reactions are acid-catalysed dehydrations of alcohols, solvolytic and base-induced eliminations from alkyl halides and sulphonates, and the well-known Hofmann elimination from quaternary ammonium salts. They proceed by both E_1 and E_2 mechanisms. Some examples are given below.

i. 

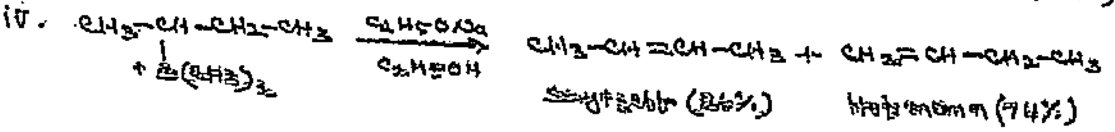
ii. $CH_3-CHBr-CH_2-CH_3 \xrightarrow[C_2H_5OH]{C_2H_5ONa} CH_3-CH=CH-CH_3 + CH_2=CH-CH_2-CH_3$

Sec. butyl bromide — Saytzeff (81%) — Hofmann (19%)

iii. 

$\underset{+N(CH_3)_3\,OH^-}{CH_3-CH-CH_2-CH_2-CH_3} \xrightarrow[130°C]{H_2O,\,KOH} CH_3-CH=CH-CH_2-CH_3 + CH_2=CH-CH_2-CH_2-CH_3$

Saytzeff (2%) — Hofmann (98%)

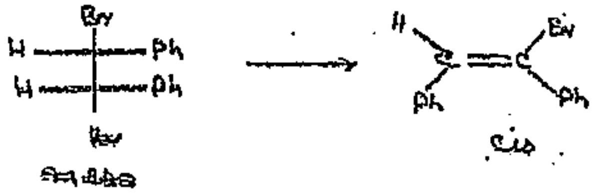
iv. 

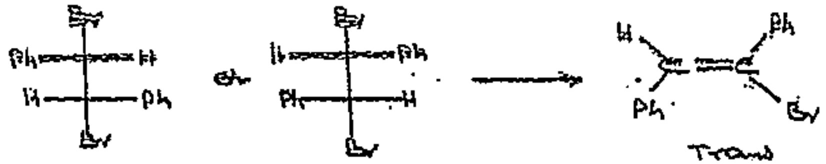
$\underset{+S(CH_3)_2}{CH_3-CH-CH_2-CH_3} \xrightarrow[C_2H_5OH]{C_2H_5ONa} CH_3-CH=CH-CH_3 + CH_2=CH-CH_2-CH_3$

Saytzeff (26%) — Hofmann (74%)

The Hofmann reaction with quaternary ammonium salts and base induced eliminations from alkyl halides and aryl sulphonates are generally 'anti' elimination processes, that is to say the hydrogen atom and the leaving group depart from opposite sides of the incipient double bond.

An example of anti-elimination is that the elimination of HBr from meso 1,2-dibromo 1,2-diphenyl ethane gave cis-2-bromostilbene, while the (+) or (−) isomer gave the trans olefin. This stereospecific result demonstrates that in this case elimination is anti.



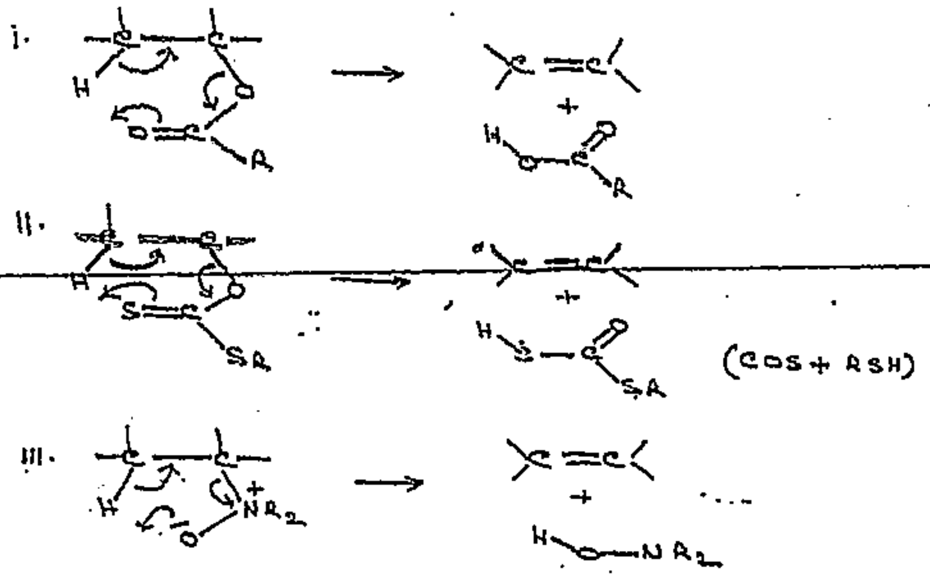


d l pair

Obviously, this type of experiment need not be restricted to compounds that have a meso form. Anti-elimination requires that an erythro d l pair (or either isomer) give the cis olefin, and the threo d l pair (or either isomer) give the trans isomer.

2. Pyrolytic Eliminations

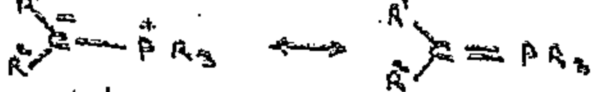
Another important group of alkene-forming reactions are pyrolytic eliminations. Included in this group are the pyrolysis of carboxylic esters, xanthates and amine oxides. For the majority of cases these reactions are believed to take place in a concerted manner by way of a cyclic transition state and they are necessarily syn eliminations; i.e., the hydrogen atom and the leaving group depart from the same side of the incipient double bond.



3. The Wittig reaction of phosphorus ylides

A carbanion attached to a heteroatom bearing a positive charge is called a ylide, i.e., $-\overset{-}{C}-\overset{+}{X}-$ where X is a heteroatom and may be N, P, or S. They are named according to the heteroatom present. Thus, a carbanion attached to a phosphorus atom bearing a positive charge is called a phosphorus ylide or phosphonium ylide. The ylides are obtained by treatment of the 'onium' salts with a strong base like NaH or n-C_4H_9Li.

Posphonium ylides are resonance stabilized structures in which there is some overlap between the carbon p-orbital and one of the d-orbitals of phosphorus as shown below.

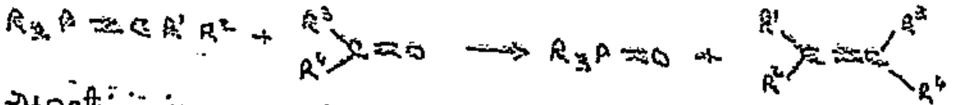


ylide form

(Trialkyl phosphonium dialkyl methylide)

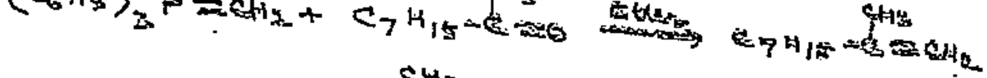
phosphorane form

The reaction between a phosphorane or phosphonium ylide and an aldehyde or ketone to form a phosphine oxide and an alkene is known as the Wittig reaction after the name of German chemist George Wittig, who first showed the value of this procedure in the synthesis of alkenes.

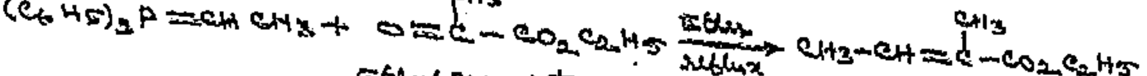


$$R_3P=CR^1R^2 + R^3R^4C=O \longrightarrow R_3P=O + R^1R^2C=CR^3R^4$$

The reaction is easy to carry out and proceeds under mild conditions. A valuable feature of the Wittig procedure is that, in contrast to the β-elimination and pyrolytic reactions, it gives rise to alkenes in which the position of the double bond is unambiguous as illustrated in the following examples.



$$(C_6H_5)_3P=CH_2 + C_7H_{15}-\overset{CH_3}{\overset{|}{C}}=O \xrightarrow{Ether} C_7H_{15}-\overset{CH_3}{\overset{|}{C}}=CH_2$$

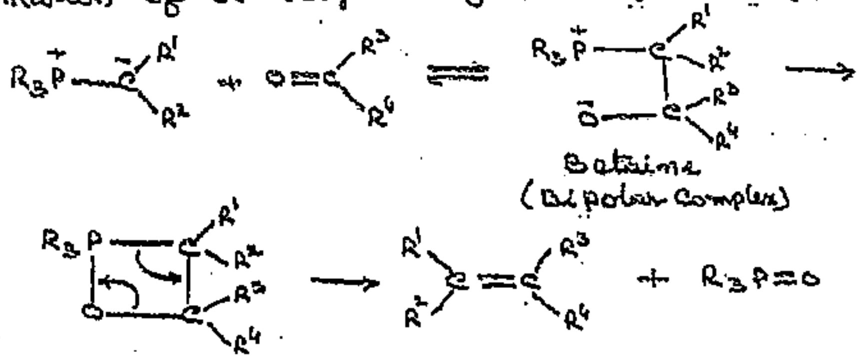


$$(C_6H_5)_3P=CH\,CH_3 + O=\overset{CH_3}{\overset{|}{C}}-CO_2C_2H_5 \xrightarrow[reflux]{Ether} CH_3-CH=\overset{CH_3}{\overset{|}{C}}-CO_2C_2H_5$$

Ethyl pyruvate

Wittig reaction mechanism

Reaction with a carbonyl compound takes place by attack of the carbanionoid carbon of the ylide form on the electrophilic carbon of the carbonyl group with the formation of a betaine which collapses to the products by way of a four-membered cyclic transition state, the driving force being provided by formation of the very strong phosphorus-oxygen bonds.



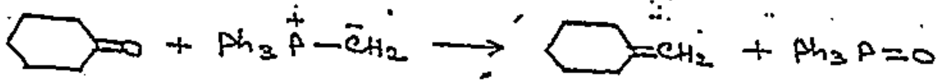
Depending on the reactants, either the first or the second step may be rate determining. It has never been observed that the last step is the slowest, and it is uncertain whether the four-membered ring compound is a true intermediate or a transition state. Evidence for the formation of a betaine in the first stage of the reaction is provided by the isolation of compounds of this type in certain cases.

The reactivity of the phosphorane depends on the nature of the groups R, R^1 and R^2. In practice, R is nearly always phenyl, and in the majority of Wittig reagents R^1 and R^2 are alkyl groups which have little effect on the carbanionoid character of the molecule. These reagents are markedly nucleophilic and react readily with carbonyl and other polar groups. Addition of the ylide to carbonyl groups takes place rapidly and decomposition of the betaine now becomes the rate-determining of the reaction. Since the polarity of the carbonyl group is of little consequence when the second step is rate determining, aldehydes and ketones usually react equally well with these reagents.

Applications

The reaction has many useful synthetic applications. Many natural products which are otherwise difficult to prepare can be synthesized by wittig reaction.

1. Formation of exocyclic methylene group



Methylene cyclohexane

This method of introducting exocyclic methylene group is extremely valuable and has been widely used in the preparation of methylene steroids.

2. Preparation of β, γ- unsaturated acids

$$R_2C=O + Ph_3\overset{+}{P}-\overset{-}{C}H-CH_2CO\overset{-}{O} \longrightarrow R_2C=CH-CH_2CO\overset{-}{O} + Ph_3P=O$$

In all other methods isomerisation to α, β- unsaturated acids results.

3. Synthesis of ethers

Methoxymethylene triphenylphosphorane reacts with carbonyl compounds to give diphenyl- substituted vinyl methyl ethers.

$$Ph_2C=O + Ph_3P=CHOCH_3 \longrightarrow Ph_2C=CHOCH_3$$

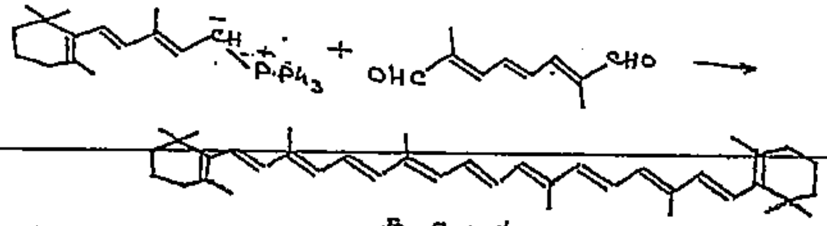
Hydrolysis of the product gives aldehyde.

$$Ph_2C=CHOCH_3 \xrightarrow{HOH} Ph_2CH-CHO$$

Diphenylacetaldehyde

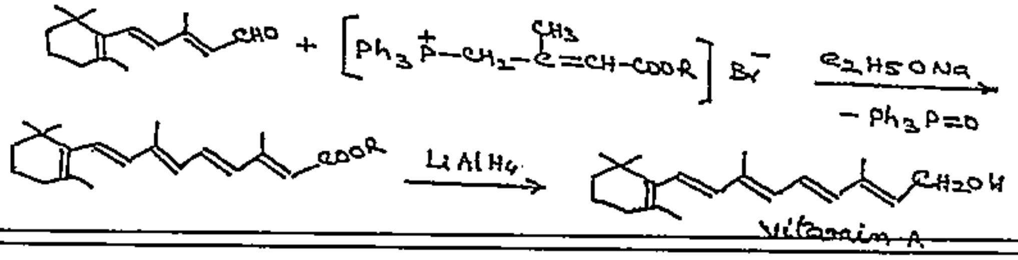
4. Preparation of natural products.

(i) β-Carotene (Pro-vitamin A)



β-Carotene

(ii) vitamin-A



Vitamin A

2. Sulphur ylides

A carbanion attached to a sulphur atom bearing a positive charge is called sulphur ylide. The two important sulphur ylides are dimethylsulphonium methylide and dimethyl oxo sulphonium methylide. They are prepared by deprotonation, with a suitable base like NaH or $n-C_4H_9Li$, of the corresponding sulphonium salts.

$$(CH_3)_2\overset{+}{S}CH_3\overset{-}{I} \xrightarrow{NaH} (CH_3)_2\overset{+}{S}-\overset{-}{C}H_2 + NaI + H_2$$

$$(CH_3)_2\underset{\underset{O}{\|}}{\overset{+}{S}}CH_3\overset{-}{I} \xrightarrow{n-C_4H_9Li} (CH_3)_2\underset{\underset{O}{\|}}{\overset{+}{S}}-\overset{-}{C}H_2 + LiI + n-C_4H_{10}$$

These ylides are formally zwitter ions in which a carbanion is stabilized by interaction with an adjacent sulphonium centre (bonding involves a sulphur 3d orbital and a carbon 2p orbital)

$$\underset{\text{ylide form}}{(CH_3)_2\overset{+}{\underset{\cdot\cdot}{S}}-\overset{-}{\underset{\cdot\cdot}{C}}H_2} \longleftrightarrow \underset{\text{sulphorane form}}{(CH_3)_2\underset{\cdot\cdot}{S}=CH_2}$$

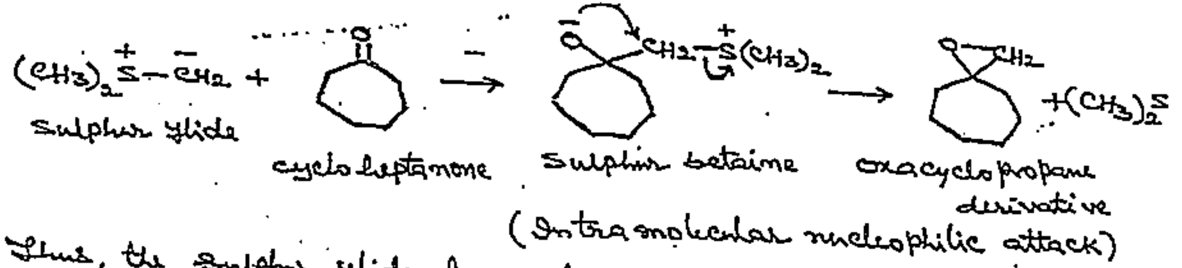
Dimethyl sulphonium methylide is more reactive and less stable compared to dimethyl oxo-sulphonium methylide.

Reactions of sulphur ylides

1. Reaction with aldehydes and ketones

Sulphur ylides on their reaction with aldehydes and ketones form epoxides. In this respect they differ from phosphorus ylides which give alkenes.

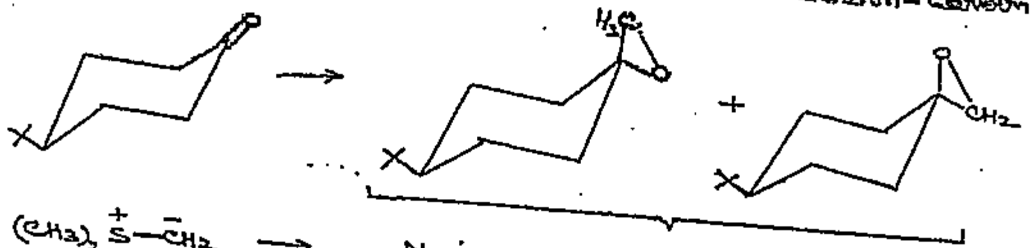
Sulphur ylides are also nucleophilic and attack the carbonyl carbon to give sulphur betaines, but as sulphur does not have that high affinity for oxygen as phosphorus has, the reaction ~~reaction~~ after sulphur betaine formation takes a different course. The dimethyl sulphide functions as a leaving group, and is displaced by intramolecular nucleophilic attack of the alkoxide ion leading to the formation of an epoxide.



Thus, the sulphur ylide here acts as a methylene transfer reagent i.e., it adds a methylene group to the carbonyl double bond.

2. Reaction with cyclohexanones

Both dimethyl sulphonium methylide as well as dimethyl-oxosulphonium methylide react the same way to give epoxides on reaction with non-conjugated aldehydes and ketones. The two reagents, however, differ in their reaction with a cyclohexanone. With the sulphonium ylide the epoxide has the new carbon-carbon bond axial, however, with the oxo-sulphonium methylide, the epoxide has an equatorial carbon-carbon bond.



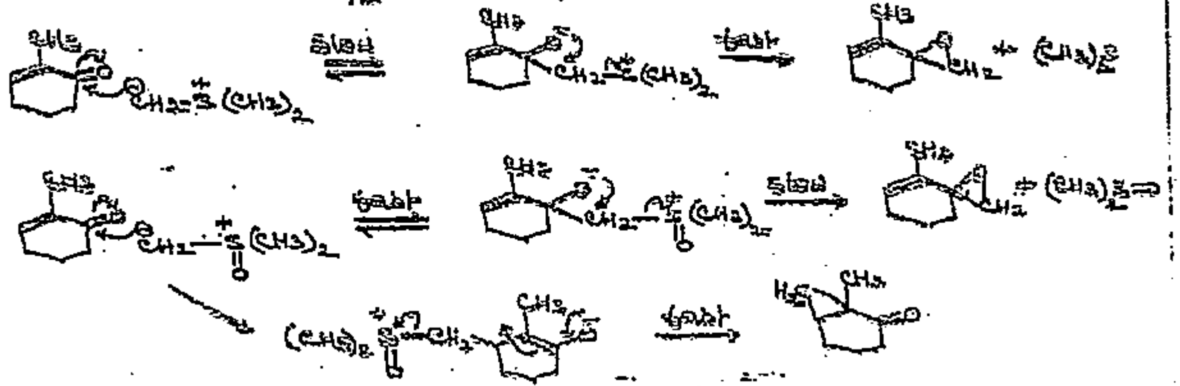
$(CH_3)_2\overset{+}{S}-\overset{-}{C}H_2$ → Major product Minor product

$(CH_3)_2\overset{+}{\underset{O}{S}}-\overset{-}{C}H_2$ → Not observed 100%

It has been suggested that the addition of sulphonium methylide to the carbonyl group of a cyclohexanone to give the sulphur betaine is irreversible, while the addition of oxo-sulphonium methylide is reversible which as a result allows the accumulation of the thermodynamically more stable betaine.

3. Reaction with α, β - unsaturated carbonyl compounds

A sharp difference in the reactivity of both the ylides is observed in the case of their reaction with α, β-unsaturated compounds. The sulphonium methylide reacts to give again an epoxide, however, the reaction with oxosulphonium methylide affords a cyclopropane, via Michael addition to the carbon-carbon double bond.



It appears that the difference is again due to the reason that the relative rates of the two reactions depends on the relative rates of the two reactions via which the betaine can collapse: (I) reversal to starting materials or (II) intramolecular nucleophilic displacement.

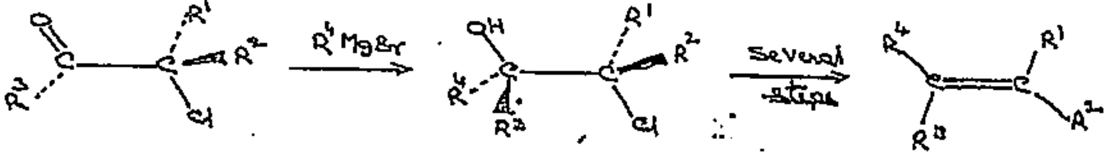
With dimethyl-sulphonium methylide, the intramolecular displacement step is faster compared to the reverse of addition, consequently epoxide formation occurs. Since dimethyl oxosulphonium methylide is more stable, the reversal is relatively more rapid and the product formation only occurs after conjugate addition.

4. Stereo-selective synthesis of tri and tetra substituted alkenes

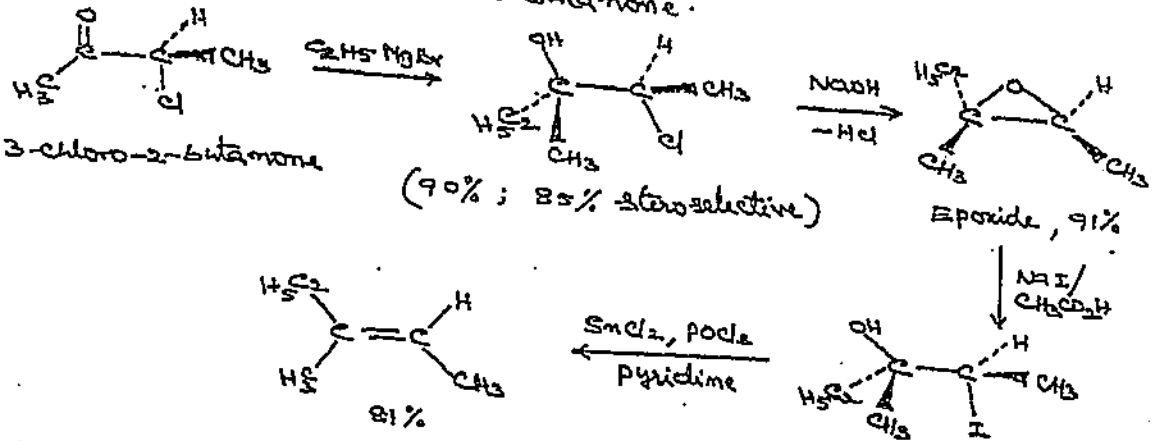
Z- and E-1,2-Disubstituted alkenes are readily available by reduction of the corresponding alkynes or by other means, but isomerically pure tri- and tetra-substituted alkenes have been more difficult to obtain. However, they can be prepared by the following methods.

1. Addition of Grignard reagent to an α-chloro aldehyde or ketone

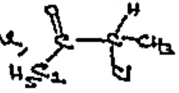
In an early method the critical step is the reaction of a Grignard reagent with an α-chloroaldehyde or ketone. The most reactive conformation of an α-chloroaldehyde or α-chloro ketone is that in which the C=O and C—Cl dipoles are antiparallel. Addition of Grignard reagent to this conformation is highly stereo-selective and takes place mainly from the side of the carbonyl group which is less sterically hindered by the groups R^1 and R^2 on the α-carbon atom, leading predominantly to the chlorohydrin in which the incoming group R^4 and larger of the groups R^1 and R^2 are anti to each other.



The resulting chlorohydrin is converted, by a series of stereo-selective reactions into the alkene in which three of the groups on the double bond are derived from the chlorocarbonyl compound and the other from the Grignard reagent. This method is exemplified below for the synthesis of E-3-methyl-2-pentene from 3-chloro-2-butanone.



A similar series of reactions beginning with the addition of methyl magnesium iodide (CH_3MgI) to 2-chloro-3-pentanone,

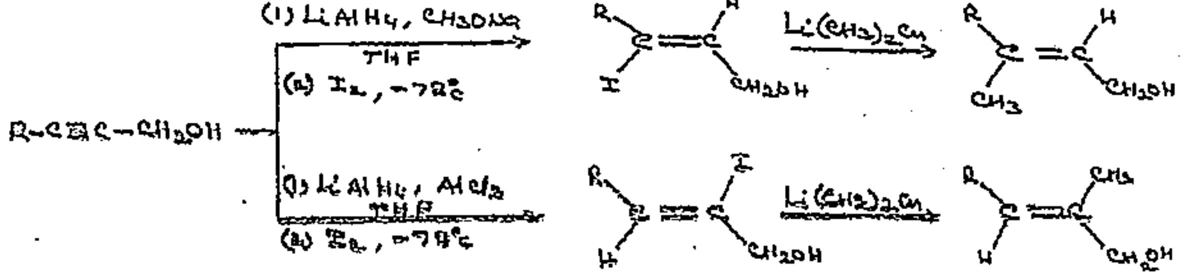


gave Z-3-methyl-2-pentene.

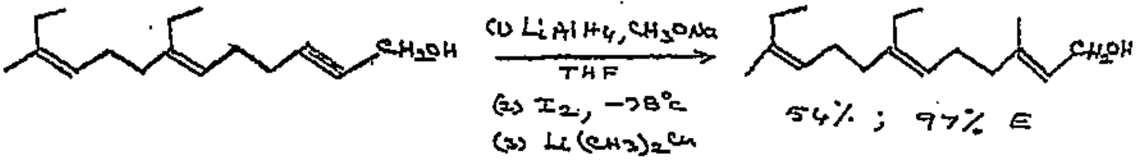
2. Reduction of propargylic alcohol with modified $LiAlH_4$ reagent

An entirely different procedure which makes possible the stereo-specific conversion of a propargylic alcohol into a 2- or 3-alkylated allylic alcohol is based on a remarkable, specific, conversion of propargylic alcohols into β- or γ-iodo-allylic alcohols by reduction with a modified $LiAlH_4$ reagent and subsequent reaction of a crude reduction product with iodine.

If the reduction is effected in the presence of sodium methoxide, the final product is exclusively the γ-iodoallylic alcohol, whereas reduction with $LiAlH_4$ and $AlCl_3$ and iodination gives finally the β-iodoallylic alcohol. Reaction of the resulting iodo compounds with lithium organocuprates then affords the corresponding substituted allylic alcohol in which the substituents originally present in the propargyl alcohol are trans to each other.

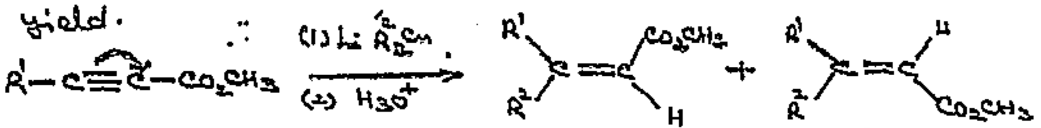


This method is applicable to a variety of synthetic problems in which the stereo-specific introduction of trisubstituted carbon-carbon double bonds is involved. For example, it formed a key step in a synthesis of juvenile hormone.



3. Addition of organocopper reagents to alkynes

Tri and tetra-substituted alkenes can also be obtained stereo-selectively from alkynes by addition of organocopper and organoborane reagents. One synthesis leads to β,β-dialkylacrylic esters from α,β-acetylenic esters. Lithium dialkylcuprates add rapidly to α,β-acetylenic esters to give the stereoisomeric acrylic esters (1) and (2) in high yield.

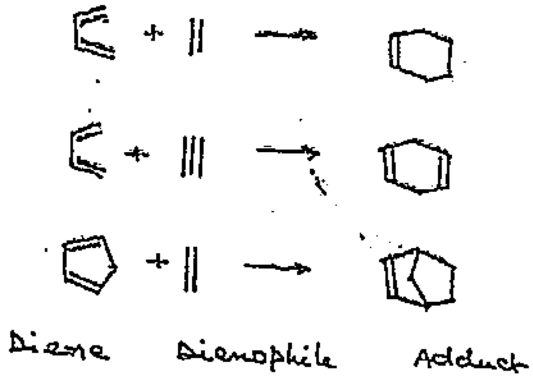


(1) (2)

The stereochemistry of the products is dependent on the reaction temperature and the nature of the solvent, and high yields of the Z-addition compound (1) are obtained by conducting the reaction at −78°c in THF-solution. In contrast to the procedure with propargyl alcohols described above, this reaction yields an alkene in which the substituents in the acetylenic precursor are cis to each other in the alkene.

5. Diels-Alder and Related Reactions

(i) A reaction in which a 1,3-diene reacts with a dienophile to form an adduct (addition product) with a six-membered hydroaromatic ring is called Diels-Alder reaction. In this reaction two new σ bonds and a new π-bond are formed at the expense of two π-bonds in the starting materials. Examples are –



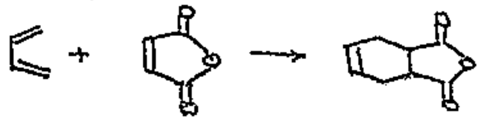
In general the reaction takes place easily, simply by mixing the components at room temperature or by gentle warming in a suitable solvent, although in some cases with unreactive dienes or dienophiles more vigorous conditions may be necessary.

The Diels-Alder reaction is reversible, and many adducts dissociate into their components at quite low temperatures. In these cases heating is disadvantageous and the forward reaction is facilitated and better yields are obtained by using an excess of one of the components, or a solvent from which the adduct separates readily. Many Diels-Alder reactions are accelerated by Lewis acid catalysts.

Many dienes can exist in a cisoid and a transoid conformation, and it is only the cisoid form which can undergo addition. If the diene does not have, or cannot adopt a cisoid conformation no reaction occurs.

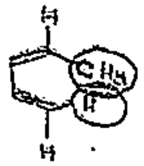
(II) The Diene

Acyclic dienes: Acyclic conjugated dienes react readily often forming the adducts in almost quantitative yield. For example, butadiene itself reacts quantitatively with maleic anhydride in benzene at 100°c in 5 h, or more slowly at room temperature, to form cis-1,2,3,6-tetrahydrophthalic anhydride.

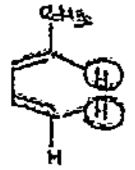


Substituents in the butadiene molecule influence the rate of cycloaddition both through their electronic nature and by a steric effect on the conformational equilibrium. The rate of the reaction is often increased by electron donating substituents (eg., $-NMe_2$, $-OMe$, $-Me$) in the diene as well as by electron-attracting substituents in the dienophile. Bulky substituents which discourage the diene from adopting the cisoid conformation hinder the reaction. Thus, whereas 2-methyl-, 2,3-dimethyl-, and 2-tert-butyl butadiene react normally with maleic anhydride, the 2,3-diphenyl compound is less reactive and 2,3-di-t-butyl butadiene is completely unreactive. Apparently the molecule of the 2,3-di-t-butyl butadiene is prevented from attaining the necessary planar cisoid conformation by the steric effects of the two bulky t-butyl substituents. In contrast, 1,3-di-t-butyl butadiene, in which the substituents do not interfere with each other even in the cisoid form, reacts readily with maleic anhydride.

Z-Alkyl or aryl substituents in the 1-position of the diene reduce its reactivity by sterically hindering formation of the cisoid conformation through non-bonded interaction with a hydrogen atom at C-4. Accordingly, an E-substituted 1,3-butadiene reacts with dienophiles much more readily than the Z-isomer. Thus, Z-1,3-pentadiene gave only 4% yield of adduct when heated with maleic anhydride at 100°C, whereas the E-isomer formed an adduct in almost quantitative yield in benzene at 0°C.



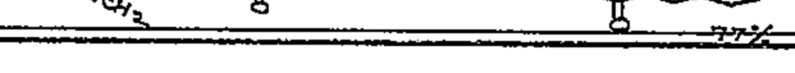
Z-1,3-pentadiene



E-1,3-pentadiene

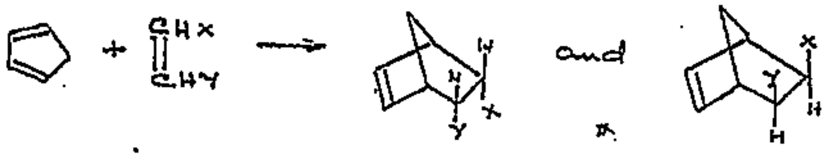
Similarly, E,E-1,4-dimethyl butadiene reacts readily with many dienophiles, but Z,E-isomer yields an adduct only when the components are heated in benzene at 150°C. Z-Substituents in both the 1- and 4- positions prevent reaction. 1,1-Disubstituted butadienes also react with difficulty, and with such compounds addition may be proceeded by isomerisation of the diene to a more reactive species. Thus, in the reaction of 1,1-dimethyl butadiene with acrylonitrile, the diene first isomerises to 1,3-dimethyl butadiene which then reacts in the "normal" way.

1,2-Dimethylenecycloalkanes: In 1,2-dimethylene cycloalkanes the cisoid conformation of the double bonds necessary for 1,4-addition is fixed and dienes of this type react readily with dienophiles, often forming the adducts in almost quantitative yield. Thus 1,2-dimethylene cyclohexane reacts exothermally with maleic anhydride, and with benzoquinone, the bis-adduct is obtained.



cyclic dienes: cyclopentadiene, in which the double bonds are constrained in a planar cisoid conformation, reacts easily with a variety of dienophiles. 1,3-cyclohexadiene is also reactive but with increase in size of the ring the reactivity of cyclic dienes rapidly decreases. In the larger rings the double bonds can no longer easily adopt the necessary coplanar configuration because of non-bonded interaction of methylene groups in the planar molecule.

Cyclopentadiene is a very reactive diene and reacts easily with dienophiles to form bridged compounds of the bicyclo [2.2.1] heptene series. The reaction of cyclopentadiene with mono- and cis-disubstituted ethenes could apparently give rise to two stereochemically distinct products, the endo- and exo- bicyclo [2.2.1] heptene derivatives.



It is found in practice, however, that the endo isomer always predominates, except under conditions where isomerisation of the first-formed adduct occurs.

(III) The dienophile

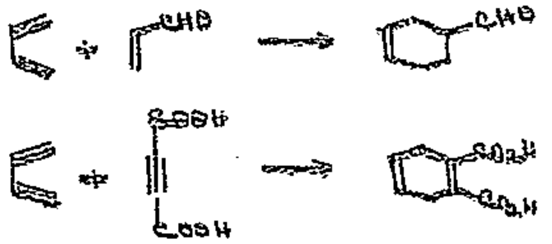
Many different kinds of dienophile can take part in the Diels-Alder reaction. They may be derivatives of ethylene or acetylene or reagents in which one or both of the reacting atoms is a hetero atom.

All dienophiles do not react with equal ease; the reactivity depends on the structure. In general, the greater the number of electron attracting substituents on the double or triple bond, the more reactive is the dienophile, due to the lowering of the energy of the lowest unoccupied molecular orbital (LUMO) of the dienophile by the substituents. Thus, whereas maleic anhydride and 1,3-butadiene afford a quantitative yield of adduct in boiling benzene or, more slowly at room temperature, tetracyanoethylene, with four electron-attracting substituents reacts extremely rapidly even at 0°c. Similarly, acetylene reacts with electron rich dienes only under severe conditions, but propiolic acid ($HC \equiv C\,COOH$), phenylpropiolic acid, and acetylene dicarboxylic acid react rapidly and have frequently been used as dienophiles in the Diels-Alder reaction.

It should be noted, however, that there are a number of Diels-Alder reactions for which the above generalisation does not hold, in which reaction takes place between an electron-rich dienophile and an electron deficient diene. The essential feature is that the two components should have complementary electronic character. These Diels-Alder reactions with reverse electron demand, as they are called, also have their uses in synthesis, but the vast majority of reactions involve an electron-rich diene and an electron-deficient dienophile.

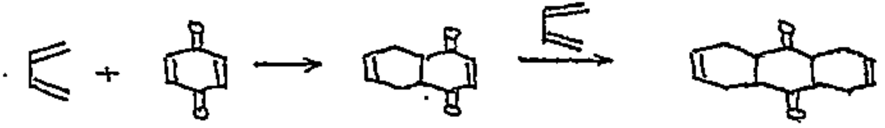
The most commonly encountered activating substituents for the 'normal' Diels-Alder reaction are CO, CO_2R, CN and NO_2 and dienophiles which contain one or more of these groups in conjugation with a double or triple bond react readily with dienes.

α,β-Unsaturated carbonyl compounds are reactive dienophiles and are probably the most widely used dienophiles in synthesis. Typical examples are acrolein (propenal), acrylic acid and its esters, maleic acid and its anhydride, 2-butyne-1,4-dioic acid (acetylene dicarboxylic acid) and numerous derivatives of 2-cyclohexenone. Thus, acrolein reacts rapidly with butadiene in benzene solution at 0°c to give tetrahydrobenzaldehyde in quantitative yield, and 2-butyn-1,4-dioic acid and butadiene give 3,6-dihydrophthalic acid.

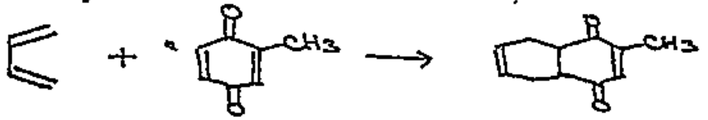


Substituents exert a pronounced steric effect on the reactivity of dienophiles. Comparative experiments show that the yields of adducts obtained in the condensation of butadiene and 2,3-dimethylbutadiene with derivatives of acrylic acid decrease with the introduction of substituents into the α-position of the dienophile, and α,β-unsaturated ketones with two alkyl substituents in the β-position react very slowly. Similarly, the reactions of butadiene and 2,3-dimethyl butadiene with methylmaleic anhydride require more vigorous conditions than those with maleic anhydride itself.

Another important group of dienophiles of the α,β-unsaturated carbonyl class are quinones. p-Benzoquinone itself reacts readily with butadiene at room temperature to give a high yield of the monoadduct, tetrahydronaphthaquinone; under more vigorous conditions a bis-adduct is obtained which can be converted into anthraquinone by oxidation of an alkaline solution with atmospheric oxygen.



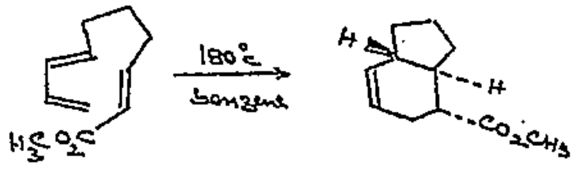
As with other dienophiles alkyl substitution on the double bonds leads to a decrease in activity and monoalkyl p-benzoquinones preferentially add dienes at the unsubstituted double bond



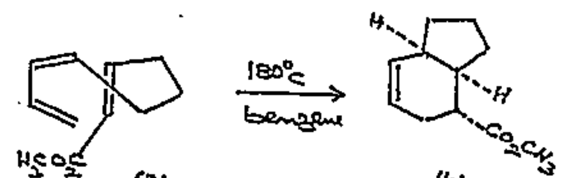
In contrast to these reactive dienophiles in which the double or triple bond is activated by conjugation with electron-withdrawing groups, ethylenic compounds such as allyl alcohol and its esters, allyl halides and vinyl esters are relatively unreactive, although they can frequently be induced to react with dienes under forcing conditions.

(IV) Intramolecular Diels-Alder Reactions

In the intramolecular Diels-Alder reaction the diene and dienophile form part of the same molecule. This reaction proceeds rather easily because of the closeness of reacting partners and the favourable entropy factor leading to the formation of two new rings with several chiral centres of predetermined configurations in one operation. Thus, the trans-dienyl acrylic ester (1) gave the trans-hydrindane (2) while the cis ester (3) gave the cis-hydrindane (4).



(1) (2)

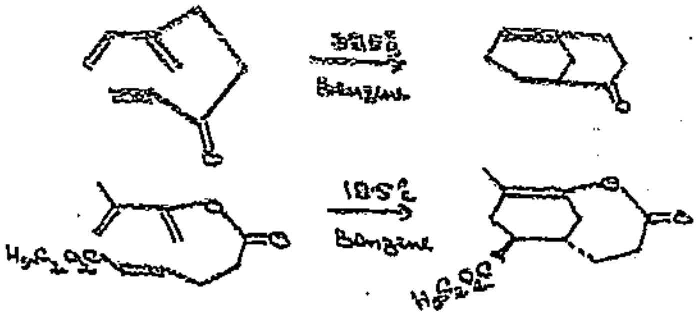


(3) (4)

In intramolecular Diels-Alder reactions involving 1-substituted butadienes (5), reaction could apparently take place in two ways to give the fused ring product (6) or the bridged ring compound (7).

(5) (6) (7)

Generally, cyclisation to give the fused ring product is highly favoured and very few examples of the formation of bridged ring compounds from 1-substituted butadienes (5) are known. With 2-substituted butadienes, however, bridged ring compounds are necessarily formed, and reactions of this kind have been used to make a series of bridgehead alkenes and bridge-head enol lactones.



Many intramolecular Diels-Alder reactions involving 2-substituted butadienes are catalysed by Lewis acids and in this way can be effected in high yield at ordinary temperatures.

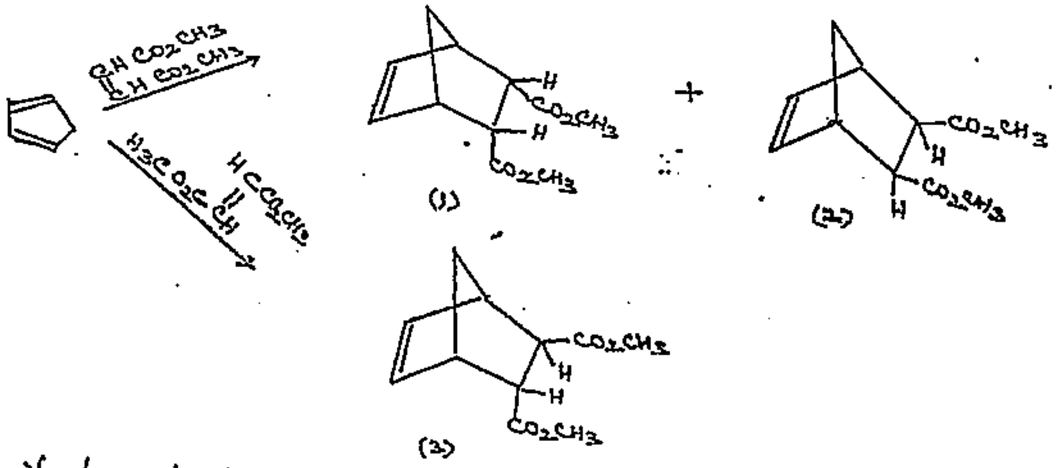
(V) Stereochemistry

The great synthetic usefulness of the Diels-Alder reaction depends not only on the fact that it provides easy access to a variety of six-membered ring compounds, but also on its remarkable stereochemistry. It should be noted, however, that the high stereo-selectivity applies only to the kinetically controlled reaction and may be lost by epimerization of the product or starting materials, or by easy dissociation of the adduct allowing thermodynamic control of the reaction.

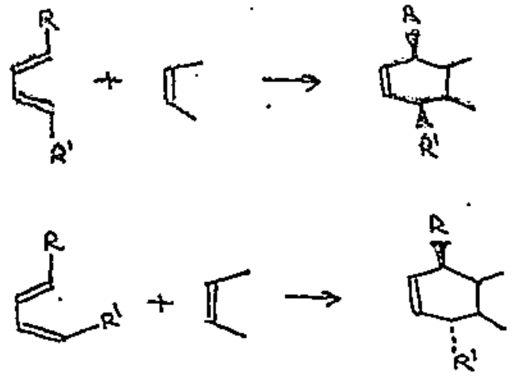
The cis principle

The stereochemistry of the adduct obtained in many Diels-Alder reactions can be selected on the basis of two empirical rules. According to the 'cis principle', which is very widely followed, the relative stereochemistry of substituents in both the dienophile and the diene is retained in the adduct. That is, a dienophile with trans substituents will give an adduct in which the trans configuration of the substituents is retained, while a cis disubstituted dienophile will form an adduct in which the substituents are cis to each other.

For example, in the reaction of cyclopentadiene with dimethylmaleate the cis adducts (1) and (2) are formed while in the reaction with dimethyl fumarate the trans configuration of the ester groups is retained in the adduct (3).



Similarly with the diene component, the relative configuration of the substituents in the 1- and 4- positions is retained in the adduct; a trans, trans-1,4-disubstituted diene gives rise to adducts in which the 1- and 4- substituents are cis to each other, and a cis, trans-disubstituted diene gives adducts with trans substituents.

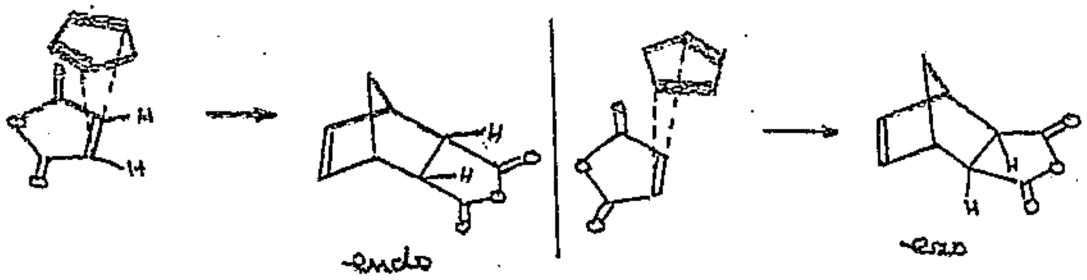


The endo addition rule

In the addition of maleic anhydride to cyclopentadiene, two different products, the endo and the exo, might conceivably be formed depending on the manner in which the diene and the dienophile are disposed in the transition state. According to Alder's endo addition rule in a diene addition reaction the two components arrange themselves in parallel planes, and the most stable transition state arises from the orientation in which there is 'maximum accumulation of double bonds'.

Not only the double bonds which actually take part in the addition are taken into account, but also the π-bonds of the activating groups in the dienophile. The rule appears to be strictly applicable only to the addition of cyclic dienophiles to cyclic dienes, but it is a useful guide in many other additions as well.

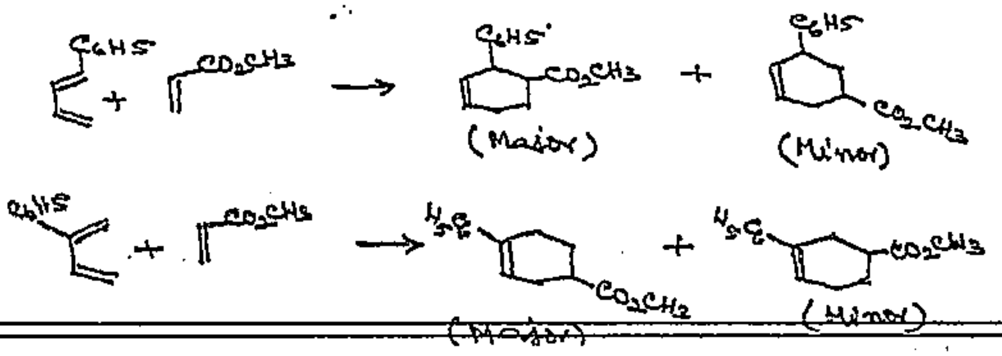
Thus, in the addition of maleic anhydride to cyclopentadiene the endo product, formed from the orientation with maximum accumulation of double bonds, is produced almost exclusively.



The thermodynamically more stable exo compound is formed in yields of less than 1.5 per cent.

Regio-selectivity (Reaction proceeding selectively in one direction)

Addition of an unsymmetrical diene to an unsymmetrical dienophile could apparently take place in two ways to yield structurally two isomeric products. The reaction, however, is regio-selective and a predominance of one isomer rather than a mixture is obtained. Thus, 1-substituted butadienes give ortho (1,2) product and 2-substituted butadienes give para (1,4) products (i.e., in which there is greater separation between the two groups.

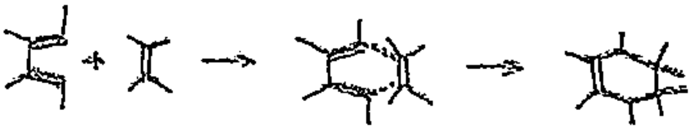


(VI) Mechanism of Diels-Alder Reaction

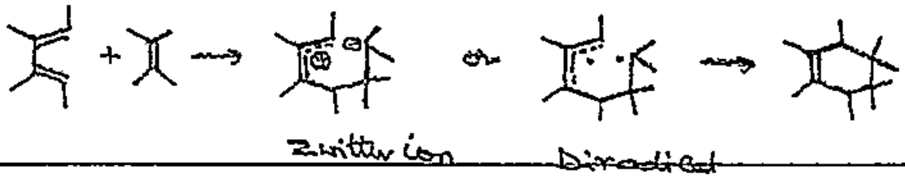
The precise mechanism of the Diels-Alder reaction has been the subject of much debate. There is general agreement that the rate-determining step in adduct formation is bimolecular and that the two components approach each other in parallel planes roughly orthogonal to the direction of the new bonds about to be formed. Formation of the two new σ bonds takes place by overlap of molecular π-orbitals in a direction corresponding to endwise overlap of atomic p-orbitals.

Two main views have been considered:

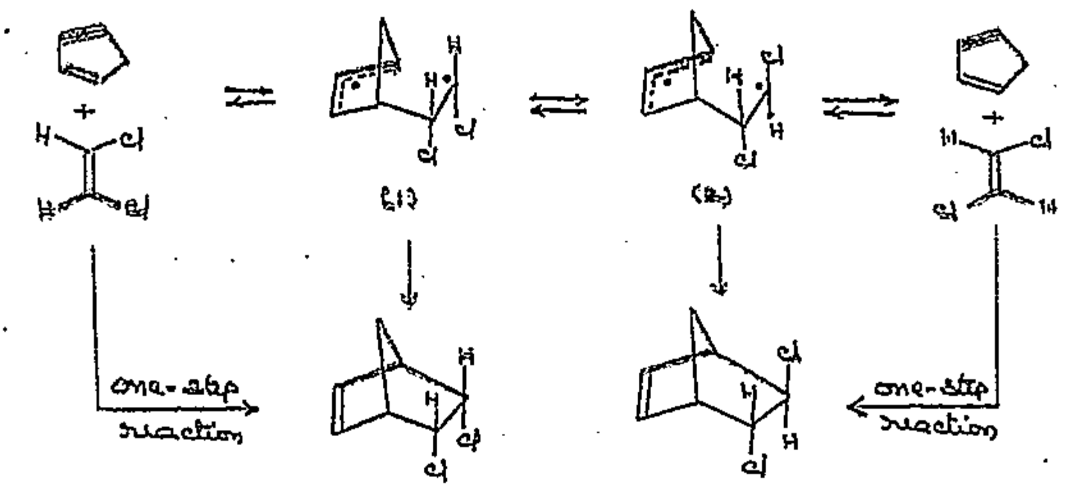
(a) The reaction is a concerted addition in which both of the new single bonds are formed at the same time



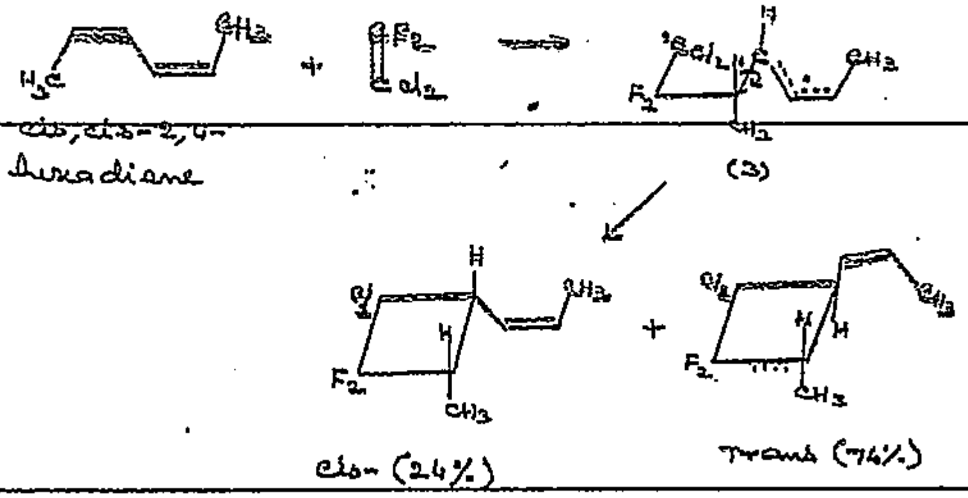
(b) The reaction takes place in two steps, the first of which, the formation of a single bond between atoms of the reactants, is rate controlling; the addition is then completed by formation of the second bond in a fast reaction. The intermediate in the second alternative may have either zwitterionic or diradical character.



It is now generally believed that most thermal Diels-Alder additions are concerted. A major factor bringing about acceptance of this view has been the high stereo-selectivity of the reactions, although a two-step mechanism is not entirely ruled out by this evidence if rotation about carbon-carbon single bonds in the "intermediate" is slow compared with the rate of ring closure. In this connection it is noteworthy that cyclo-addition of cis- and trans-1,2-dichloroethylene to cyclopentadiene is completely stereospecific. A two-step mechanism would have given the diradicals (1) and (2) which might have been expected to be long-lived enough to undergo some interconversion, resulting in a mixture of products.



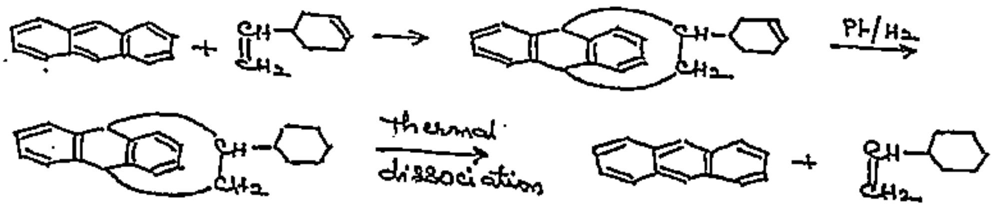
Addition of dichlorodifluoroethylene to cis,cis- and trans,trans-2,4-hexadiene, which certainly proceeds by a two-step mechanism with a biradical intermediate, is not stereospecific because the rate of rotation about a carbon-carbon single bond in the intermediate (3) is comparable with the rate of ring closure.



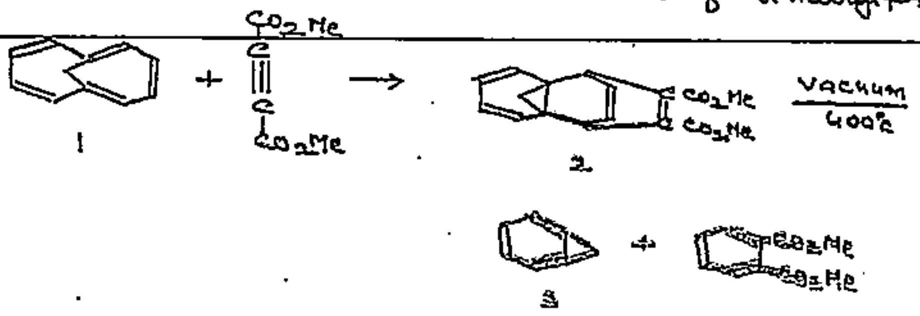
(VII) The retro Diels-Alder reaction

Diels-Alder reactions are reversible, and on heating many adducts dissociate into their components, sometimes under quite mild conditions.

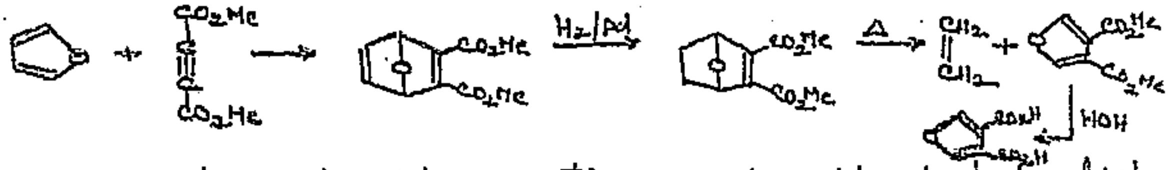
1. More interesting are reactions in which the original adduct is modified chemically and subsequently dissociated to yield a new diene or dienophile. Thus, catalytic hydrogenation of the adduct obtained from 4-vinylcyclohexene and anthracene followed by thermal dissociation affords vinylcyclohexane, whereas direct hydrogenation of vinylcyclohexene itself results in reduction of both double bonds. In this case adduct formation has been used to protect one of the double bonds of the vinylcyclohexene.



2. It is not always the bonds formed in the original diene addition which are broken in the retro reaction. A reaction of this kind was used in an ingenious synthesis of benzocyclopropene (3). Addition of methylacetylene dicarboxylate to 1,6-methanocyclodecapentaene (1) afforded the adduct (2) from which benzocyclopropene was obtained in 45% yield on pyrolysis at 400°c, with elimination of dimethylphthalate.



3. In another example furan-3,4-dicarboxylic acid was readily prepared by decomposition of the hydrogenated adduct from furan and acetylene dicarboxylic ester.

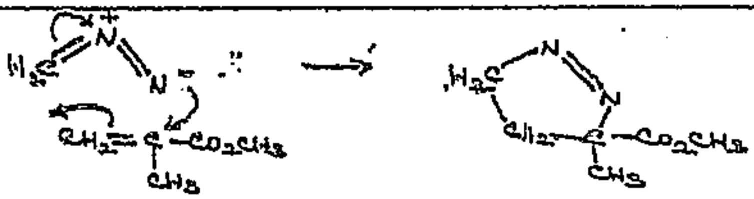


Most retro Diels-Alder reactions are brought about by heat, but some photo-induced reactions have been observed.

6. 1,3-Dipolar cycloaddition Reactions

Closely related to the Diels-Alder and ene reactions are the so called 1,3-dipolar cycloaddition reactions. These also are 6 π-electron pericyclic reactions, but here the 4 π-electron component, called the 1,3-dipole, is a three atom system a b c containing at least one hetero-atom and represented by a zwitter ionic octet structure, and the two π-electron component, here called the dipolarophile, is a compound containing a double or triple bond.

A typical example is the well-known reaction between diazomethane, the 1,3-dipole, and an α,β-unsaturated ester to form a pyrazoline



A considerable number of 1,3-dipoles containing various combinations of carbon and heteroatoms is theoretically possible and many of these have been made and their reactions with dipolarophiles studied. Some of the more commonly encountered classes among those containing C, O and N are given below.

$HC\equiv\overset{+}{N}-\overset{-}{C}H_2$ Nitrile ylides

$HC\equiv\overset{+}{N}-\overset{-}{N}H$ Nitrile imines

$HC\equiv\overset{+}{N}-\overset{-}{O}$ Nitrile oxides

$H_2C=\overset{+}{N}=\overset{-}{N}$ Diazoalkanes

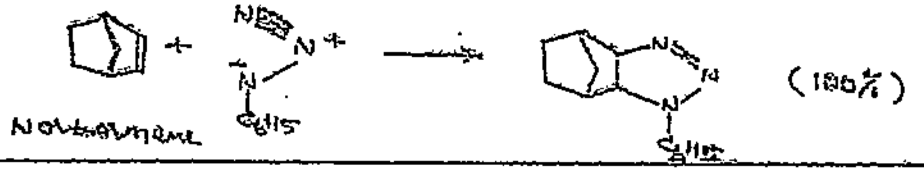
$HN=\overset{+}{N}=\overset{-}{N}$ Azides

$R'CH=\overset{R}{\overset{|}{\overset{+}{N}}}-\overset{-}{O}$ Nitrones

Applications

1. 1,3-Dipolar cycloadditions provide a versatile route to a wide variety of five-membered heterocyclic compounds. In most reactions the 1,3-dipole is not isolated but generated in situ in presence of the dipolarophile. In many cases the dipolarophile is an alkene or an alkyne but this is not essential and dipolarophiles containing hetero-multiple bonds have also been used, for example, imines, nitriles and carbonyl compounds

The most widely studied reaction of the addition of phenyl azides is to prepare strained bicyclo[2.2.1]heptane derivatives. Addition of phenyl azides to norbornene or norbornadiene leads to triazoline derivatives.

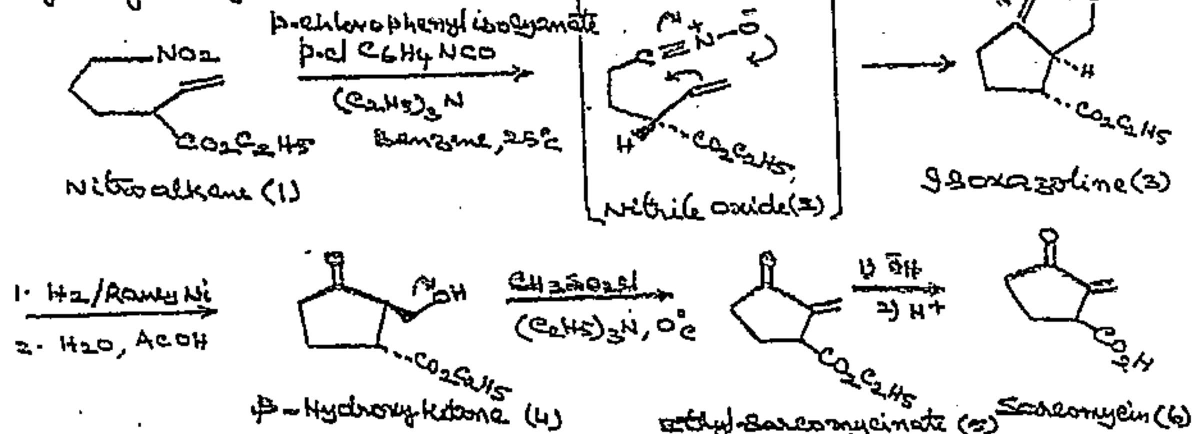


(100%)

(100%)

2. Intramolecular reactions take place readily and some of the most useful applications of 1,3-dipolar cycloadditions

in synthesis have involved reactions of this kind. This is nicely illustrated in a recent synthesis of the antitumour agent sarcomycin. Dehydration of the nitroalkene (1) gave the isoxazoline (3) directly in 55% yield by way of the nitrile oxide (2). Hydrogenolysis with Raney nickel in aqueous acetic acid then led to the β-hydroxy ketone (4) which by dehydration gave (5) and thence sarcomycin (6) by hydrolysis.



Nitroalkane (1)
Nitrile oxide (2)
Isoxazoline (3)
β-Hydroxy ketone (4)
ethyl sarcomycinate (5)
Sarcomycin (6)

Stereochemistry and Mechanism

Like Diels-Alder reaction, 1,3-dipolar cycloaddition reactions are both regio-and stereo-selective, features which enhance their synthetic usefulness. Thus, although reaction of an unsymmetrical 1,3-dipole with an unsymmetrical dipolarophile could apparently give two products, in general, one is formed predominantly or even exclusively, and in the reactions with geometrically isomeric alkenes the "cis rule" holds, that is the steric disposition of the substituents about the double bond in the alkene is retained in the adduct.

~~There has been some~~ controversy about the mechanism of 1,3-dipolar cycloaddition reactions. But it is now generally agreed that, like the Diels-Alder reaction they are concerted 6 π-electron reactions and take place through a five-membered cyclic transition state in which the two components approach each other in parallel planes. This view is supported by the relative insensitivity of the reactions to solvent polarity, and by ~~their stereoselectivity~~.

Paper-II: Organic Synthesis & Reaction Mechanisms-II

UNIT - II

4. Organic Synthesis : The Disconnection Approach

1. Technical Terms for the Disconnection Approach

1. Target Molecule (TM) : The molecule to be synthesised

2. Analysis or Retrosynthetic Analysis : The process of breaking down a T.M. into available starting materials by Functional Group Interconversion (FGI) and disconnection.

3. Functional Group Interconversion (FGI) : The process of converting one functional group into another by substitution, addition, elimination, oxidation, or reduction, and the reverse operation used in analysis.

4. Disconnection : The reverse operation to a reaction. The imagined cleavage of a bond to 'break' the molecule into possible starting materials.

5. $\Longrightarrow$: Symbol for disconnection or FGI

6. ∼ : The curved line drawn through the bond being broken.

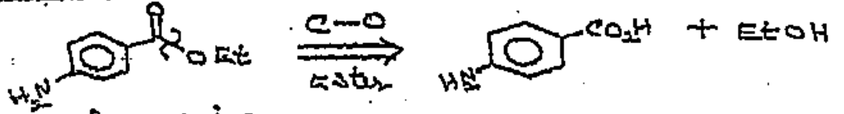
7. Synthon : An idealised fragment, usually a cation or an anion resulting from a disconnection. May or may not be an intermediate in the corresponding reaction.

8. Synthetic equivalent : A reagent carrying out the function of a synthon which cannot itself be used, often because it is too unstable. Thus CH_3I is the reagent for the CH_3^+ synthon.

2. Disconnection and FGI

Disconnections are the reverse of synthetic steps or reactions and we disconnect only when we have a reliable reaction in mind. In designing a synthesis of the local anaesthetic benzocaine we know that esters are made from alcohols and acids, so we can write a C—O disconnection. Usually, disconnection will be labelled to show the reason for making them.

Benzocaine : Analysis-1

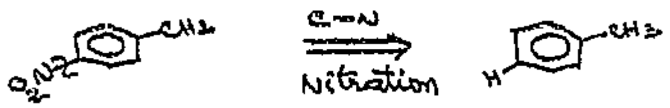


Benzocaine

We should now like to disconnect either CO_2H or NH_2 from the aromatic ring but we know of no good reactions corresponding to these disconnections. We must therefore first do functional group interconversion (FGI) to change these functional groups into others which can be disconnected. Aromatic acids can be made by the oxidation of methyl groups, and amino groups by the reduction of nitro groups. We can write these as follows:

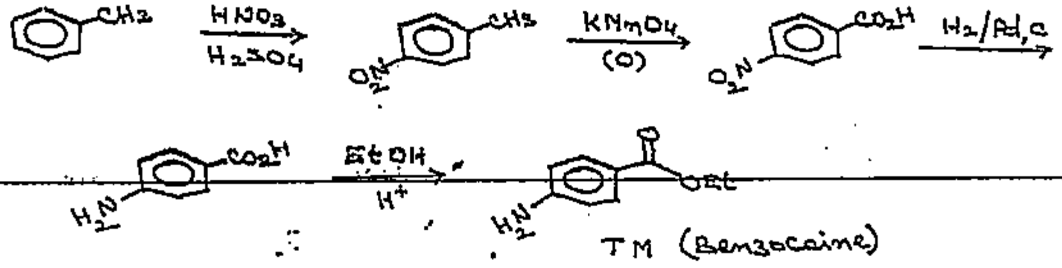
Analysis-2.

Now, disconnection of the nitro group is rational because we know that nitration of toluene occurs easily, and toluene is available.



This completes the analysis and we should now write out the synthesis with suggested reagents.

Synthesis

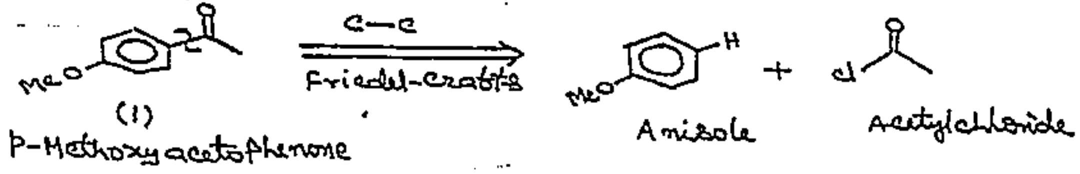


TM (Benzocaine)

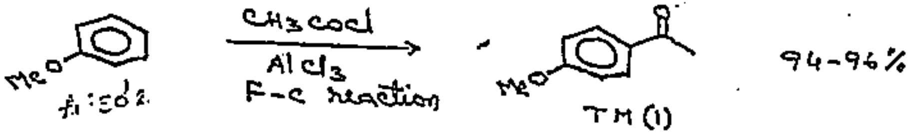
3. Synthons and Synthetic Equivalents

In designing a synthesis of the hawthorn blossom perfume compound (1) we can write a C–C disconnection corresponding to the Friedel-Crafts acylation reaction

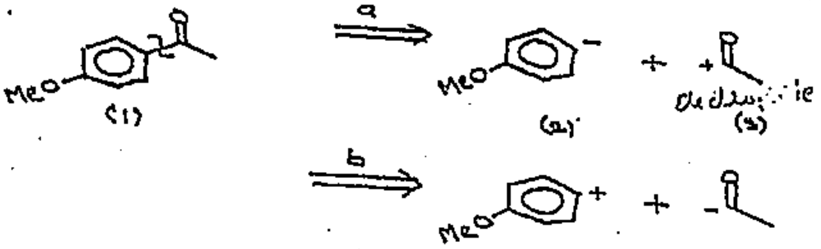
Analysis



Synthesis: The synthesis is one step from an available ether.

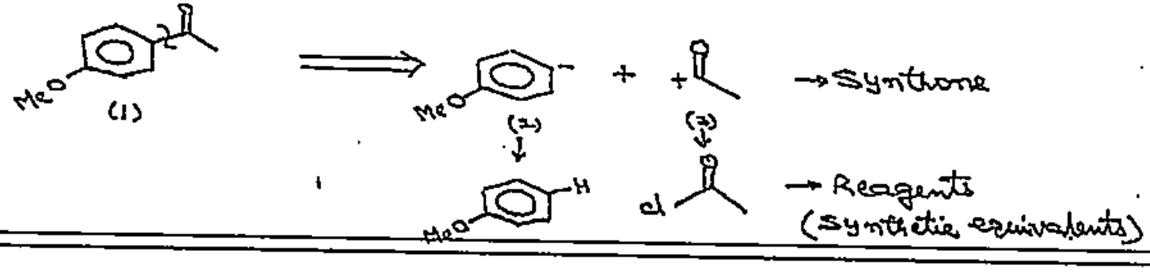


In this reaction the reagent which carries out the attack on the benzene ring is a cation, $CH_3C\ddot{O}^+$. When we disconnect a bond to an aromatic ring we normally expect this type of reaction and so we can choose not only which bond to break but which way, electronically, to break it. Here we write (a) and not (b) because the aromatic ring behaves as the nucleophile and the acid chloride as the electrophile.

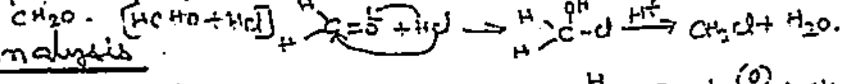


[illegible]

These fragments (2) and (3) are synthons – that is idealised fragments which may or may not be involved in the reaction but which help us to work out which reagents to use. Here, as it happens, (3), but not (2) is an intermediate in the synthesis. When the analysis is complete, the synthons must be replaced by reagents (synthetic equivalents) for practical use. For an anionic synthon, the reagent is often the corresponding hydrocarbon: for a cationic synthon, the reagent is often the corresponding halide.

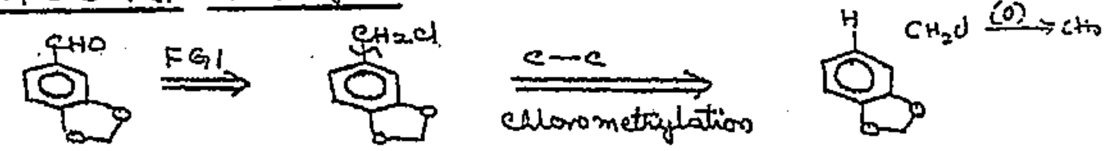


4. <u>Chloromethylation.</u> If we wish to add just one carbon atom, as in the synthesis of aromatic aldehydes, we cannot use HCOCl since it does not exist. one of the most reliable methods is chloromethylation with CH_2O and HCl giving a CH_2Cl group which can easily be oxidised to CHO (FGI). The important perfumary compound piperonal can be made this way.



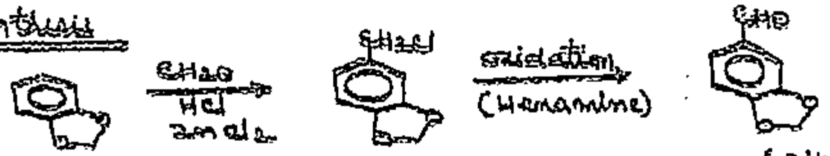
$CH_2O \cdot [HCHO + HCl] \quad \overset{H}{\underset{H}{>}}C{=}\ddot{O} + HCl \rightarrow \overset{H}{\underset{H}{>}}\overset{OH}{C}{-}Cl \xrightarrow{H^+} CH_2Cl + H_2O.$

Piperonal : Analysis



piperonal
(3,4-Methylenedioxybenzaldehyde)

Synthesis



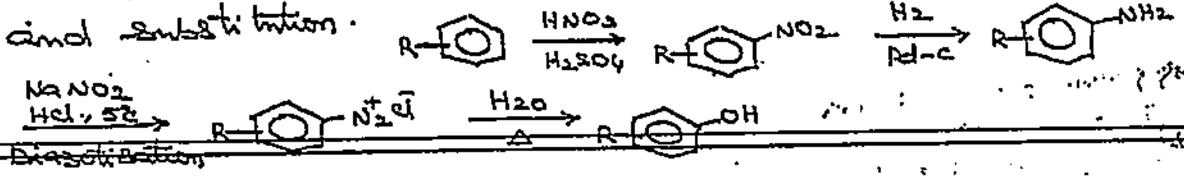
1,2-Methylenedioxybenzene

TM (Piperonal)

when heteroatoms are required, nitration gives the NO_2 group and halogenation puts in Cl or Br directly (OR and I are generally added by nucleophilic substitution). other side chains are best added by FGI on these products.

5. <u>Nucleophilic Aromatic Substitution</u>

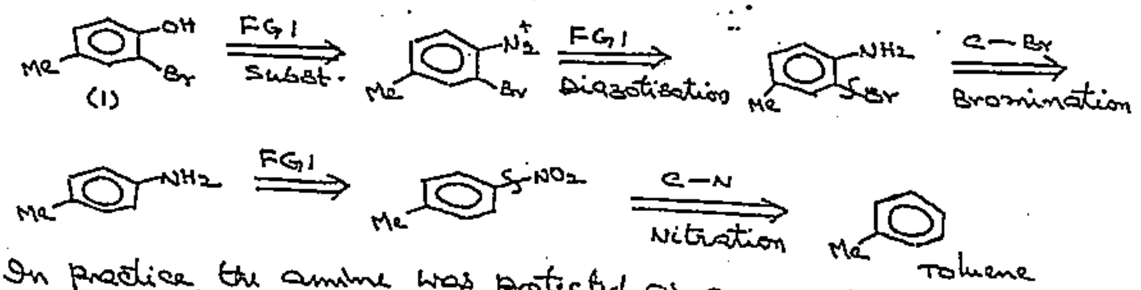
In nitration, acylation and chloromethylation reactions cationic synthons are added to the aromatic ring (electrophilic aromatic substitution). But suitable reagents are not available for the synthon $R{-}O^+$. If we wish to add an oxygen atom to an aromatic ring we must use the alternative approach, and add anionic reagents $R{-}O^-$ to an aromatic compound <u>with</u> a leaving group. This is nucleophilic aromatic substitution and works best when the leaving group is N_2 (diazonium salts). The synthetic sequence is nitration, Reduction, diazotisation and substitution.



Diazotisation

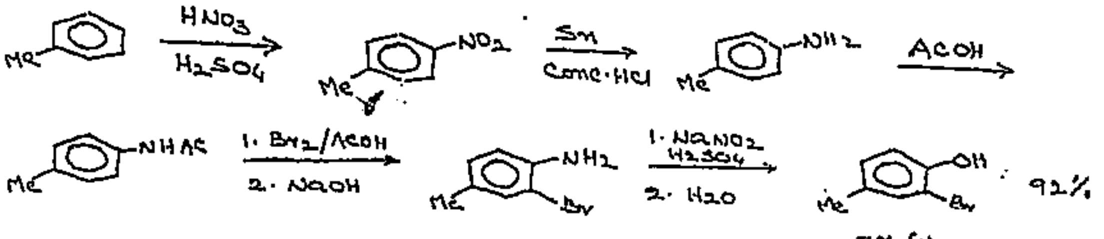
The synthesis of 2-bromo-4-methylphenol (1) can be analysed in this way, the -OH reverting to NO_2. The bromine could be added at the amine or the phenol stage, but the amine stage gives better control. NO_2 - OH [illegible] but Here OH & NO_2 [illegible]

Analysis



In practice, the amine was protected as an amide to prevent the bromine adding to the other orthoposition as well.

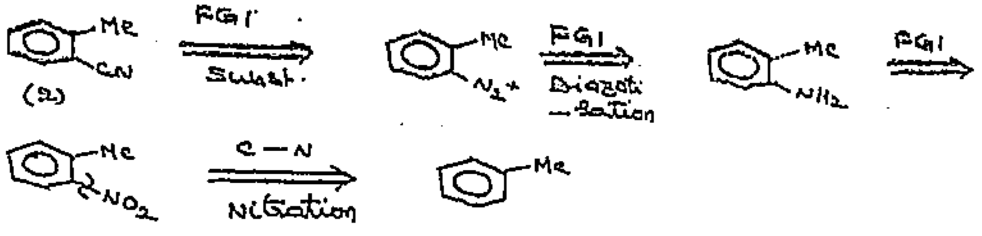
Synthesis [illegible] more reactive than benzene. B'coz CH_3 is [illegible]



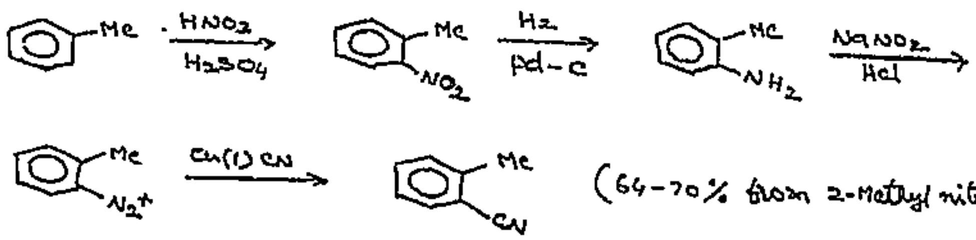
TM (1)

Some nucleophiles (CN^-, Cl^-, Br^- for example) are best added as Cu(I) derivatives. The aromatic cyanide (2) is most easily disconnected this way. CuCN. CuCl. [illegible]

Analysis



Synthesis



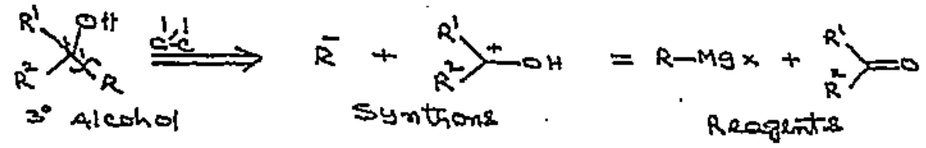
(64-70% from 2-Methyl nitrobenzene)

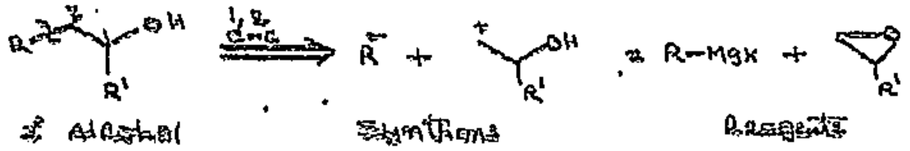
TM (2), 2-Methylphenyl cyanide

6. One-Group C—C Disconnections

(i) Alcohols

The C—C disconnections are more challenging because organic molecules contain many C—C bonds and we must learn which to disconnect. In one way they are easier than C—X disconnections. Reagents are available for both electrophilic (eg., R—Br) and nucleophilic (eg., R—MgBr) carbon whereas heteroatoms are almost always added as nucleophiles. The C—C disconnections in alcohols are shown below.

(a) 

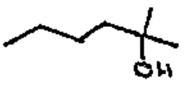
(b) 

These disconnections require organolithiums or Grignard reagents as reagents for the carbanion synthon $\bar{R}$.

Any alcohol can be disconnected at the C—C bond next to oxygen (a) to give an aldehyde or ketone and a Grignard reagent as starting materials. An epoxide route, (b) also works very well provided that the epoxide does not have too many substituents.

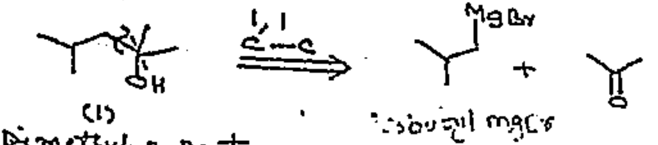
(1) Synthesis of alcohols with branched (1) and unbranched (2) side chains.


(1)

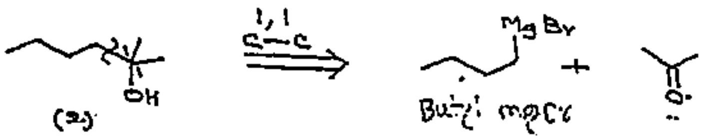

(2)

Disconnections of C—C bond next to the hydroxyl group (route reveals that both these compounds can be made from acetone and a Grignard reagent. Both the alkyl halides are commercially available, so the syntheses are trivial. The full method drawn out for TM (1), is usually summarised as drawn for TM (2).

Analysis

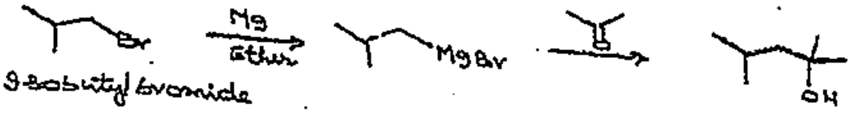


(1)
2,4-Dimethyl-2-pentanol

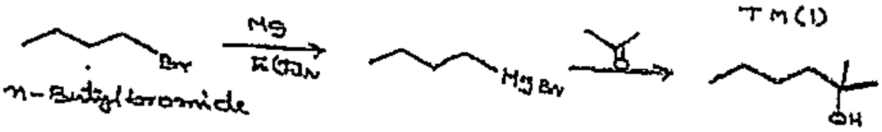


(2)
2-Methyl-2-hexanol

Synthesis



TM(1)

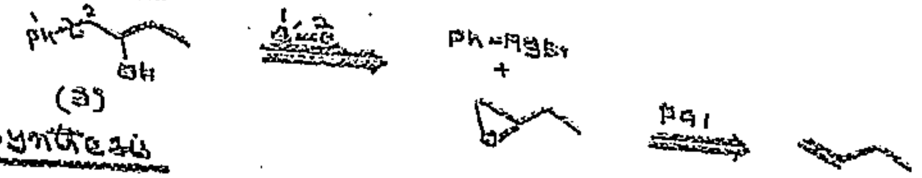


TM (2)

(2) Synthesis of 1-phenyl-2-butanol, (3)

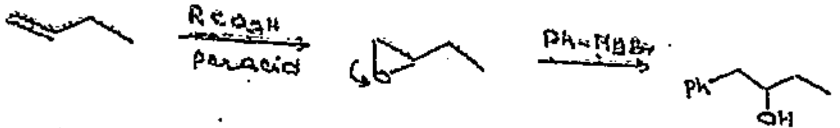
The alcohol (3), used in perfumery, can be made by epoxide route(6).

Analysis



(3)

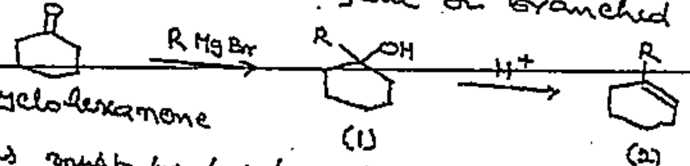
Synthesis



TM(3)

(II) Alkenes (olefins)

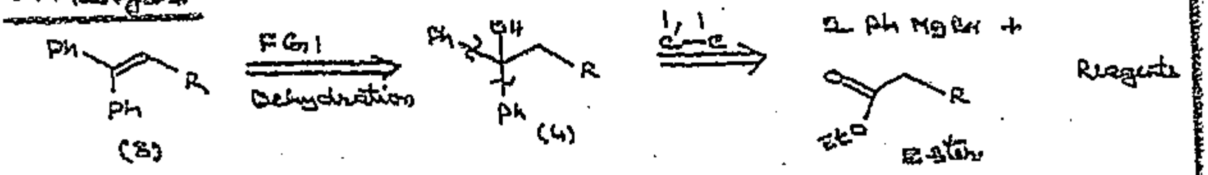
(1) Alkenes (olefins) can be made by the dehydration of alcohols (eg., 1), usually under acidic conditions. This route is particularly good for cyclic or branched olefins (e.g., 2)



Acids must be fairly strong for this job and must have a non-nucleophilic counter ion or substitution may occur. popular ones are KHSO4 (crystalline and easier to handle than H_2SO_4) and phosphoric acid, or less acidic $POCl_3$ in pyridine.

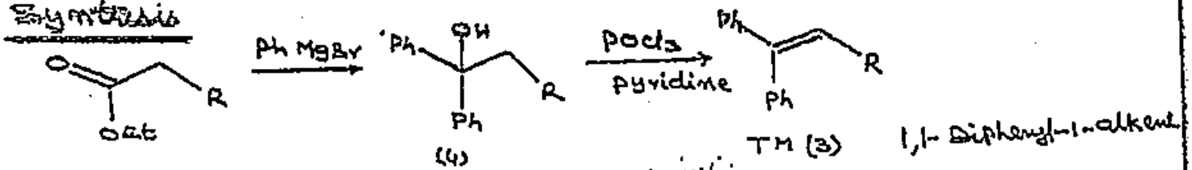
In the synthesis of alkenes of general structure (3), the OH group can be placed at either end of the double bond. putting OH at the branch point is better strategy as disconnection of the alcohol (4) then gives simpler starting materials.

Analysis



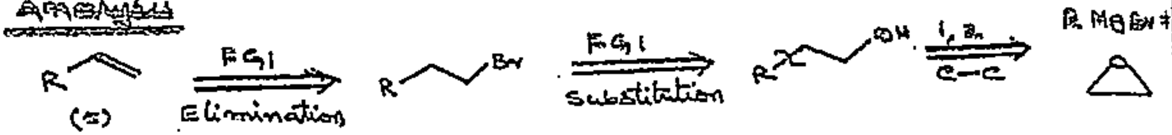
The dehydration of this tertiary alcohol (4) will be very rapid by an E_1 mechanism and there is no doubt about the position or geometry of the double bond.

Synthesis

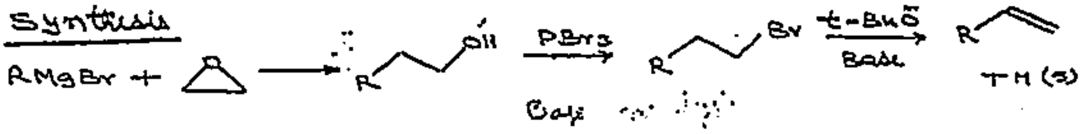


(2) Alkenes can also be acid [illegible] made by the dehydrohalogenation of alkyl halides. These elimination reactions follow essentially the same strategy used in the synthesis of alkenes from alcohols, because the alkyl halides are usually made from alcohols. Eliminations of primary groups are better done this way with base instead of acid catalysis.

Analysis



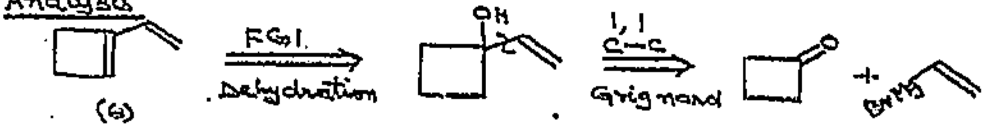
Synthesis



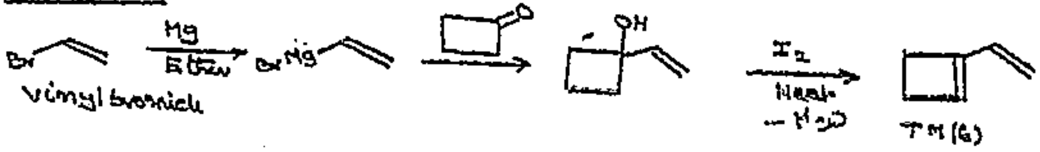
(3) Dienes can be made by this approach if vinyl Grignards are used because the vinyl group blocks dehydration in one direction and makes the reaction faster by E_1 as the

intermediate is an allylic cation. An interesting example is the four membered ring compound (6): it is to be noted that the OH group is again added at the branch point.

Analysis



Synthesis



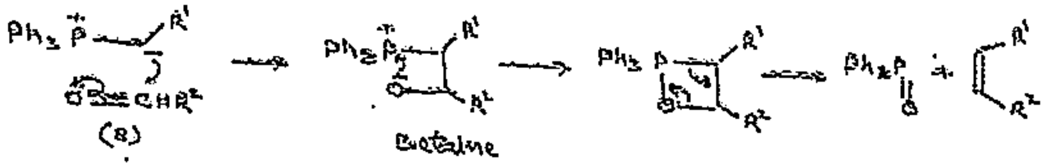
(4) The Wittig Reaction is a reaction between carbonyl compd. or ketone & phosphorus ylide – it gives alkene

The Wittig method gives total control over the position of the double bond and partial control over its geometry.

The Wittig Reagent : Phosphorous ylide. It is prepared as shown below.

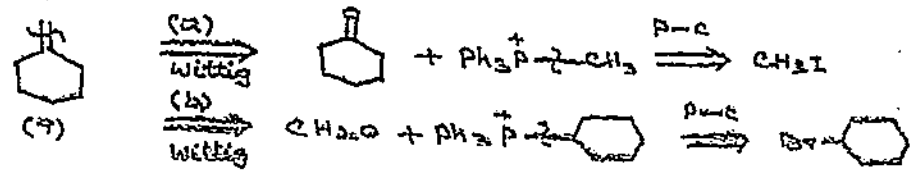
$$\underset{(7)}{R^1CH_2Br} \xrightarrow{PPh_3} Ph_3\overset{+}{P}-CH_2R^1 \xrightarrow[\text{NaH or } n\text{-}C_4H_9Li]{\text{Base}} \underset{\text{Phosphorus ylide}}{Ph_3\overset{+}{P}-\overset{-}{C}HR^1}$$

The Wittig Reaction

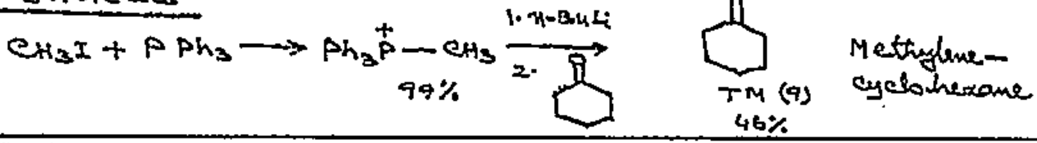


The Wittig reaction forms both σ and π bonds in one reaction, so the disconnection is at the double bond with a nearly free choice of which end comes from the alkyl halide (7) and which from the carbonyl compound (8). Hence the exo-olefin (9), all but impossible to make by elimination, is easily made by either Wittig route. Route (a) is perhaps easier as cyclohexanone is easier to handle than formaldehyde (a gas).

Analysis



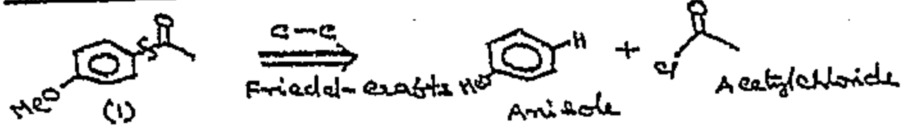
Synthesis



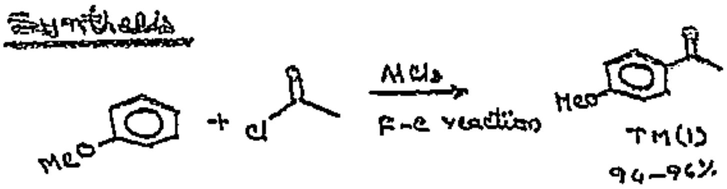
(III) Aryl ketones

Aryl ketones may be synthesised by the Friedel-Crafts acylation of aromatic rings. So the disconnection approach involves the aromatic disconnection corresponding to the Friedel-Crafts reaction. This would be used in the synthesis of the hawthorn blossom perfume compound (1). The synthesis is one step from an available ether.

Analysis



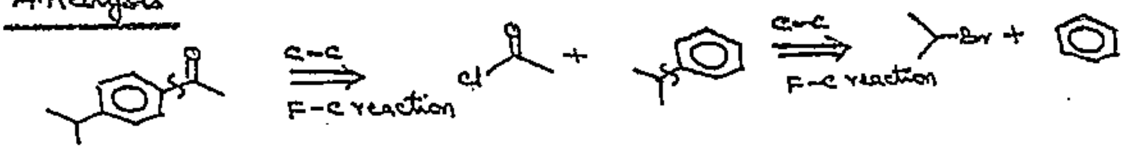
Synthesis



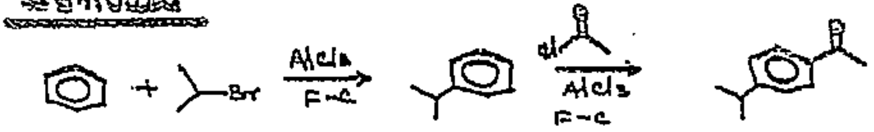
p-Methoxyacetophenone

Example-2. The analysis of the orris odour ketone (2) could be tackled by the following disconnections.

Analysis



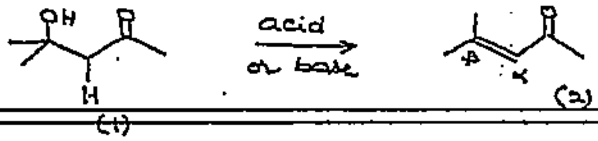
Synthesis



7 TWO-GROUP C–C DISCONNECTIONS

(1) α,β-Unsaturated carbonyl compounds

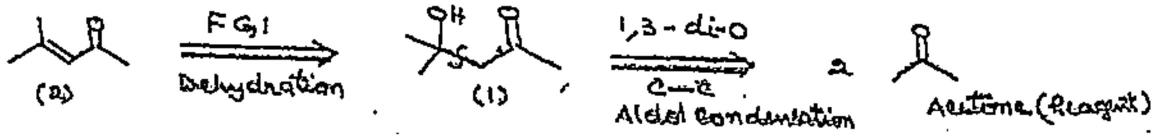
Dehydration of β-hydroxy carbonyl compounds is very easy because the proton to be removed (H in 1) is enolic and the product (2) is conjugated.



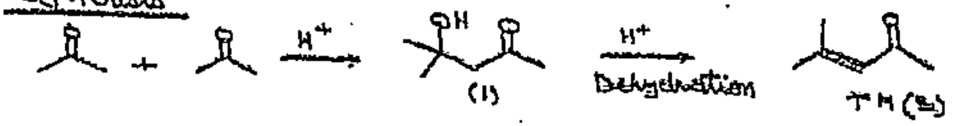
(2) 4-Methylpent-3-en-2-one
Mesityl oxide (An enone)

The full analysis of an enone or other α,β-unsaturated carbonyl compound should be an F.G.I followed by a 1,3-di-O disconnection.

Analysis



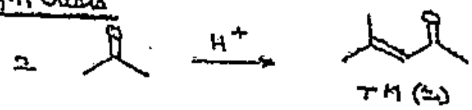
Synthesis



In practice, the dehydration often occurs during the condensation so that the intermediate (1) need not be isolated. We therefore usually write a short hand disconnection of the enone directly to the two carbonyl components:

Analysis

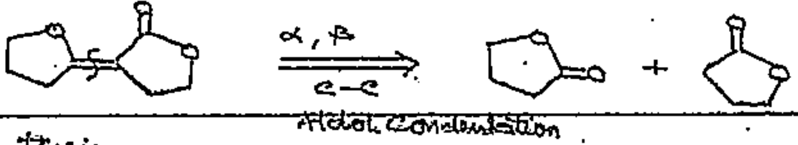
Synthesis



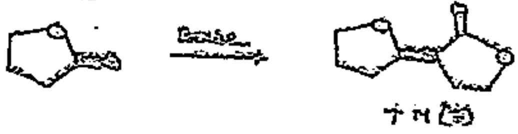
In this example, acid catalysis gave a good yield.

This is a very important disconnection and one should learn to look for it in unlikely places, eg.(3). Simply disconnect the double bond and write a carbonyl group at the β-atom. In this case we get two identical lactones and the reaction can be carried out in base.

Analysis

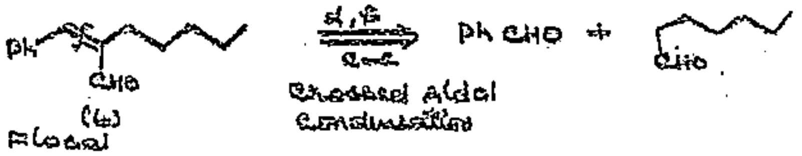


Synthesis



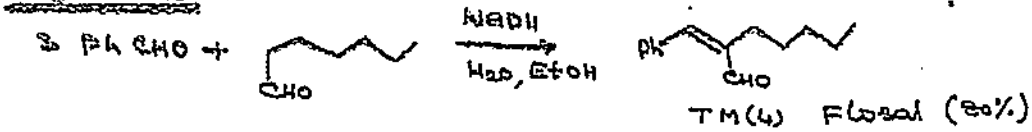
The famous French perfume ingredient Floral (4) is an enal and can be disconnected in this way.

Analysis



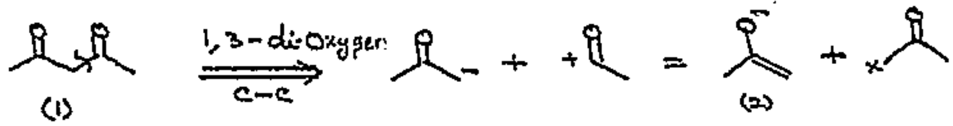
The synthesis is carried out in base with a large excess of benzaldehyde to minimise self condensation of the aliphatic aldehyde.

Synthesis



(II) 1,3-Dicarbonyl compounds

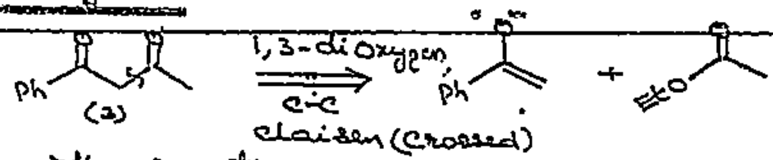
Direct disconnection of 1,3-dicarbonyl compounds is possible at two oxidation levels.



Disconnection (1) means that we are looking for a reaction which is the acylation of an enolate anion (2). This is possible with esters (X = OR) or acid chlorides (X = Cl)

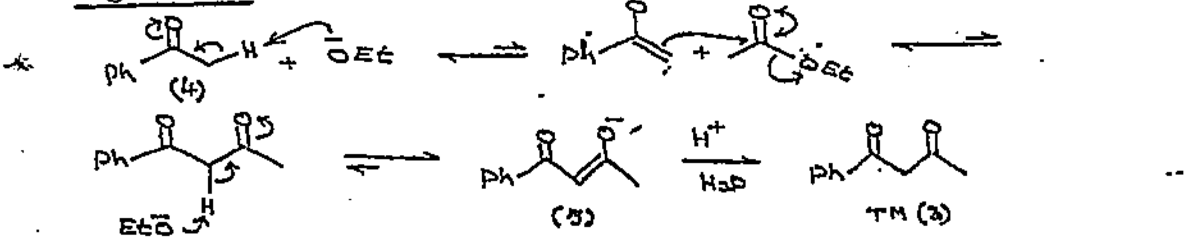
Example-1. The perfumary compound (3) can be disconnected to the enolate of a ketone and an ester.

Analysis



The reaction can be carried out by combining Ketone (4) with the ester and a base strong enough to produce only a small concentration of the enolate, often EtO^-. The reaction is therefore an equilibrium and it is driven over by formation of the stable delocalised enolate (5) of the product. Acid work-up then releases TM (3). This last step applies to all reactions of this sort but is not usually written down.

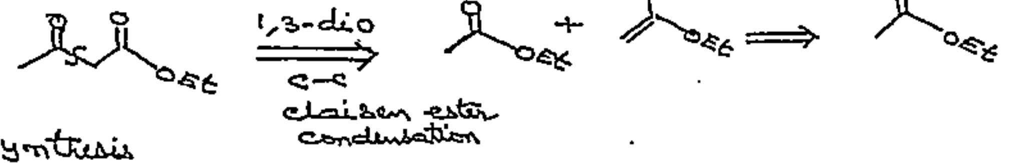
Synthesis



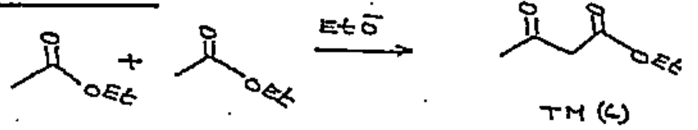
This synthesis was carried out by Claisen and the reaction is known as Claisen condensation

Example-2. Ethyl acetoacetate (6) is also made this way. This time the starting materials are two molecules of the same compound, ethyl acetate. The synthesis, known as the Claisen ester condensation, simply involves treating ethyl acetate with base.

Analysis



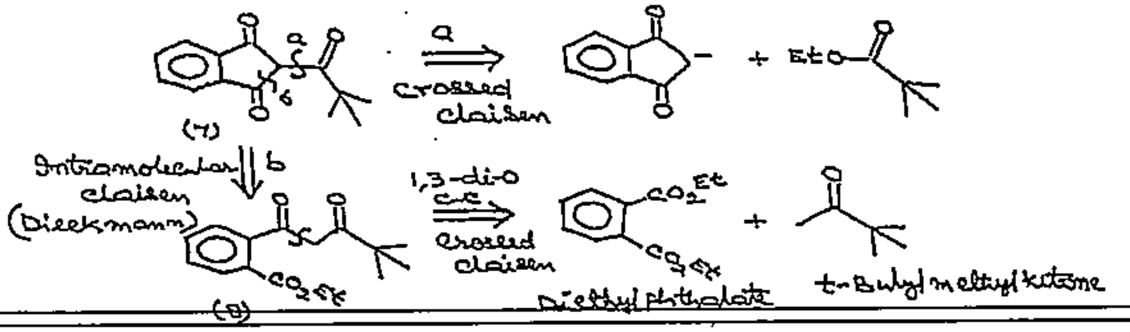
Synthesis



TM (6)
60%

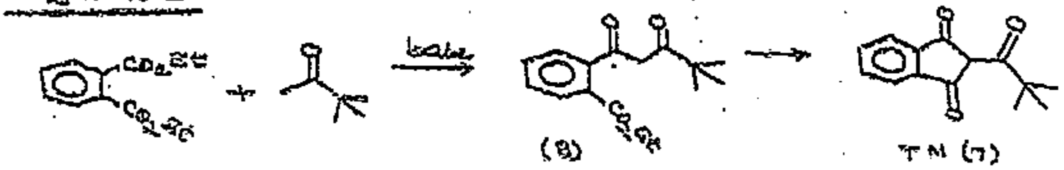
Example-3. Pival (7) is a rat poison with three ketone groups each having a 1,3-relationship to the others. Of the two possible disconnections, (b) quickly leads back to available starting materials.

Analysis



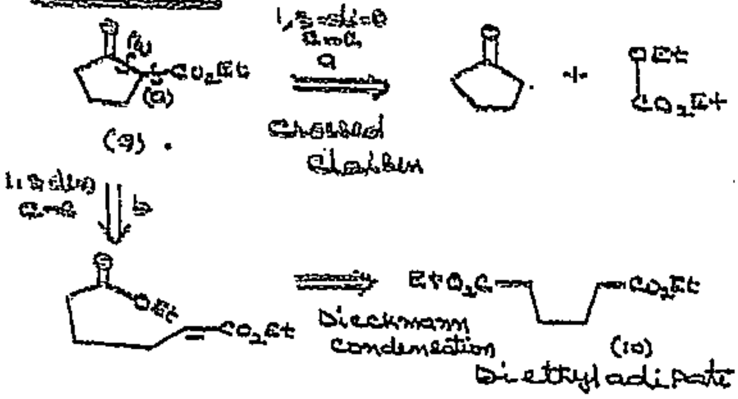
The synthesis, as so often when a cyclisation is involved, is easier than expected as (8) cyclises to (7) under the conditions of its formation.

Synthesis



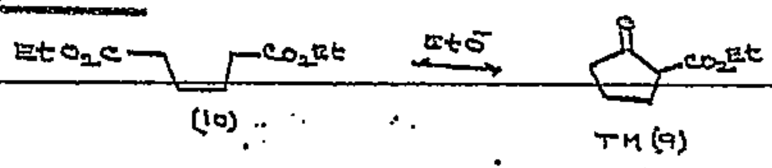
Example-4. The important keto ester (9) can be disconnected in two ways. One (a) removes only one carbon atom and is bad strategy but the other (b) gives the symmetrical and readily available diester (10) as starting material.

Analysis



The reaction is intramolecular and hence fast and clean. Compound (9) is thus readily available and is used as a starting material for other five membered rings.

Synthesis



Paper-II: Organic Synthesis & Reaction Mechanisms-II

UNIT - III

V.R.S. & Y.R.N. COLLEGE: CHIRALA

M.Sc. (Final) Organic Chemistry, Semester – IV

Paper – II, Organic Synthesis & Mechanisms – II

UNIT – ~~IV~~ III

Organic Photochemistry

Organic photochemistry is the chemistry of electronic excited states of organic molecules, which are generated by excitation of organic compounds using appropriate wavelengths of light in the ultraviolet or visible regions of the spectrum. Excited states of organic molecules exist with either paired (singlet) or unpaired (triplet) electron spins, and these states have different physical properties (e.g., energies, lifetimes, and molecular geometries) and different chemical reactivities. These reactivities are very different from the reactivity of the compound in its ground state. Chemical reactions of electronic excited states must be extremely fast to compete with rapid deactivation of excited states by inherently fast radiative (fluorescence and phosphorescence) and nonradiative pathways (internal conversion and intersystem crossings). Typical reactions include isomerization around carbon – carbon double bonds, molecular rearrangements and fragmentations, intra- and intermolecular hydrogen abstraction, cycloadditions, and dimerization.

Laws of Photochemistry

There are three laws which govern the effect of radiation on chemical reactions. These laws are:

1. Grotthuss – Draper law: It may be stated as follows: "When light falls on any substance, only the fraction of incident light which is absorbed by the substance can bring

about a chemical change; reflected and transmitted light do not produce any such effect."

It is important to remark that all light radiations which are absorbed by reacting systems are not effective in producing desired chemical reactions. When conditions are not favourable for the molecules to react, some portion of the whole light absorbed by reacting substances is converted into heat in some cases. while in some other cases, the absorbed light is reemitted as radiations of the same or another frequency.

2. Law of photochemical Equivalence: In 1905, Einstein applied quantum theory to photochemical reactions and enunciated the law of photochemical equivalence which states that: "When an atom or molecule absorbs light of a given frequency, it absorbs one quantum only"

3. In 1912, Einstein restated his law as:
"Each molecule which takes part in a chemical reaction absorbs one quantum of light which induces the reaction" or briefly "one molecule one quantum"

The term one quantum (or one photon) means energy equal to $h\nu$, where h is Planck's constant and ν is the frequency of radiation. $AB + h\nu \rightarrow AB^*$

Thus, in the primary process, the number of molecules that are activated is equal to the number of quanta absorbed. Therefore, amount of energy E, for activation of 1 mole will be $Nh\nu$, where N is the Avogadro's number and is equal to 1 mole, i.e., $E = Nh\nu = Nh\frac{c}{\lambda}$

This quantity of energy 'E' absorbed per mole of the substance is called an Einstein.

Substituting the values in the above equation

$$E = \frac{6.02\times10^{23}\,(6.63\times10^{-27})\,(3\times10^{10})\times10^{7}}{4.184\times10^{7}\ \lambda\,(nm)}\ \text{cal./mol.}$$

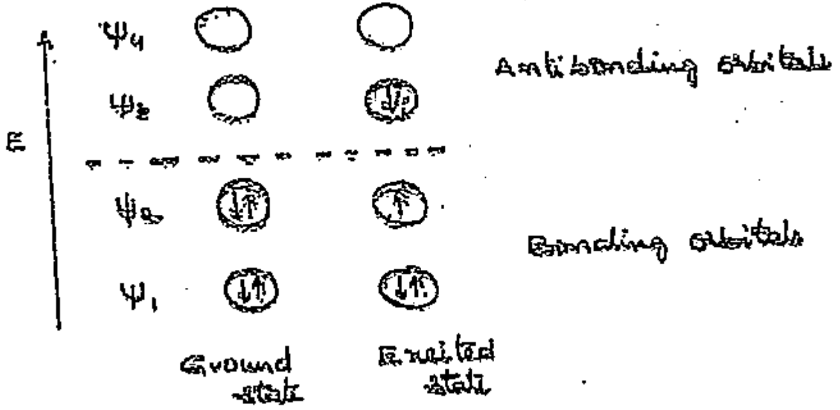
$$= \frac{2.86\times10^{4}}{\lambda\,(nm)}\ \text{k.cal./mol.}$$

Radiations in the infrared region of the spectrum correspond to 1–10 k.cal/mole of energy which is capable of producing only vibrationally or rotationally excited molecules. On the other hand, light in the visible and ultraviolet region has sufficient energy to cover the range of chemical bond energies and is often able to induce chemical changes by exciting molecules to higher electronic states. The energy of visible light varies from 38 k.cal/mole (750 nm) to 71 k.cal/mole (400 nm), whereas ultraviolet light is still more effective as it provides energy upto 143 k.cal/mole (200 nm).

Electronic Excitation

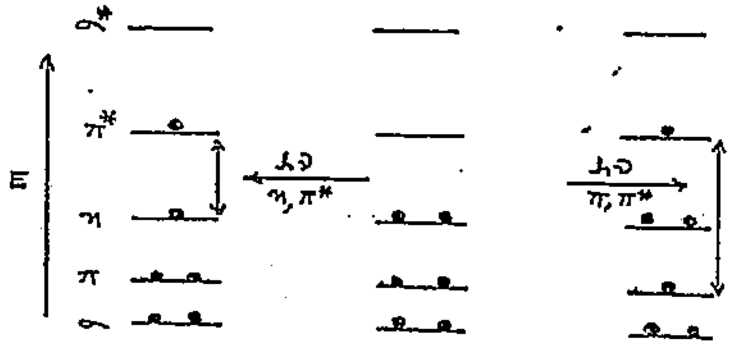
The absorption of light energy by molecules in the visible and ultraviolet region involves promotion of an electron from the bonding orbital to the corresponding antibonding orbital. The antibonding orbitals corresponding to σ and π bonds are called σ^* (sigma starred) and π^* (pi starred) respectively. As the nonbonding electrons (n) are not involved in the bond formation, there are no anti-bonding orbitals corresponding to them. Excitation promotes a nonbonding electron either to a σ^* or a π^*

We have the following types of electronic transitions involved in the visible and ultraviolet regions: σ, σ^*; n, σ^*; n, π^*; and π, π^*. The energies required for σ, σ^* and $n\ \sigma^*$ transitions are usually very high, requiring a wavelength of far less than 200 nm (~ 180 nm). Although photochemical excitation may be effected using such light, this is relatively less common because strong absorption by atmospheric oxygen below 200 nm creates complications and hence irradiation must be done in vacuum. Butadiene provides a typical example of a π, π^* transition in which an electron is promoted from ψ_2 (bonding orbital) to ψ_3 (anti bonding orbital) on excitation. The molecular orbital description of the process is given in the following figure.



π, π^* Excitation of butadiene

By far the most interesting types of electronic excitation in organic molecules are the n, π^* and the π, π^* transitions. These transitions have lower energy requirements and occur at longer wavelengths. Both types may be illustrated with a saturated aldehyde or ketone which absorbs at two wavelengths, one around 285 nm and the other around 180 nm. The absorption at 285 nm is due to the excitation of an electron from the nonbonding orbital (n) to the lowest unoccupied π anti bonding orbital (π^*) and since this transition requires less energy than other electronic transitions (σ, σ^*; π, π^*, etc.), it occurs at the highest wavelength. The other absorption around 180 nm is attributed to the promotion of an electron from the π bonding orbital to the π^* antibonding orbital. Obviously it requires more energy than the n,π^* transition. The following figure schematically displays n,π^* and π,π^* transition energies in such a system.



4 excitations
σ,σ^*, π,π^* high excited state
n,σ^*, n,π^* lower excited state

Schematic molecular orbital diagram showing n,π^* and π,π^* transitions

For exciting a molecule, it must be irradiated with light in the region where it absorbs, and so it is helpful to determine the ultraviolet absorption spectrum before irradiation.

Antibonding $<^{\sigma}_{\pi}$
non bonding – n
Bonding $<^{\pi}_{\sigma}$

Excited states, Modes of dissipation of energy

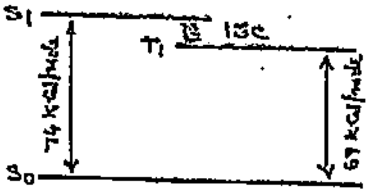
There are an even number of electrons in a typical organic molecule, and these electrons are usually paired in the ground state. Absorption of light of the correct energy occurs without spin inversion and so the electron spins remain paired in the excited state. This state is commonly called excited singlet state or S_1. However, in many cases, electronic excitation is followed by spin inversion thus giving rise to a new excited state with two unpaired electrons. This state is called an excited triplet state or T_1. Direct excitation of the ground state (S_0) to a triplet state is not possible and hence T_1 is invariably populated via S_1.

The terms singlet and triplet arise from the fact that singlet states do not split in a magnetic field, while triplet states have three possible energy states in an applied magnetic field. A triplet state is more stable than the corresponding excited singlet state because the two electrons do not get very close together in space when their spins are parallel and hence lesser inter-electronic repulsion is expected with unpaired than with paired electrons.

Let us now describe the major events that occur following light absorption by a molecule thus raising it to a higher electronic state, say from S_0 to S_2 (S_2 represents the higher vibrational level of the upper excited singlet state) in detail. The life time of upper excited singlet states is usually less than 10^{-11} second and they rapidly decay to the lowest level (S_1) by a process called 'internal conversion'. Decay of S_1 to S_0 may also occur but it is usually a slower process than decay from higher electronic singlet states (S_2 etc.) to S_1. Consequently, S_1 has the longest life ($\sim 10^{-8}$ s) of all the excited singlet states and is very important in photochemistry. S_1 may undergo one of the following four energy-degrading processes.

1. It may emit the energy as a photon and drop to S_0. This process is called 'fluorescence' and generally occurs within 10^{-9} to 10^{-6} s.
2. It may return to S_0 by nonradiative processes in which excess energy of the excited state is shuffled into vibrational modes.
3. S_1 may undergo chemical reactions, and
4. Its decay to a triplet state (T_1) may occur before any of the above processes takes place. This conversion of S_1 to T_1 is energetically gainful and is called 'inter-system crossing'.

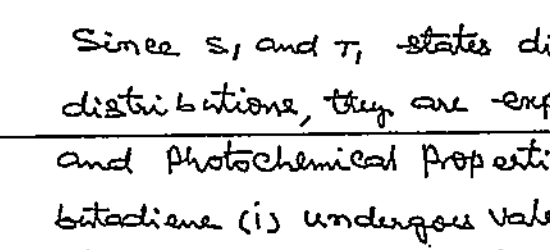
Inter-system crossing is a very important phenomenon in photochemistry as T_1 exists for a much longer period of time (10^{-3} to 1 s) than a singlet state and, therefore, photochemical reactions are favoured by the longer life of the T_1 state. Inter-system crossing is more efficient in the molecules where the energy gap between S_1 and T_1 is rather small. A typical example is benzophenone. In this case intersystem crossing has 100% efficiency because of the small energy gap (5 K·cal/mole)



Intersystem crossing in benzophenone

Olefins have a lower tendency to intersystem crossing due to the high energy gap (50–60 K·cal/mole) between the two states.

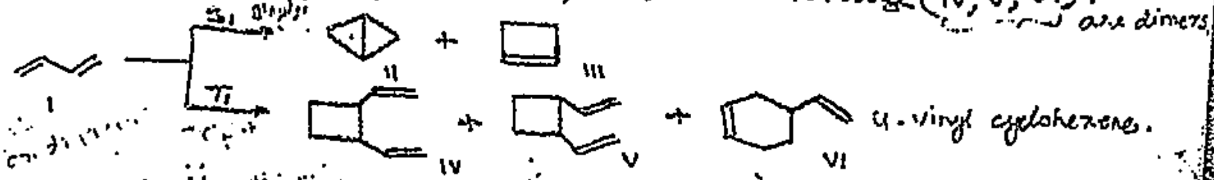
Let us now describe probable paths for T_1 states. A T_1 state may not be converted to S_1 again since T_1 is of lower energy. However, it may either undergo a chemical reaction or may return to the ground state (S_0) by emission of a photon, a process known as 'phosphorescence'. The lifetime of phosphorescence is usually in the range of 10^{-3} to 10 s. The third alternative for the triplet state is to return to S_0 by radiationless decay. All these consequences of the absorption of light are summarized in the following figure.



ISC = Intersystem crossing
IC = Internal conversion
F = Fluorescence
P = Phosphorescence
RD = Radiationless decay
— = Transition with absorption or emission of radiation
∿∿ = Non-radiative transitions.

Since S_1 and T_1 states differ in energy contents and electronic distributions, they are expected to possess different chemical and photochemical properties. For example the S_1 state of butadiene (I) undergoes valence isomerization (II, III) while the T_1 state, attained by energy transfer, prefers to dimerize (IV, V, VI).

are dimers



Energy Transfer

We have referred to energy transfer as a means of populating the T_1 state. Energy transfer refers specially to the one step radiationless transfer of excitation energy from an electronically excited molecule (donor) to the ground state of another molecule (acceptor). Depending upon the multiplicity (singlet or triplet state) of the donor molecule, there may be a triplet – triplet or a singlet – singlet energy transfer. However, the life time of S_1 is short compared to that of T_1 and hence there is greater probability of energy transfer through a triplet state.

A typical mechanism for triplet energy transfer involves the excitation to S_1 of donor molecule on irradiation, and the subsequent decay of S_1 to T_1. Collision of the T_1 donor with the ground state acceptor molecule produces a T_1 acceptor and ground state donor molecule.

$D \xrightarrow{h\nu} {}^1D$
${}^1D \xrightarrow{ISC} {}^3D$ Triplet state donor
$A + {}^3D \xrightarrow{collision} {}^3A + D$
${}^3A \longrightarrow$ Products

D = Donor
A = Acceptor
1 = Singlet
3 = Triplet

Let we consider the specific example of butadiene, a molecule which possesses a sufficiently low triplet energy (E_T = 60 K.cal/mole) to be an excellent triplet acceptor. In practice, the only way to generate the T_1 state of butadiene is through energy transfer by a triplet donor. Absorption of light by butadiene is negligible above 250 nm and so no photochemistry is to be expected under such conditions. However, when it is mixed with benzophenone and irradiated at 366 nm, which is a region where benzophenone absorbs appreciable amount of light, butadiene undergoes a change to yield dimers, IV, V & VI.

$E = \frac{2.26 \times 10^4}{\lambda (nm)}$ K.cal

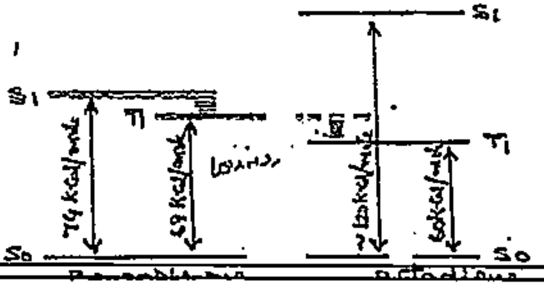


Fig. The mechanism of energy transfer.

Apparently, the light is being absorbed by benzophenone while the reaction is taking place with butadiene, or in other words, benzophenone is acting as a photosensitizer. Benzophenone absorbs light at about 366 nm and is excited to its S_1 state which is then transferred to T_1 state by inter-system crossing. When the benzophenone triplet collides with butadiene, a triplet energy transfer occurs resulting in the formation of the triplet state of butadiene which then reacts to produce dimers. Triplet energy transfer is possible here only because the triplet state of butadiene is of lower energy than that of benzophenone.

Butadiene has lower energy level than the [illegible] 69 > 60 k.c.

1. Photochemistry of olefins

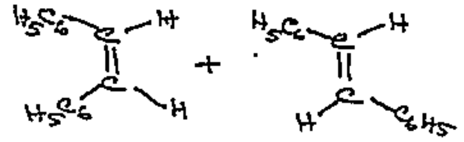
The photochemistry of olefins involves only two types of electronic excitations: σ,σ^* and π,π^*. Promotion of an electron from σ to σ^* requires more energy (available only from the light of wavelength lower than 150 nm) and hence difficult to achieve under usual experimental conditions. The $\pi\text{-}\pi^*$ excitation, on the other hand, is experimentally accessible as it requires the absorption of light of about 180-210 nm for nonconjugated olefins and of about 220 nm or more for the conjugated olefins. The initial excitation (π, π^*) usually occurs with no change in multiplicity and so a singlet excited state is obtained. The singlet excited state of olefins has less tendency to inter-system crossing and they themselves are capable of initiating many photochemical reactions. However, the T_1 states of olefins are conveniently generated by intermolecular energy transfer from a triplet donor to an olefin molecule. More often, the photochemistry of singlet excited state of an olefin differs considerably from that of its triplet state.

cis-trans isomerizations

Olefins usually undergo cis-trans isomerizations upon irradiation with ultraviolet light. The transformation can be effected by direct irradiation of the olefins or by irradiation in the presence of a sensitizer, and it may either take place through a singlet or a triplet excited species. It is, however, known that isomerization in the triplet state possesses a lower barrier to rotation around the carbon-carbon bond. Triplets are frequently involved since simple olefins absorb light at about 200 nm and experimentally it is more convenient to sensitize these reactions by using a triplet donor which usually absorbs at longer wavelengths.

The photoisomerization of the stilbenes is probably the most completely understood process of this type. Direct irradiation of solutions of either cis- or trans-stilbene (1) yields a constant mixture containing 93% cis-stilbene and 7% trans-stilbene.

$$\underset{(1)}{C_6H_5\,CH=CH\,C_6H_5} \xrightarrow{h\nu}$$



Initial absorption of light by either of these isomers is rapidly followed by intersystem crossing to the respective triplet states. Photoisomerization then occurs via interconversion or probably via a common triplet intermediate.

$$\left.\begin{array}{l}\text{cis-stilbene}\\ \text{trans-stilbene}\end{array}\right] \xrightarrow{h\nu} \begin{array}{l}{}^1[\text{cis-stilbene}] \longrightarrow {}^3[\text{cis-stilbene}]\\ {}^1[\text{trans-stilbene}] \quad\; {}^3[\text{trans-stilbene}]\end{array}$$

$$\equiv {}^3[C_6H_5CH\overset{\dots}{=}CH\,C_6H_5] \longrightarrow \underset{93\%}{\text{cis-stilbene}} + \underset{7\%}{\text{trans-stilbene}}$$

Photoisomerization of stilbene can be sensitized by an excited triplet molecule having more triplet energy than cis- (50 k.cal/mole) and trans-stilbene (57 k.cal/mole). Energy transfer from T_1 of the donor to either stilbene generates the corresponding stilbene triplet state which either interconverts to the triplet of the other isomer or goes to a common triplet intermediate and in either case final decay to the ground state isomer occurs. Thus the benzophenone sensitized process may be depicted in following steps:

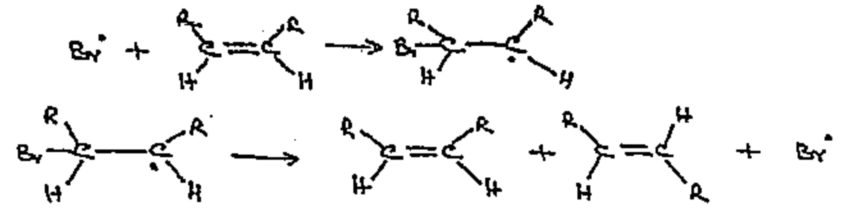
$(C_6H_5)_2CO \xrightarrow{h\nu} {}^1[(C_6H_5)_2CO] \longrightarrow {}^3[(C_6H_5)_2CO]$

$\left.\begin{array}{l}\text{cis-stilbene}\\ \text{trans-stilbene}\end{array}\right] + {}^3[(C_6H_5)_2CO] \longrightarrow {}^3[C_6H_5\,CH{=}CH\,C_6H_5] + (C_6H_5)_2CO$

${}^3[C_6H_5\,CH{=}CH\,C_6H_5] \longrightarrow \underset{93\%}{\text{cis-stilbene}} + \underset{7\%}{\text{trans-stilbene}}$

Sometimes photochemical cis-trans isomerization may take place in the presence of halogens. It appears that under these conditions there is a photochemical production of halogen atoms which add to the olefin yielding a radical. Elimination of the halogen atom from this radical yields a constant ratio of the cis and trans isomers.

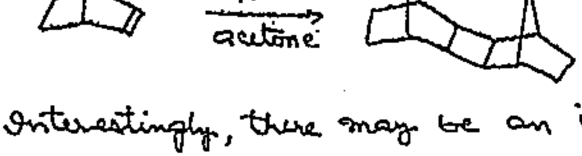
$Br_2 \xrightarrow{h\nu} Br^{\bullet} + Br^{\bullet}$



Dimerisation Reactions

Like αβ-unsaturated ketones, olefins may also undergo dimerization reactions. The process involves the generation of an excited triplet molecule which subsequently reacts with a ground state olefin molecule. A well known example is the acetone-sensitized photodimerization of norbornene. Two units combined to form

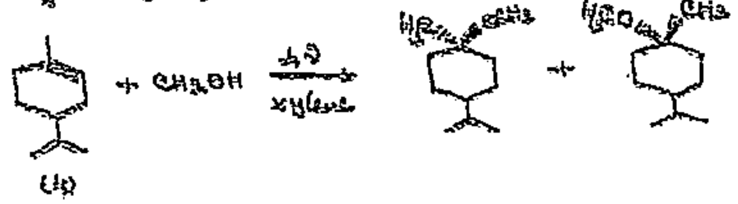
Dimerisation



Interestingly, there may be an intramolecular reaction between two properly situated double bonds in a molecule yielding an isomeric substance. The photoisomerization of norbornadiene (2) to quadricyclene (3) for instance, occurs on irradiation.

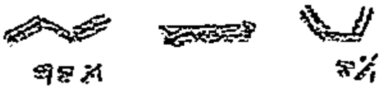
(2) (3)

cyclic olefins undergo addition reactions, instead of dimerization on irradiation in methanol. The reaction of (4) with methanol is sensitized by xylene.

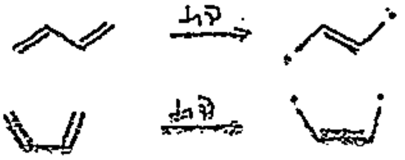


Photochemistry of conjugated olefins (Butadiene)

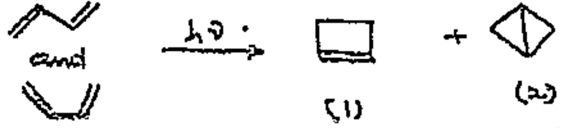
Butadiene may be considered as an example for conjugated olefins. It exists in solution as a mixture of s-trans (95%) and s-cis (5%) conformers.



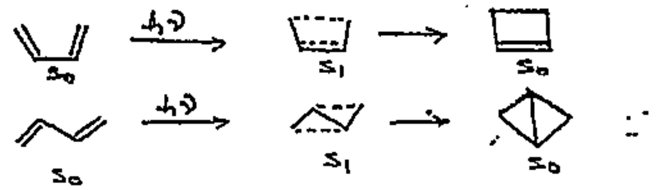
Irradiation of butadiene promotes an electron from ψ_2 to ψ_3 (π, π^* transition) which results in the increased bonding between C_2 and C_3 at the expense of $C_1 - C_2$ and $C_3 - C_4$. In other words, the lowest excited states of s-trans and s-cis butadiene should exhibit still larger barriers to rotation about the $C_2 - C_3$ bond because of its double bond character. Thus conformational character of butadienes are retained in the excited states.



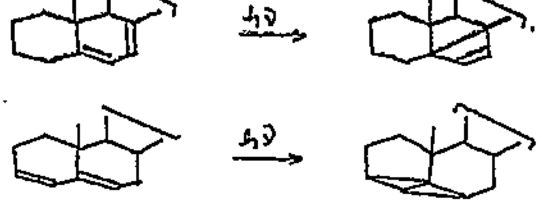
Direct irradiation of butadiene yields cyclobutene (1) and bicyclo [1.1.0] butane (2).



The formation of these products occur directly from the S_1 state of the butadiene and, assuming that the conformational characters of butadiene are retained in the S_1 state, it appears quite reasonable to speculate that s-cis butadiene is the precursor of cyclobutene while the excited state resembling s-trans butadiene gives rise to bicyclobutane

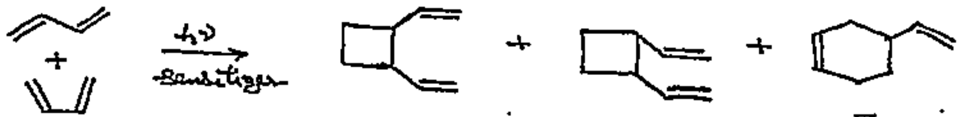


The formation of cyclobutene and bicyclobutane on irradiation of 1,3-butadienes is a fairly general photochemical reaction.



The singlet excitation energies of the two conformers of butadiene are not exactly known (roughly they are in the range of 110–120 K·cal/mole), but it appears from the product composition (more cyclobutene than bicyclobutane) that the energy required for the singlet excitation of s-cis butadiene is lower than that required for the s-trans isomer. The triplet excitation energies for the s-cis and s-trans isomers have been found to be 53 and 60 K·cal/mole, respectively. The large energy gap between S_1 and T_1 accounts for the diminished intersystem crossing in butadienes.

The photochemistry of the T_1 states of butadienes has been investigated through energy transfer from the triplet state sensitizers. A mixture of three dimers 3, 4 and 5 is obtained on sensitized irradiation of butadiene



3 4 5

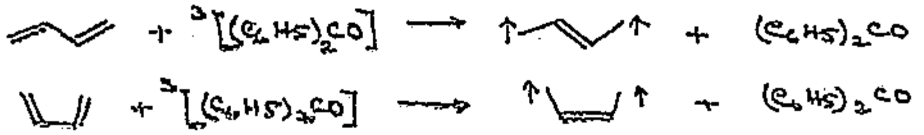
Moreover, the composition of the dimer mixture varies with the triplet energy of the sensitizers employed to populate the T_1 state of

3

butadiene. Typical results from two sensitizers are given in the table below.

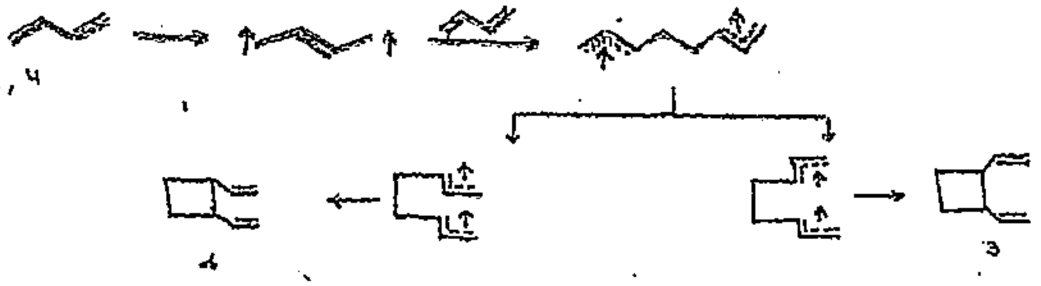
Sensitizer	E_T	3	4	5
Benzophenone	69	80	16	4.
Benzil	54	49	8	43

The T_1 states of butadienes are of lower energy than the T_1 of benzophenone, so triplet energy transfer takes place efficiently to both the butadiene conformers.

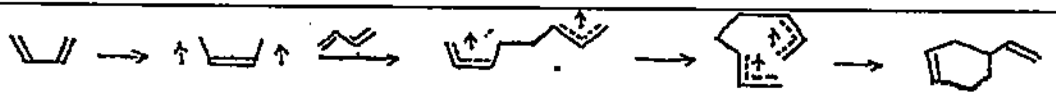


The trans triplet of butadiene is formed predominantly, because the diene is mostly trans. Subsequent reaction of the trans triplet with s-trans butadiene leads to an intermediate hexadienyl biradical in which both the allylic units have the trans configuration and so a cyclization leading to 3 and 4 is favored.

trans → 3, 4
cis → 5.



A similar reaction of the cis triplet, which is formed in small amounts, with a molecule of s-trans butadiene leads to a biradical in which one allylic unit has cis configuration, and in one conformation it is favourably disposed toward cyclization to 5

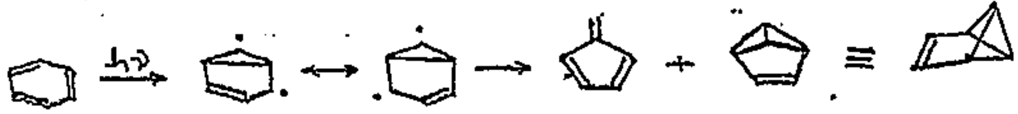


In contrast to benzophenone (E_T 69 k·cal/mole), a triplet sensitizer with E_T below 60 k·cal/mole but above 53 k·cal/mole preferentially should form the cis-butadiene triplet by energy transfer to s-cis butadiene. This explains the predominance of 5 when benzil is employed as a sensitizer.

3. Photochemistry of Aromatic Compounds

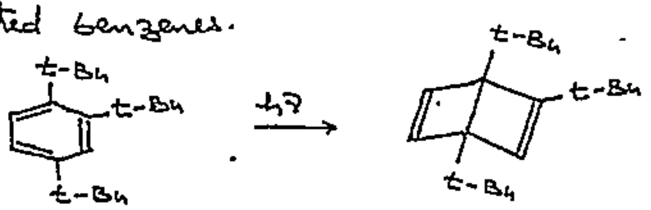
(i) Isomerisation

Benzene itself on irradiation with light of 254 nm gives both fulvene and benzvalene via prefulvene.

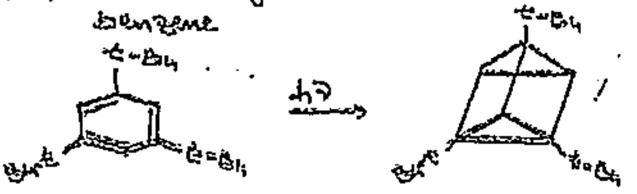


Prefulvene   Fulvene   Benzvalene

Several strained systems like that in Dewar benzene and a prismane have been reached by irradiation of substituted benzenes.

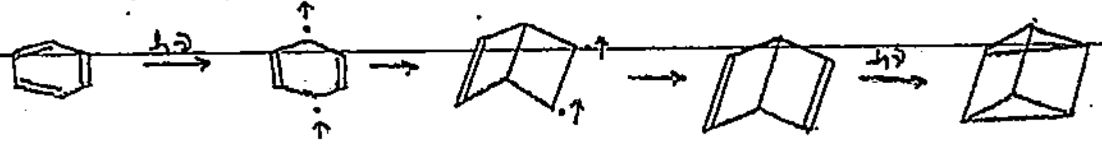


1,2,4-tritertiarybutyl benzene   a Dewar benzene



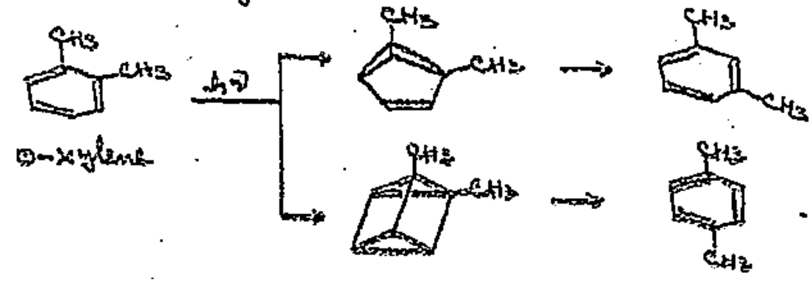
1,3,5-tri-t-butyl benzene   a Prismane

These photoproducts are all valence isomers of the normal benzenoid structure. These products are no doubt reached from the excited state, but a precise mechanism is not clear. Probably the skeletons of Dewar benzene and a prismane arise from the bent triplet state as shown below by ignoring the substituents, for simplicity.



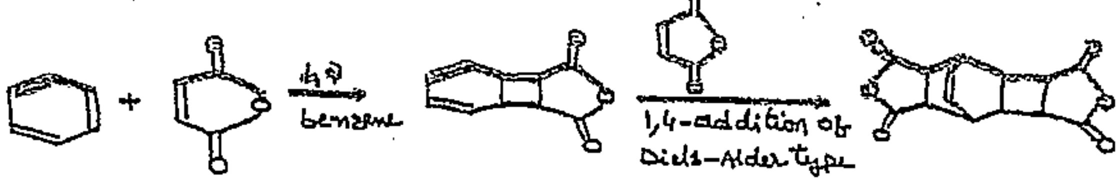
Dewar benzene   Prismane

The presence of bulky t-butyl groups introduces a steric factor which is favourable for the photochemical valence isomerism. The t-butyl groups are coplanar in the aromatic system, in photoproducts, their geometry results in reduced steric interactions between adjacent t-butyl groups. All these strained systems i.e., Dewar benzene, Prismane, benzvalene as well as their derivatives are likely intermediates in photochemical reactions of benzenoid compounds. Thus o-xylene on irradiation ends up in mixtures containing m- and p- isomers.

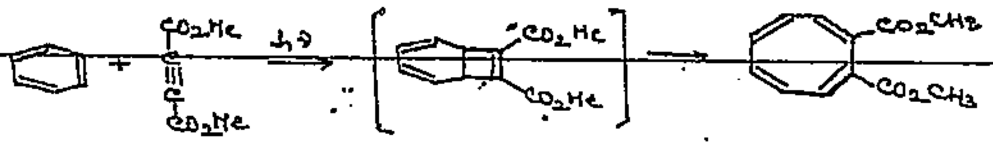


(II) Addition of olefins and amines

Interesting products of cycloaddition are formed when both olefins and acetylenes undergo photochemical addition to benzene. Thus photochemical 1,2-addition to the benzene ring initiated by the $n \to \pi^*$ excitation of the maleic anhydride is followed by a spontanious 1,4-addition of Diels-Alder type to the 1,3-diene.

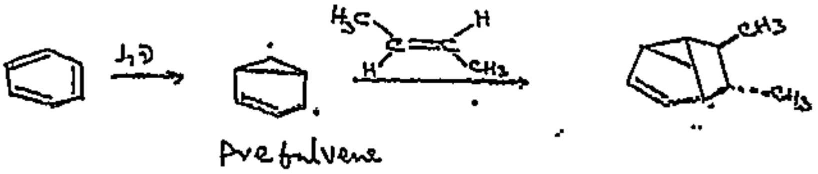


An extremely strained cyclobutene ring, formed in the photochemical reaction between benzene and dimethyl-2-butynoate, undergoes a spontaneous electrocyclic ring opening.

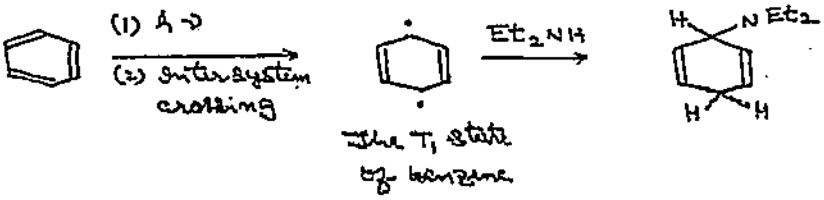


Both 1,3- and 1,4- addition to benzene ring are known. Irradiation of solutions of alkenes in benzene (or substituted benzenes) gives primarily 1:1 adducts where the alkene bridges meta positions of the aromatic ring. Thus, the key step in the

1,3- addition of olefins with benzene is the formation of intermediate prefulvene which is formed from a high vibrational level of the first excited singlet of benzene.



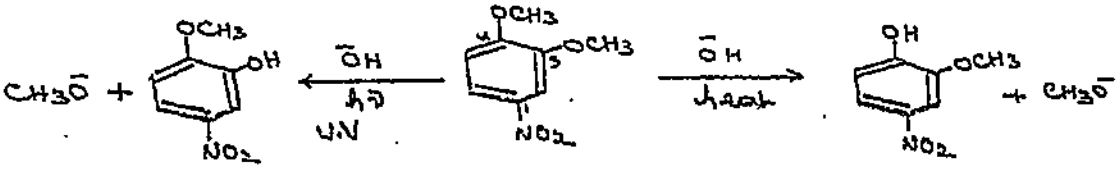
During 1,4- addition of a primary or a secondary amine to benzene (via irradiation), the T_1 state of benzene is involved



1,4- Addition to benzene

(III) Substitution

Compared to the ground state, the distribution of charge in an excited species can be entirely different. Several examples are available where one can control the positional selectivity in nucleophilic aromatic substitutions by working under photochemical conditions. Thus the reaction of 3,4- dimethoxynitrobenzene on heating with $\bar{O}H$ ion leads to the replacement of 4-methoxy group, while at room temperature under u.v. irradiation, instead the 3- methoxy substituent $\overset{OH}{\times}$ is substituted.

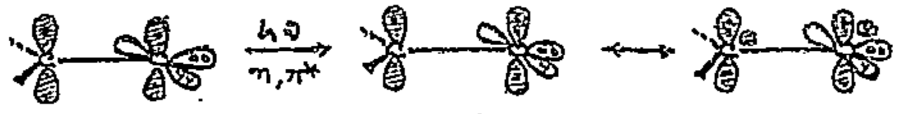


~~under the influence of heat the nitro group through its -M effect~~ makes the ortho and para positions positive compared with the meta position. Under irradiation, however, the ortho and meta positions are rendered positive compared to the para position.

4. Photochemistry of Carbonyl Compounds

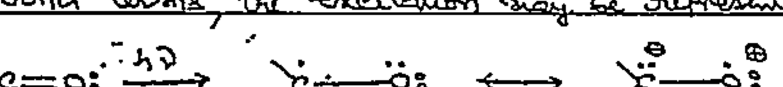
Carbonyl compounds especially ketones, undergo many interesting and versatile reactions on irradiation. Two absorption regions of interest in the ultraviolet spectra of ketones are around 285 nm (n,π^*) and 180 nm (π,π^*). Most commonly, the lowest energy transition is n,π^* in which a non-bonding oxygen electron is promoted to a π^* orbital. For many ketones S_1 and T_1 are derived from n,π^* excitation.

The molecular orbital construction of n,π^* transition may be visualized by the following description. The sigma (σ) skeleton of the ketone is formed by the sp^2 hybrid orbitals leaving an unused p-electron on the carbon. The oxygen atom has two sp hybrid orbitals, one to form a σ bond with carbon and the other to accommodate a pair of electrons (represented as ••). A single electron in a p-orbital of oxygen overlaps with its counterpart in the carbon atom to form a π bond. The remaining two electrons of oxygen atom (××) are accommodated in another p-orbital and it is this pair of electrons that is commonly known as the lone pair or n electrons. n,π^* excitation promotes an electron of the lone pair to a vacant π^* orbital.



n,π^* excitation of the carbonyl group

In valence bond terms, the excitation may be represented as:

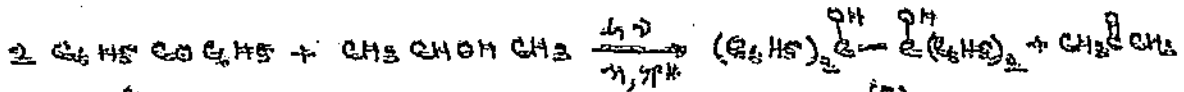


The n,π^* excited state has a singly occupied n orbital and it, therefore, undergoes reactions that place an electron in this orbital.

Due to the small energy gap between S_1 and T_1 states, ketones undergo inter-system crossing with a high degree of efficiency. As a result most of the photochemistry of ketones arises from their triplet states. Very frequently, the structure of the ketone, along with the medium of irradiation, dictates the nature of the products.

(1) Photoreduction

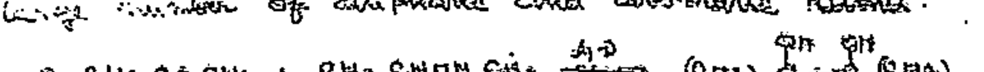
The photoreduction of benzophenone (1) leading to benzpinacol (2) is one of the oldest and most thoroughly investigated photochemical reactions. The reaction is carried out by irradiating a solution of benzophenone in isopropyl alcohol with light of wavelength of 345 nm. Isopropyl alcohol does not absorb light at this wavelength but benzophenone undergoes an n, π* transition.



$$2\ C_6H_5COC_6H_5 + CH_3CHOHCH_3 \xrightarrow[n,\pi^*]{h\nu} (C_6H_5)_2\overset{OH}{C}-\overset{OH}{C}(C_6H_5)_2 + CH_3\overset{O}{\overset{\|}{C}}CH_3$$

(1) (2)

The reaction is very general, and it can be performed with a large number of aliphatic and aromatic ketones.



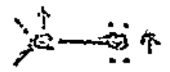
$$2\ CH_3COCH_3 + CH_3CHOHCH_3 \xrightarrow[n,\pi^*]{h\nu} (CH_3)_2\overset{OH}{C}-\overset{OH}{C}(CH_3)_2$$

In addition to isopropyl alcohol, a variety of solvents such as toluene, cyclohexane and methanol have been used for carrying out the reaction.

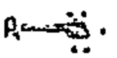
In case of benzophenone, the initial light absorption is followed by rapid inter-system crossing from S_1 to T_1

$$(C_6H_5)_2CO \xrightarrow{h\nu} {}^1[(C_6H_5)_2CO] \xrightarrow{ISC} {}^3[(C_6H_5)_2CO]$$

The carbonyl n, π* triplet (3) has a structure which closely resembles the structure of alkoxy radicals (4)



(3)



(4)

Like alkoxy radicals, the n, π* triplet is capable of abstracting the α-hydrogen of isopropyl alcohol thus giving rise to two radicals, (5) and (6).

$$^{3}\left[(C_6H_5)_2CO\right] + CH_3CHOHCH_3 \longrightarrow \underset{(5)}{(C_6H_5)_2\dot{C}OH} + \underset{(6)}{(CH_3)_2\dot{C}OH}$$

Combination of two units of (5) leads to benzpinacol

$$2\ \underset{(5)}{(C_6H_5)_2\overset{OH}{\overset{|}{C}}\cdot} \longrightarrow \underset{(2)}{(C_6H_5)_2\overset{OH}{\overset{|}{C}}-\overset{OH}{\overset{|}{C}}(C_6H_5)_2}$$

Since the quantum yield, Φ, for benzpinacol formation is about 1, the second unit of (5) does not form as a result of the absorption of a fresh quantum of light; rather it is generated by the reaction between benzophenone and (6)

$$(C_6H_5)_2CO + \underset{(6)}{(CH_3)_2\dot{C}OH} \longrightarrow (C_6H_5)_2\dot{C}OH + (CH_3)_2CO$$

Benzpinacol formation can also be achieved by irradiating benzophenone and benzhydrol in benzene solution.

$$(C_6H_5)_2CO + (C_6H_5)_2CHOH \xrightarrow{h\nu} (C_6H_5)_2\overset{OH}{\overset{|}{C}}-\overset{OH}{\overset{|}{C}}(C_6H_5)_2$$

The mechanism of this reaction is similar to that of the above except that there is simultaneous formation of two radicals, which subsequently dimerize.

$$^{3}\left[(C_6H_5)_2CO\right] + (C_6H_5)_2CHOH \longrightarrow 2\ (C_6H_5)_2\overset{OH}{\overset{|}{C}}\cdot \longrightarrow \underset{(2)}{(C_6H_5)_2\overset{OH}{\overset{|}{C}}-\overset{OH}{\overset{|}{C}}(C_6H_5)_2}$$

α-Keto esters such as (7) also undergo photoreduction to yield pinacols:

$$\underset{(7)}{C_6H_5COCOOC_2H_5} + CH_3CHOHC_2H_5 \xrightarrow{h\nu} \begin{array}{l} \quad\ \ OH \\ C_6H_5\overset{|}{C}COOC_2H_5 \\ \qquad | \\ C_6H_5\underset{|}{C}COOC_2H_5 \\ \quad\ \ OH \end{array}$$

(II) NORRISH TYPE I REACTION

α-[illegible] cleavage.

The bond dissociation energy of a carbon-carbon bond adjacent to a carbonyl is comparitively small and consequently photochemical excitation of ketones usually results in the homolytic fission of the α-carbon-carbon bond. This process is known as α-cleavage or Norrish type I reaction.

The most thoroughly studied example is acetone which has been photolysed in the vapour phase as well as in the

~~Homolysis of carbon and carbon~~ [illegible] liquid phase. Absorption of light results in the formation of an n,π^* excited state of acetone which undergoes a carbon-carbon cleavage yielding a methyl radical and an acetyl radical.

$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow[n-\pi^*]{h\nu} \left[CH_3\overset{O}{\overset{\|}{C}}CH_3\right] \longrightarrow \dot{C}H_3 + CH_3-\overset{O}{\overset{\|}{C}}\cdot$$

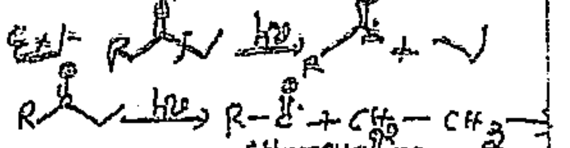
At room temperature, two acetyl radicals combine to form biacetyl.

$$2\,CH_3\overset{O}{\overset{\|}{C}}\cdot \longrightarrow \underset{\text{Biacetyl}}{CH_3\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}CH_3}$$

At temperatures above 100°, acetyl radicals decarbonylate with the ultimate production of ethane and carbon monoxide.

$$CH_3\overset{O}{\overset{\|}{C}}\cdot \longrightarrow \dot{C}H_3 + CO$$

$$2\,\dot{C}H_3 \longrightarrow CH_3-CH_3$$



In the case of unsymmetrical ketones, splitting takes place in a way as to generate the more stable of the two possible radicals.

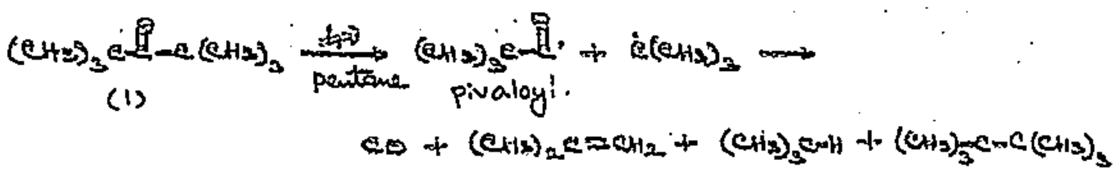
$$R\overset{O}{\overset{\|}{C}}R \xrightarrow{-CO} R-R$$

$$CH_3CO\,CH(CH_3)_2 \xrightarrow{h\nu} CH_3\dot{C}O + (CH_3)_2\dot{C}H$$

$$CH_3CO\,CH_2CH_3 \xrightarrow{h\nu} CH_3\dot{C}O + CH_3\dot{C}H_2$$

Both the singlet and the triplet n,π^* excited states are capable of undergoing α-cleavage. In the case of acetone, most of the excited singlet molecules undergo intersystem crossing to T_1 at room temperature, but with increase in temperature, there is less intersystem crossing and thus both the species participate in Norrish type I reaction. Similarly, at room temperature nearly half of the molecules of diethylketone react in the S_1 state before the intersystem crossing to T_1 occurs.

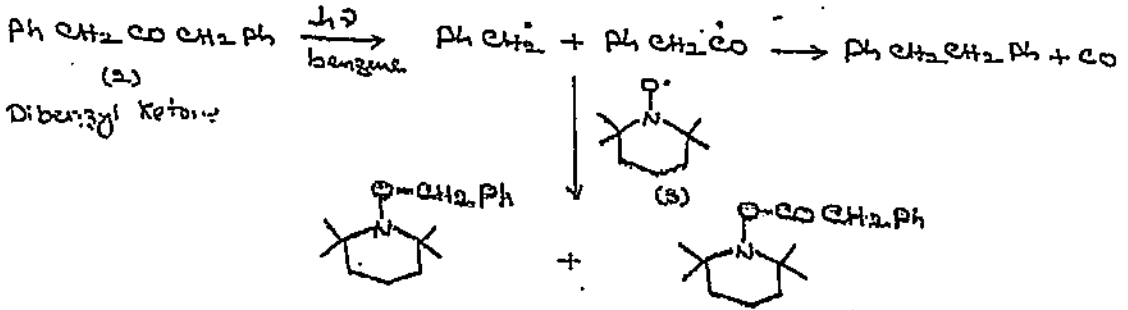
~~Another example of this reaction is the photo-fragmentation of di-t-butyl-ketone (1)~~ at elevated temperatures in the gas phase, which produces a t-butyl and a pivaloyl radical. Subsequent decarbonylation of the acyl radical, dimerization and disproportionation of the alkyl radical affords the final products.



$$\underset{(1)}{(CH_3)_3C-\overset{O}{\overset{\|}{C}}-C(CH_3)_3} \xrightarrow[\text{pentane}]{h\nu} \underset{\text{pivaloyl}}{(CH_3)_3C-\overset{O}{\overset{\|}{C}}\cdot} + \dot{C}(CH_3)_3 \longrightarrow CO + (CH_3)_2C=CH_2 + (CH_3)_3C-H + (CH_3)_3C-C(CH_3)_3$$

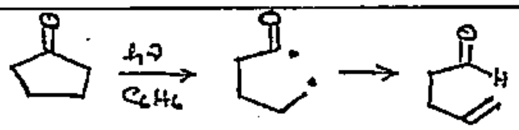
The same products are produced upon irradiation of the ketone in solution where the reaction takes place from both the singlet and the triplet excited states.

Another solution-phase reaction is the triplet state decarbonylation of dibenzyl ketone (2). The decarbonylation is efficient ($\Phi = 0.7$) and as with the gas-phase reaction a two-step radical mechanism is operative. Substantiation of this mechanism was obtained by several approaches, e.g., the absence of viscosity effects in product formation which shows that the radicals produced by the Norrish Type I fission are sufficiently separated to prevent cage recombination and also by the use of trapping experiments. 2,2,6,6-Tetramethylpiperidine-1-oxyl (3) was used for the trapping and the radical fragments produced by the fission of dibenzyl ketone were trapped as an ester and an ether.

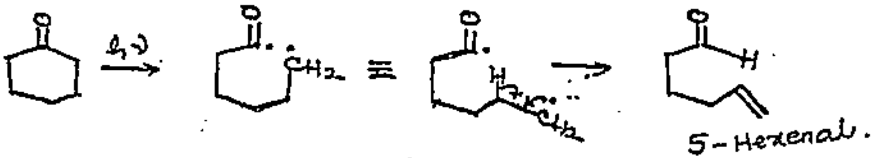


Cyclic ketones, in contrast to the acyclic ketones, show a greater tendency to undergo α-cleavage to furnish acyl-alkyl biradicals. Available information indicates that the electronically excited state responsible for the photo-process is the triplet state. This was demonstrated first for the irradiation of cyclopentanone, either neat or in solution, which forms pent-4-enal on excitation either at 313 or 254 nm. The formation of the aldehyde is an intramolecular disproportionation arising within the biradical

formed by α-fission.



cyclohexanone also forms an aldehyde when irradiated in solution. Again a triplet state is implicated.

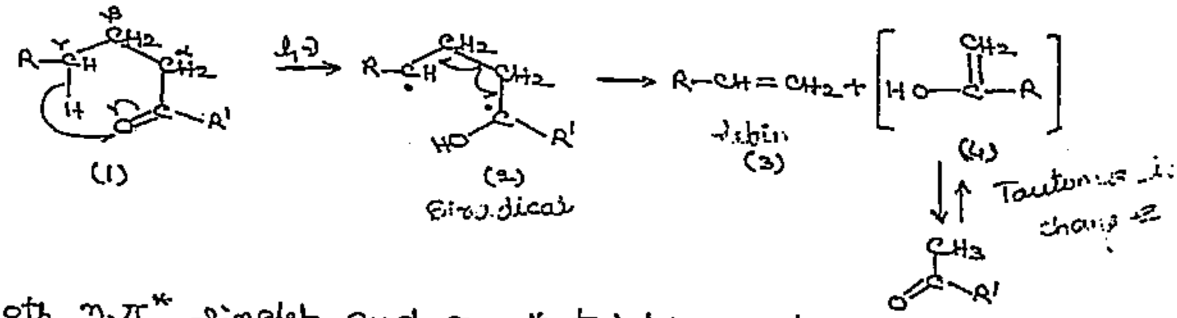


5-Hexenal.

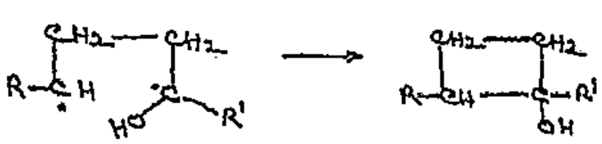
(III) Norrish Type II Reactions

γ C–H Bond cleavage.

Ketones possessing a γ-hydrogen atom (1) undergo a very interesting photochemical reaction which results in the formation of an olefin and the enol of a smaller ketone. Spectroscopic studies have demonstrated that the disappearance of the starting ketone occurs at the same rate as the appearance of the enol form. The reaction proceeds by the initial γ-hydrogen abstraction by the oxygen atom yielding a 1,4-biradical (2) which subsequently cleaves to an olefin (3) and an enol (4)

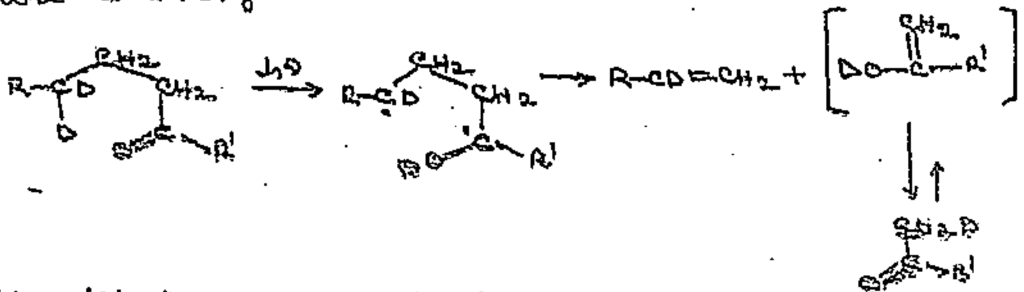


Both n,π* singlet and n,π* triplet participate in the intramolecular hydrogen abstraction reactions while ketones with a low-lying π,π* state do not undergo this reaction. γ-Hydrogen abstraction is sometimes followed by ring closure of the 1,4-biradical.

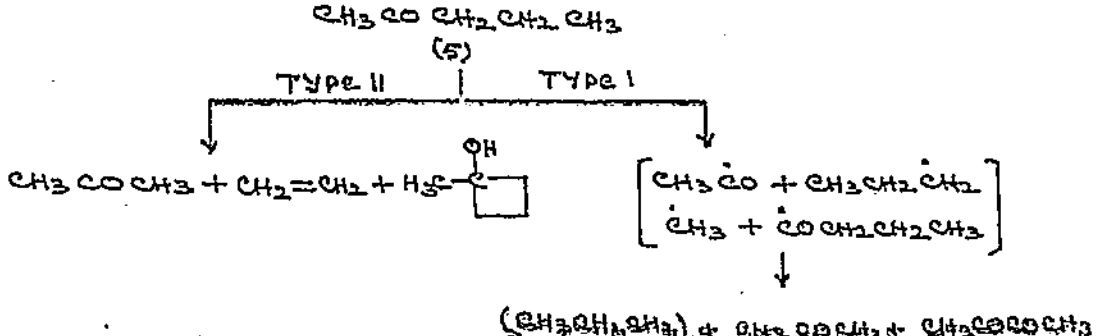


(2)

The formation of the 1,4-biradical is a reversible process and the equilibrium between the reactant and the products depends upon the structure of the starting ketone and the conditions of irradiation. When γ-hydrogens are replaced by deuterium, the resultant 1,4-biradical has an O—D bond and since more energy is required to break it than an O—H bond, the reaction proceeds in the forward direction more smoothly.

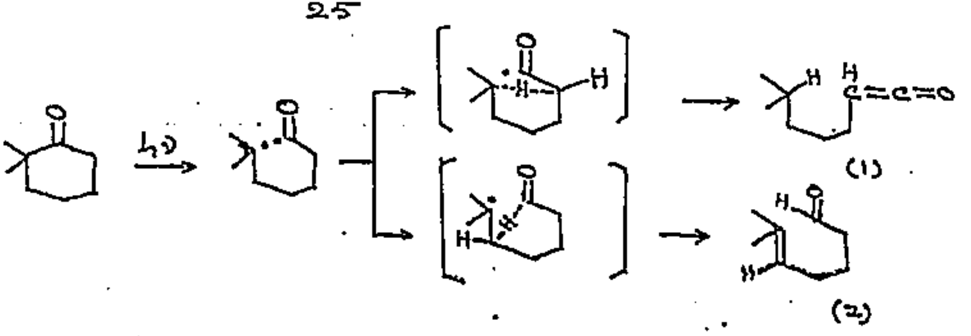


Norrish type II cleavage is often accompanied by a type I split; for instance, irradiation of 2-pentanone (5) yields the following products:

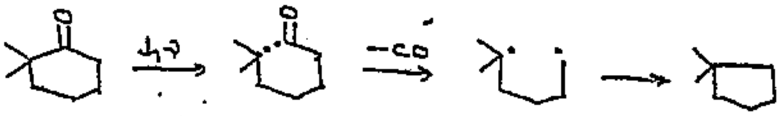


(IV) Photochemical Reactions of cyclic ketones

The photochemical reactions of saturated cyclic ketones resemble rather closely the photochemical reactions of open chain analogues. Usually, the photochemistry begins with the n,π* excitation of the carbonyl group followed by α-fission in which formation of the most stable radical is preferred. The biradical, thus formed, may then undergo a hydrogen transfer reaction from the carbon atom α- to the carbonyl group yielding a ketene (1) or it may give rise to an unsaturated aldehyde (2) by hydrogen transfer to the carbonyl group.

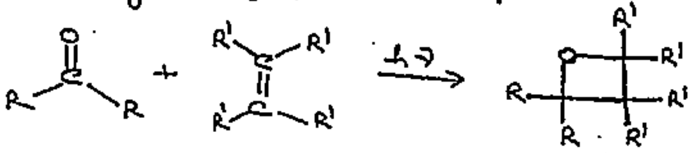


Alternatively, the biradical may prefer to decarbonylate.



5. The Paterno-Buchi Reaction

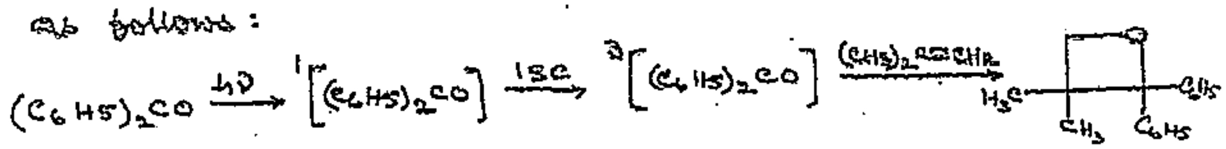
Carbonyl compounds yield oxetanes on irradiation in the presence of olefins.



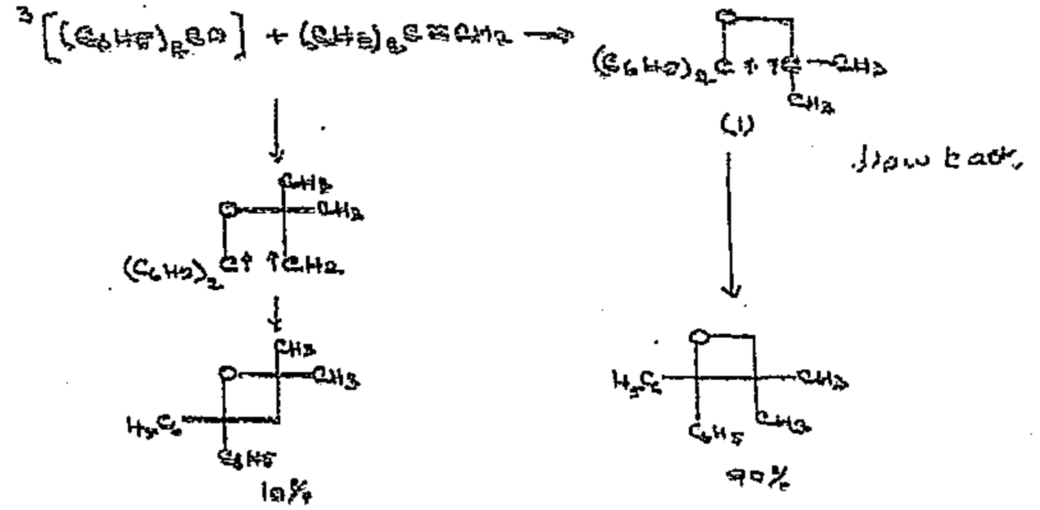
oxetane

This photocycloaddition is usually referred to as the Paterno-Buchi reaction. Since the addition is usually performed by irradiation with the light of wavelengths absorbed only by the carbonyl group, it involves the excited state of the carbonyl compound rather than that of the olefin. The light energy required for the n,π^* transition initiates the reaction in simple carbonyl compounds, while for some conjugated ketones it is difficult to distinguish between n,π^* and π,π^* transitions. Available evidence favours participation by both the excited states in the latter case.

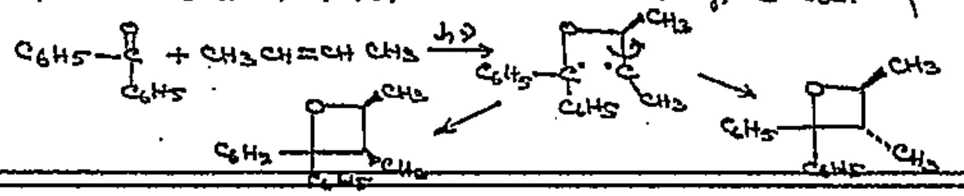
It has been established that carbonyl compounds undergoing Paterno-Buchi reaction can also be photoreduced upon irradiation in the presence of protic solvents, such as isopropyl alcohol, leading to the formation of pinacols. The inability of a carbonyl compound to undergo photo-cycloaddition is always coupled with a similar inertness toward photoreduction. These facts illustrate that the two reactions are initiated by the same type of excited state. That this excited state is a triplet species has been shown in the case of photoreduction processes and on that basis the mechanism of the Paterno-Buchi reaction can be written as follows:



Since the olefin used in the above reaction is unsymmetrical, theoretically two products should arise from this cycloaddition. The other product is, indeed, obtained but only in 10% yield. Preferential formation of the major product indicates intermediacy of biradical and logically the addition takes place to yield preferentially the most stable biradical intermediate (1).



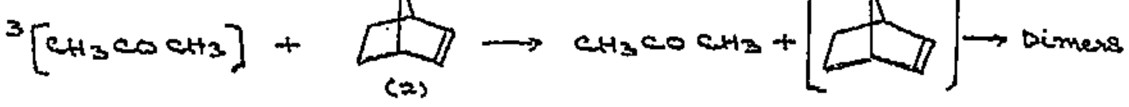
(Moreover, irradiation of benzophenone with either cis or trans-2-butene yields the same mixture of both isomeric oxetanes. Had it been a concerted reaction in which both the bonds were formed simultaneously, different products would have been formed in each case. The above result thus confirms intermediacy of a biradical in which the stereochemistry is lost.)



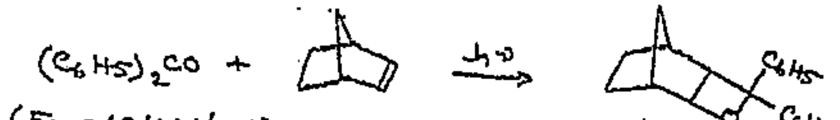
A serious drawback of the Paterno-Buchi reaction is the competing energy transfer process from the excited ketone to the olefin, in cases where the triplet energy of the former exceeds that of the latter. Irradiation of acetone with norbornene (2), for instance, yields dimers of norbornene rather than oxetanes.

$$CH_3COCH_3 \xrightarrow{h\nu} {}^1[CH_3COCH_3] \xrightarrow{ISC} {}^3[CH_3COCH_3]$$

$(E_T = 78\ \text{k·cal/mole})$

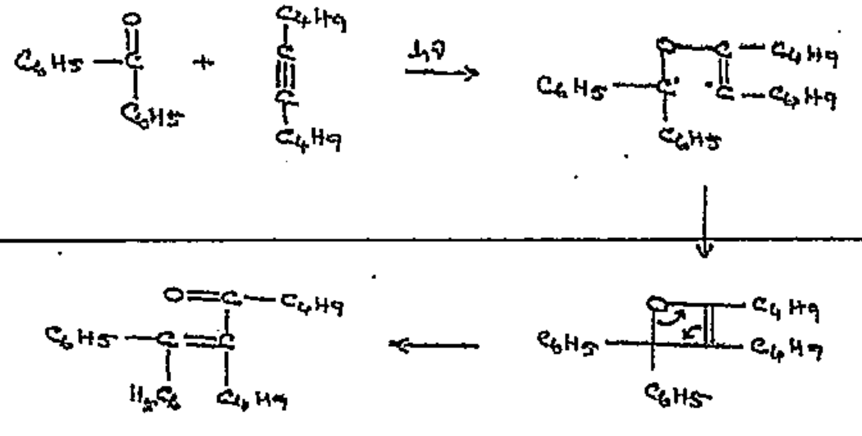


However, when a ketone having less triplet energy is used we get the oxetane of norbornene



For similar reason, the Paterno-Buchi reaction fails to occur with conjugated dienes whose triplet excitation energy is far below the triplet excitation energy of the ketones. Here again, energy transfer becomes the predominant reaction between the ketone triplet ($E_T \sim 70$ k·cal/mole) and the conjugated diene ($E_T \sim 60$ kcal/mol).

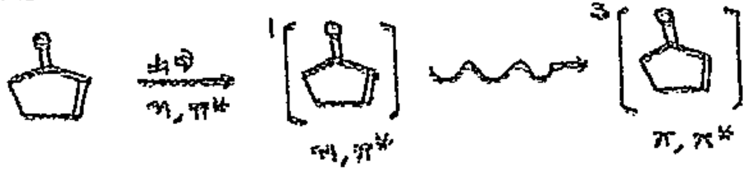
Acetylenes also participate in the Paterno-Buchi reaction to yield products which probably arise via an unstable oxetene (3)



(3)

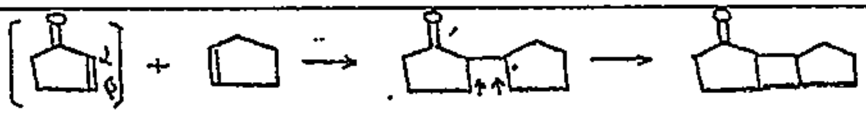
6. Photochemistry of αβ-unsaturated ketones

Conjugation of the carbonyl group with a carbon–carbon double bond in an αβ-unsaturated ketone raises the energy of the highest π orbital and lowers the energy of the π* orbital. In other words, there is now a lesser energy gap between π and π* states and so less energy (and hence light of a longer wavelength) is required for the π, π* transition in which the entire C=C–C=O system is involved. Although there is no change in the energy level of the n orbital, the lowering of the level of the π* orbital shifts the n, π* transition to a longer wavelength. A typical αβ-unsaturated ketone displays two absorption maxima at 220 nm (π, π*) and at 310 nm (n, π*) and irradiation may induce either of these transitions. The excited state of such a ketone usually has more π, π* than n, π* triplet character even though there may be an initial n, π* excitation.

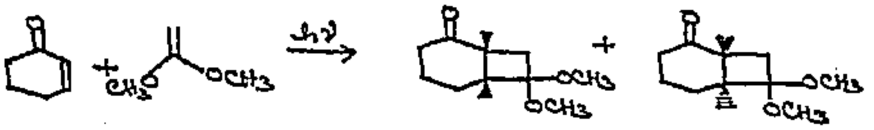


Two important reactions initiated by π, π* states of the αβ-unsaturated ketones are olefin addition across the double bond and photocyclodimerization. Both the reactions have long been used for preparing cyclobutane derivatives.

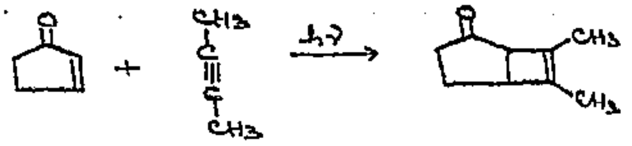
- Photocycloaddition reaction involves the initial formation of a carbon–carbon bond between the α carbon of αβ-unsaturated ketone and the olefin, followed by cyclization.



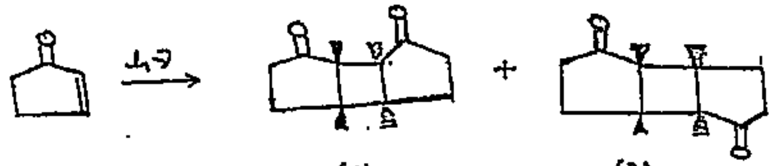
The reaction is of a considerable synthetic utility since substituted olefins such as 1,1-dimethoxyethylene undergo photocycloaddition.



Acetylenes yield cyclobutenes in a similar fashion.



The photodimerization of α,β-unsaturated ketones occurs most readily in cyclic systems. Irradiation of cyclopentenone, for instance, yields head-to-head (1) and head-to-tail (2) dimers in almost equal amounts.

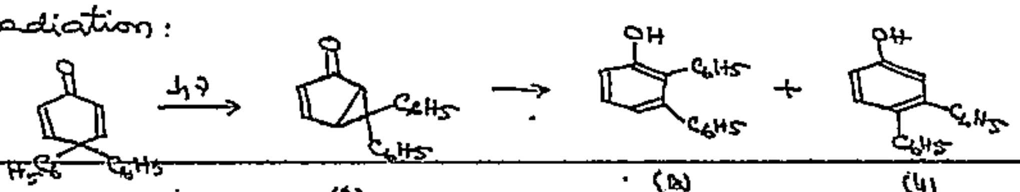


(1) (2)

Head-to-head dimers are preferred in polar solvents, while non-polar media favour head-to-tail dimers. The dimerization of cyclohexenone occurs in a similar manner.

7. Photorearrangement of Cyclohexadienones

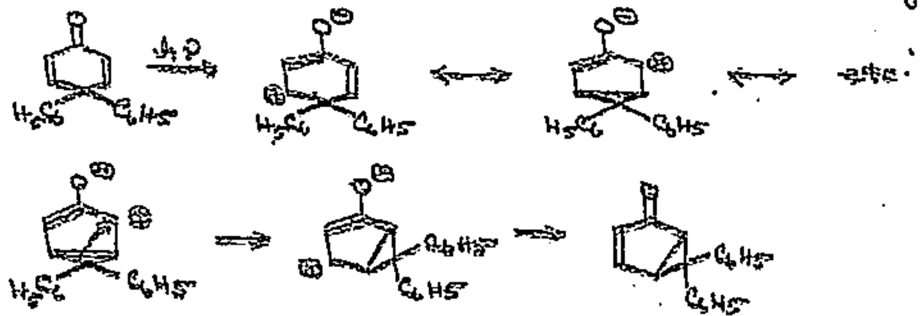
The photochemical rearrangement of compounds containing the cyclohexadienone chromophore is a complex process. 4,4-Diphenylcyclohexadienone (1), for instance is rapidly isomerized to a ketone (2) and two phenols (3) and (4) on irradiation:



(1) (2) (3) (4)

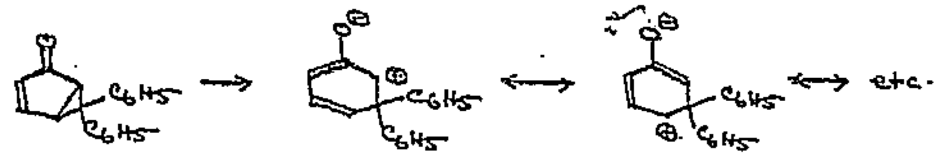
cyclohexadienone displays absorption at about $300\,nm\ (n,\pi^*)$ and at about $240\,nm\ (\pi,\pi^*)$. Since the above photochemical transformation may be brought about by irradiation at either wavelength, it is reasonable to assume that the lower energy transition (n, π*) is involved in the initial excitation process. It has been shown that the energy transfer takes place when (1) is irradiated with triplet energy sensitizers such as aceto-phenone. These observations suggest that the photochemical rearrangements of (1) proceed via an n, π* triplet state.

It appears that the excitation of ketone moity of the molecule involves electron redistribution which renders the molecule more polarisable with respect to the ground state. The intermediates thus have a polar character in which negative charge is localized on the oxygen atom and positive charge is spread over the carbon skeleton. Based on the polar state concept, as advanced by Chapman, we may write the mechanism of the above reaction in the following steps.



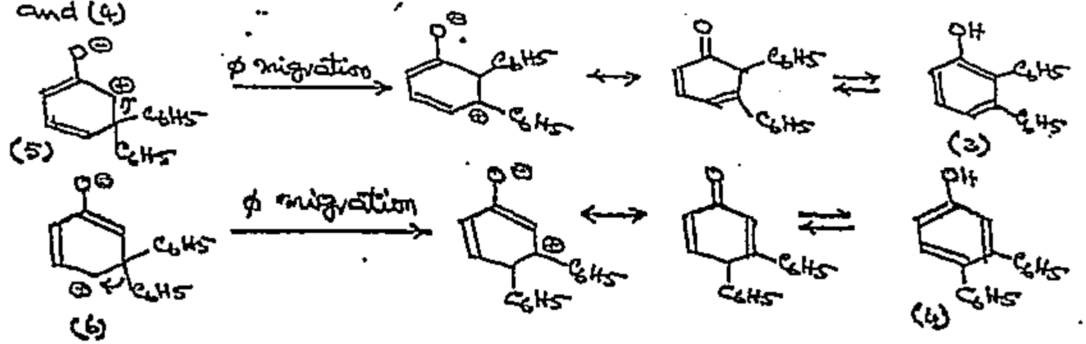
(2)

Since (2) still possesses a chromophore; it can undergo further n, π* excitation to produce the following resonance hybrid.



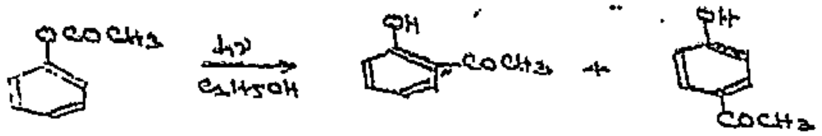
(2) (5) (6)

Structures (5) and (6) undergo phenyl migration leading respectively to (3) and (4)



8. Photo-Fries Rearrangement

Phenolic esters can be rearranged to ortho and para-hydroxy ketones by heating in the presence of Friedel-crafts catalysts like $AlCl_3$. These rearrangements, known as Fries rearrangements can also be carried out in solution by irradition with ultraviolet light



The photo-Fries rearrangement does not need a catalyst and is predominantly an intramolecular free radical process. Significantly, the phenol (ArOH) is always a side product which arises from some ArO· which leaks from the solvent cage and abstracts a hydrogen atom from a neighbouring molecule.

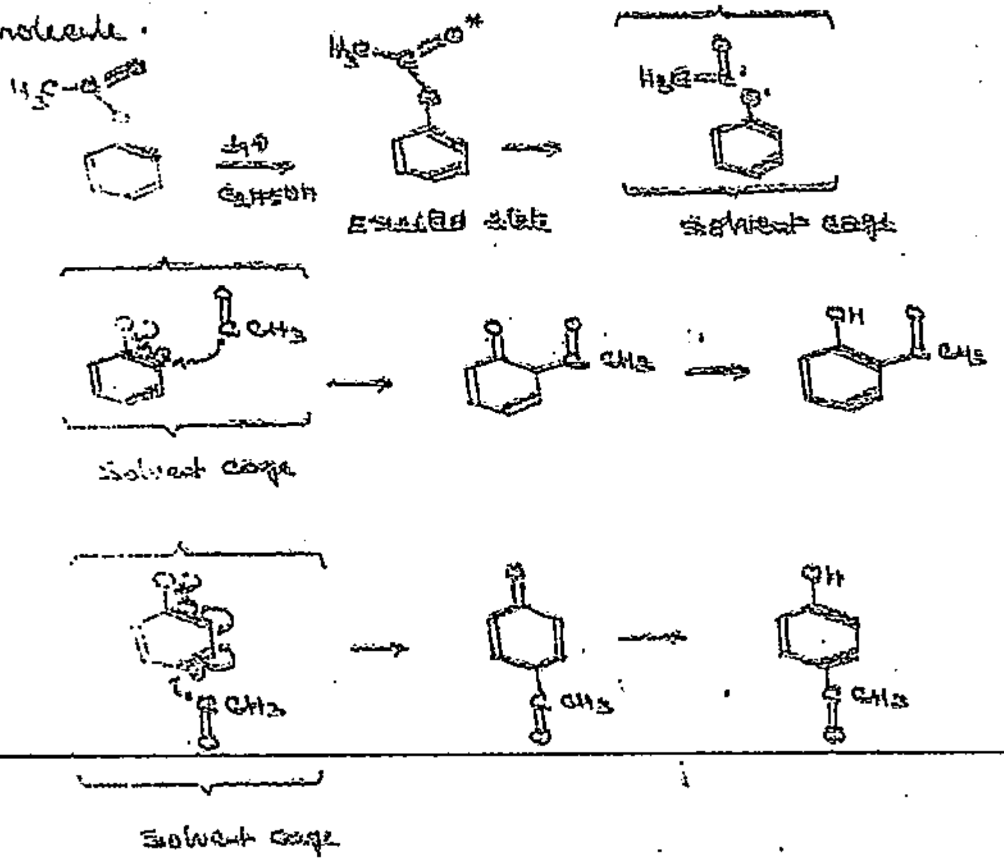
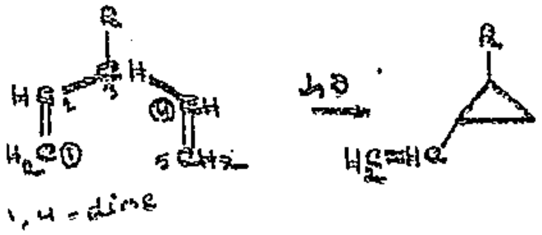
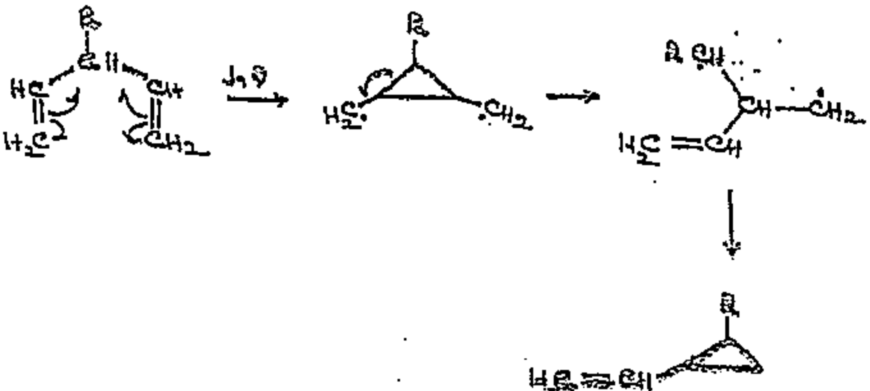


Photo-Fries Rearrangement

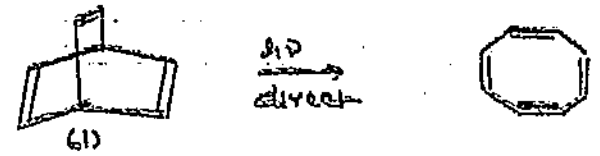
Di-π-Methane Rearrangement (DPM)

In this rearrangement a 1,4-diene system, in which the two π components are separated by an sp^3 carbon gives a cyclopropane derivative photochemically. The rearrangement can involve either a singlet or a triplet excited state, and proceeds through a diradical formed via bonding between C-2 and C-4. When the central sp^3 carbon in a substrate is unsubstituted, the rearrangement becomes unfavourable. This is so because the second step would involve energetically unfavourable primary radical:

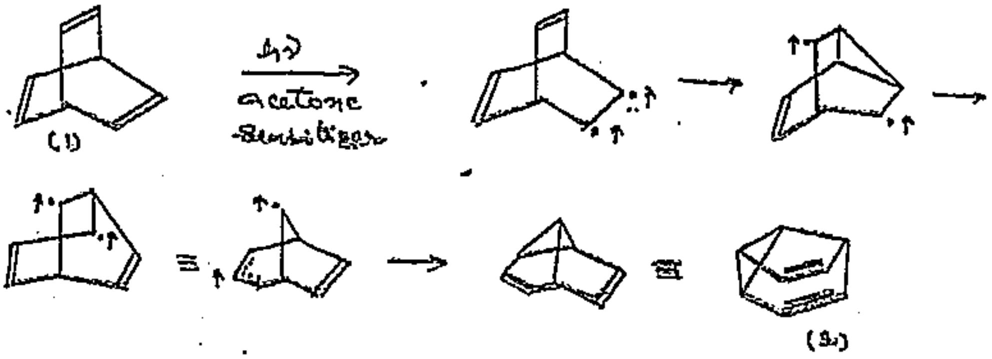




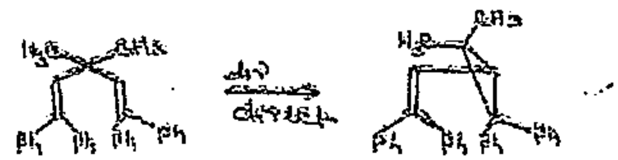
It has been established by Zimmerman and coworkers that bicyclic systems undergo this rearrangement by way of triplet excited state in contrast to acyclic systems where the singlet reacts smoothly but the triplet excited state is unreactive. Barrelene (1) for instance, on sensitized photolysis yields semibullvalene (2) but cyclooctatetraene by direct photolysis.



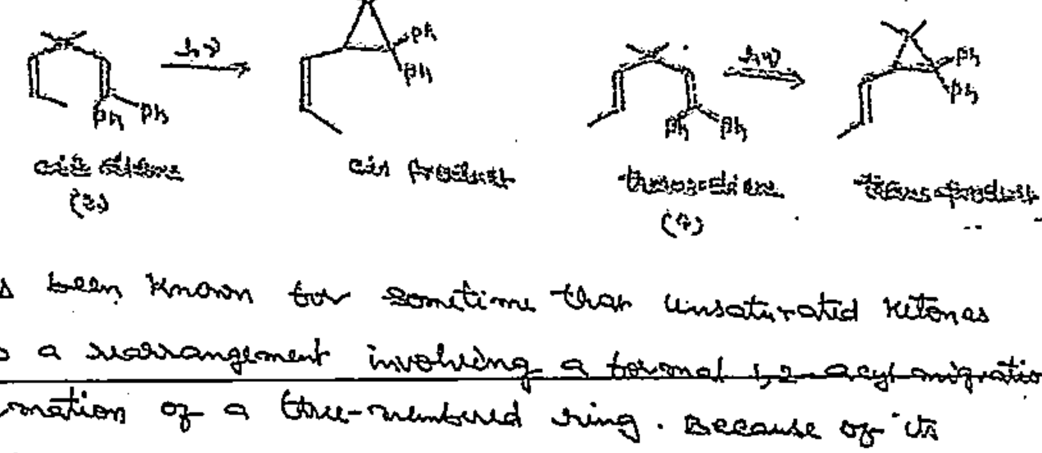
(1)



on the other hand, direct photolysis of 3,3-dimethyl-1,1,5,5-tetraphenylpenta-1,4-diene has been found to give vinylcyclopropane derivative.

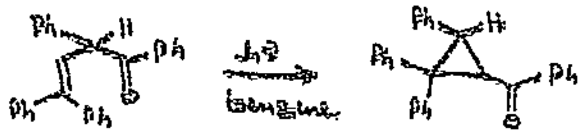


Furthermore, the reaction is stereospecific, as isomeric cis (3) and trans (4) 1,1-diphenyl-3,3-dimethyl-1,4-hexadiene rearrange to give the corresponding vinyl-cyclopropanes, respectively with retention of configuration.



cis diene (3) cis product trans diene (4) trans product

It has been known for sometime that unsaturated ketones undergo a rearrangement involving a formal 1,2-acyl migration and formation of a three-membered ring. Because of its similarity to the DPM rearrangement the reaction has been referred to as oxadi-π-methane rearrangement (ODPM). The irradiation of 1,2,4,4-tetraphenyl-3-butenone gives 2,2,3-triphenyl-1-benzoyl cyclopropane on photolysis in a low yield (7%).



The carbonyl group functions as one of the π-component. The mechanism may be formulated as follows:

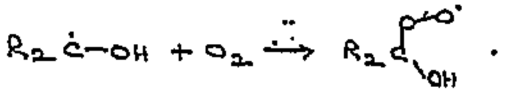
1. Photo-oxidations

A. Formation of peroxy-compounds

Certain types of peroxy-compounds can be formed by irradiating the parent organic compound in the presence of oxygen and a sensitizer. Reaction occurs by the excitation of the sensitizer to its triplet state, and thereafter in one of two ways — either the triplet abstracts a hydrogen atom from the substrate to form a radical which then reacts with oxygen, or it interacts with the oxygen molecule so as to activate it.

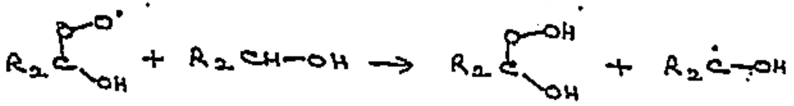
The best known example of the first type of reaction is the oxidation of a secondary alcohol to give a hydroxy-hydroperoxide, with benzophenone as the sensitizer. The triplet benzophenone reacts with the alcohol to give a carbon radical which adds oxygen —

$$^3[Ph_2C{=}O] + R_2CH{-}OH \longrightarrow Ph_2\dot{C}{-}OH + R_2\dot{C}{-}OH$$

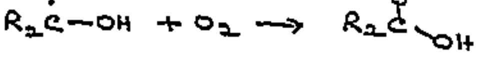


$$R_2\dot{C}{-}OH + O_2 \longrightarrow R_2C(OO^{\bullet})(OH)$$

A chain reaction is now propagated —

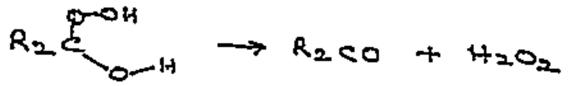


$$R_2C(OO^{\bullet})(OH) + R_2CH{-}OH \longrightarrow R_2C(OOH)(OH) + R_2\dot{C}{-}OH$$



$$R_2\dot{C}{-}OH + O_2 \longrightarrow R_2C(OO^{\bullet})(OH)$$

The usefulness of the reaction was in the fact that hydroxy-hydroperoxides readily eliminate hydrogen peroxide to form carbonyl compounds—

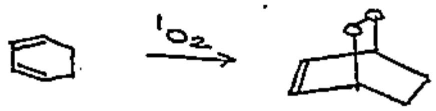


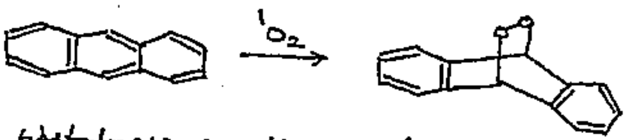
$$R_2C(OOH)(OH) \rightarrow R_2CO + H_2O_2$$

In the second type of sensitized oxidation, the sensitizer in its triplet state interacts with the triplet oxygen molecule, ie, the ground state of oxygen, to give singlet oxygen, $^1O_2$, ie, an excited oxygen molecule, while the sensitizer returns to its ground state, S_0. Singlet oxygen then interacts directly with the organic substrate. The common sensitizers are dyes such as fluorescein and Rose Bengal (a halogenated fluorescein)$^{\alpha}$.

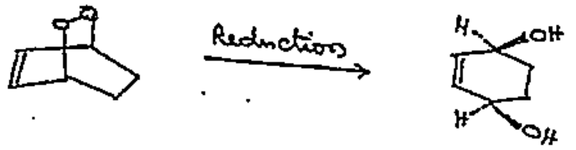
Three types of oxidation can be brought about in this way.

(I) First conjugated dienes yield cyclic peroxides in a reaction of Diels-Alder type. Examples are —

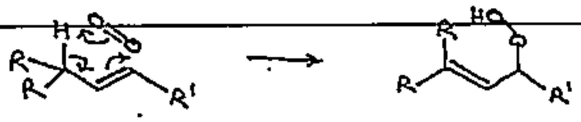




The usefulness of the reaction lies in the reducibility of the peroxides to diols—

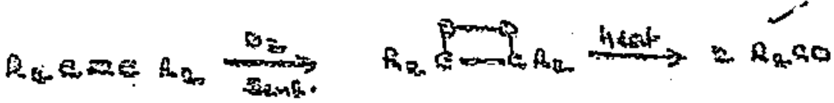


(II) Second, alkenes with an allylic hydrogen atom form hydroperoxides, probably as follows



The products can be reduced to allyl alcohols.

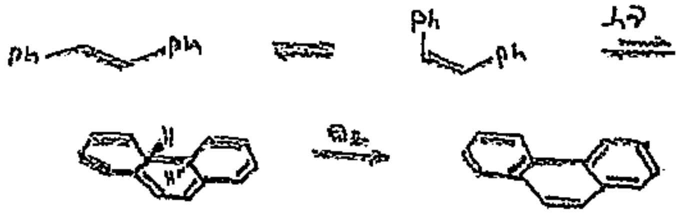
(III) Third, alkenes with no allylic hydrogen form dioxetanes which, on warming, yield carbonyl compounds —



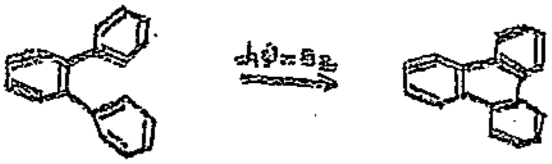
$$R_2C=CR_2 \xrightarrow[\text{Sens.}]{O_2} R_2C(O-O)CR_2 \xrightarrow{\text{heat}} 2\,R_2CO$$

B. Oxidative coupling of aromatic compounds

Although the irradiation of cis- or trans-stilbene in the absence of oxygen gives simply a mixture of the two, in the presence of oxygen phenanthrene is formed. It has been inferred that cis-stilbene photocyclizes reversibly to give a small proportion of dihydrophenanthrene which, in the presence of oxygen, is oxidized irreversibly to phenanthrene—



Compounds related to stilbene react analogously, providing a useful method for obtaining polycyclic systems, eg.,



Stilbene-related compd.

Paper-II: Organic Synthesis & Reaction Mechanisms-II

UNIT - IV

V·R·S·& Y·R·N· COLLEGE : CHIRALA

M·Sc·(Final), Semester–IV Organic Chemistry

Paper–II : Organic Synthesis & Mechanisms–II

UNIT- : PERICYCLIC REACTIONS
'IV'

1. **Definition:** Pericyclic reactions are defined as the reactions that occur by a concerted cyclic shift of electrons in olefinic molecules.

Characteristics: (i). These reactions do not involve ionic or free radical intermediates.

(ii) They are remarkably insensitive to the presence or absence of solvents and catalysts

(iii) Many of them are characterised by the making or breaking of two or more bonds in a single concerted step through cyclic transition states wherein all first-order bonding changes occur. Because of their cyclic transition states, they are known as pericyclic reactions.

(iv) They are initiated by heat (thermolysis) or light (Photolysis)

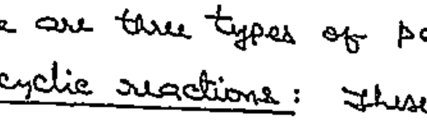
(v) They are highly stereospecific.

(vi) Very often, thermal and photochemical processes yield products with differing stereochemistry.

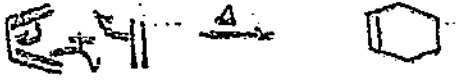
Classification of Pericyclic reactions

There are three types of pericyclic reactions–

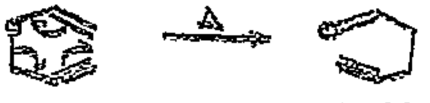
(1) **Electrocyclic reactions:** These are intramolecular pericyclic reactions which involve either the formation of a ring, with the generation of one new σ-bond and the consumption of one π-bond, or the converse. An example is the thermal interconversion of 1,3,5-hexatriene and 1,2-dihydrobenzene.



(II) Cycloaddition reactions: These are reactions in which two σ-bonds are formed between the terminals of two isolated π-systems. The classical example is the Diels-Alder reaction



(III) Sigmatropic rearrangements: In these, an atom or a group migrates with a π-electron system without change in the number of σ- or π-bonds. An example is the claisen rearrangement.



Allylvinyl ether

Atomic orbitals — one nucleus

Molecular orbital [illegible] nuclei

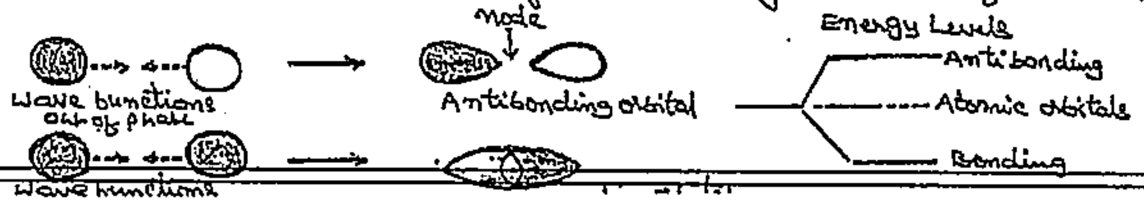
[illegible]

ψ = positional [illegible]

[illegible]

Molecular orbital theory (M.O. Theory)

Whenever two atoms with half-empty orbitals (two hydrogen atoms, for instance) approach each other, two results are possible. If the wave function of the electrons are in phase the atoms can form a bond, resulting in the formation of a molecule that is lower in energy than the "zero energy level" of the two unbonded atoms. In effect, a new molecular orbital is formed by combining the two atomic orbitals of the individual atoms. Mathematically, this can be done by the linear combination of atomic orbitals (LCAO), so that if ϕ_1 and ϕ_2 are the wave functions for the atomic orbitals, the wave function for the molecular orbital, ψ (psi), can be approximated by the equation $\psi = c_1\phi_1 + c_2\phi_2$ the coefficients, c_1 and c_2, are proportional to the contributions of the two atomic orbitals to the molecular orbital, and the squares of the coefficients are proportional to the electron density in the neighborhood of each atom.

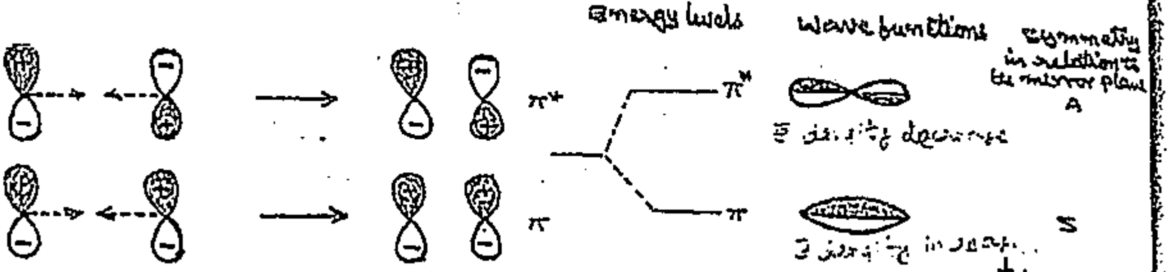


If the wave functions of the two atoms are out of phase, there will be a net repulsion rather than a net attraction between the two atoms. (The molecular wave function would then be $\psi = c_1\phi_1 - c_2\phi_2$) If the atoms are held at bonding distance, a new molecular orbital would still be formed, but this orbital would be an antibonding orbital, with an energy that exceeds that of the "zero level" to the same degree that the bonding orbital would be lower in energy. whereas the electron density in a bonding orbital is highest at the mid-point between the two atomic nuclei (if the two atoms are identical), the electron density in an antibonding orbital is lowest at that point. The wave function of the antibonding orbital is said to have a node at that point.

It would be noted that the number of molecular orbitals will always be the same as the number of atomic orbitals from which they are formed. Mathematically, bonding molecular wave functions will form when the wave functions of the individual atoms have the same sign: either both + or both −.

Instead of discussing only the interactions of two half-filled orbitals, we can consider orbitals in the abstract, free of any electrons they may hold. orbitals by themselves cannot form bonds; but we can imagine the interaction of any two orbitals as resulting in the formation of one low energy bonding orbital and one high-energy antibonding orbital that can potentially form new bonds (or new "antibonds") if electrons are inserted into them.

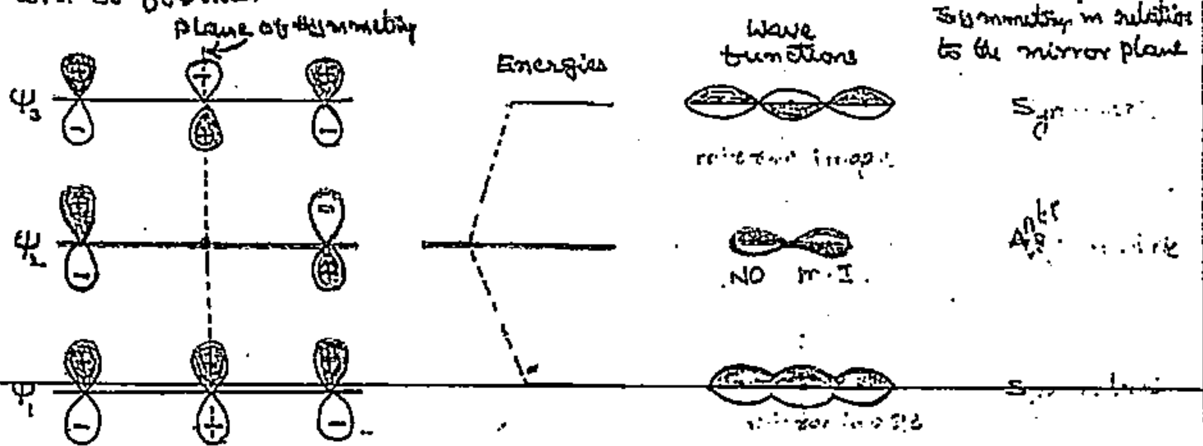
In the preceding discussion, we pictured spherical s-orbitals. If, instead, we consider the interaction of two p-orbitals, we should remember that each lobe of a p-orbital is opposite in phase to the other lobe. Thus, if two p-orbitals approach each other in a "side-by-side" manner, whether bonding or antibonding orbitals are formed will depend on whether the lobes coming together are in phase or out of phase (that is, whether they have the same or opposite signs). The bonding orbital formed from the side-by-side interaction of two p-orbitals is called a π-orbital, and the antibonding orbital is called a π^* orbital. The wave function for the π-orbital will have its largest value at the centre of the new orbital, while the wave function for the π^* orbital will have a node at the centre of the orbital.



Formation of π and π^* orbitals.

S = Symmetric
A = Anti-Symmetric

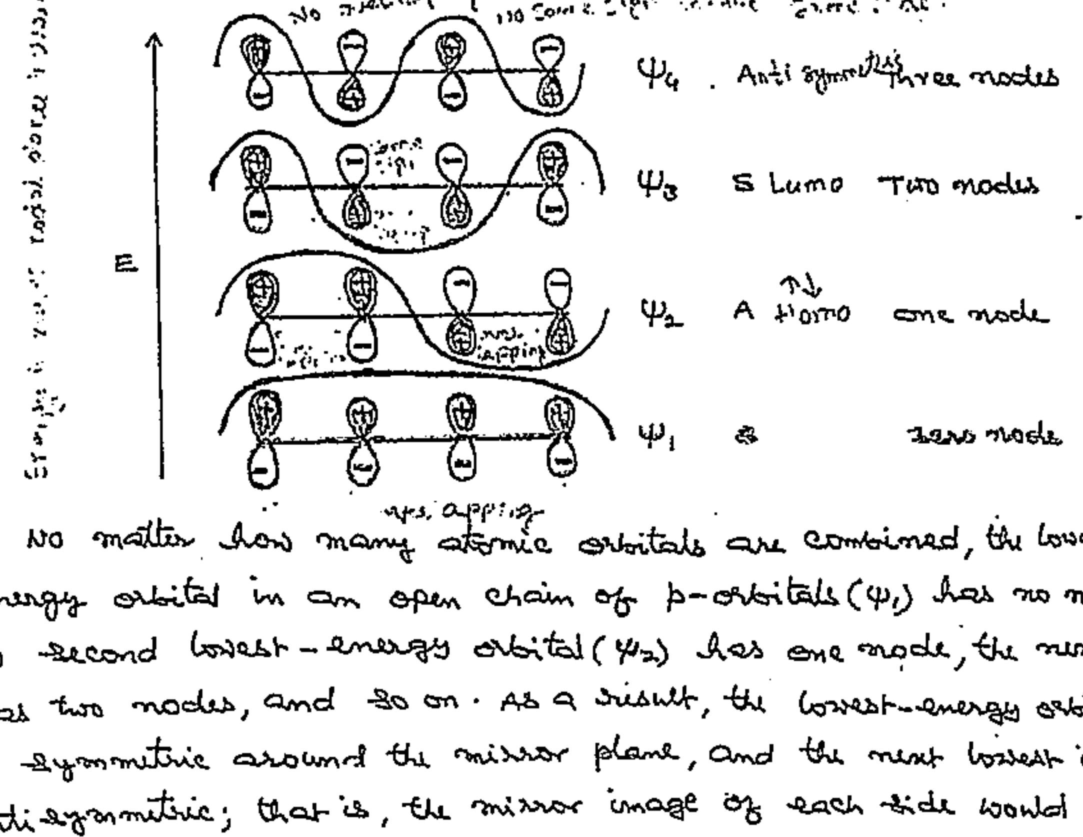
Suppose we try to combine atomic orbitals for three p-orbitals side by side. Three atomic orbitals must give rise to three new molecular orbitals. It is easy to see how two of these orbitals are formed. If all three orbitals are in phase, as shown in the diagram below, a new, very low energy molecular orbital (ψ_1) will be formed. If the center orbital is out of phase with both end orbitals, a high energy molecular orbital (ψ_3) with two nodes — that is, one in which each orbital repels the orbital next to it — will be formed.



combination of three atomic orbitals

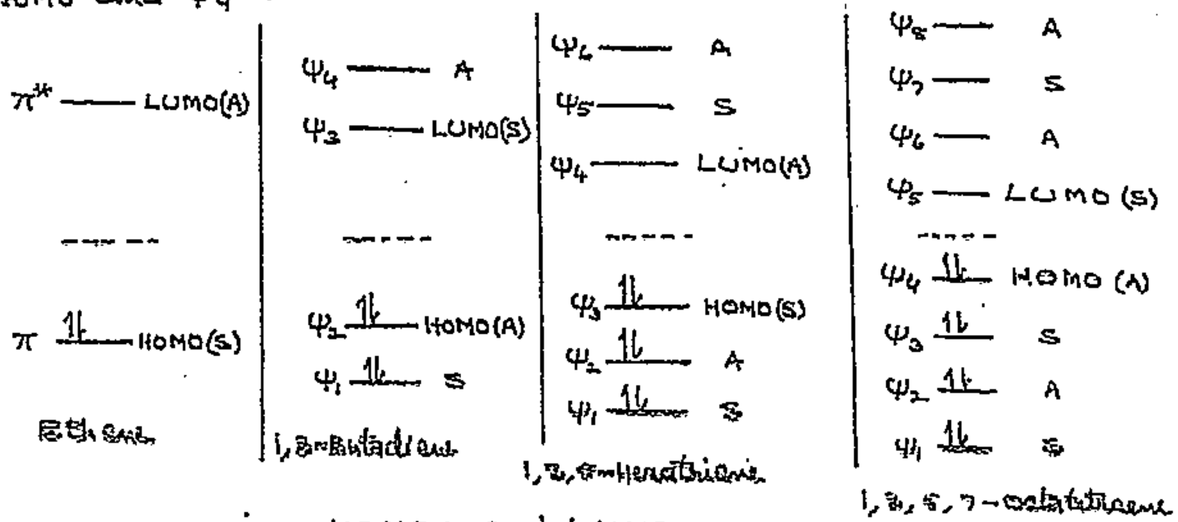
But how about the third orbital? There are constraints as to how you can combine atomic orbitals. When p-orbitals are lined up side by side, the array has a vertical plane of symmetry (a mirror plane) as a symmetry element. Therefore, the molecular orbitals formed by combining the atomic orbitals must also have a mirror plane as a symmetry element — that is, the central atomic orbital must have the same relationship to both end orbitals. However, molecular orbitals with the central orbital in phase and out of phase with the end orbitals were already constructed. The only other possibility is to eliminate the centre atomic orbital completely; that is, to have the coefficient of the wave function of the molecular orbital drop to zero at that point, so that the new orbital has a node at that atom. Since the two remaining atomic orbitals are far from each other, the third molecular orbital (ψ_2) will essentially remain at the "zero energy level" of atomic orbitals.

Molecular orbitals from the linear combination of four atomic orbitals can be formed in a similar manner as shown below.



No matter how many atomic orbitals are combined, the lowest-energy orbital in an open chain of p-orbitals (ψ_1) has no nodes, the second lowest-energy orbital (ψ_2) has one node, the next has two nodes, and so on. As a result, the lowest-energy orbital is symmetric around the mirror plane, and the next lowest is antisymmetric; that is, the mirror image of each side would replace each + lobe with a − lobe, and vice versa. The third lowest orbital is again symmetric, and the next is antisymmetric, around the mirror plane, until the highest-energy orbital is reached.

Of course, real molecules have electrons in some of their orbitals, so let us insert electrons into the orbitals to make neutral molecules. Following the standard "aufbau" approach, electrons will go into the lowest available orbitals, with, of course, a maximum of two electrons in each orbital. For the two atom system, the two electrons will fill the π orbital, while the π^* orbital will remain empty. The π orbital will therefore be the highest occupied molecular orbital (HOMO) and the π^* orbital will be the the lowest unoccupied molecular orbital (LUMO). In a four orbital system, the four electrons necessary to make a neutral molecule will fill orbitals ψ_1 and ψ_2, so that ψ_2 would be the HOMO and ψ_3 the LUMO. In a six orbital system, ψ_3 would be the HOMO and ψ_4 the LUMO.

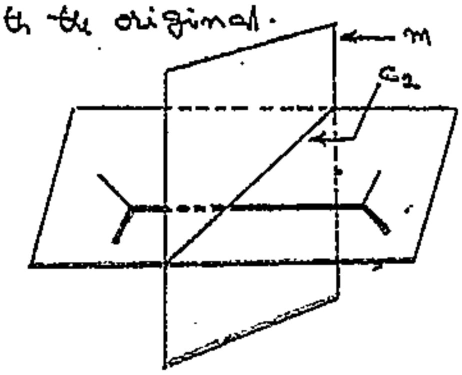


HOMOs and LUMOs

Notice that in systems containing $4n+2$ electrons the HOMO is symmetric, and in systems containing $4n$ electrons the HOMO is antisymmetric.

Symmetry properties of Molecular orbitals

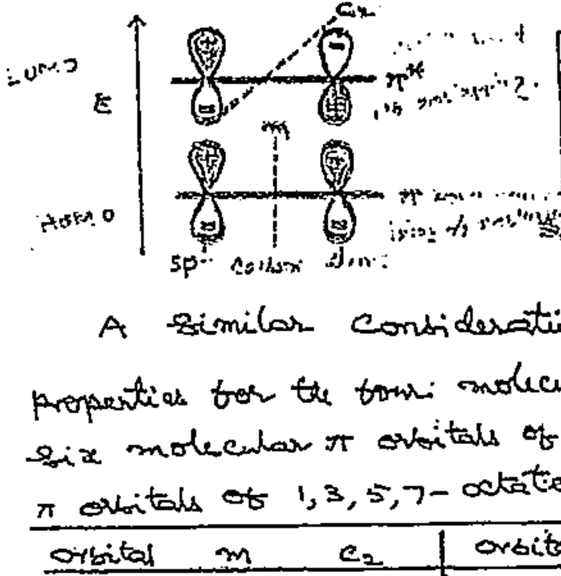
Various molecular orbitals are classified according to their two independent symmetry properties. Some molecular orbitals have the symmetry about a mirror plane (m) which bisects the molecular orbital and is perpendicular to the plane of the atoms. If the left half of the molecular orbital is the mirror image of the right half, the molecular orbital is symmetrical (S), and if not, it is antisymmetric (A). On the other hand, there are other molecular orbitals which do not have m symmetry but do display another type of symmetry about a two-fold axis (C_2) passing at right angles in the same plane, and through the centre of the frame work of the atoms forming the molecular orbital. Symmetry of this type is said to be present if the rotation of the molecule around the axis by 180° (360/2) results in a molecular orbital identical with the original.



starting material obtained by the rotation by 180°.

∴ C_2 - 180° rotate same

Let us examine symmetry properties of π orbitals of ethylene in ground state and also in the excited state. The ground state π-orbital is symmetric (S) with respect to the mirror plane, m, and anti-symmetric (A) with respect to the rotation axis, C_2. On the other hand, the antibonding orbital, π*, of ethylene is anti-symmetric (A) with respect to m and symmetric (S) with respect to the C_2 axis.



orbital	m	C_2
π*	A	S
π	S	A

✓

Symmetry properties π M.O.s in ethylene

A similar consideration leads to the following symmetry properties for the four molecular π orbitals of 1,3-butadiene, six molecular π orbitals of 1,3,5-hexatriene and eight molecular π orbitals of 1,3,5,7-octatetraene.

orbital	m	C_2
ψ_4	A	S
ψ_3	S	A
ψ_2	A	S
ψ_1	S	A

Symmetry properties of the π-M.O.s of 1,3-butadiene

orbital	m	C_2
ψ_6	A	S
ψ_5	S	A
ψ_4	A	S
ψ_3	S	A
ψ_2	A	S
ψ_1	S	A

Symmetry properties of the π M.O.s of 1,3,5-Hexatriene

orbital	m	C_2
ψ_8	A	S
ψ_7	S	A
ψ_6	A	S
ψ_5	S	A
ψ_4	A	S
ψ_3	S	A
ψ_2	A	S
ψ_1	S	A

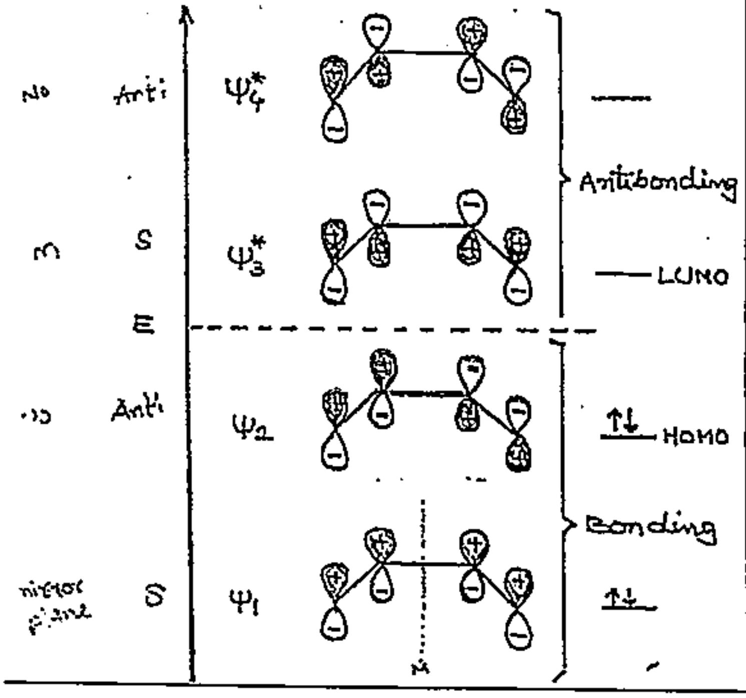
Symmetry properties of the π-M.O.s of 1,3,5,7-octatetraene

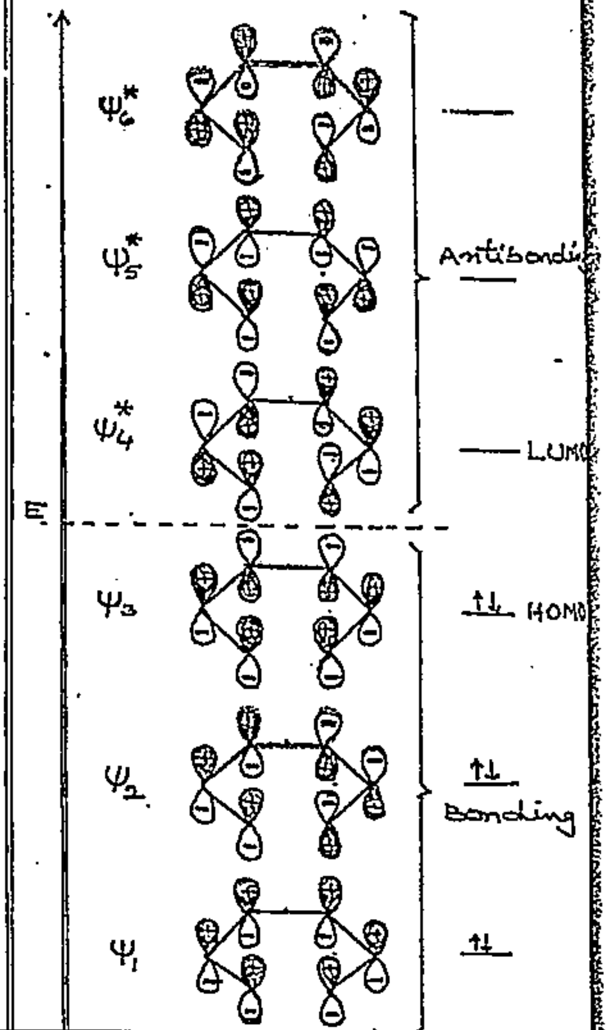
The four p-electrons of butadiene are accommodated in the first two π-molecular orbitals (ψ_1 & ψ_2) while the remaining two higher energy π molecular orbitals (ψ_3^* & ψ_4^*) remain unoccupied. Similarly, the six p-electrons of hexatriene are accommodated in the first three π molecular orbitals (ψ_1, ψ_2 & ψ_3) while the remaining three higher energy π molecular orbitals (ψ_4^*, ψ_5^* & ψ_6^*) remain unoccupied in the ground state.

(4n) π Homo (A)

(4n+2) π Homo (S)

Fmo - frontier molecular orbital





Molecular orbitals of Butadiene | Molecular orbitals of Hexatriene

The σ orbital of a C—C covalent bond has a mirror plane symmetry, and since a rotation of 180° through a mid point regenerates the same σ orbital, it has also a C_2 symmetry. A σ* orbital is antisymmetric with respect to both m and C_2

Orbital	m	C_2
σ*	A	A
σ	S	S

Symmetry [illegible]

For a linear conjugated π system the wave function ψ_n will have $n-1$ nodes. When $n-1$ is zero or an even integer, ψ_n will be symmetric with respect to m and antisymmetric with respect to C_2. When $n-1$ is an odd integer, ψ_n will have the symmetry exactly reversed. For any orbital, no. of nodes = $(n-1)$ nodes.

Node $(n-1)$	m	C_2
zero or even integer	S	A
odd integer	A	S

Symmetry elements in the orbital ψ_n of a linear conjugated π system

✓ [illegible] symmetry is over [illegible] symmetry allowed

4. Conservation of Molecular orbital symmetry

Woodward and Hoffmann in 1965 pointed out that symmetry of the molecular orbitals which participate in the chemical reaction determines the course of the reaction and they proposed the Principle of the conservation of orbital symmetry. This principle states that orbital symmetry is conserved in concerted reactions.

Concerted reactions are those in which a reactant is converted into the product without the intervention of an intermediate, and bond formation and bond breakage occur synchronously, though not necessarily symmetrically. In a cyclic concerted reaction, i.e., reaction involving a cyclically conjugated transition state, orbitals in the reactant can only transform into those orbitals in the product, which have the same symmetry properties with respect to the elements of symmetry preserved in the reaction. The energy of the transition state of a symmetry-allowed process will necessarily be lower than that of the alternative symmetry-forbidden path and even when this difference is small, a concerted reaction will take the path of least resistance, i.e., the symmetry-allowed path, if that path is available.

for Pericyclic reaction symmetry and [illegible]
to energy shows [illegible]

5. Methods to explain pericyclic reactions

(I) Woodward-Hoffmann rules – Correlation Diagrams

These rules require the smooth passage of the participating molecular orbitals of the reactants into the molecular orbitals of the product. The process is described by a correlation diagram. In case the conversion of the reactant orbitals into the product orbitals is favoured in terms of energy and if orbital symmetry is <u>conserved</u> in the process, the reaction is called symmetry-allowed (The symmetries of the orbitals to be maintained are around the mirror plane, m, and the two fold axis of rotation as a symmetry element). In case either of these conditions (energy and orbital symmetry) is not met the reaction is called symmetry-forbidden.

highest occupied m.o. lowest unoccupied m.o.

(II) HOMO-LUMO Method – FMO Approach

It is depends on [illegible] m.o.

The Fuki's method concentrates on the so called Frontier Molecular orbitals (FMO), the Highest occupied Molecular orbital (HOMO) and the Lowest Unoccupied Molecular orbital (LUMO). In ground state butadiene, for example, ψ_2 is the HOMO since it has two electrons and ψ_3^* is the LUMO since it is vacant.

The Fuki's FMO approach examines as to how the orbitals of HOMO or in some cases, the orbitals of HOMO of one component and the LUMO of the other <u>overlap</u> to form new bonds. If the overlaps are favourable (<u>bonding overlaps</u>) then the reaction is allowed and if not favourable (antibonding overlaps) then the reaction is forbidden.

Here energy decrease.

Bonding overlap → Inphase overlap. (+)(+) — [illegible] ... Antibonding ... no bond formation.

(III) Mobius-Huckel Analysis – Perturbational Molecular orbital (PMO) Method.

Twisted.

The idea behind this method is that a pericyclic reaction which proceeds through a transition state which has aromatic characteristics (electron interaction is energetically favourable) is allowed process. For systems of $4n+2$ electrons Huckel transition states are aromatic; for systems of $4n$ electrons Mobius transition states are aromatic.

(4n+2) anti aromatic.

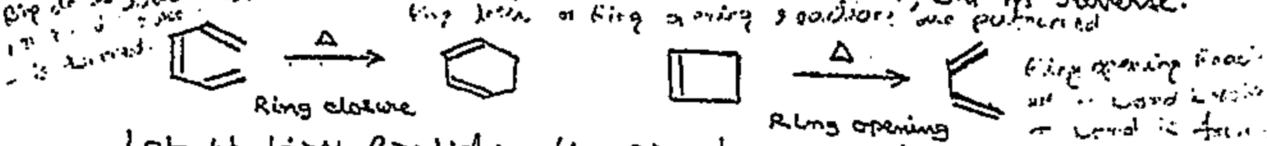
[illegible] anti [illegible] (or) Mobius system. It appears rarely [illegible] twisting exist [illegible] rotation

6. Correlation Diagrams

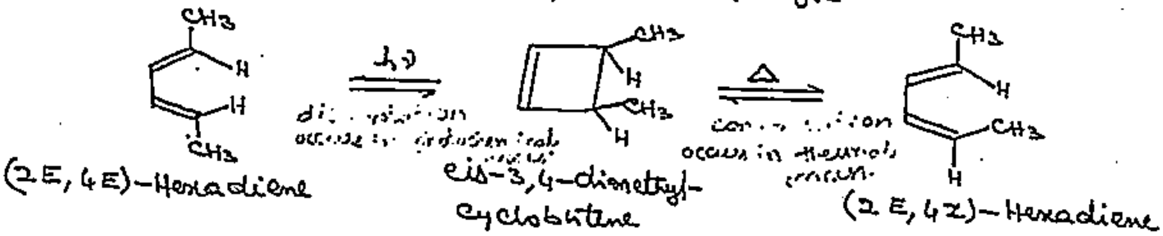
A correlation diagram is a chart that follows the molecular orbitals of the starting materials in a reaction and shows how they are converted to the molecular orbitals of the products.

(i) Correlation diagrams for Electrocyclic Reactions.

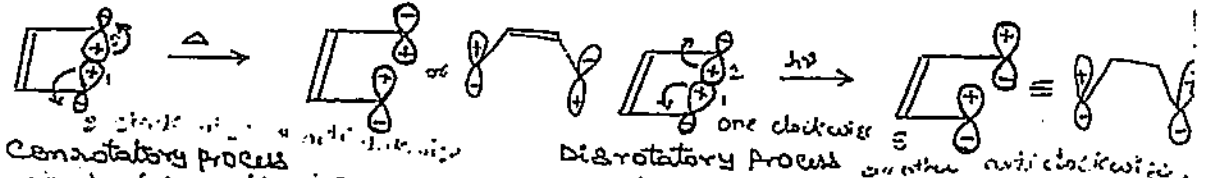
Electrocyclic reactions are intramolecular pericyclic reactions which under the influence of heat or light involve either the formation of a ring with the generation of one new σ-bond and the consumption of one π-bond, or the reverse. The reverse reaction, ring opening proceeds by the same mechanism, but in reverse.



Let us first consider the simplest example in which a cyclobutene system opens to a 1,3-butadiene. The reaction can be performed thermally or photochemically, and under either condition the rearrangement is completely stereospecific.



A σ bond of cyclobutene must break to yield the open-chain diene and obviously this bond may break in two ways. First, the two atomic orbital components of the σ bond may both rotate in the same direction, clockwise or anticlockwise (Conrotatory process) as under thermal condition. Second, the atomic orbitals may rotate in opposite directions, one clockwise, and the other anticlockwise (Disrotatory process) as under photochemical condition.



Depending upon these modes of rotation, the substituents may rotate in the same direction (conrotatory) or in opposite directions (disrotatory).

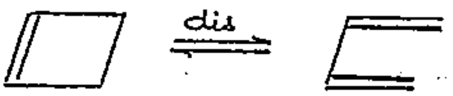
However, from the above analysis it is incorrect to infer that all electrocyclic reactions proceed in a conrotatory fashion under thermal condition and in a disrotatory mode on irradiation. For instance, irradiation of (2E, 4Z, 6E)-octatriene (1) yields trans-5,6-dimethylcyclohexa-1,3-diene (2), while thermal ring-closure leads to cis-5,6-dimethylcyclohexa-1,3-diene (3).

An electrocyclic reaction is a concerted and cyclic process in which reactant orbitals transform into product orbitals. The transition-state of such reactions should be intermediate between the electronic ground state of starting material and product. Obviously, the most stable transition-state will be the one which conserves the symmetry of the reactant orbitals in passing to product orbitals. In other words, a symmetric (S) orbital in the reactant must transform into a symmetric orbital in the product and that an antisymmetric (A) orbital must transform into an antisymmetric orbital. If the symmetries of the reactant and product orbitals are not the same, the reaction will not take place in a concerted manner.

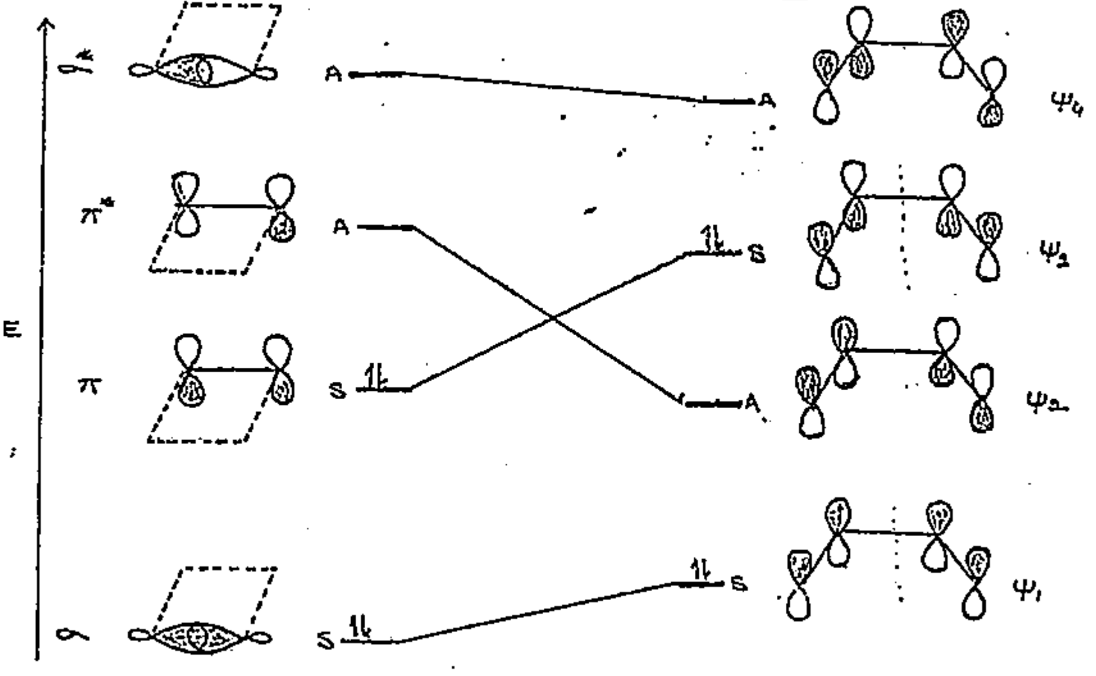
Let us exemplify the above principle by analysing the cyclobutene-butadiene transformation. In the case of the disrotatory ring-opening, cyclobutene preserves a plane of symmetry (m) throughout the transformation while a two-fold (C_2) symmetry axis is maintained at all times in the conrotatory mode of ring-opening. The orbitals of cyclobutene which are directly involved are σ and π and the related antibonding orbitals σ* and π*; these orbitals pass on to the four molecular π orbitals of butadiene, viz., ψ_1, ψ_2, ψ_3 & ψ_4. In the ground state of cyclobutene and butadiene, only σ, π and ψ_1, ψ_2 orbitals are filled with electron pairs.

Let us first analyse a disrotatory opening of cyclobutene in which a mirror plane symmetry (m) is maintained.

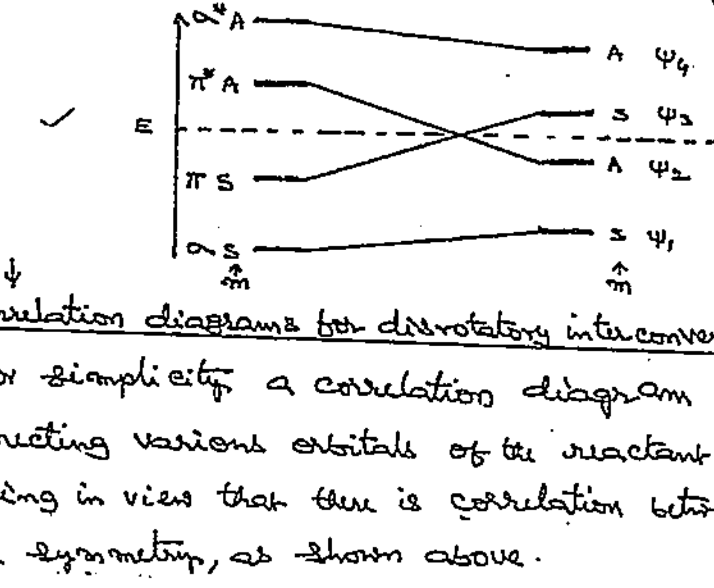
under thermal condition
disrotation not allowed.



m symmetry maintained



mirror plane symmetry



Ground state orbitals of reactants transformed to ground state orbitals of products.
hν — excited state ground state of correlation.
so hν applied

Correlation diagrams for disrotatory interconversion of cyclobutene-butadiene

For simplicity a correlation diagram can be constructed by connecting various orbitals of the reactant and product by lines keeping in view that there is correlation between orbitals of the same symmetry, as shown above.

The following two conclusions can be drawn by a close inspection -

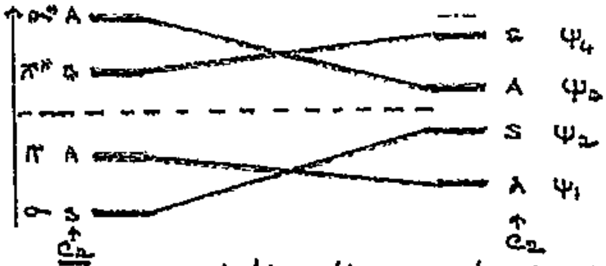
(A) We expect a thermal transformation to take place only when the ground state orbitals of the reactants correlate with the ground state orbitals of the products. Although in the above diagram the cyclobutene ground state orbital σ correlates with the butadiene ground state orbital ψ_1, the π orbital of the former does not correlate with ψ_2 of the latter. Instead it correlates with ψ_3 which is an excited state and an antibonding orbital. Thermal transformation of cyclobutene ⇌ butadiene system by disrotatory process is thus symmetry-forbidden.

(B) Irradiation of cyclobutene produces the first excited state in which an electron is promoted from π to π^* orbital and in this case σ, π and π^* orbitals of cyclobutene correlate with ψ_1, ψ_2 & ψ_3 orbitals of butadiene. In other words, the first excited state of cyclobutene correlates with the first excited state of butadiene and hence disrotatory ring-opening (and ring closing) is photochemically a symmetry allowed process.

$$\underset{\text{Ground state}}{\sigma^2\pi^2} \xrightarrow{h\nu} \underset{\text{First excited state}}{\sigma^2\pi\pi^*} \rightleftharpoons \underset{\text{First excited state}}{\psi_1^2\psi_2\psi_3} \xleftarrow{h\nu} \underset{\text{Ground state}}{\psi_1^2\psi_2^2}$$

Working on similar lines, we can construct another correlation diagram (as shown below) for the conrotatory opening in which a C_2 axis of symmetry is maintained throughout the reaction.

C_2 symmetry maintained.



Correlation diagram for conrotatory process.

Two conclusions may again be drawn from the above correlation diagram.

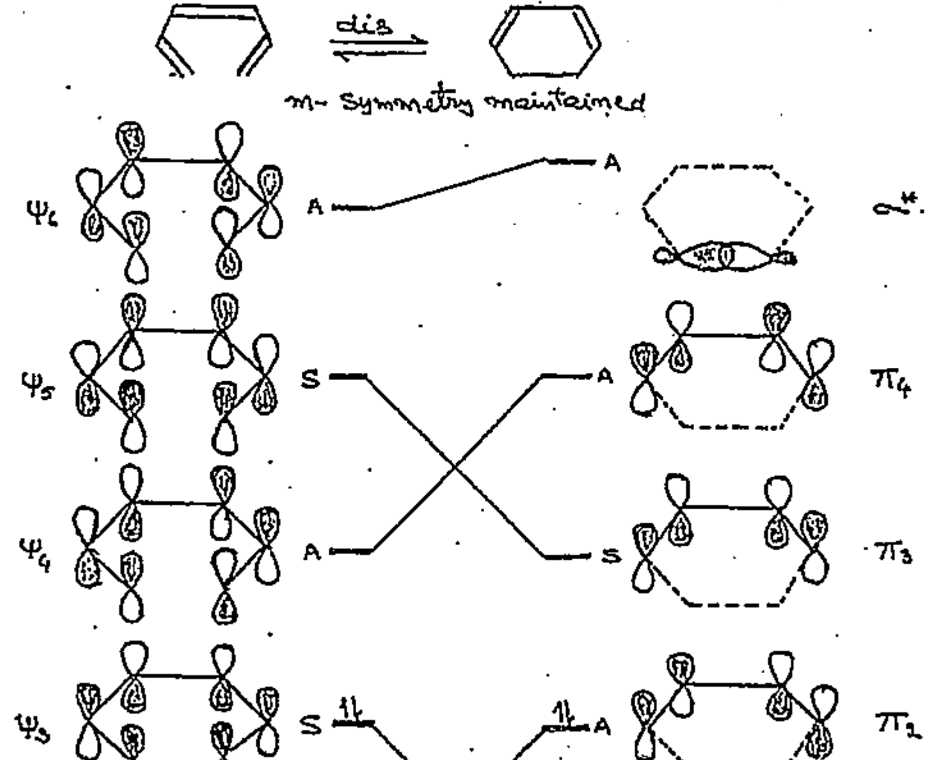
(A) Since there is correlation between the ground state orbitals of cyclobutene and butadiene ($\sigma^2\pi^2 \rightleftharpoons \psi_1^2\psi_2^2$) a thermal conrotatory process in either direction is a symmetry-allowed process.

(B) The first excited state of cyclobutene ($\sigma^2\pi\pi^*$) correlates with the upper excited state ($\psi_1^2\psi_2\psi_4$) of butadiene thus making it a high energy symmetry-forbidden process. Similarly, the first excited state of butadiene ($\psi_1^2\psi_2\psi_3$) correlates with a high energy upper excited state ($\sigma^2\pi\sigma^*$) of cyclobutene. In other words, a photochemical conrotatory process in either direction is symmetry-forbidden.

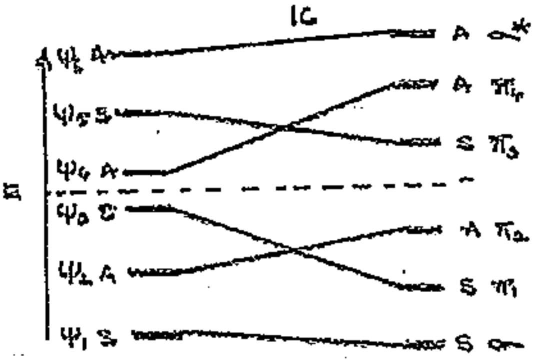
Thus it becomes clear from the above considerations that thermal opening of the cyclobutene proceeds in a conrotatory process while photochemical interconversion involves a disrotatory mode.

These generalisations are true for all systems containing $4n$ π electrons where $n = 1, 2, 3$, etc. However, for systems containing $(4n+2)$ π electrons theoritical predictions are entirely different and are in conformity with the actual observations. A typical system of this type is the interconversion of cyclohexadiene and hexatriene. In this transformation six molecular orbitals (ψ_1 to ψ_6) of hexatriene and six molecular orbitals (four π and two σ) of cyclohexadiene are actually involved and, therefore, need to be considered.

The correlation diagram for the disrotatory pathway is constructed



Disrotatory interconversion of a 1,3,5-hexatriene and a cyclohexadiene



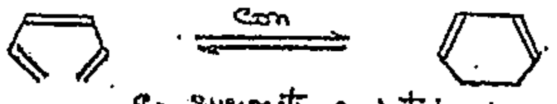
Disrotatory interconversion of a 1,3,5-hexatriene and a cyclohexadiene

The following conclusions may be drawn from these correlation diagrams.

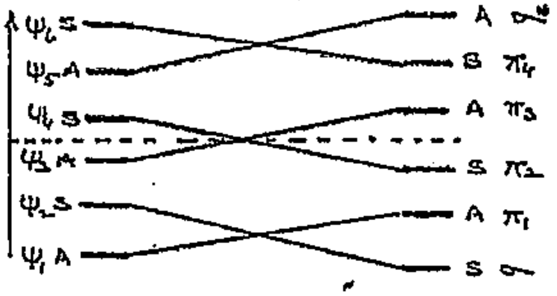
(A) In the disrotatory mode, ground state bonding orbitals of 1,3,5-hexatriene correlate with the ground state bonding orbitals of cyclohexadiene and so it is a thermally allowed process.

(B) But in the conrotatory mode (C_2 symmetry), ground state bonding orbitals of hexatriene do not correlate with the ground state bonding orbitals of cyclohexadiene. Since the presence of two electrons in π_3 is a very high energy process, a conrotatory mode is prohibited under thermal conditions.

(C) However, if we promote an electron to ψ_4 in hexatriene (obviously by irradiation) then the orbitals of the reactant with C_2 symmetry correlate with the first excited state of the product.



C_2 symmetry maintained



Conrotatory interconversion of a hexatriene and a cyclohexadiene

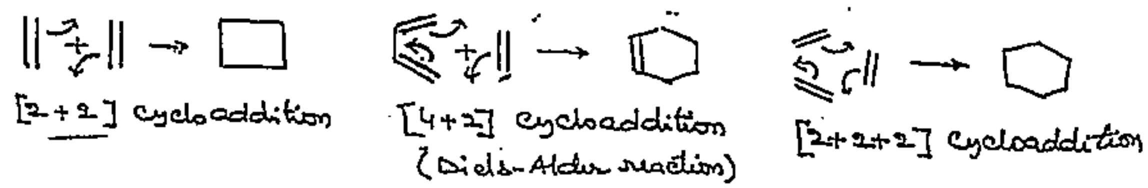
Therefore, photochemical interconversion is allowed in the conrotatory pathway. These generalisations are true for all the systems containing $(4n+2)\pi$ electrons, where $n = 0, 1, 2$ etc. Thus, Woodward–Hoffmann rules for electrocyclic reactions may be summed up as in the following Table.

Selection rules for electrocyclic reactions

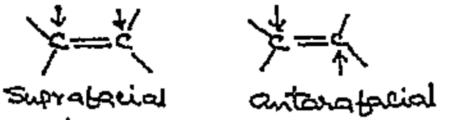
Number of π-electrons	Thermal condition	Photochemical condition
4n	con	dis
4n+2	dis	con

(ii) Correlation diagrams for cycloaddition reactions

Cycloadditions are reactions in which at least two new σ bonds are formed simultaneously, so as to convert two or more open-chain molecules into rings. These reactions are classified on the basis of π electrons involved in each component.

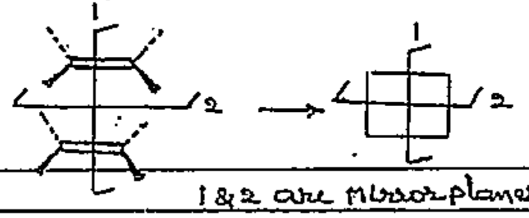

[2+2] cycloaddition
[4+2] cycloaddition (Diels-Alder reaction)
[2+2+2] cycloaddition

Since in a typical cycloaddition reaction, there is addition of two systems containing double bonds, it is logical to expect the addition to occur on the same or the opposite side of the system. Addition to the lobes on the same side of a π system is called suprafacial addition, while addition to lobes on opposite sides of a π system is termed Antarafacial addition. These modes of addition are identified by the symbols 's' and 'a' respectively. Thus cycloaddition of two π bonds each reacting suprafacially would be called $[\pi 2_s + \pi 2_s]$ reaction.



Orbital symmetry in cycloaddition reaction

To illustrate the control of orbital symmetry on cycloaddition reactions, we choose the simplest example in which the two ethylene molecules approach each other vertically $(2_s + 2_s)$ to form a molecule of cyclobutane. Such a system has vertical and horizontal planes of symmetry which shall be referred to as as 1 and 2, respectively.



1 & 2 are Mirror planes

In this transformation we are mainly concerned with the four π orbitals of the two ethylene molecules and the four σ orbitals of cyclobutane.

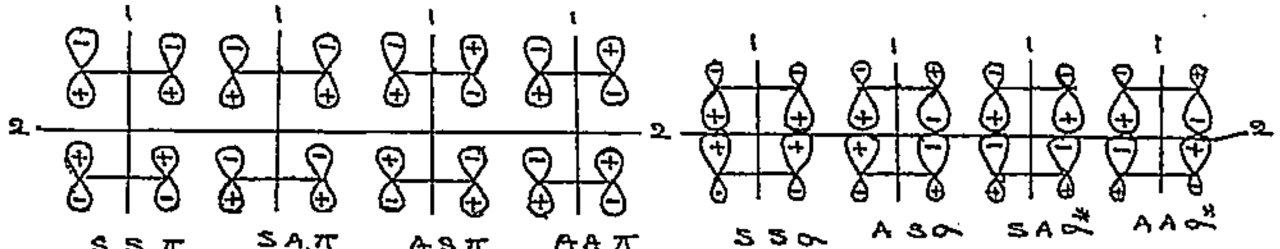
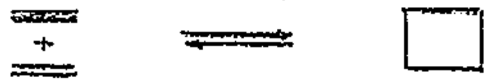


Fig. 1 S = Symmetric & A = Antisymmetric with respect to mirror plane (σ).

The symmetry properties of the remaining orbitals remain unchanged during the reaction and need not be considered further. The shapes and symmetry properties of these four π orbitals (π, π bonding; π^*, π^* antibonding) and four σ orbitals (σ, σ bonding; σ^*, σ^* antibonding) are listed in Fig. 1. The symmetry classifications (SS, SA, AS and AA) are with respect firstly to plane of symmetry 1 and then to 2.

On the basis of the above information, a correlation diagram (Fig. 2) may be drawn in which the levels of like symmetry are connected by lines.

3m



2+2 has [illegible]
Ethylene

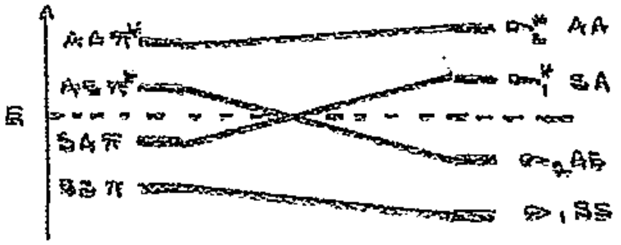


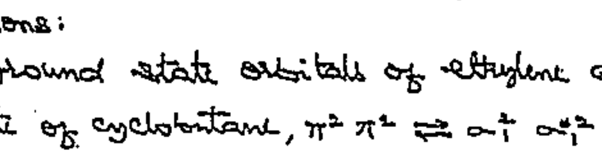
Fig. 2. Correlation diagram for cycloaddition of ethylene to cyclobutane

A close examination of the diagram leads us to the following two conclusions:

(A) The ground state orbitals of ethylene correlate with an excited state of cyclobutane, $\pi^2 \pi^2 \rightleftharpoons \sigma_1^2 \sigma_1^{*2}$. Consequently, the combination of two ground state ethylene molecules cannot result in the formation of ground state cyclobutane while conserving the orbital symmetry. Hence the thermal process is symmetry-forbidden.

(B) As there is correlation between the first excited state of the ethylene system and cyclobutane, $\pi^2 \pi \pi^* \rightleftharpoons \sigma_1^2 \sigma_2 \sigma_1^*$, the photochemical process is symmetry-allowed.

A similar correlation diagram may be constructed for the Diels-Alder reaction which is a [4+2] cycloaddition reaction. In this case there is only a single vertical plane of symmetry bisecting the carbon framework of two reactants and the product.



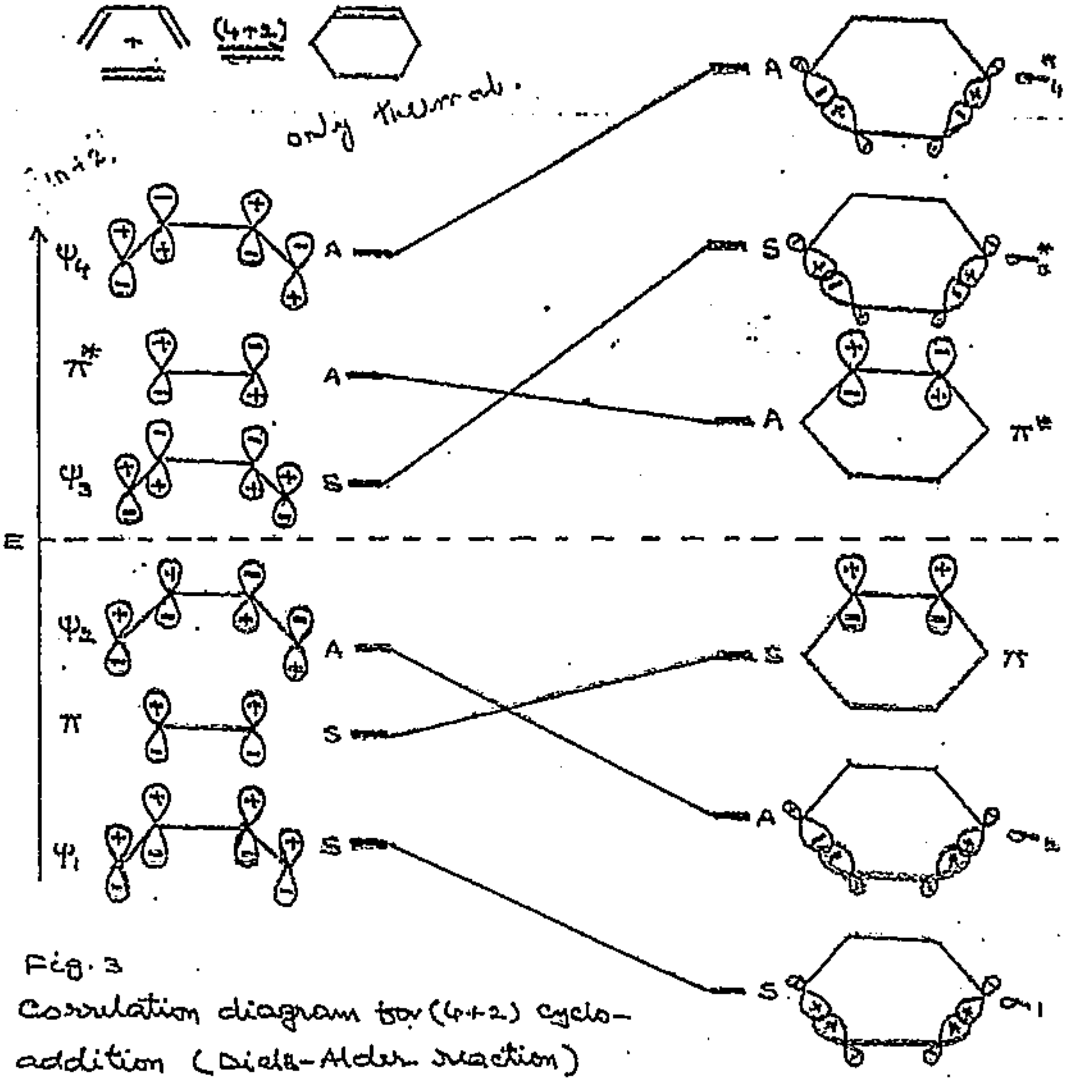


Fig. 3
Correlation diagram for (4+2) cyclo-addition (Diels-Alder reaction)

In this transformation, we have to consider six orbitals each of the reactants and the product. The ground state orbitals of the reactants are ψ_1, ψ_2 (of butadiene) and π (of ethylene) while ψ_3, π^* and ψ_4 are the corresponding antibonding orbitals. Similarly, the ground orbitals of cyclohexene are represented by σ_1, σ_2 and π; the remaining three orbitals are antibonding. All these orbitals along with their symmetry properties are shown in the above correlation diagram (Fig.3)

It becomes immediatily clear from an inspection of the above diagram that there is a smooth transformation of the reactant orbitals into the product orbitals. The Diels-Alder reaction (4+2) cycloaddition is, therefore, a thermally allowed process. on the other hand, photochemical transformation is not possible as the first excited state of the reactant does not correlate with the first excited state of the product. Rather it correlates with the upper excited state of the product.

20 further [illegible]

⑦ HOMO-LUMO Method - FMO Approach

(1) Electrocyclic reactions

In FMO analysis of electrocyclic reactions, the following points may be considered.

- HOMO and LUMO are the Frontier Molecular orbitals (FMOs).
- The normal electronic configuration of a molecule is called its ground state.
- In the ground state of ethylene ψ_1 is the HOMO and ψ_2^* is the LUMO (since it is vacant). When ethylene is raised to its excited state in a photochemical reaction the ψ_2^* orbital with one electron in it then becomes HOMO.

Ground state of ethylene			Excited state of ethylene	
ψ_2^* —	LUMO	$\xrightarrow{h\nu}$	ψ_2^* ↓	HOMO
ψ_1 ↑↓	HOMO		ψ_1 ↑	

Ground state energy levels — Excited state energy levels

- In ground state of 1,3-butadiene, ψ_2 is the HOMO and ψ_3^* is the LUMO. When it absorbs a photon during a photochemical reaction, an electron is promoted from the HOMO (i.e., ψ_2) to the LUMO (i.e., ψ_3^*) which then becomes the new HOMO

Ground state of 1,3-butadiene			Excited state of 1,3-butadiene	
ψ_4^* —			ψ_4^* —	LUMO
ψ_3^* —	LUMO	$\xrightarrow{h\nu}$	ψ_3^* ↓	HOMO
ψ_2 ↑↓	HOMO		ψ_2 ↑	
ψ_1 ↑↓			ψ_1 ↑↓	

- In the ground state of 1,3,5-hexatriene, ψ_3 is the HOMO and ψ_4^* is the LUMO. In its excited state ψ_4^* is HOMO and ψ_5^* is LUMO

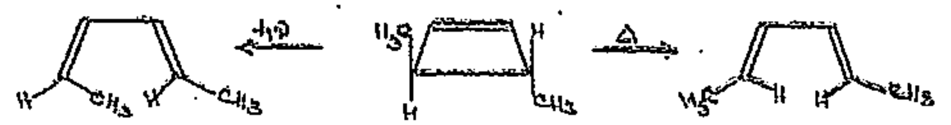
Ground state of hexatriene			Excited state of hexatriene	
ψ_6^* —			ψ_6^* —	
ψ_5^* —			ψ_5^* —	LUMO
ψ_4^* —	LUMO	$\xrightarrow{h\nu}$	ψ_4^* ↓	HOMO
ψ_3 ↑↓	HOMO		ψ_3 ↑	
ψ_2 ↑↓			ψ_2 ↑↓	
ψ_1 ↑↓			ψ_1 ↑↓	

- The ground state HOMO and the excited state HOMO always have opposite symmetries

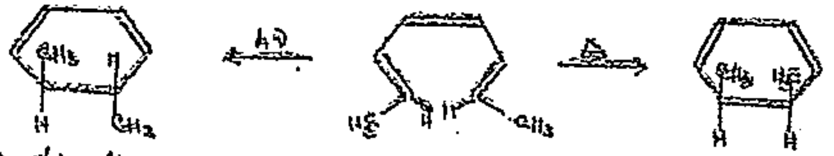
- Electrocyclic reactions are stereoselective (a stereoselective reaction leads to the exclusive formation of one of the several possible stereoisomeric compounds) and are also completely stereospecific (in a stereospecific reaction a given isomer gives one product or d,l pair while another stereoisomer gives the opposite product). The stereoisomer formed in an electrocyclic reaction depends on whether the reaction is thermally induced or photo-induced. The stereochemistry of electrocyclic reactions can be studied by using suitably substituted molecules as shown below.

4

(2E,4E)-hexadiene   cis-3,4-dimethylcyclobutene   (2Z,4Z)-hexadiene

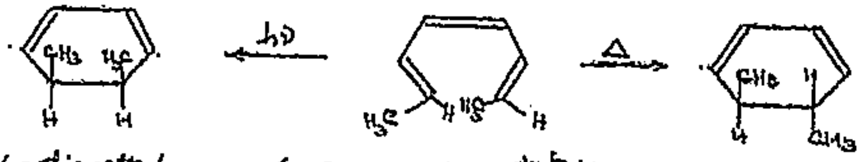


2 (2E,4Z)-hexadiene   Trans-3,4-dimethylcyclobutene   (2E,4E)-hexadiene



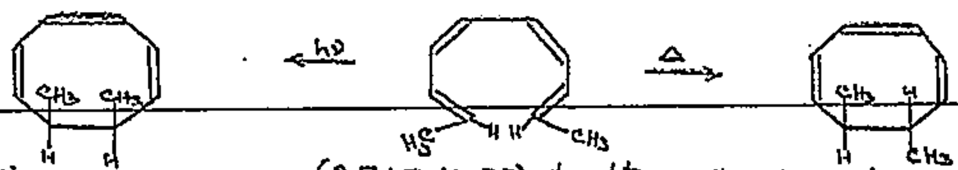
10 Trans-5,6-dimethyl-1,3-cyclohexadiene   (2E,4Z,6E)-octatriene   cis-5,6-dimethyl-1,3-cyclohexadiene

12

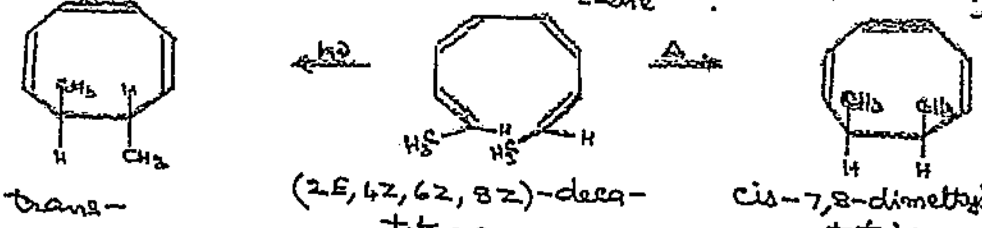


cis-5,6-dimethyl-1,3-cyclohexadiene   (2E,4Z,6Z)-octatriene   Trans-5,6-dimethyl-1,3-cyclohexadiene

#4

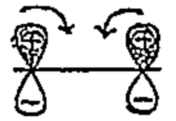


cis-   (2E,4Z,6Z,8E)-decatetraene   Trans-7,8-dimethyl-1,3,5-octatriene

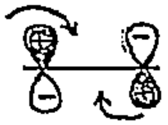


trans-   (2E,4Z,6Z,8Z)-decatetraene   cis-7,8-dimethyl-1,3,5-octatriene

- All the electrocyclic reactions are accounted for by orbital symmetry arguments by looking only at the symmetries of two outermost lobes of the polyene. Thus the inner lobes may not be shown and if shown, these may not be labelled +ve or –ve.
- For bond formation the outermost lobes must rotate – a positive lobe overlapping a positive lobe or a negative lobe overlapping a negative lobe. When the two lobes of like sign are on the same side of the molecule (symmetry arrangement) the two orbitals (on the ends of the π system) must rotate in different direction (clockwise and counterclockwise) and this motion is termed DISROTATORY. When, however, the lobes of like sign are on opposite sides of the molecule (anti-symmetric arrangement) both orbitals must rotate in the same direction (both clockwise or both counter clockwise) and this motion is termed CONROTATORY.



Disrotation



Conrotation

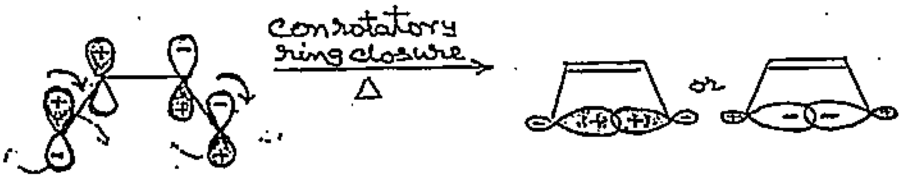
- The stereochemical outcome of an electrocyclic reaction depends on the number of double bonds in a polyene and on whether the reaction is thermal(Δ) or photochemical ($h\nu$). A thermal electrocyclic reaction involving $4n$ π electrons ($n = 1, 2, 3 \cdots$) proceeds with conrotatory motion (i.e., a motion in which the bonds rotate in the same direction) while the photochemical reaction involves disrotatory motion (a motion in which the bonds rotate in opposite directions).

A thermal reaction involving $(4n+2)$ π electrons (where $n = 0, 1, 2 \cdots$) proceeds with disrotatory motion while the photochemical reaction proceeds with conrotatory motion.

- The direction taken by an electrocyclic reaction is dependent on the relative stabilities of the ring and open-chain reactants. In the case of cyclobutanes the open-chain structure is favoured because of the strain in the ring, during the thermal reaction.

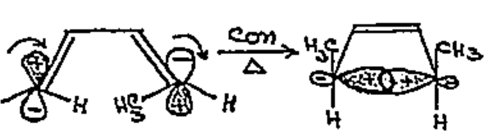
Thermal cyclisation of Butadienes (4n systems)

The ground state HOMO of a conjugated diene is ψ_2. For the bond formation, the overlap of lobes on C_1 and C_4 of the diene is required. For this to happen, the two end carbons of the conjugated π system need only to rotate so that their p-orbitals begin to overlap to form the new σ bond e.g. of the cyclobutene.

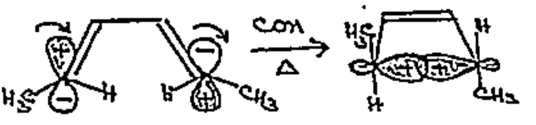


It is only the conrotatory motion (both carbons rotate in the same direction, shown in a clockwise way in the above figure) which brings the lobes of the same phase together for bond formation. In case the conrotatory motion occurs in the opposite, counter clockwise direction, even then the lobes of the same phase sign will still overlap. However, the disrotatory motion will bring the lobes of opposite phase together and this will be repulsive and antibonding

Conrotatory motion, therefore, explains the observed stereochemistry of the product on thermal cyclisation of a disubstituted butadiene as shown below. Thus during cyclisation of (2E,4Z)-hexadiene, both the methyl groups rotate in the same direction to end up on the same side of the ring to give cis products. (2E,4E)-Hexadiene similarly cyclise to form trans products.



(2E,4Z)-Hexadiene cis-3,4-dimethyl cyclobutene



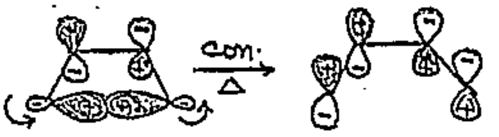
(2E,4E)-Hexadiene Trans-3,4-dimethyl-cyclobutene

Thus, conrotation of a diene (or 4n π-system) is thermally allowed, while disrotation is forbidden.

Thermal ring opening of Cyclobutenes

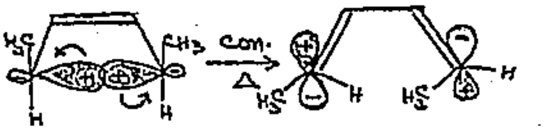
In keeping with the principle of microscopic reversibility, the reverse process of thermal ring opening takes exactly the same path as that of cyclisation (4π electrons in the transition state)

Due to conrotatory motion a σ bond will open so as to give the resulting p-orbitals which will have the symmetry of the highest occupied molecular π orbital of the product. Since in the case of cyclobutenes the HOMO of the product (i.e., a butadiene) in the thermal reaction is ψ_2, therefore, the cyclobutene must open so that on one side the positive lobe lies above the plane, while on the other side it is below it. This process also forces the stereochemistry in the product formed from a substituted cyclobutene.



σ-HOMO for thermal reaction

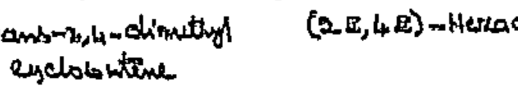
Diene-HOMO for thermal reaction



cis-3,4-dimethyl cyclobutene

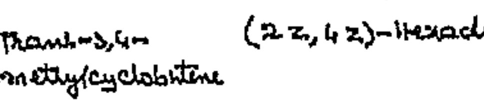
(2E,4Z)-Hexadiene

Trans-3,4-dimethylcyclobutene can undergo conrotatory ring opening which could in principle give two products depending on the sense of rotation. When, however, both methyl groups turn inwards a severe steric crowding would result in the formation cis,cis-dimethyldiene. This process will raise the activation energy compared with the process of formation of trans,trans-isomer. As a result only the trans,trans-isomer is formed.



Trans-3,4-dimethyl cyclobutene

(2E,4E)-Hexadiene

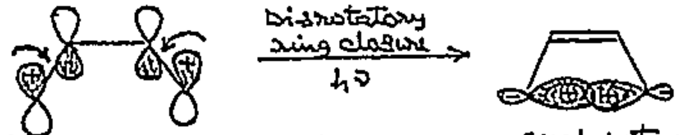


Trans-3,4-dimethylcyclobutene

(2Z,4Z)-Hexadiene

Photochemical interconversion of 3,4-Dimethylcyclobutene and 2,4-Hexadiene

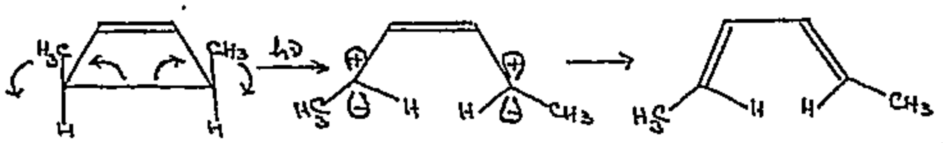
The irradiation of the diene will lead to the promotion of an electron into the orbital of next higher energy level i.e. ψ_3^* (symmetric) and consequently the HOMO to be considered now is ψ_3^*. It is now the disrotatory motion which results in bonding situation.



Excited state ψ_3^*; HOMO is symmetric

cyclobutene

Similarly, the reverse reaction also involves a disrotatory motion, which establishes the stereochemistry on suitably substituted substrates.



Disrotatory motion
cis-3,4-dimethylcyclobutene

(2E,4E)-Hexadiene

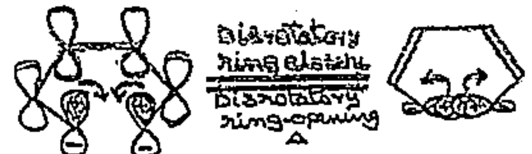
The stereochemical outcome of these reactions is that a thermal electrocyclic reaction involving $4n$ π electrons (where $n = 1,2,3\cdots$) takes place by conrotatory motion, and the photochemical reaction proceeds with disrotatory motion.

Stereochemistry. In case the bonds to the substituents in the reactant are in opposite directions, the substituents will be cis in the product, if the ring closure is disrotatory, and trans if ring closure is conrotatory. In case these are in the same direction, these will be trans in the product for disrotatory ring closure and cis if ring closure is conrotatory.

Interconversion of 1,3-cyclohexadiene and 1,3,5-hexatriene ($4n+2$ π-systems)

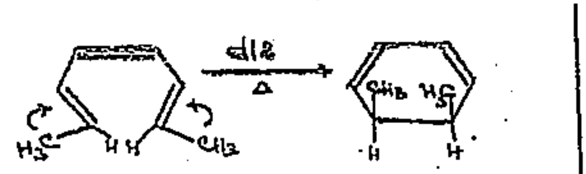
A thermal electrocyclic reaction involving $(4n+2)$ π electrons where $n = 0,1,2\cdots$, proceeds with disrotatory motion, and the photochemical reaction proceeds with conrotatory motion. Stereochemistry is the same as seen for $4n$ systems.

The HOMO for the ground state of a hexatriene is $\psi_3(S)$ and when compared with the HOMO of the ground state of butadiene i.e. $\psi_2(A)$ one finds that the relative symmetry about the terminal carbons is opposite. Thus unlike the thermal opening of a cyclobutene (or the reverse reaction – the ring closure) which requires conrotatory motion, in the thermal ring-opening of a 1,3-cyclohexadiene and likewise the ring-closure requires a disrotatory motion. Based on these arguments 2E,4Z,6E-octatriene gives specifically cis-5,6-dimethylcyclohexadiene. Similarly, for the reverse reaction, Since the positive lobes must lie on the same side of the plane (consider ψ_3 i.e. HOMO of a triene) a disrotatory motion has to occur.



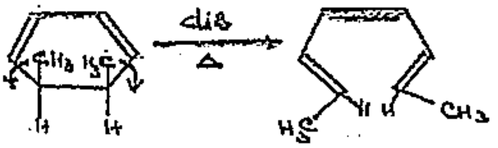
Ground state HOMO, ψ_3 of hexatriene is symmetric

1,3-cyclohexadiene



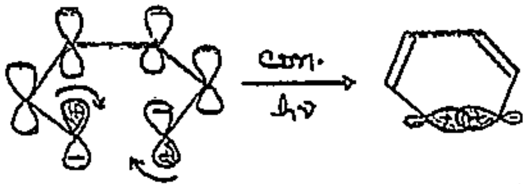
(2E,4Z,6E) octatriene

cis-5,6-dimethyl-1,3-cyclohexadiene



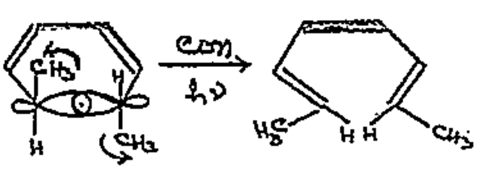
(2E,4Z,6E)-octatriene

In the excited state of hexatriene, ψ_4^* is the HOMO (irradiation results in the promotion of an electron into the orbital of the next higher energy level). Therefore, photochemical opening of a 1,3-cyclohexadiene, and likewise, the ring closure requires conrotatory motion. Thus, the ring-opening of trans-5,6-dimethyl-1,3-cyclohexadiene proceeds by conrotation.



Excited state HOMO, ψ_4^* of hexatriene is antisymmetric conrotatory motion is bonding

1,3-cyclohexadiene



Trans-5,6-dimethyl-1,3-cyclohexadiene

(2E,4Z,6E)-octatriene

✱ Selection Rules (Woodward-Hoffmann Rules) for Electrocyclic Reactio

The selection rules for electrocyclic reactions may be summarised as follows:

1. A conjugated diene and a conjugated triene react in opposite (alternating) stereochemical senses during thermal reactions. The diene opens and closes by a conrotatory path while the triene opens and closes by a disrotatory path. These results are due to different symmetries of the HOMO of a diene and a triene. Polyenes with an even number of electron pairs (double bonds)

undergo conrotatory thermal electrocyclic reactions. However, the polyenes with an odd number of electron pairs displays the same reaction in a disrotatory fashion.

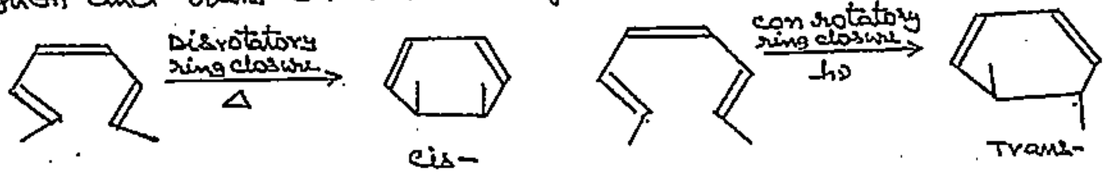
2. on electronic excitation (Photochemical reactions) the symmetry of HOMO and LUMO changes and with it, changes the reaction stereochemistry (which is reversed).

Selection rules for electrocyclic reactions are given in the table below.

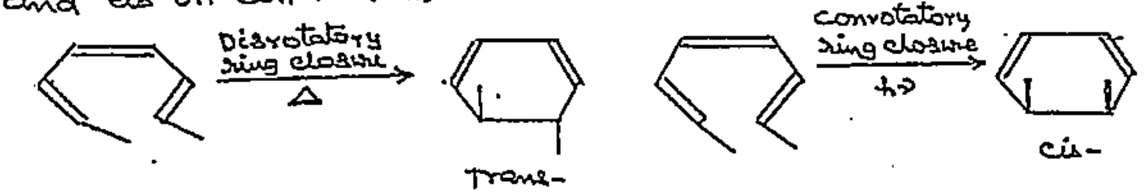
Electron Pairs (Double bonds)	Thermal reactions	Photochemical reactions
Even number (4n π systems)	conrotatory	Disrotatory
odd number (4n+2 π systems)	Disrotatory	conrotatory

stereochemistry of products can be easily established by the following rules coupled with the above rules.

3. If in the reactant the bonds to the substituents point in opposite directions, then the substituents will be cis in the product on disrotatory motion and trans on conrotatory motion.

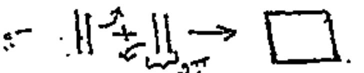


4. If in the reactant the bonds to the substituents point in the same direction then the substituents will be trans on disrotation and cis on conrotation.

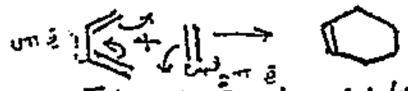


(II) cycloaddition reactions

cycloadditions are reactions in which at least two new σ bonds are formed simultaneously, so as to convert two or more open chain olefin molecules into rings. These reactions are classified on the basis of π electrons involved in each component.

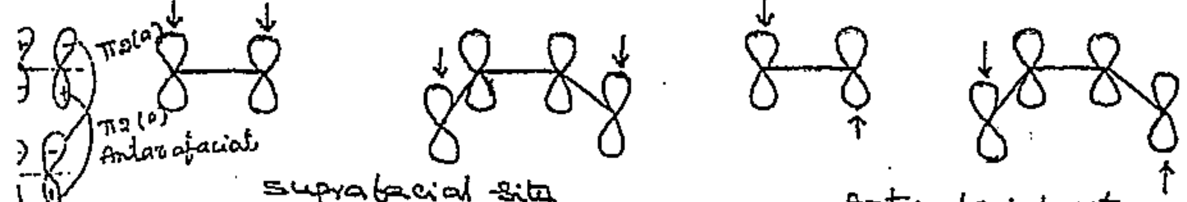


[2+2] cyclo addition



[4+2] cycloaddition (Diels-Alder reaction).

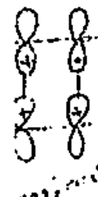
There are two possible ways to form bonds to the two atoms of a π bond or to the two terminal atoms of a set of conjugated π bonds. The two new bonds may be formed either from lobes on the same side of the π bond system or from lobes on opposite sides. Addition to the lobes on the same side of a π system is called Suprafacial addition, while addition to lobes on opposite sides of a π system is termed Antarafacial addition. These modes of addition are identified by the symbols 's' and 'a' respectively. Thus, cycloaddition of two π bonds, each reacting suprafacially, would be classified as a $[\pi^{2s} + \pi^{2s}]$ reaction. cycloaddition of a four-electron unit reacting antarafacially with a two-electron unit reacting suprafacially would be classified as a $[\pi^{4a} + \pi^{2s}]$ reaction.



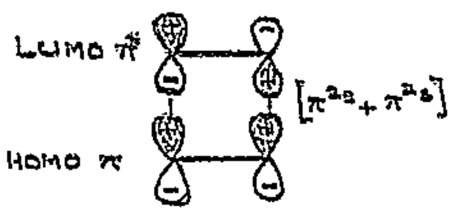
Suprafacial sita

Antarafacial sites

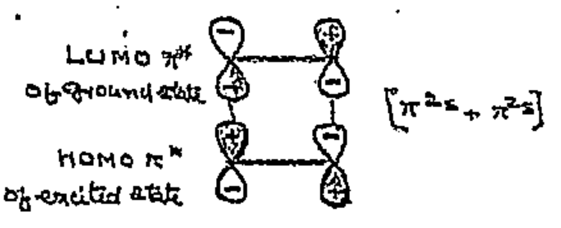
[2+ 2] - cycloaddition



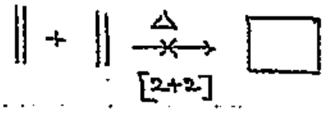
In the dimerisation of ethylene, a thermal [2+2] cyclisation would involve overlap of HOMO, π of one molecule with the LUMO, π* of the other. Now π and π* are of opposite symmetry. Its in this concerted reaction both bonds to a component are formed on the same face, i.e., the process is suprafacial, the lobes of opposite phase would approach each other. This interaction which is suprafacial with respect to both components $[\pi^{2s} + \pi^{2s}]$ is therefore, antibonding and repulsive and the concerted reaction, does not take place (symmetry-forbidden process).

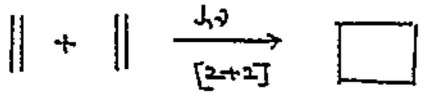


Symmetry-forbidden
thermal [2+2] cycloaddition

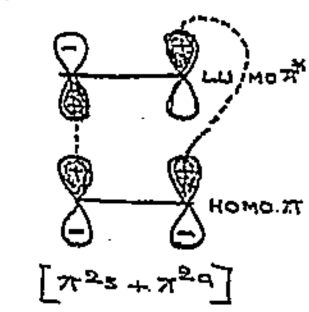


Symmetry-allowed
Photochemical [2+2] cycloaddition





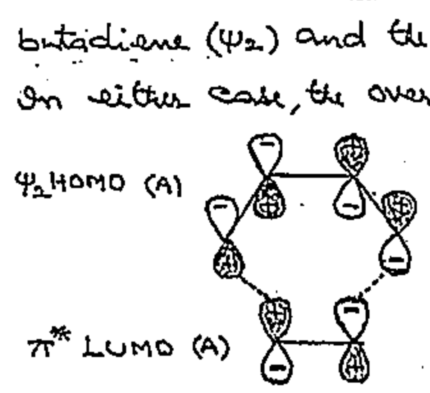
The photochemical [2+2] cycloadditions which are suprafacial with respect to both the components [$\pi^{2s}+\pi^{2s}$] will, however, permit a previously forbidden reaction to become a symmetry allowed process. This is so, since here, one has the overlap of the HOMO π^* of an excited molecule with the LUMO (also π^*) of a ground state molecule. However, a thermal [2+2] cycloaddition could occur provided it is suprafacial with respect to one component and antarafacial with respect to the other i.e., it is [$\pi^{2s}+\pi^{2a}$]. This process, though symmetry-allowed is geometrically very difficult. - - - →



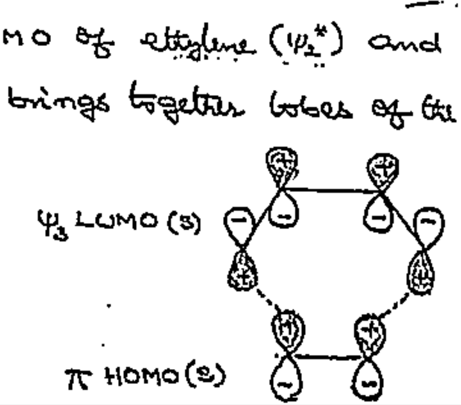
Thus the photochemical [2+2] cycloaddition reaction occurs smoothly and represents one of the best techniques to synthesise cyclobutane rings and cage compounds.

[4+2]- Cycloadditions – Diels-Alder reactions

These are concerted, thermal [4+2] cycloadditions. A consideration of orbital interactions (two combinations) accounts for this, i.e., the overlap can take place between the HOMO of butadiene (ψ_2) and the LUMO of ethylene (ψ_2^*) and vice-versa: In either case, the overlap brings together lobes of the same phase.



Interaction of ψ_2 orbital of butadiene and π^* orbital of ethane – [$\pi^{4s}+\pi^{2s}$]



Interaction of ψ_3 orbital of butadiene and π orbital of ethene – [$\pi^{4s}+\pi^{2s}$].

In [4+2] photocycloadditions, the HOMO of a molecule in an excited state would have the opposite symmetry from the LUMO of a molecule in the ground state. So, only antarafacial-suprafacial [4+2] cycloadditions would be symmetry-allowed.

Stereochemical rules (Woodward-Hoffmann rules) for cycloaddition reactions

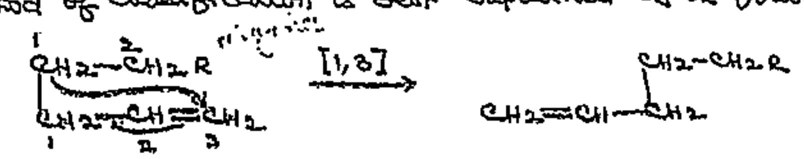
Electron pairs (Double bonds)	Allowed or preferred mode	
	Thermal	Photochemical
Even number-(4n)	Antarafacial-suprafacial	suprafacial-suprafacial
odd number - (4n+2)	suprafacial-suprafacial	Antarafacial-suprafacial

(III) Sigmatropic Rearrangements

A sigmatropic rearrangement is a concerted intramolecular shift of an atom or a group of atoms. During this rearrangement a sigma bond is broken in the reactant and a new σ bond is formed in the product and the π bonds rearrange. The number of π and σ bonds remain separately unchanged. These reactions are called sigmatropic rearrangements because a σ bond appears to move from one place to another during the reaction.

classification of sigmatropic rearrangements

Sigmatropic rearrangements are classified by a double numbering system (i,j or m,n) that refers to the relative positions of the atom or group involved in the migration. This method of classification is best explained by the following example.



In sigmatropic rearrangement the substrate can be divided into two parts alkenyl (or polyalkenyl) chain and the migrating group. All the substrates will have at least one allylic carbon in alkenyl chain for sigmatropic rearrangement.

Numbering of alkenyl chain and migrating group

Numbering of alkenyl chain is always started from the allylic carbon and it is numbered -1. Similarly, the atom (H, C or hetero atom) of migrating group bonded with allylic carbon by sigma bond is always given number -1

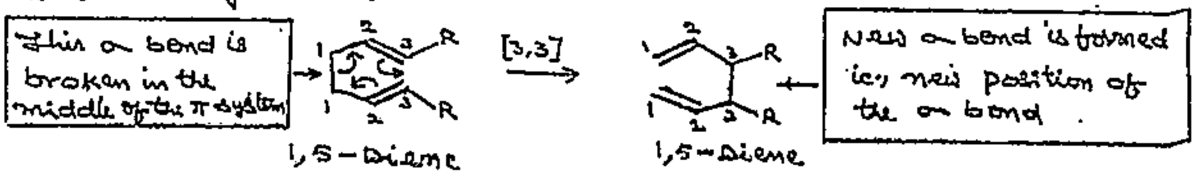
$\overset{1}{C}H_2 - \overset{2}{C}H_2R$ ← Migrating group

$\underset{1}{C}H_2 - \underset{2}{C}H = \underset{3}{C}H_2$ ← Alkenyl chain

Name of the sigmatropic rearrangement

In the above example, atom-1 of the migrating group migrates to the atom-3 of the alkenyl chain. Therefore, this rearrangement would be classified as a [1,3]-sigmatropic rearrangement. In 1,3 (i.e., i, j) i = 1 and j = 3.

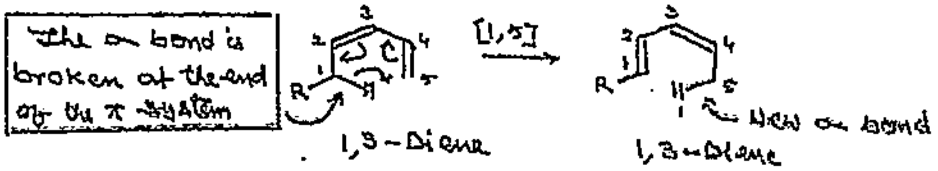
It is not always the first atom of the migrating group that becomes bonded to the alkenyl chain in the arrangement. Consider the following example:


This σ bond is broken in the middle of the π system

New σ bond is formed i.e., new position of the σ bond

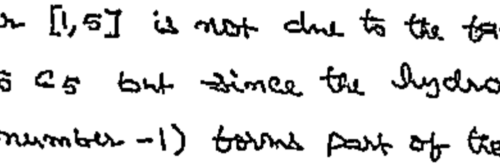
A [3,3]-sigmatropic rearrangement

Similarly, the migration of hydrogen is another example of [1,5] sigmatropic shift.


The σ bond is broken at the end of the π system

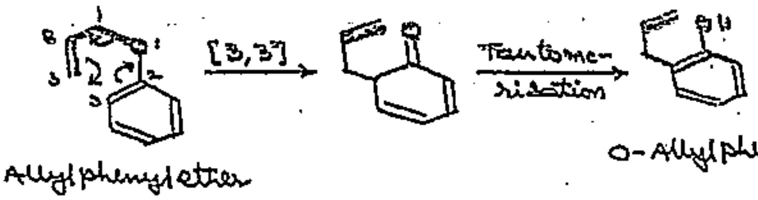
A [1,5]-sigmatropic rearrangement

The order [1,5] is not due to the fact that hydrogen migrates from C_1 to C_5 but since the hydrogen (one of the two atoms given the number -1) forms part of the new σ bond and had also formed part of the old σ bond. Only all the atoms taking part in the reaction have to be counted. Thus, the rearrangement of cyclohexadiene cannot be labelled as [1,3] shift since the methylene group linking 1 and 5 is not involved in the reaction.



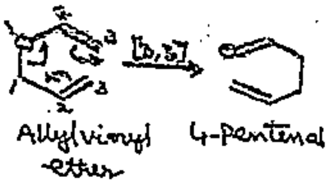
A [3,3]-sigmatropic rearrangement of 1,5-diene (when the six atoms involved are all carbons) is known as the Cope rearrangement—

The oxygen analog of the cope rearrangement is called the claisen rearrangement. Often one of the π bonds is part of an aromatic ring. Allylvinyl ethers also undergo claisen rearrangement.



Allylphenylether

O-Allylphenol



Allylvinyl ether

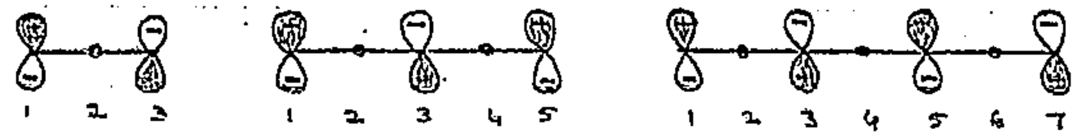
4-Pentenal

(A) Sigmatropic Migration of Hydrogen – Suprafacial & Antarafacial Migrations

A hydrogen atom is reported to migrate from one end of a system of π bonds to the other, under thermal or photochemical rearrangements. In the transition state the hydrogen atom must be in contact with both ends of the chain at the same time. There are two distinct processes by which a sigmatropic migration can occur. If the hydrogen moves along the top or bottom face of the π system ie., migrating group remains associated with same face of the conjugated system throughout the process, the migration is termed suprafacial. When the hydrogen moves across the π system either from top to bottom or vice versa ie., the migrating group moves to the opposite face of the π system during the course of migration then it is called Antarafacial.

In a given sigmatropic rearrangement, the migrating group is bonded to both the migration source and the migration terminii in the transition state. It is imagined that the migrating hydrogen atom breaks away from the rest of the system which is then treated as a free radical. Thus in a simplest case involving a [1,3] shift of hydrogen, the frontier orbital analysis treats this system as a hydrogen atom interacting with an allyl radical.

The electron of the hydrogen atom is in a 1s orbital which has only one lobe. The HOMO of an allylic free radical depends on the number of carbons in the π frame work.



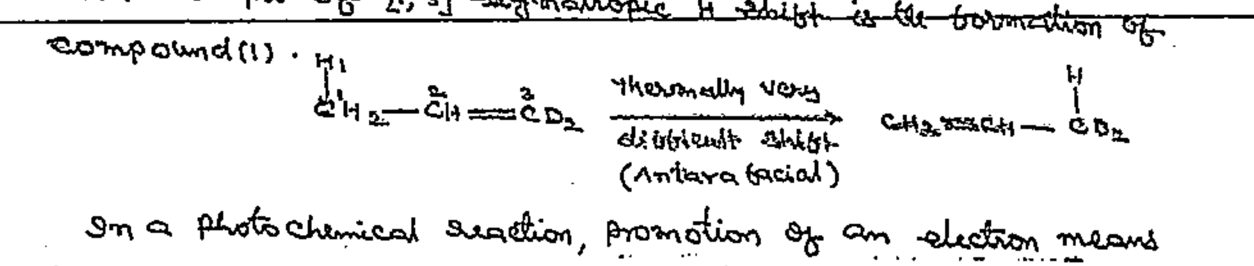
(I) ψ_2 is HOMO, (A)　(II) ψ_3 is HOMO, (S)　(III) ψ_4 is HOMO, (A)

HOMO of the allylic radicals

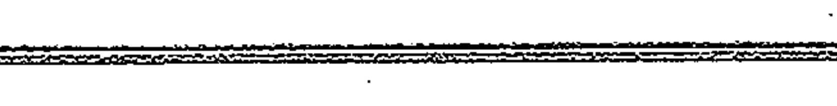
[1,3] sigmatropic Hydrogen shift

A [1,3] sigmatropic rearrangement involves a π bond and a pair of σ electrons, so in all two pairs of electrons are involved. In the migration of hydrogen, the H must move from a plus to plus or from minus to minus lobe of the HOMO. It cannot move to a lobe of opposite sign.

During a thermal [1,3] sigmatropic migration of a hydrogen, the overlap of the hydrogen 1s orbital with the HOMO of the allyl radical (I, Antisymmetric) is bonding at one end and antibonding at the other end for the suprafacial migration. Thus, [1,3] sigmatropic suprafacial migration of hydrogen, under thermal conditions, is symmetry forbidden. However, in the antarafacial process the hydrogen atom shall have to cross over the π system to the other face to form a four membered ring transition state, a geometrically very difficult situation.

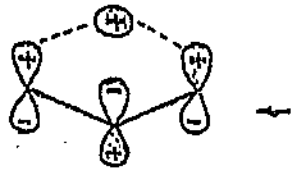


An example of [1,3] sigmatropic H shift is the formation of compound (1).



$$\overset{H^1}{\overset{|}{\overset{1}{C}}}H_2-\overset{2}{C}H=\overset{3}{C}D_2 \xrightarrow[\text{difficult shift (Antarafacial)}]{\text{Thermally very}} CH_2=CH-\overset{H}{\overset{|}{C}}D_2$$

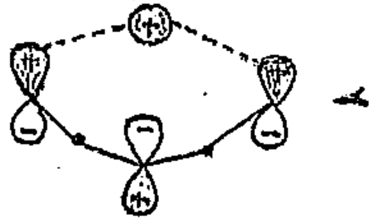
In a photochemical reaction, promotion of an electron means that now ψ_3 becomes the HOMO which is symmetrical. Suprafacial pathway for [1,3] shift now becomes an allowed process and antarafacial pathway forbidden



Photochemical [1,3]
Suprafacial process
Symmetry-allowed

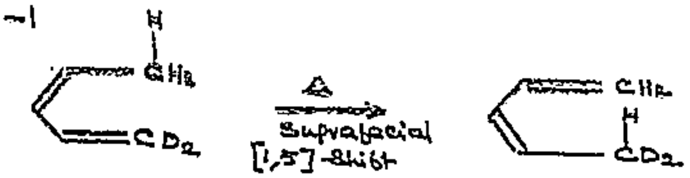
[1,5] sigmatropic Hydrogen shift

A [1,5]-sigmatropic rearrangement involves three pairs of electrons. The [1,5]-sigmatropic shift of hydrogen or deuterium atom is well known. These shifts occur via a suprafacial pathway under thermal conditions. They can be analysed by examining a hydrogen atom and a pentadienyl radical whose HOMO is bonding at both the migration origin and the migration terminus. Thus the migration maintains orbital symmetry when the migrating group remains on the same side of the conjugated system (suprafacial process).

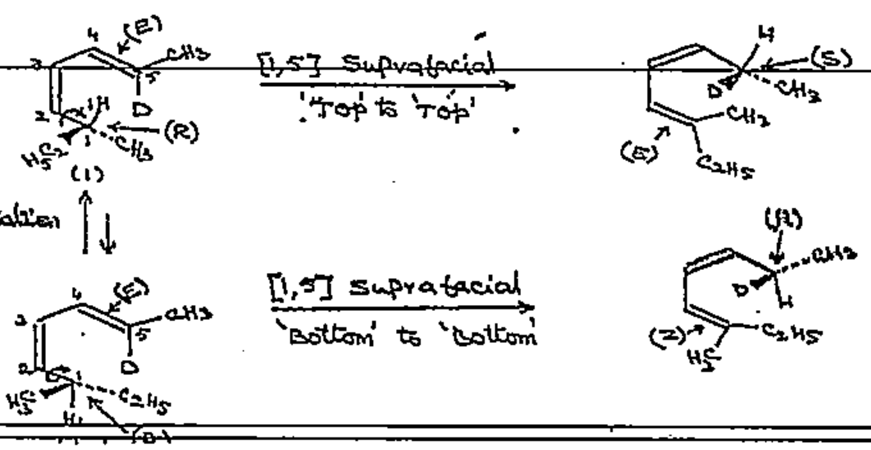


Thermal [1,5] hydrogen shift. Suprafacial process
Symmetry-allowed

Example-1



Example-2. Another remarkable example is in the 1,3-diene of known stereochemistry both at the double bond and at the stereocentre. This 1,3-diene gave a two component mixture compatible with only suprafacial migration.

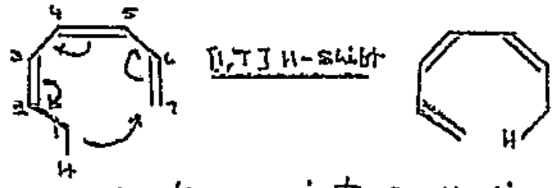


These results are explained as under

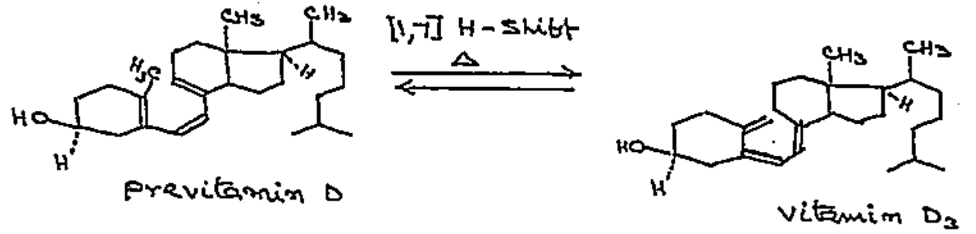
- One has to consider two rotational isomers (1 and 1a) for the reaction
- In (1) the methyl group is directed toward C_4–C_5 double bond while in (1a) it is now ethyl group that is directed toward C_4–C_5 bond.
- There are two suprafacial [1,5] pathways for the hydrogen in these two conformations (1 and 1a), 'top to top' as in (1) or 'bottom to bottom' as in (1a)
- Each of these suprafacial pathways gives a product with specific stereochemistry.

[1,7] Sigmatropic Hydrogen Shift

In the case of [1,7] hydrogen shifts, in a triene, the orbital symmetry rules predict that the transfer of hydrogen must be antarafacial. Compared to [1,3] shift, the transition state is not much strained and the shift is sterically feasible.



This is seen in the thermal interconversion of Vitamin D series.



Previtamin D

Vitamin D3

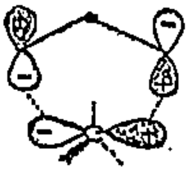
Nagendra

B. Sigmatropic Migrations of Carbon

As compared to a hydrogen atom which has its electron in a 1s orbital that has only one lobe, a carbon free radical (for imaginary transition state) has its odd electron in a p-orbital which has two lobes of opposite sign. [It is known that a [1,3] sigmatropic suprafacial migration of hydrogen (thermally) is symmetry forbidden while an antarafacial reaction though allowed is geometrically improbable. Interestingly an additional possibility would exist if an alkyl group (carbon) rather than a hydrogen was a potential migrator. A [1,3] shift can now be suprafacial migration (II) if the migrating group does so antarafacially, i.e., it would result in inversion of configuration of the migrating group. Thus carbon can simultaneously interact with the migration source and the migration terminus using either of its lobes or both of its lobes. Considering suprafacial rearrangement, carbon will migrate using one of its lobes if the HOMO is symmetric (III). This happens during a thermal suprafacial [1,5] process.

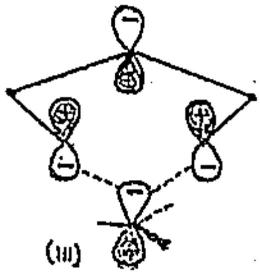
(I)

A thermal [1,3] suprafacial shift is forbidden, antarafacial shift is allowed but geometrically improbable (For H-[1,3] shift)



(II)

A thermal suprafacial [1,3] shift of carbon is allowed, inversion of configuration in migrating carbon (In fact it is supra-antara shift)



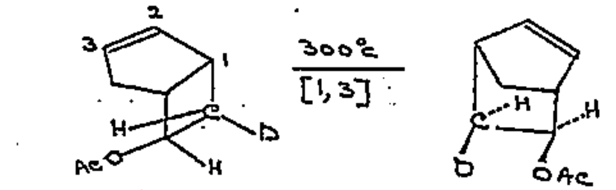
(III)

A thermal suprafacial [1,5] shift of carbon is allowed with retention of configuration in migrating carbon (In fact it is supra-supra shift)

When carbon migrates with only one of its lobes interacting with migrating source and migration terminus, the migrating group retains its configuration since bonding is always to the same lobe. When the carbon migrates using both of its lobes (antisymmetric HOMO, (III)), a [1,3] thermal suprafacial migration would involve opposite lobes. Thus, if the migrating carbon was originally bonded via its positive lobe, it must now use its negative lobe to form the new C–C bond. The stereochemical outcome of such a process is the inversion of configuration in the migrating group.

In summary, a suprafacial [1,5] thermal rearrangement proceeds with retention of configuration at the migrating carbon, while the related [1,3] suprafacial process proceeds with inversion.

For example, compound (1) when heated at 300°C gives compound (2). This is [1,3] sigmatropic carbon shift with inversion at the migrating centre.



(1)
Trans
(Both H are trans)

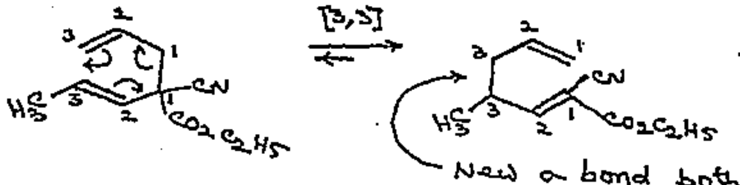
(2)
cis
(Both H are cis)

Woodward–Hoffmann rules for sigmatropic rearrangements are given in the following table.

Electron pairs (Double bonds)	Allowed or Preferred mode	
	Thermal	Photochemical
Even number (4n)	Antarafacial	Suprafacial
Odd number (4n+2)	Suprafacial	Antarafacial

Cope Rearrangement [illegible]

The thermal rearrangement of 1,5-dienes by [3,3] sigmatropy involving carbon-carbon bond is called cope rearrangement. The reaction proceeds in the thermodynamically favoured direction.

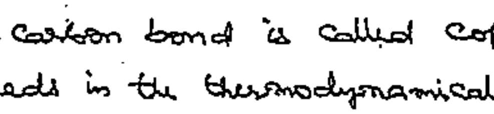


cope rearrangement
[3,3] sigmatropic

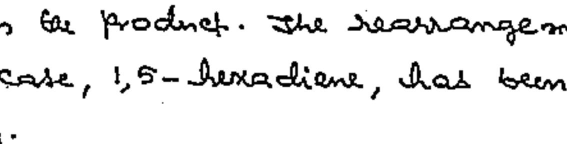
New σ bond, both ends numbered 3

This particular reaction is called a [3,3] sigmatropic rearrangement because the new σ bond has a 3,3 relationship to the old σ bond

The equilibrium in this case is controlled by the conjugation present in the product. The rearrangement of the simplest possible case, 1,5-hexadiene, has been studied using deuterium labeling.



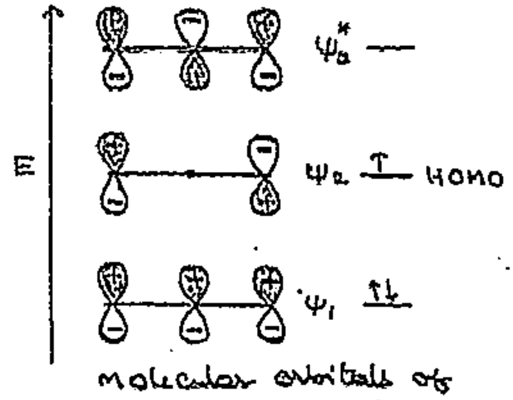
For this reaction activation energy is 33.5 K.Cal/mole and the entropy of activation is −13.8 e.u. The substantially negative entropy conforms the formation of cyclic transition state



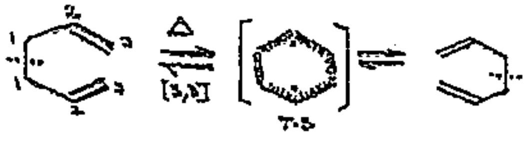
b = bond breaking
f = bond formation.

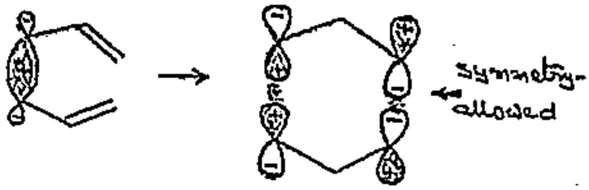
✓ Conjugated substituents at C-2, C-3, C-4 or C-5 accelerate the rearrangement. Donor substituents at C-2 and C-3 have an ↑ increase accelerating effect.

In Cope rearrangement the migrating group is allyl radical. An analysis of the symmetry of the orbitals involved shows why this reaction is a relatively facile thermal process but is not commonly observed on photochemical activation. As we break the C_1-C_1 bond the phases of the overlaping lobes must be the same. The HOMO of the allyl radical is ψ_2 and that information allows us to fill the symmetries of the two allyl radicals making up of transition state.

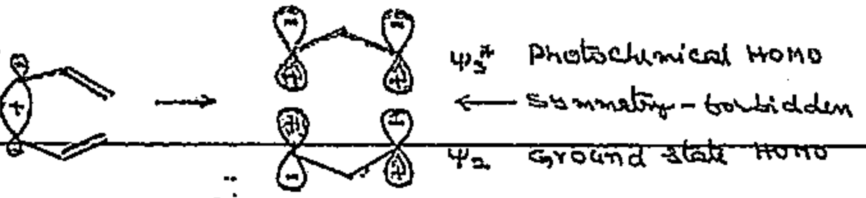


Molecular orbitals of allyl free radical





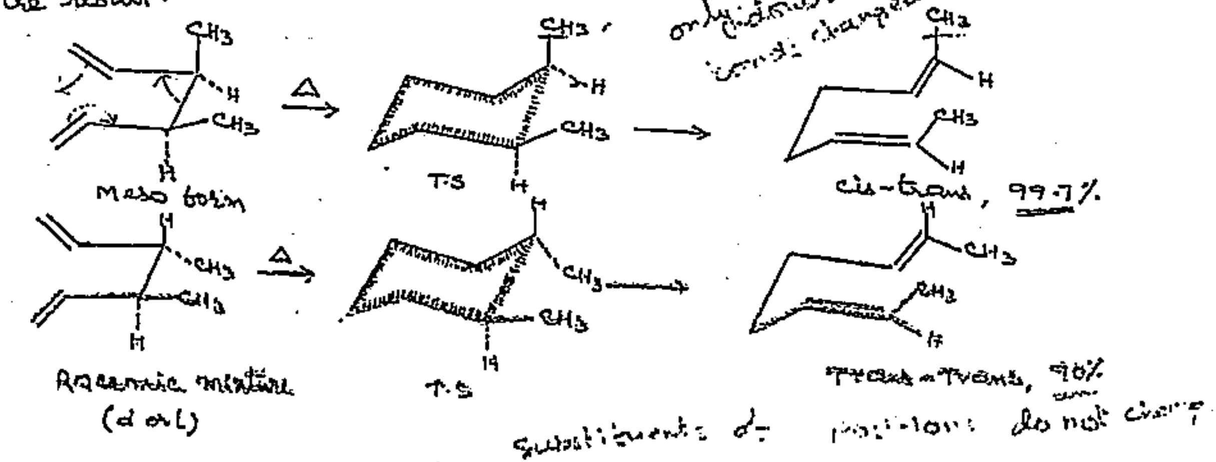
Reattachment at the two C-3 positions is allowed because the interaction of the two lobes on the two C-3 carbons is bonding. If the interaction is carried out in the presence of UV light then one electron is promoted from the HOMO to the LUMO and LUMO will become photochemically HOMO.



✓ Interaction between HOMO ground and HOMO photochemical is a symmetry-forbidden process.

Stereochemistry of Cope rearrangement

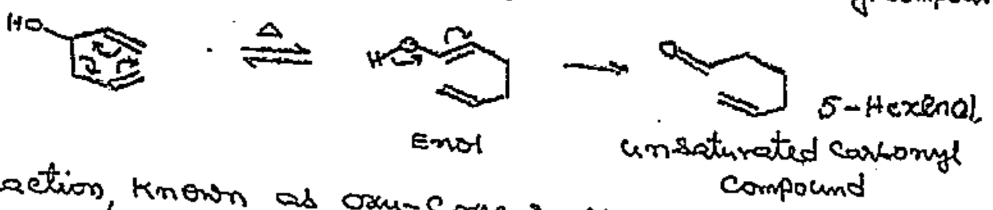
The cope rearrangement usually proceeds through the chair like transition state. The stereochemical feature of the reaction can usually be predicted and analysed on the basis of a chair transition state that minimises steric interactions between substituents. Rearrangement of the meso diene through such transition state then would give the cis-trans isomer while in the case of the rearrangement of the racemic mixture, the trans-trans isomer is the major product and this is actually the result.



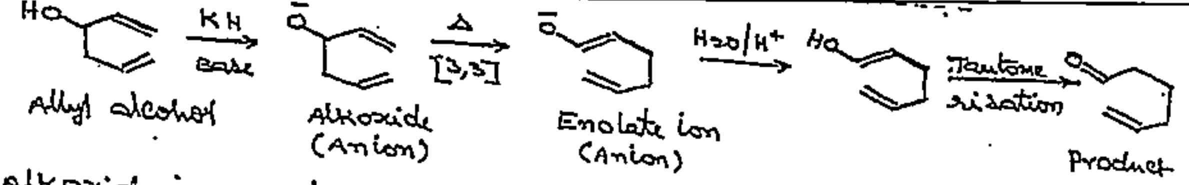
The above result establishes that chirality is maintained throughout the course of the reaction. This stereospecificity is a general feature of [3,3] sigmatropic shifts and has made them valuable reactions in enantiospecific synthesis.

Preparation of carbonyl compounds from cope rearrangement

1,5-Hexadien-3-ol on heating undergoes cope rearrangement with the formation of unsaturated carbonyl compounds.



This reaction, known as oxy-cope rearrangement, is accelerated by a strong base. In the presence of a strong base allyl alcohol is converted into alkoxide ion which is very stable.



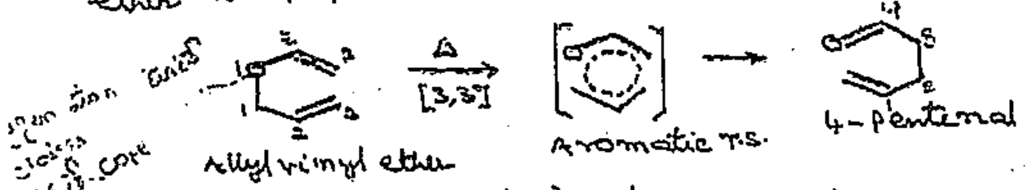
Alkoxide ion undergoes cope rearrangement to give the product in which negative charge is in conjugation to π bond. This conjugation makes the anion very stable.

This is also [3,3] [illegible] by [illegible]

40

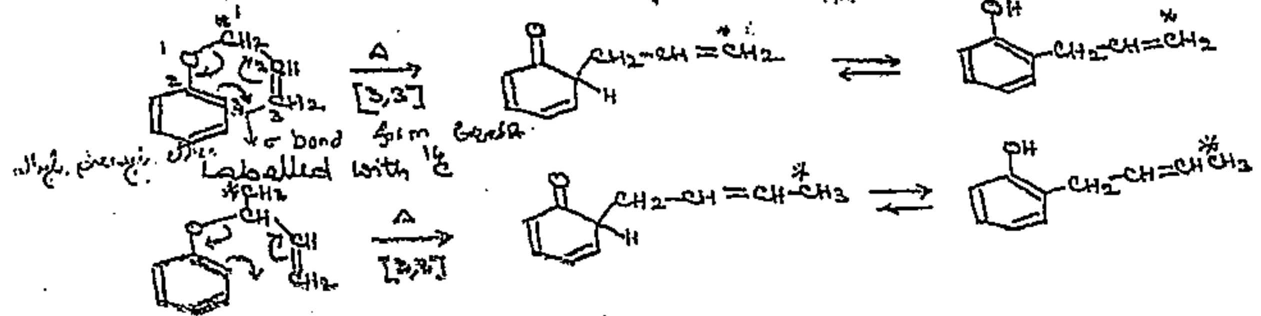
★ Claisen Rearrangement

This rearrangement also involves a [3,3] sigmatropic path-way like cope rearrangent, however, in claisen rearrangement the substrates incorporate one or more heteroatoms in place of carbon in the 1,5-hexadiene system. The simplest example of claisen rearrangement is the thermal conversion of allyl vinyl ether to 4-pentenal



The transition state involves a cycle of six orbitals and six electrons. With six electrons the transition state has aromatic character. Similarly allylaryl ethers on heating rearrange to o-allyl phenols.

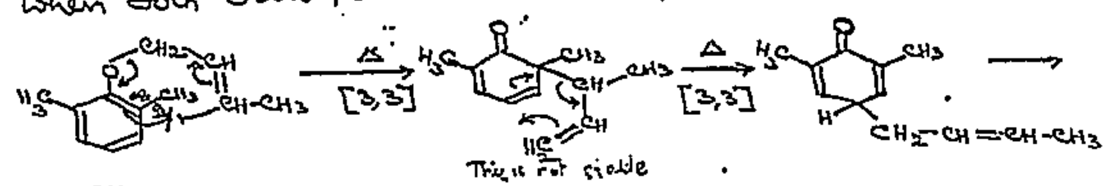
Studies using migrating groups labelled with ^{14}C or with substituents show that the allyl group is end-interchanged during the ortho rearrangement.

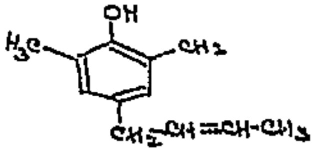


Labelled with CH3 substituent

These and other results which show that the claisen rearrangement is intramolecular provide strong support for a concerted mechanism.

~~When both ortho positions are filled~~, the allyl group migrates to the p-position





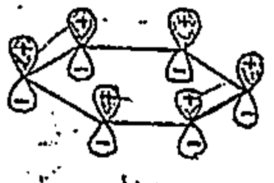
Two successive allylic rearrangements restore the original orientation of the allyl group.

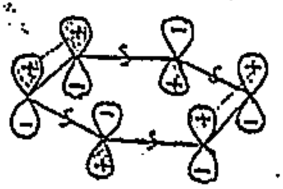
8. Aromatic and Antiaromatic Transition states

(i) Huckel system

Benzene is an especially stable conjugated compound, and calculations show that it is much lower in energy than the hypothetical, undelocalised cyclohexatriene. cyclobutadiene is much destabilised by interaction of the two π bonds. These are the two examples of the generalisation that 4n+2 electrons in a cyclic array are aromatic and 4n electrons are antiaromatic. A necessary condition of this description of aromaticity is that a number of p-orbitals of the same type (p_x, p_y or p_z) overlap in a sideways manner. A planar carbon skeleton is implied.

Figure 1(a) illustrates the basis set of atomic orbitals used in the construction of the molecular orbitals for benzene. In this


1(a)
Lobes of the same phase are adjacent



1(b)
Randomly assigned orbital phases
The wavy lines indicate phase dislocation

representation we have chosen to label the lobes on the same side of the molecular plane with the same sign. For the treatment we shall adopt this is unnecessary. The same molecular orbitals are obtained on combination of the atomic orbitals, no matter how the phase relationships in the basis set are displayed. The same basis set for benzene is shown in Fig. 1(b), but the phases are randomly assigned. The wavy lines indicate phase dislocations, where a positive and negative lobe are adjacent. Every possible combination of phases in the benzene basis set gives rise to either zero or an even number of phase dislocations. Such a cyclic system with a zero or even number of phase dislocations is called a Huckel system.

(A Huckel system with 4n+2 electrons is aromatic and with 4n electrons is antiaromatic

[illegible]

(ii) Anti-Huckel System (or mobius system)

Stable π-systems with an odd number of phase dislocations are unknown, and the only way that they can be visualised is through a 'twisted', or Mobius system. Such an array with an odd number of phase dislocations is called an anti-Huckel system. It can be shown that the condition for aromaticity in anti-Huckel system is opposite to that for Huckel systems

An anti-Huckel system with 4n electrons is aromatic and with 4n+2 electrons is antiaromatic

Except for very large rings, where aromatic stabilisation is small anyway, the twist in the Mobius system reduces the π electron overlap too much for the observation of stable molecules. Transition states may have twisted π systems and their energy can be lowered by aromaticity.

Although the concepts described above apply strictly to planar molecules, it is assumed that non-planar transition states can be 'aromatic' or 'antiaromatic'. The transition states are examined for the number of electrons, and the number of phase dislocations. Each transition state can therefore be treated, to a first approximation, as being stabilised or destabilised by aromaticity. In general, for any pericyclic reaction, a choice of routes is possible and the one (or ones) leading to an 'aromatic' transition state will be favoured for thermal reactions.

9. Mobius-Huckel Analysis – PMO Approach

Anti-Huckel (π)

twisted orbitals → (Perturbational Molecular Orbital Approach)

The concerted reactions are analysed by the classification of transition states as aromatic or antiaromatic. These predictions yield the same results as by other methods. Huckel's rule of aromaticity states that a monocyclic planar conjugated system with (4n+2) π electrons is aromatic and, therefore, stable in the ground state. On the other hand a system with (4n) π electrons is unstable and is called antiaromatic.

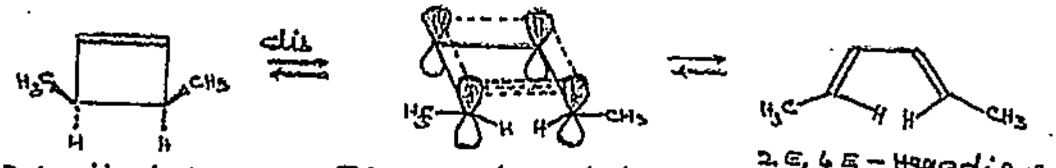
Further it has been shown that these rules are reversed by the presence of a node (a phase dislocation) in the array of atomic orbitals. The Mobius-Huckel concept is used to analyse the pericyclic reactions without using the actual molecular orbitals. The following points may be noted:

- Each atom of the interacting system is assigned a p-orbital with one lobe black and one white (or some other designation). A hydrogen atom is represented by a circle of one colour representing an s-orbital.
- One draws each reactant with the black lobes on one side and white on the other. Then one considers the transition state of a particular reaction, counts the number of electrons and the nodes in the array to reach the conclusion if that reaction is symmetry allowed or forbidden.
- Any array with a zero or even number of nodes (phase dislocations) is called a Huckel system. A Huckel system with $4n+2$ electrons is aromatic and with $4n$ electrons is antiaromatic. Any array of orbitals with an odd number of nodes (phase changes) is called an anti-Huckel system (or Mobius system). An anti-Huckel system with $4n$ electrons is aromatic and with $4n+2$ electrons is antiaromatic.
- The condition for aromaticity in anti-Huckel system is opposite to that for Huckel system.
- Thermal reactions take place via aromatic transition-states whereas photochemical reactions proceed via antiaromatic transition-states.

(I) Electrocyclic Reactions

Interconversion of cyclobutene and 1,3-butadiene – $4n$ system

Let us consider the disrotatory and conrotatory processes for the system cyclobutene ⇌ 1,3-butadiene

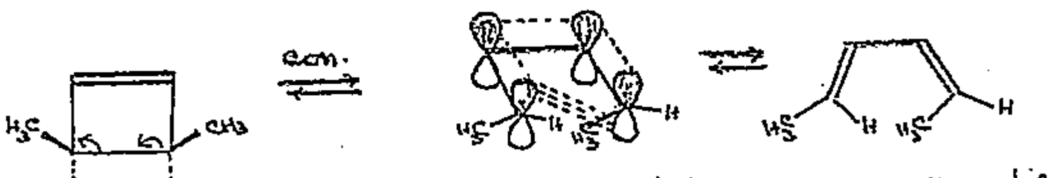


cis-3,4-dimethyl cyclobutene

T.S., 0 node, 4 electrons antiaromatic, hν allowed

2E, 4E – Hexadiene

in dis rotation → same [illegible] can be taken [illegible]



cis-3,4-dimethyl cyclobutene

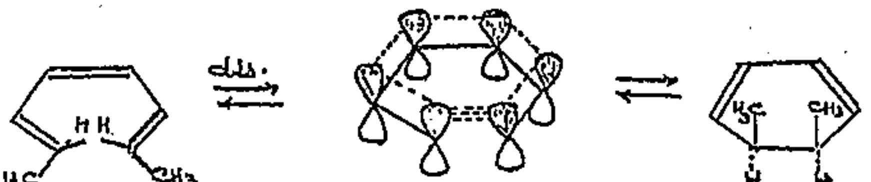
T.S., 1 node, 4 electrons, aromatic, Δ allowed

2E,4Z-Hexadiene

The transition state for conrotatory interconversion of cyclobutene-butadiene system has 1 node (phase dislocation) with 4 electrons. It is aromatic, and thus it is an allowed process under thermal conditions. But, the transition state for disrotatory interconversion has no node and with 4 electrons it is antiaromatic. It is thus an allowed process under photochemical conditions.

Interconversion of hexatriene and cyclohexadiene — 4n+2 system

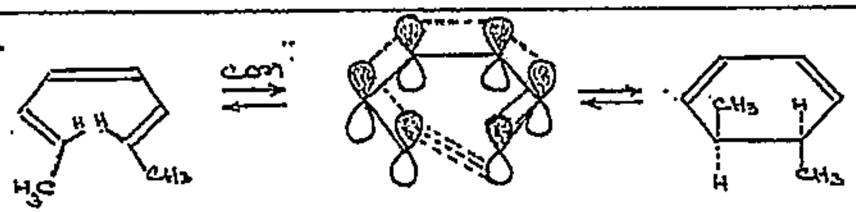
Starting from hexatriene basis set, the transition state for disrotatory ring closure has a zero node, and with six electrons it is aromatic. The conrotatory ring closure proceeds through an antiaromatic transition state. It is therefore correctly predicted that thermal ring closure of substituted hexatrienes should be disrotatory and photochemical reaction should proceed via the opposite conrotatory path.



2E,4Z,6E-octatriene

T.S. for disrotatory process; 0 node, 6 electrons aromatic, Δ allowed

cis-5,6-dimethyl cyclohexadiene



2E,4Z,6E-octatriene

T.S. for conrotatory process, 1 node, 6 electrons, antiaromatic, hν allowed

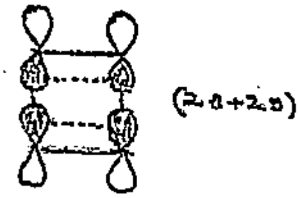
trans-5,6-dimethyl cyclohexadiene

Thus we reach the same conclusions as described under correlation diagram and F.M.O. methods. The stereochemical rules by this approach to electrocyclic reactions are tabulated below.

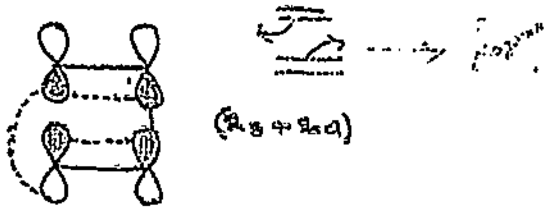
Array of electrons involved	Number of nodes (Phase dislocations)	Type of Aromaticity	Δ Allowed	$h\nu$ Allowed
4n	zero or even	Antiaromatic	—	disrotatory
4n	odd	Aromatic	conrotatory	—
4n+2	zero or even	Aromatic	disrotatory	—
4n+2	odd	Antiaromatic	—	conrotatory

(II) Cycloaddition Reactions

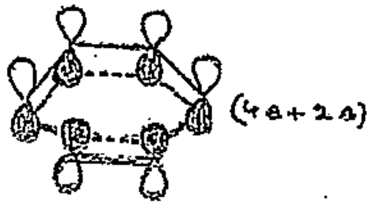
The transition state for 2_s+2_s cycloaddition has 4 electrons with zero node, and is therefore antiaromatic, and hence the reaction is thermally-forbidden and photochemically-allowed. Similarly for 4_s+2_s cycloaddition (Diels-Alder reaction), the transition state has 6-electrons with zero node. Therefore it is aromatic and hence the reaction is thermally-allowed and photochemically-forbidden.



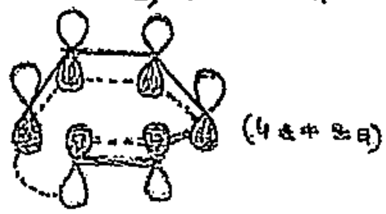
0 node, 4 electrons
antiaromatic, $h\nu$ allowed



1 node, 4 electrons
aromatic, Δ allowed



0 node, 6 electrons
aromatic, Δ allowed



1 node, 6 electrons
antiaromatic, $h\nu$ allowed

Thus we come to the same conclusions as by other methods.

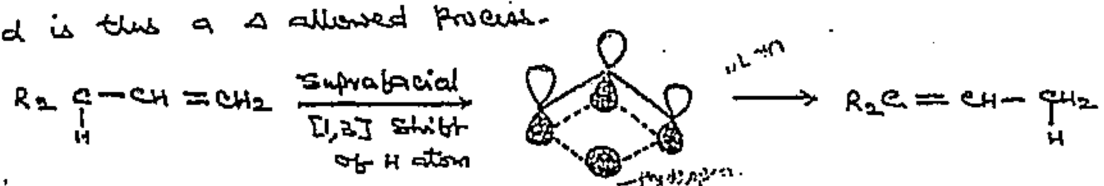
Stereochemical rules for cycloaddition by PMO method

No. of electrons involved	No. of nodes	Type of aromaticity	Δ Allowed	$h\nu$ Allowed
4n	0 or even	Antiaromatic	—	Supra-Supra Antara-Antara
4n	odd	Aromatic	Supra-Antara Antara-Supra	
4n+2	0 or even	Aromatic	Supra-Supra Antara-Antara	
4n+2	odd	Antiaromatic	—	Supra-Antara Antara-Supra

(III) Sigmatropic Rearrangements

(A) Sigmatropic Hydrogen shift

Consider the simplest case of [1,3]-sigmatropic shift of a hydrogen atom. [1,3] supra facial shift occurs via a transition state with 0 node and 4 electrons (Antiaromatic) and thus is an $h\nu$ allowed process, wheras the [1,3] antara facial shift can occur via a transition state with 1 node, 4 electrons (Aromatic) and is thus a Δ allowed process.



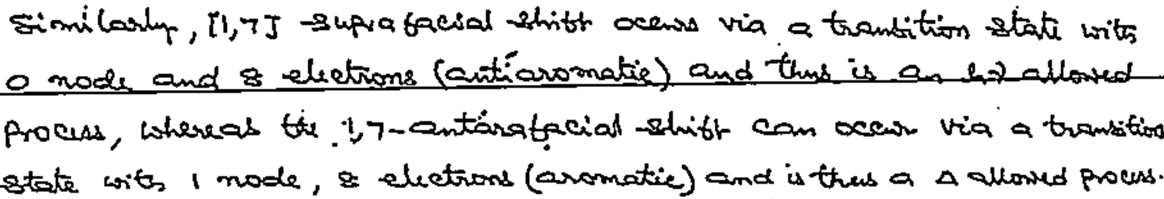
$$R_2\underset{\substack{|\\H}}{C}-CH=CH_2 \xrightarrow[\text{[1,3] Shift of H atom}]{\text{Suprafacial}} \longrightarrow R_2C=CH-\underset{\substack{|\\H}}{CH_2}$$

0 node, 4 electrons
antiaromatic, $h\nu$ allowed

$$R_2\underset{\substack{|\\H}}{C}-CH=CH_2 \xrightarrow[\text{[1,3] Shift}]{\text{Antarafacial}} \longrightarrow R_2C=CH-\underset{\substack{|\\H}}{CH_2}$$

1 node, 4 electrons
aromatic, Δ allowed

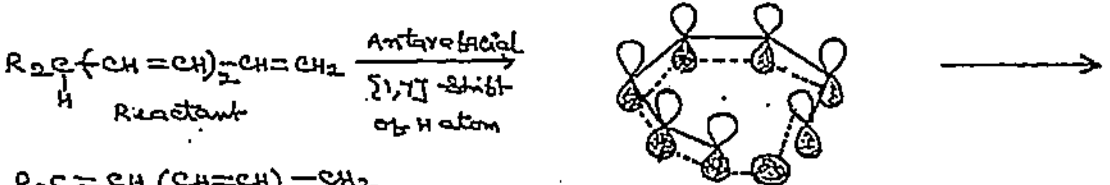
In [1,5] suprafacial shift of hydrogen atom, the transition state has 0 node with 6-electrons (aromatic) and thus is a Δ allowed process, whereas in [1,5] antarafacial shift, the transition state has 1 node with 6-electrons (antiaromatic) and is thus an $h\nu$ allowed process.



$$R_2\underset{\substack{|\\H}}{C}-CH=CH-CH=CH_2 \xrightarrow[\text{[1,5] Shift of H atom}]{\text{Suprafacial}} \longrightarrow R_2C=CH-CH=CH-\underset{\substack{|\\H}}{CH_2}$$

0 node, 6 electrons
aromatic, Δ allowed

Similarly, [1,7] suprafacial shift occurs via a transition state with 0 node and 8 electrons (antiaromatic) and thus is an $h\nu$ allowed process, whereas the 1,7-antarafacial shift can occur via a transition state with 1 node, 8 electrons (aromatic) and is thus a Δ allowed process.



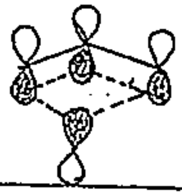
$$\underset{\text{Reactant}}{R_2\underset{\substack{|\\H}}{C}\!-\!(CH=CH)_2\!-\!CH=CH_2} \xrightarrow[\text{[1,7] Shift of H atom}]{\text{Antarafacial}} \longrightarrow$$

$$\underset{\text{Product}}{R_2C=CH(CH=CH)_2-\underset{\substack{|\\H}}{CH_2}}$$

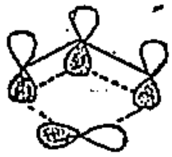
1 node, 8 electrons
aromatic, Δ allowed

(B) Sigmatropic carbon shift

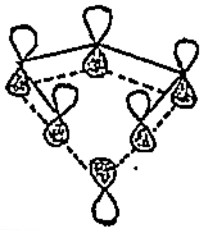
When an alkyl group (carbon) migrates an additional stereochemical feature has to be considered. The allowed processes include, the suprafacial [1,3] shift with inversion and the suprafacial [1,5] shift with retention of configuration under thermal condition.



[1,3] suprafacial shift
0 node, 4 electrons
antiaromatic, hν allowed
with retention



[1,3] suprafacial shift
1 node, 4 electrons
aromatic, Δ allowed
with inversion



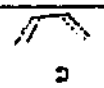
[1,5] suprafacial shift
0 node, 6 electrons
aromatic, Δ allowed
with retention

classification of sigmatropic shifts of alkyl groups (carbon) with respect to basis set orbitals.

Selection rules for sigmatropic rearrangements by PMO method

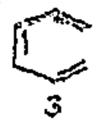
No. of electrons involved	No. of nodes	Type of aromaticity	Δ allowed	hν allowed
$4n$	0 or even	Antiaromatic	—	Supra
$4n$	odd	Aromatic	Antara	—
$4n+2$	0 or even	Aromatic	Supra	—
$4n+2$	odd	Antiaromatic	—	Antara

In conclusion it must be said that while the prediction rules under different methods have dramatic success for thermolytic reactions (symmetry-allowed reactions on heating), photolytic reactions are more complex. Photolysis is initiated by light absorption first to a high-energy excited state which may also collapse via other, not necessarily concerted, pathways.

(4n):


Δ/con hν/Dis

(4n+2)


Δ/Dis hν/con..

[1,3] – shift [1,5] – shift

Δ Antarafacial

hν Suprafacial

✓ Huckel system — 4n → Antiaromatic – Photochemical process [illegible] by Δ [illegible]

4n+2 → Aromatic – Thermal process Δ ✓ [illegible]

✓ Mobius system — 4n → Aromatic – Thermal process [illegible]

Anti aromatic — → Antiaromatic – [illegible]

aromatic and antiaromatic energy [illegible] [illegible] sold energy [illegible] [illegible] antiaromatic [illegible] decrease [illegible] [illegible] Delocalisation [illegible] [illegible] [illegible] Because of [illegible] in Quinolines [illegible]

Aromatic ex – Benzene, [illegible]