

DAMIETTA UNIVERSITY

CHEM-405: PERICYCLIC REACTIONS

LECTURE 6

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LEARNING OUTCOMES

LECTURE 6

➤ (1) [2 + 2] photocycloaddition

Regioselectivity in photochemical [2 + 2] cycloadditions

➤ (2) Thermal [2 + 2] cycloaddition

The ketene–alkene cycloaddition (Regioselectivity)
The isocyanate-alkene cycloaddition

➤ Cycloadditions involving more than six electrons.

➤ Not all cycloadditions are pericyclic

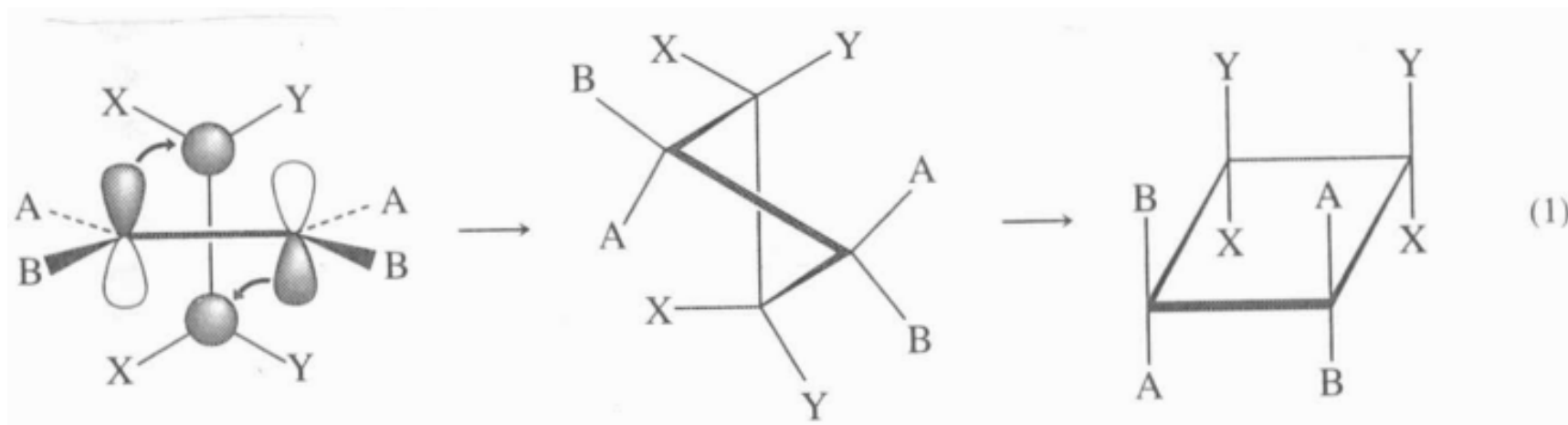
Zwitterionic and biradical intermediates

➤ [$\pi 2_s + \pi 2_s + \pi 2_s$] cycloadditions

➤ Sigmatropic Reactions

Thermal [2 + 2] cycloaddition¹

- Orbital overlap in the TS for the theoretically allowed $[\pi 2_s + \pi 2_a]$ reaction would be extremely poor, and the reaction would initially give rise to a **badly twisted** cyclobutane.¹



- Therefore, $[\pi 2_s + \pi 2_a]$ reactions are also rare, if they exist at all.¹
- The component that is undergoing an antarafacial mode of addition would result in **inversion of the geometry** about that bond.¹

[2 + 2] cycloaddition¹

➤ There are basically 3 situations in which concerted [2 + 2] cycloadditions are seen:

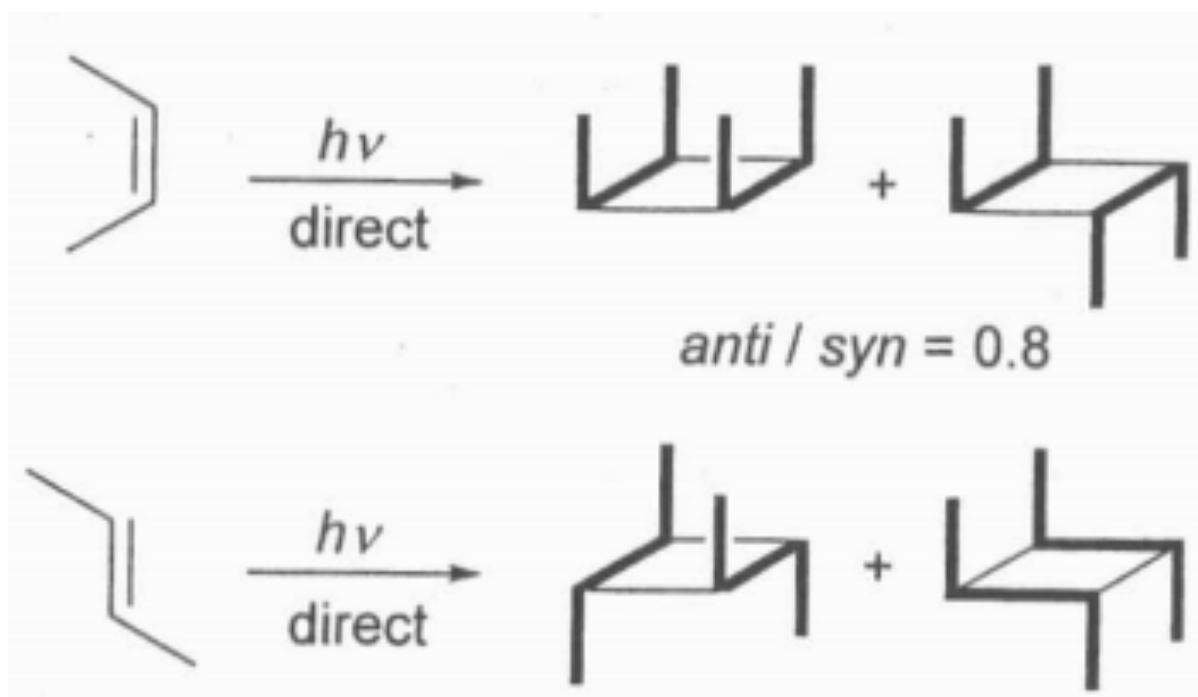
(1) Reaction is promoted by light

(2) Thermal reaction between alkene and a ketene ($R_2C=C=O$) or another *cumulene*.

(3) Thermal reaction between alkene and a component, which has a pi bond between C and a second-row or heavier element (e.g., $Ph_3P=CH_2$ or $R_2Ti=CH_2$).

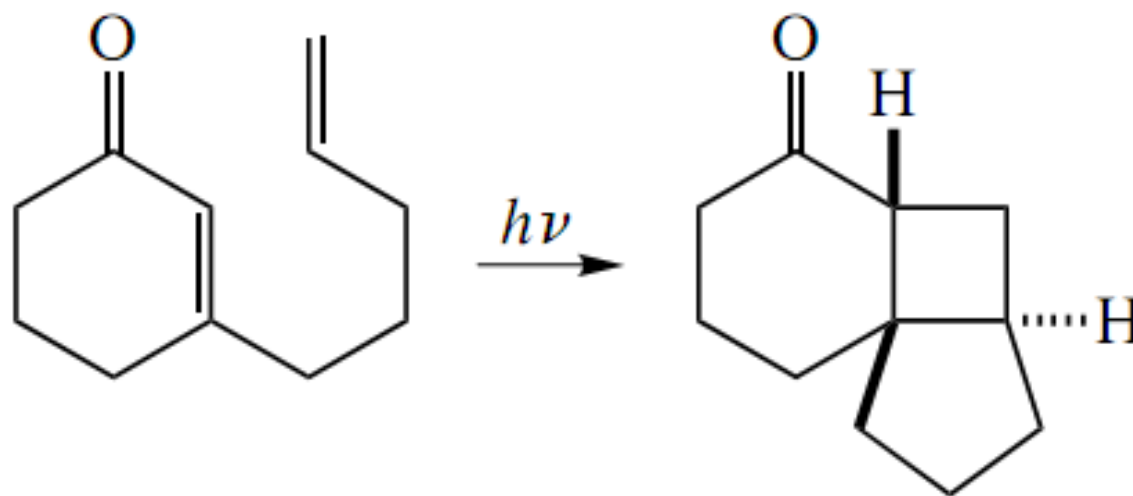
(1) [2 + 2] photocycloaddition

- The [2 + 2] photocycloaddition of two alkenes is widely used to form cyclobutanes.
- The [2 + 2] photocycloaddition reaction is highly **stereospecific** and **suprafacial** in each of the reacting partners.^{1,2}



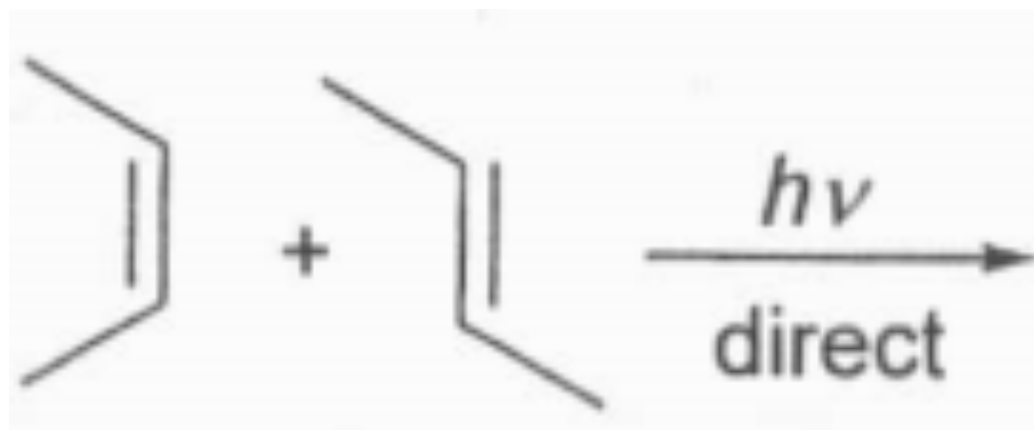
Scheme 3.2 Photochemical cycloaddition reactions of *cis*- and *trans*-2-butene.

(1) [2 + 2] photocycloaddition



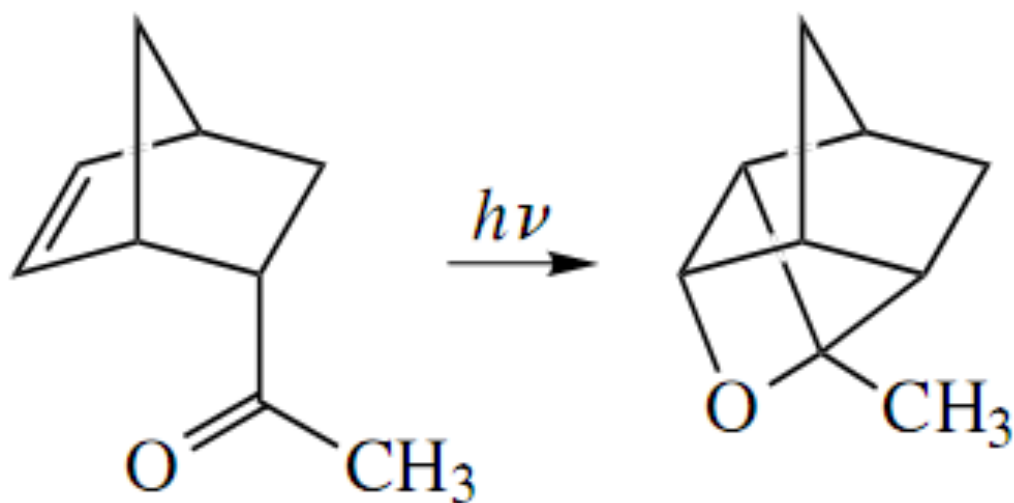
(1) [2 + 2] photocycloaddition

➤ **Homework:** Draw all possible products of the following reaction:



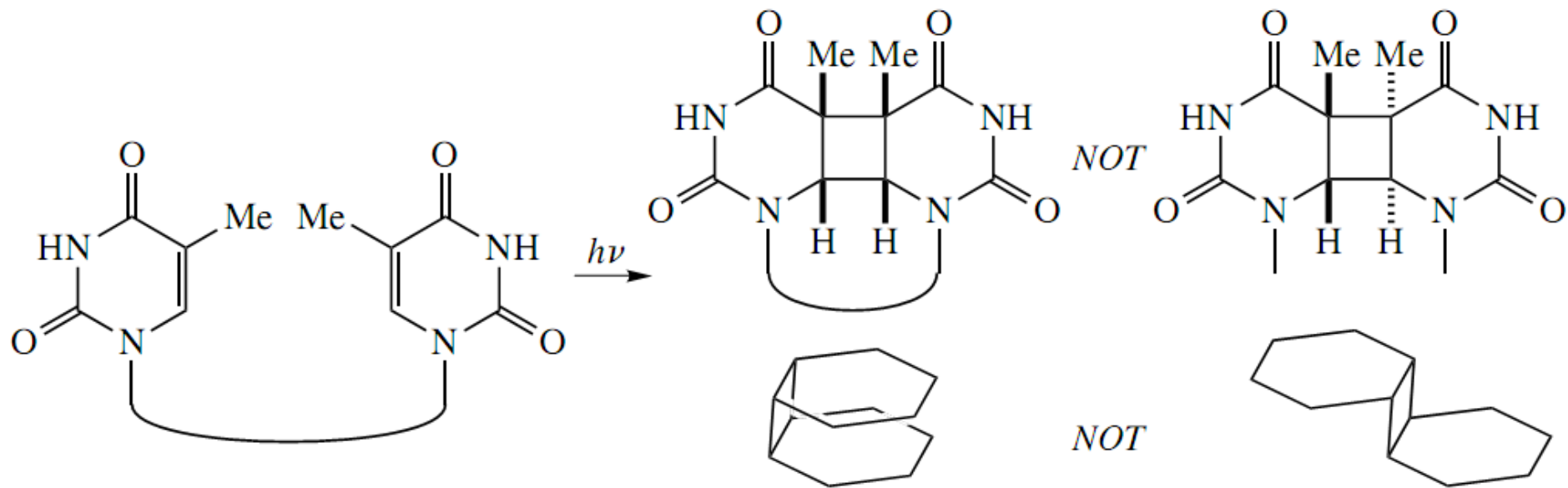
[2 + 2] photocycloaddition

- The photochemical reaction of ketone or an aldehyde with alkene to form an **oxetane** is called *Paterno–Büchi* reaction.¹



[2 + 2] photocycloaddition

- The light-induced [2 + 2] cycloaddition can occur **in vivo**. Two adjacent thymidine residues in DNA can undergo a [2 + 2] cycloaddition to give a *thymine dimer* with **endo** selectivity.¹
- DNA repair enzymes remove the dimer and usually repair it correctly, but occasionally they make a **mistake**, and a **mutation** occurs. The mutation can lead to **skin cancer**.¹

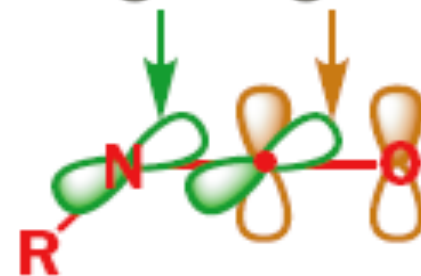
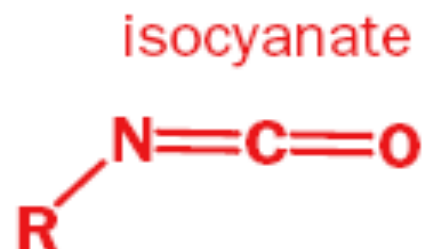
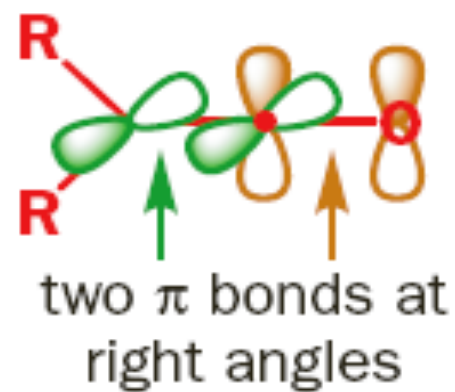
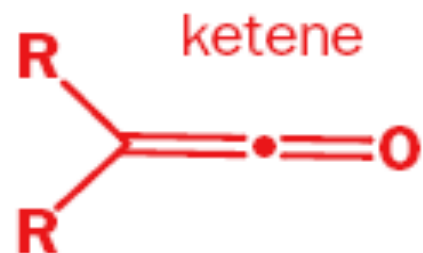


Why!!!!!!!!!!!!

- Why does [2 + 2] cycloaddition reaction work at all, given the strain in a four-membered ring: why doesn't the product just go back to the two starting materials?^{1,2}
- This reverse reaction is governed by the Woodward–Hoffmann rules, just like the forward one, and to go back again the four-membered ring products **would have to absorb light**. But since they have now lost their *pi* bonds they cannot absorb light of the wavelengths that the starting material can absorb. *i.e.* the reverse photochemical reaction is simply not possible because there is **no mechanism for the compounds to absorb light**.^{1,2}

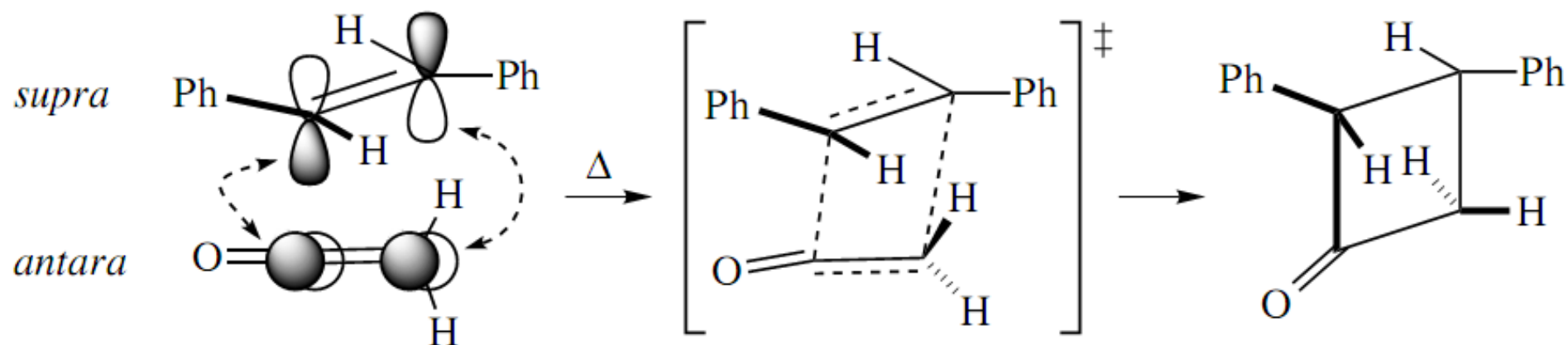
(2) [2 + 2] cycloaddition

- The structures of *cumulenes* have two pi bonds at right angles and they have a **central sp carbon atom**.¹



(2) [2 + 2] cycloaddition

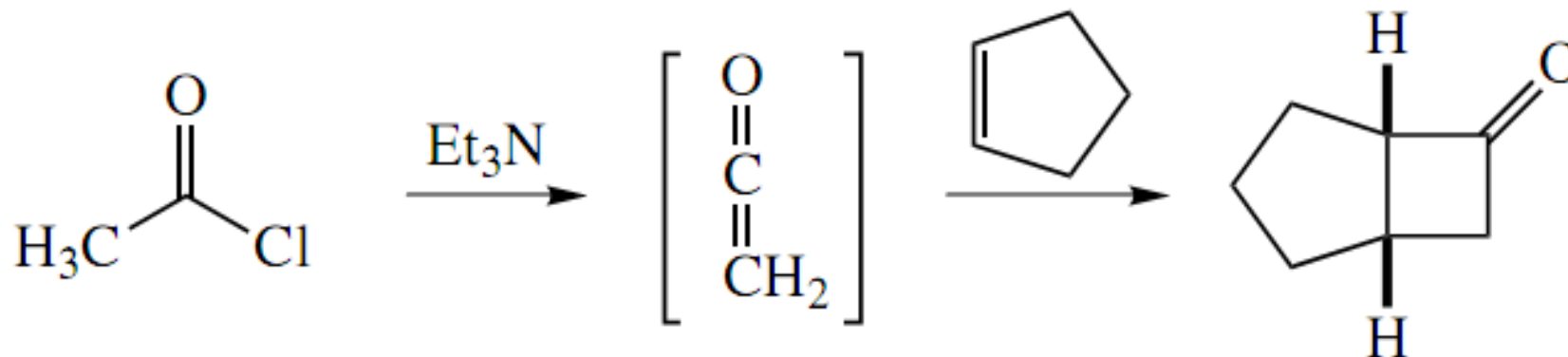
- Ketenes ($R_2C=C=O$) undergo concerted cycloadditions to alkenes under **thermal conditions** because the ketene can react *antarafacially* with an alkene that reacts *suprafacially*. The two termini of the C=C pi bond of the ketene react from opposite faces of the *pi* bond.¹
- Because the ketene must react antarafacially, the alkene **approaches** the ketene **with the two pi bonds nearly perpendicular** to each other.¹



- The **ketene–alkene** cycloaddition gives **cyclobutanones** in a *thermal* reaction.

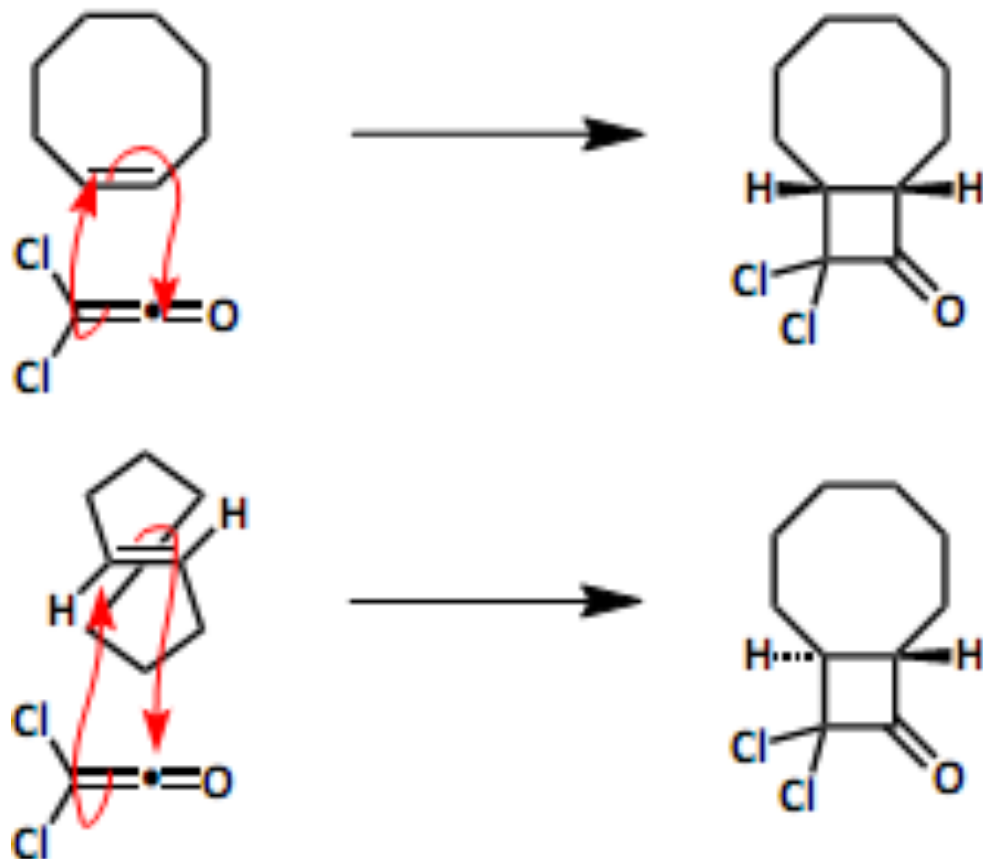
(2) [2 + 2] cycloaddition

- The antarafacial nature of the ketene **does not have any stereochemical** consequences, as there is no *cis-trans* relationship in the ketene to preserve in the product.¹
- The **alkene** component of the [2 + 2] cycloaddition with ketenes, however, reacts suprafacially, and its stereochemistry **is preserved** in the product.¹



(2) [2 + 2] cycloaddition

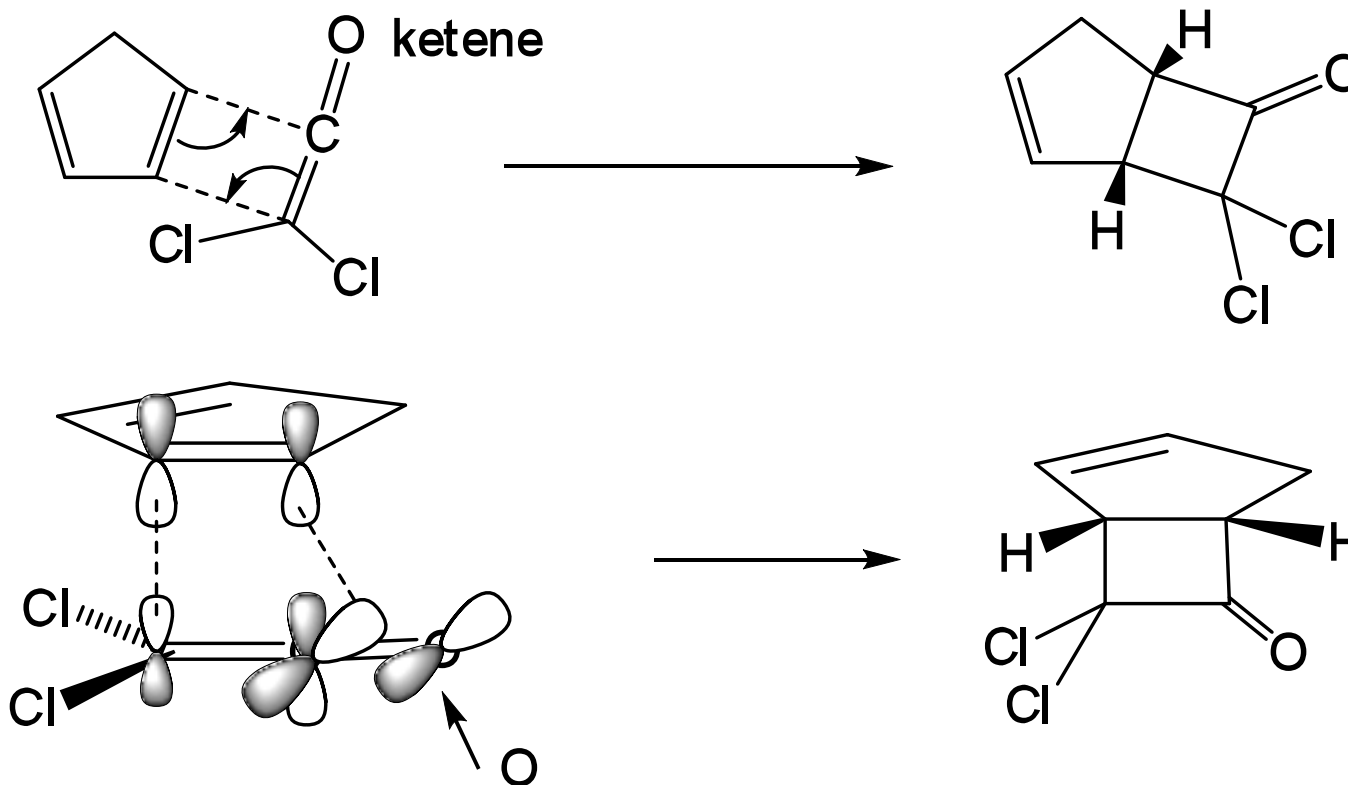
➤ The stereospecificity of cycloaddition of dichloroketene to olefins has been demonstrated by its reaction with *cis*- and *trans*-cyclooctene. In each case the cycloadduct is formed with very high stereospecificity clearly indicating that the olefin adds in a **suprafacial** manner.¹



(2) [2 + 2] cycloaddition^{1,2}

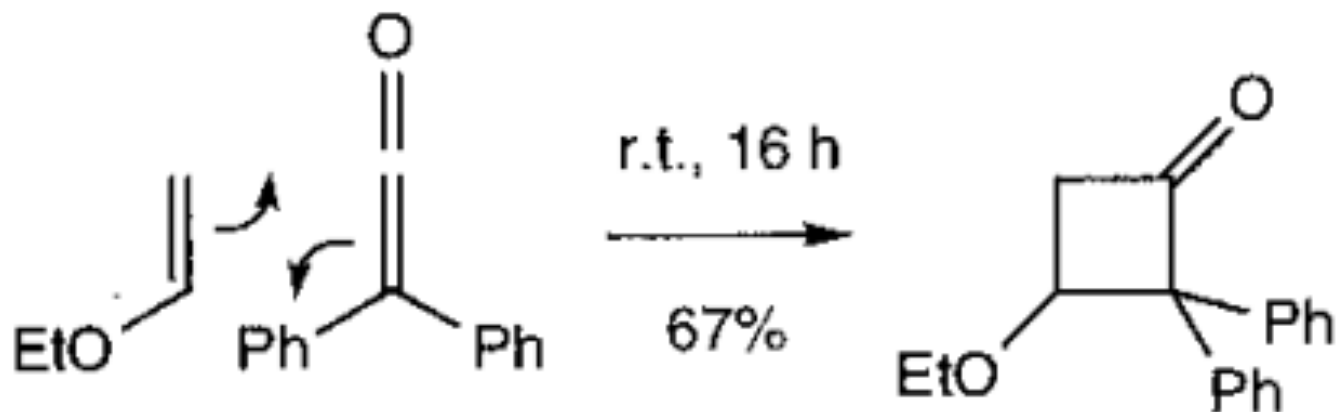
There are many explanations:

- (b) The other explanation is that the ketene uses **both** the C=C and C=O p-orbitals in the reaction, through a 'twisted' transition state.



Regioselectivity

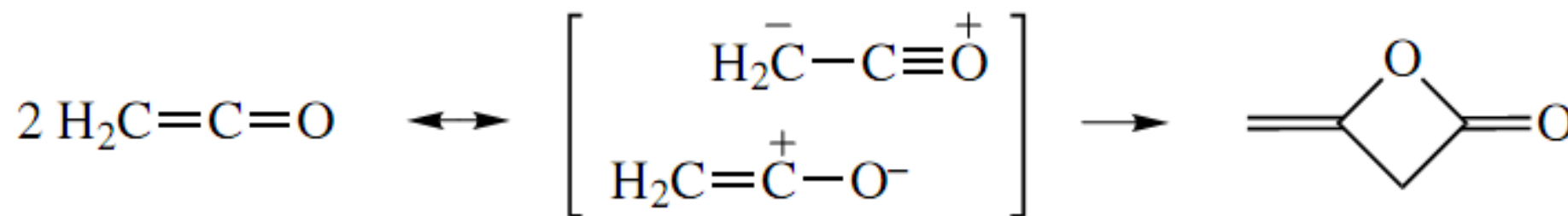
- Regioselectivity for the reaction of ketene with alkene can be predicted using the **ionic approach** and taking into consideration that the **carbonyl carbon** of ketenes is **very electrophilic** or by using orbital coefficients approach.¹



- The reaction of ketene with alkene is a **very efficient** regio- and stereospecific [2 + 2] cycloaddition.²

Dimerization of ketenes

➤ In the absence of other substrates, ketenes dimerize by a [2 + 2] cycloaddition. The electron-rich **C=C pi bond** combines with the electron-poor **C=O pi bond** to give a β -lactone.¹



Disconnection of a four-membered ring

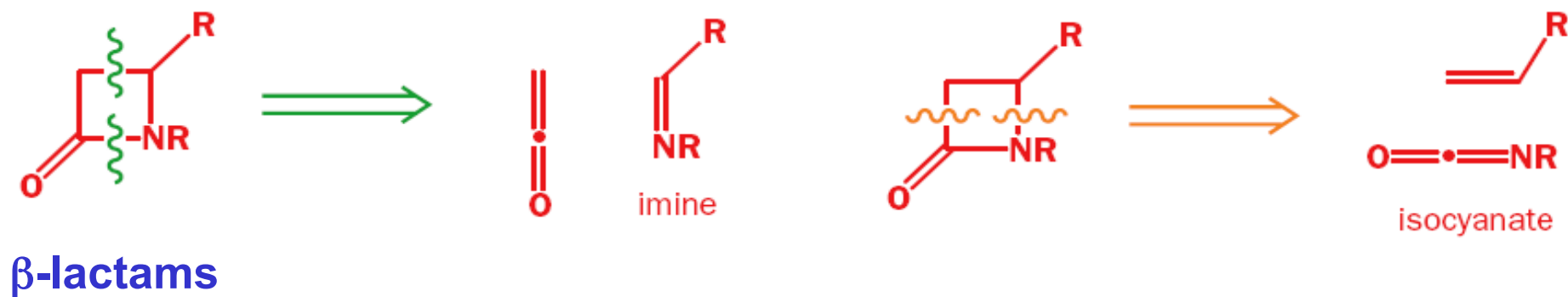
- The disconnection of a four-membered ring is very simple—you just split in half and draw the two alkenes. There may be **two ways** to do this.¹



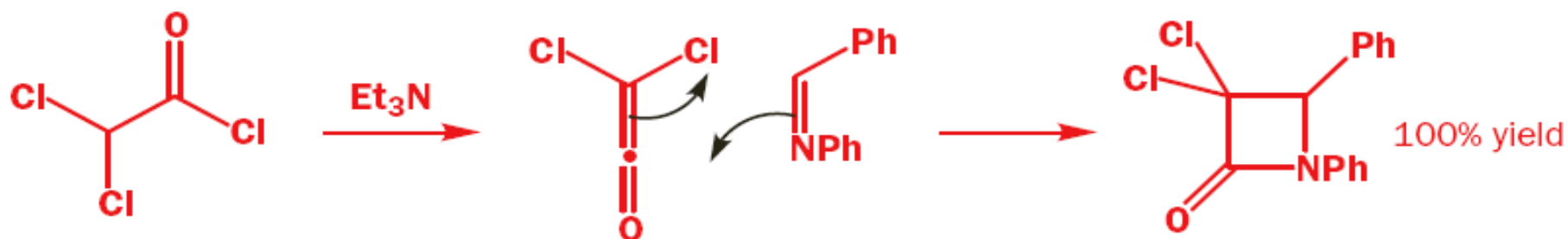
- However, we prefer the **second one** because we can control the stereochemistry by using *cis*-butene as the alkene.¹

Synthesis of β -lactams by [2 + 2] cycloadditions^{1,2}

- Other cumulenes such as **isocyanates** ($\text{RN}=\text{C}=\text{O}$) can also undergo thermal [2 + 2] cycloadditions. The [2 + 2] cycloaddition of an **isocyanate and an alkene** is a useful route to **β -lactams**, the key functional group in the penicillin and cephalosporin antibiotics, as is the [2 + 2] cycloaddition of a **ketene and an imine**.



Synthesis of β -lactams by [2 + 2] cycloadditions¹



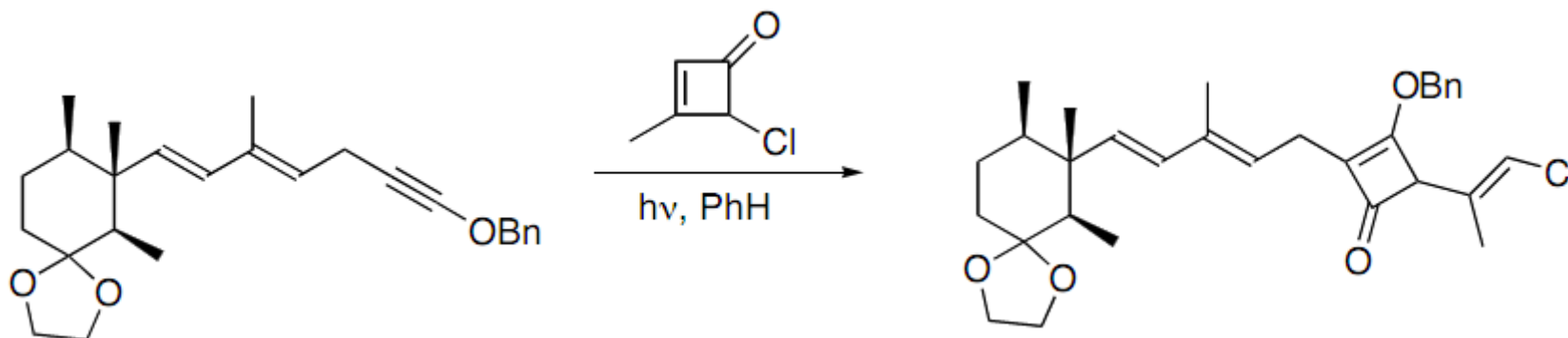
- As we expect, the more **nucleophilic nitrogen** atom attacks the carbonyl group of the ketene so that the **regioselectivity is right** to make β -lactams.

Homework: Write the product of this reaction



Homework

➤ Write the mechanism of the following reaction?

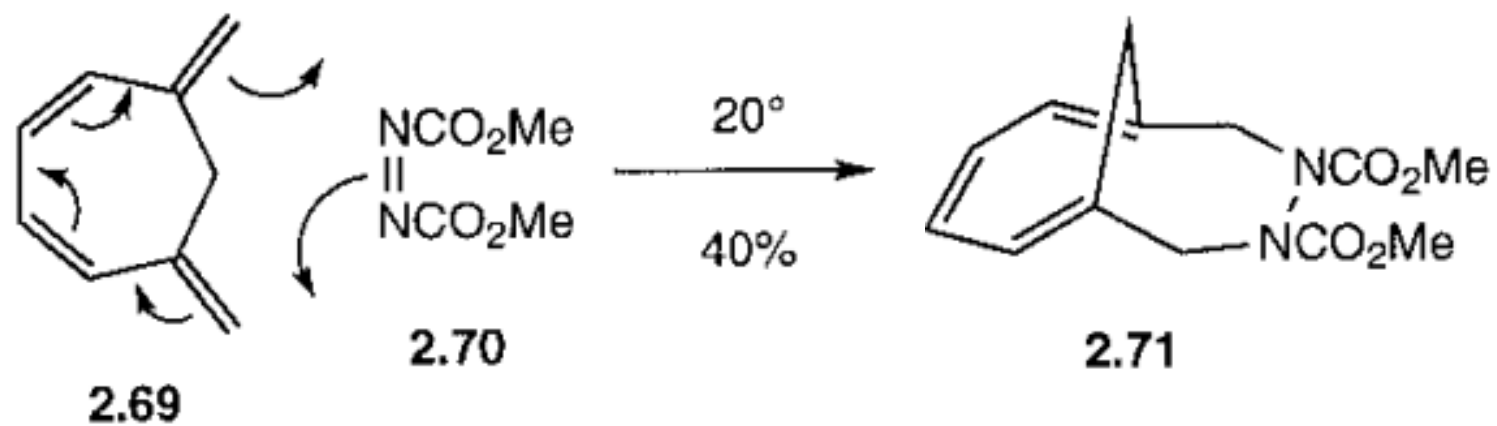


LEARNING OUTCOMES

LECTURE 7

- **Cycloadditions involving more than six electrons.**
- **$[\pi 2_s + \pi 2_s + \pi 2_s]$ cycloadditions**
- **Sigmatropic Reactions**

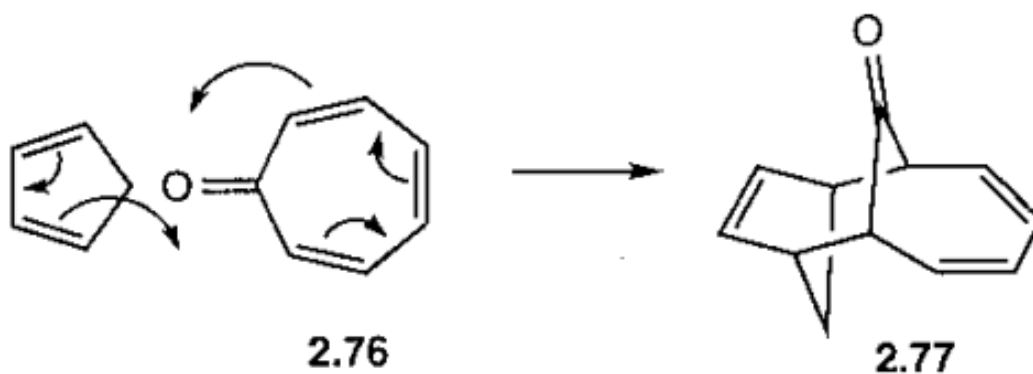
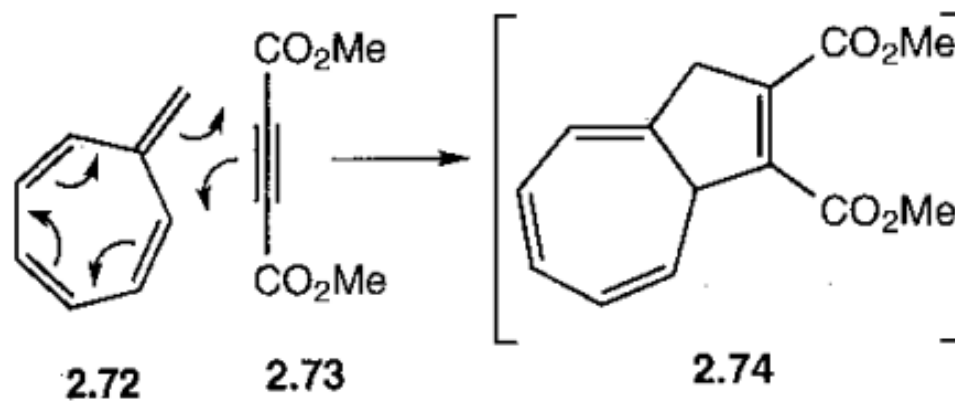
Cycloadditions involving more than six electrons



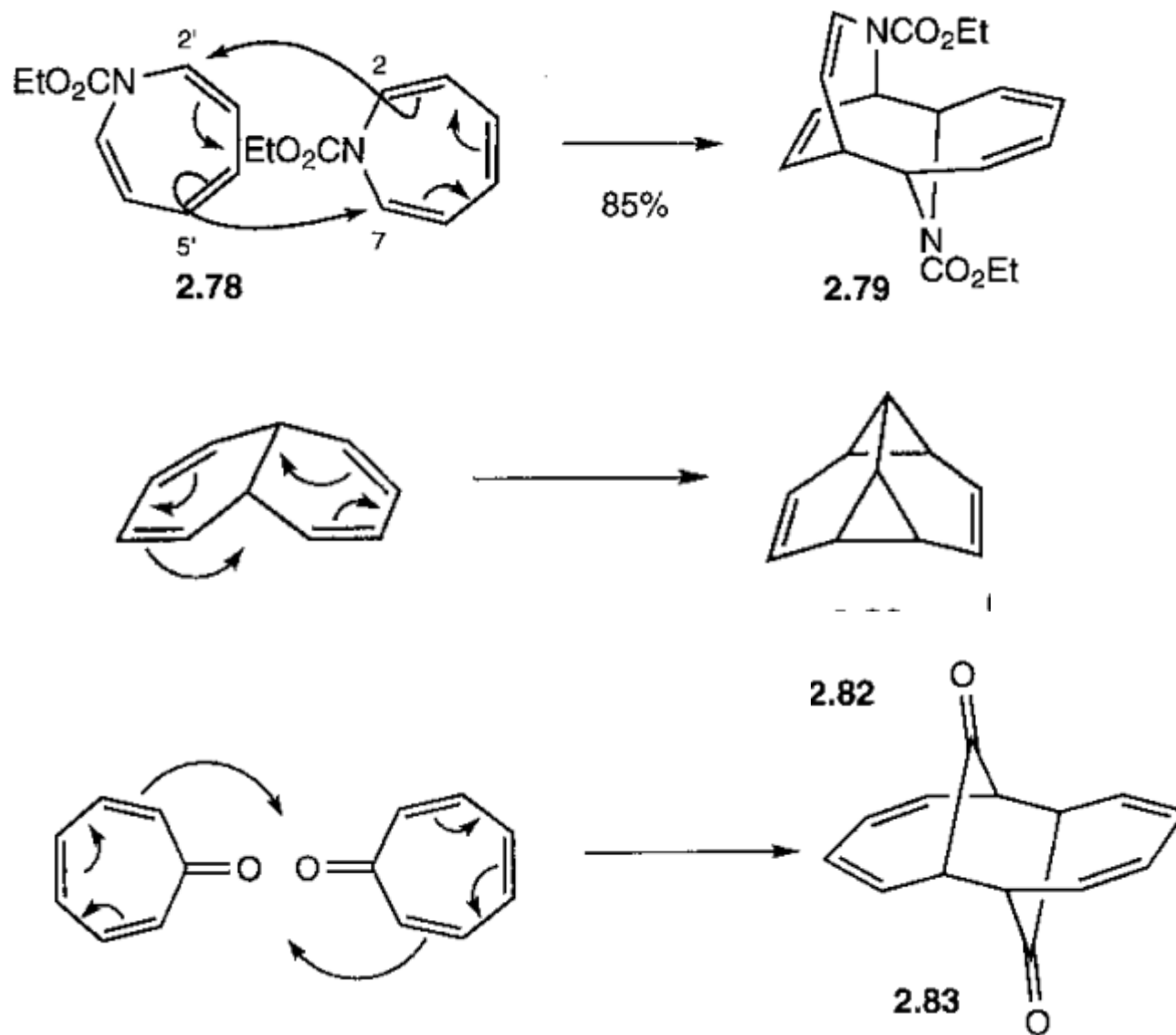
[8 + 2] cycloaddition

Homework

- Complete the following equations and (1) define the type of cycloaddition?
(2) Will the pericyclic reaction proceed under thermal or photochemical conditions?

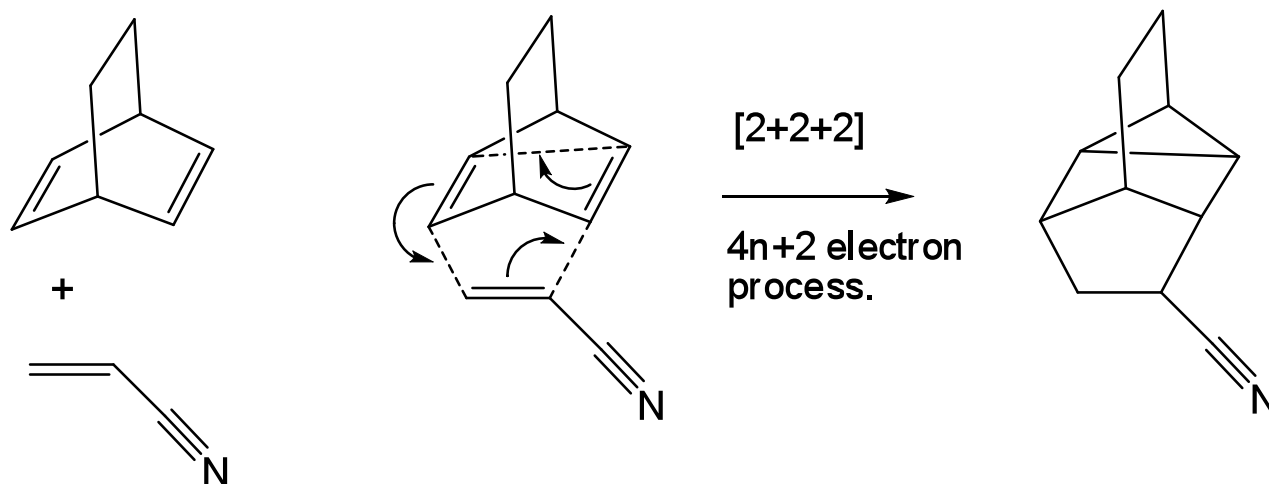


Homework



$[\pi 2_s + \pi 2_s + \pi 2_s]$ cycloadditions

- Although thermal $[\pi 2_s + \pi 2_s + \pi 2_s]$ cycloadditions are theoretically allowed, the **simultaneous combination of three molecules** would suffer from a **large, negative, entropy effect**. This would be particularly unfavorable at the high temperatures necessary for many cycloaddition reactions. Thus there appear to be no examples of concerted thermal cycloadditions of three molecules.¹
- Several examples of thermal cycloaddition reactions of unconjugated dienes with alkenes are known e.g. the reaction of norbornadiene with acrylonitrile.¹

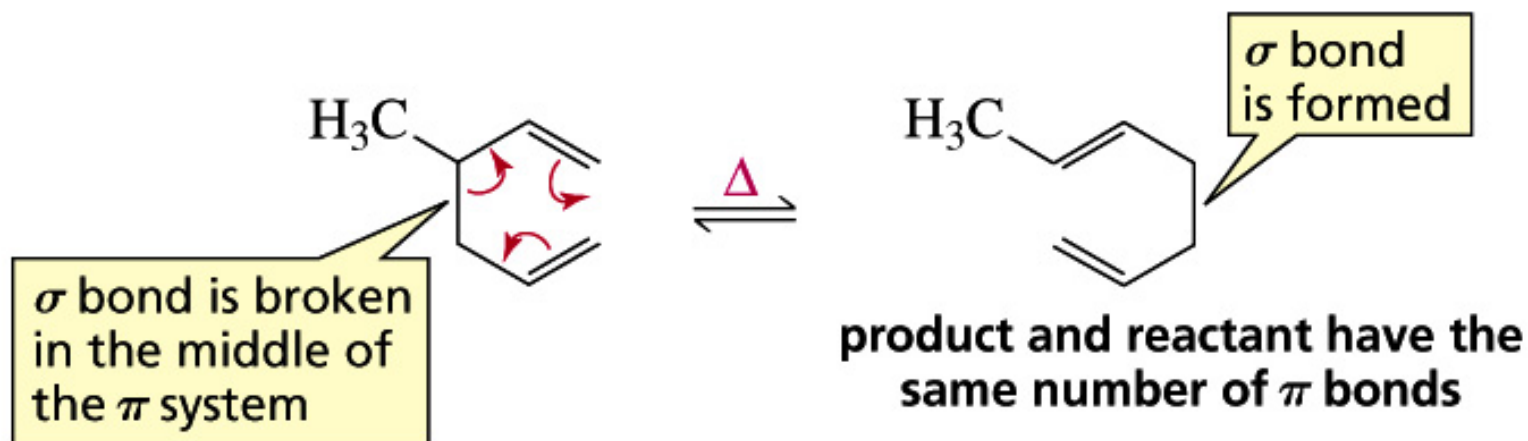


- Because the two π bonds in the norbornadiene **are not conjugated**, each is designated separately in the description of the reaction so this is a $[\pi 2_s + \pi 2_s + \pi 2_s]$ cycloadditions.²

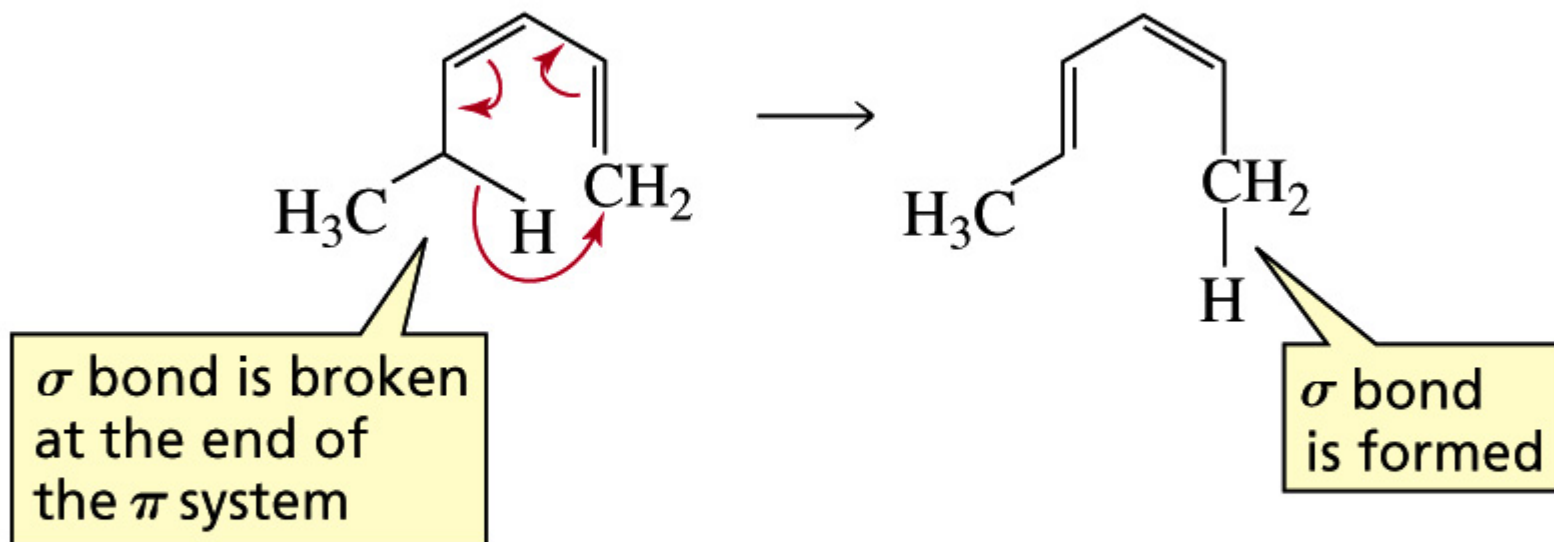
Pericyclic Reaction III

A σ bond is broken in the reactant, a new σ bond is formed in the product, and the π bonds rearrange

sigmatropic rearrangements



- A sigmatropic rearrangement produces a new sigma bond at the expense of a sigma bond, so this reaction is the most inherently **reversible** of all pericyclic reactions. The **position of the equilibrium** depends on the relative thermodynamic and kinetic stabilities of the starting material and products.¹

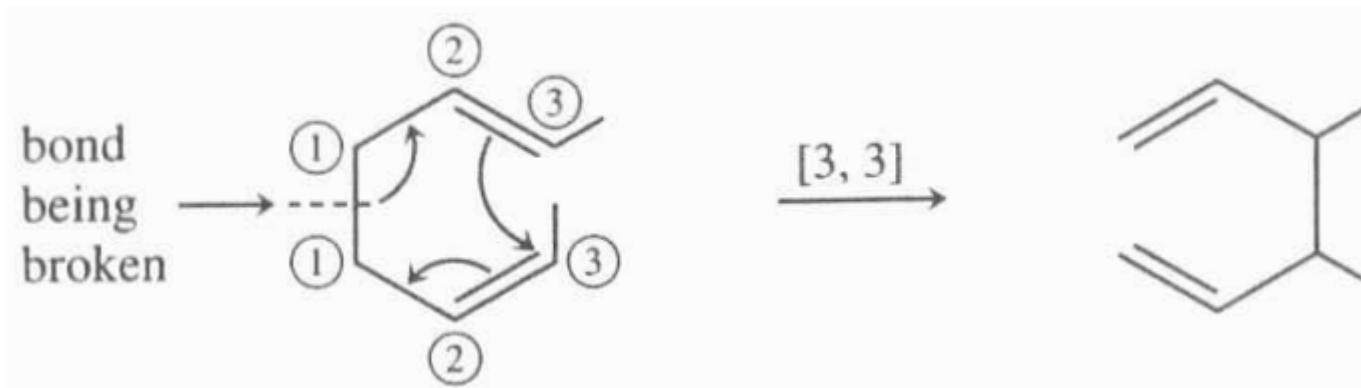


Sigmatropic Reactions

- **Sigmatropic reactions:** A concerted reaction in which a group migrates with its sigma bond within a pi framework, an ene or a polyene, and the migration is accompanied by a shift in pi bonds.¹
- Since in these reactions a change in the position of **one sigma bond** takes place, Woodward and Hofmann coined the term “**sigmatropic shifts**” to describe them.²⁻⁴
- In a sigmatropic reaction, a sigma bond that breaks is bonded to an **allylic carbon**.²⁻³

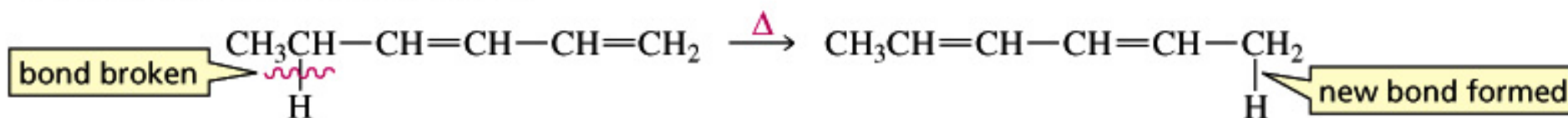
Sigmatropic Reactions¹

- To identify the type of a particular sigmatropic reaction, the two atoms forming the bond being **broken** are both numbered **as atom 1**.
- Then the atoms in each direction from the bond being broken, up to and including the atoms that form the new sigma bond in the product, are numbered consecutively as atoms 2,3, and so on.
- The numbers assigned to the atoms forming the new bond, separated by commas, are placed within brackets to designate the reaction type.

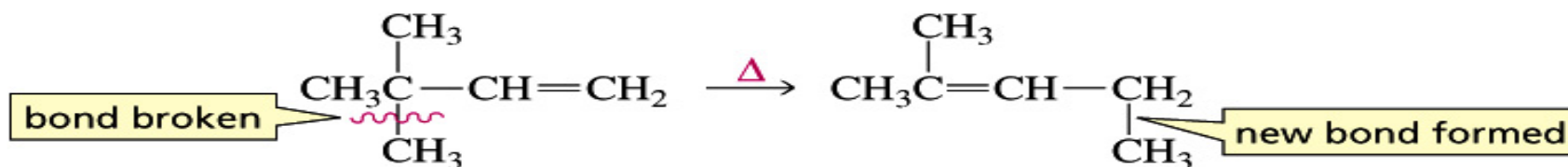


Sigmatropic Rearrangements

a [1,5] sigmatropic rearrangement



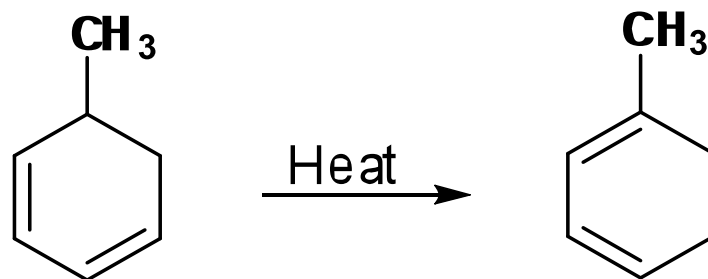
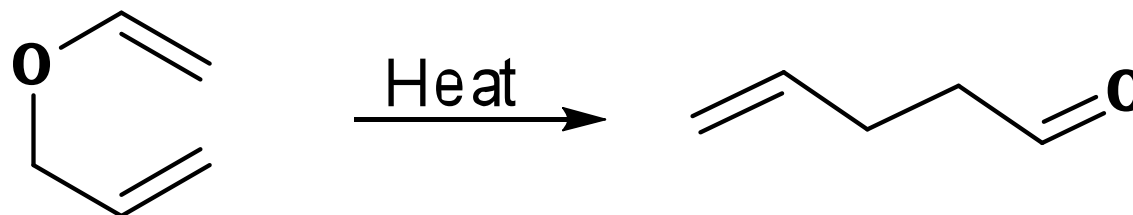
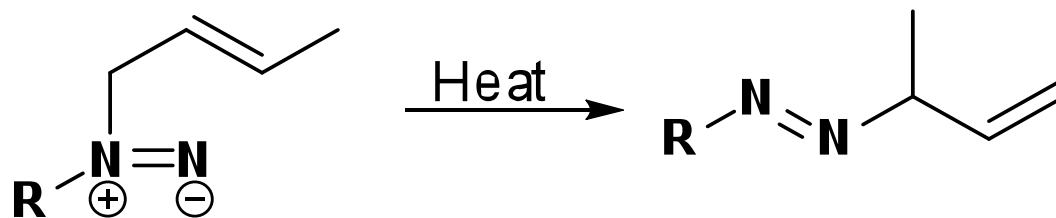
a [1,3] sigmatropic rearrangement



- In the designations [1,3] and [1,5] the “3” and “5” refer to the number of the carbon to which migrating group is moved to (the migration terminus). The “1” **does not** refer to the migration source; instead it specifies that in both reactant and product bonding is to the **same atom** (number 1) in the migrating group.¹

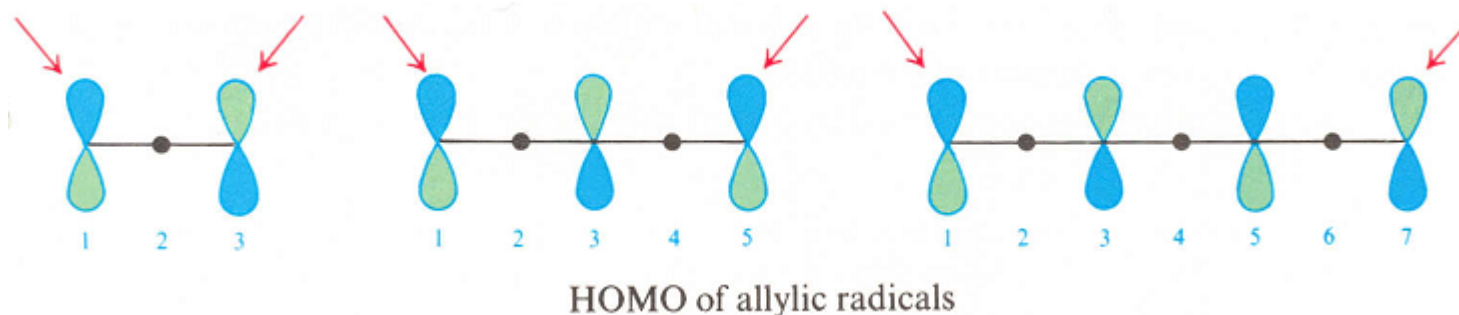
Homework

➤ Indicate **the order** of each of the sigmatropic shifts shown in the equations below.



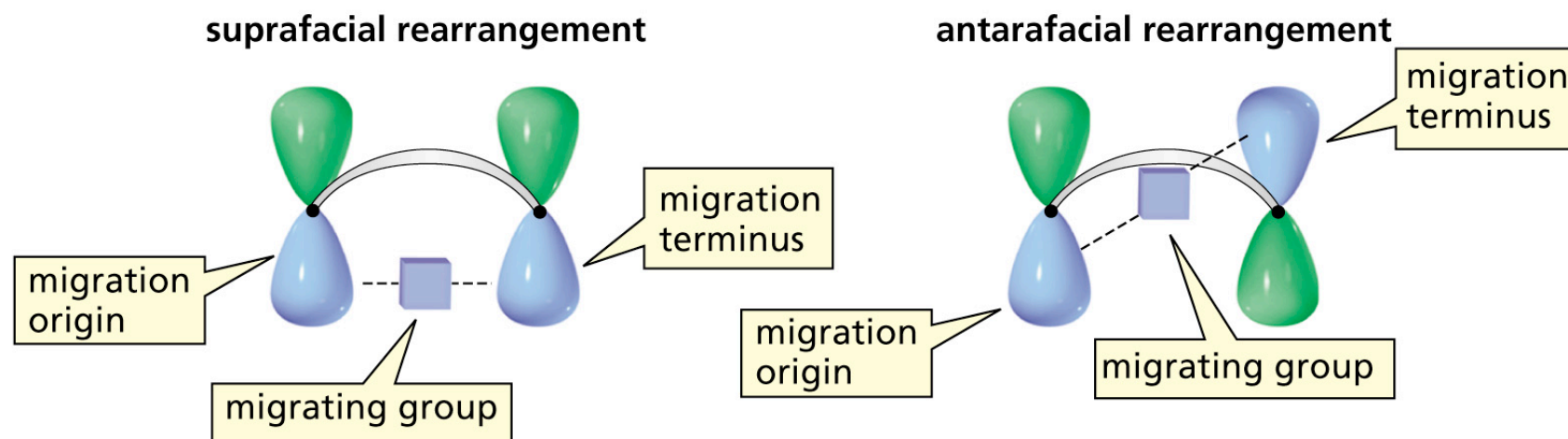
Sigmatropic Rearrangements

- We consider the bonding in the TS for sigmatropic reactions to arise from **overlap between an orbital of an atom or free radical (G) and an orbital of an allylic free radical** (the pi framework).
- In the TS, there is overlap between the HOMO of one component and the HOMO of the other. Each HOMO is singly occupied, and together they provide a pair of electrons.¹
- The HOMO of an allylic radical depends on the number of carbons in the pi framework. The migrating group is passed from one end of the allylic radical to the other, and so it is the **end carbons** that we are concerned with.¹



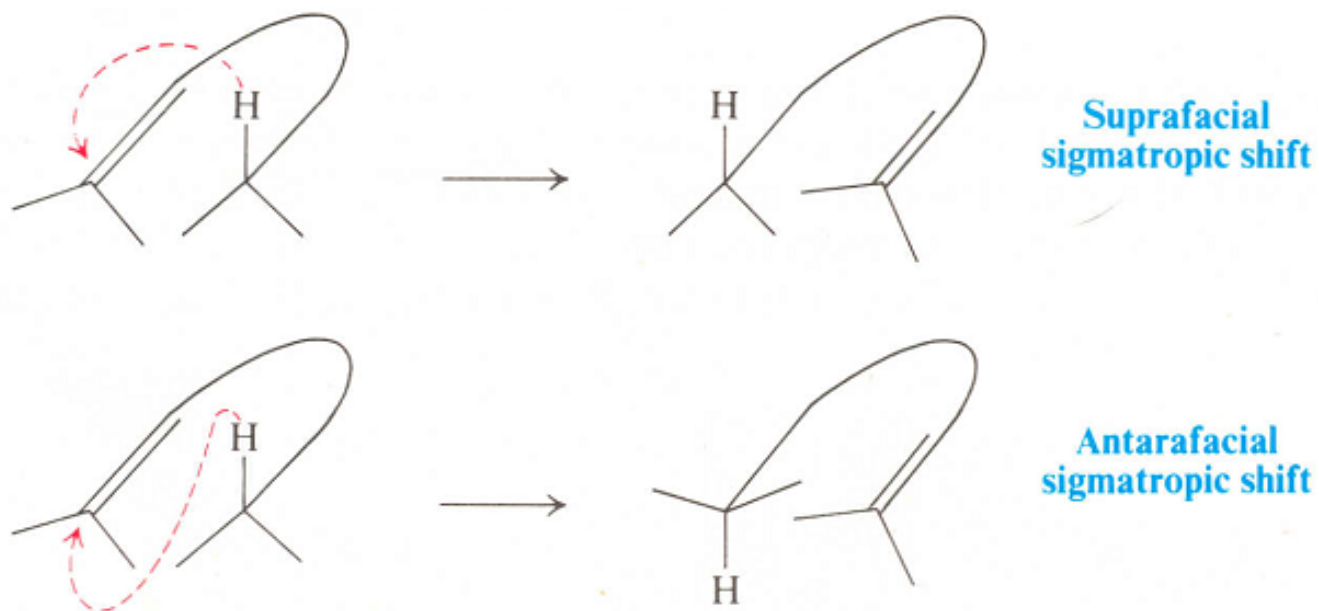
Sigmatropic Rearrangements

- In the **TS** of sigmatropic reaction, the migrating group is bonded to both the migration source and the migration terminus.



Sigmatropic Rearrangements

Migration of Hydrogen

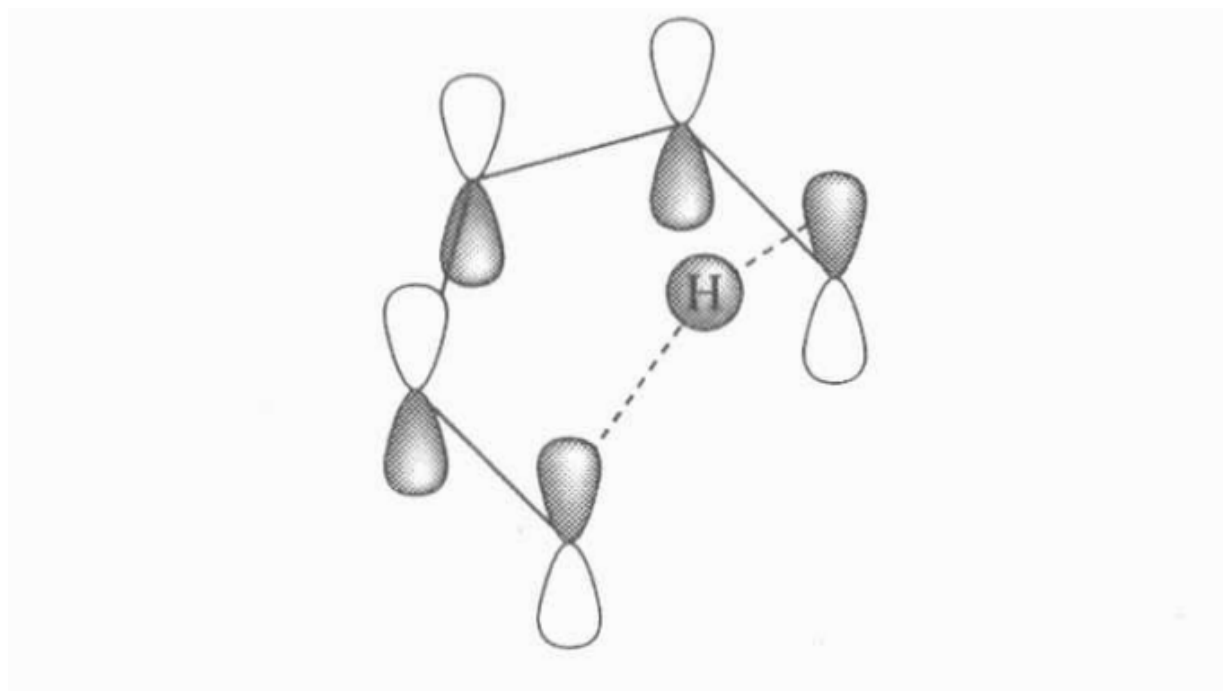


Sigmatropic Rearrangements

Migration of Hydrogen

- In the TS, a *three-center* bond is required, and this must involve overlap between the **s orbital** of the hydrogen and the **lobes of p orbitals** of the two terminal carbons.¹

For [1,5] hydrogen shift:

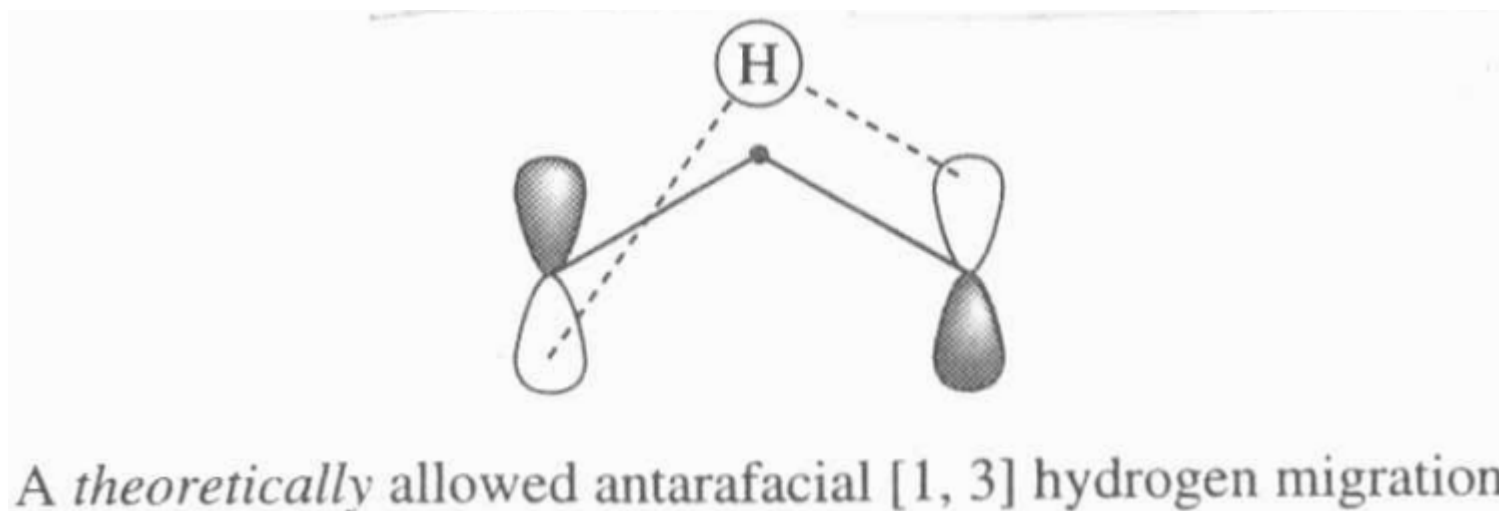


HOMOs in the transition state for a [1, 5] hydrogen shift

Sigmatropic Rearrangements

Migration of Hydrogen

For [1,3] hydrogen shift:



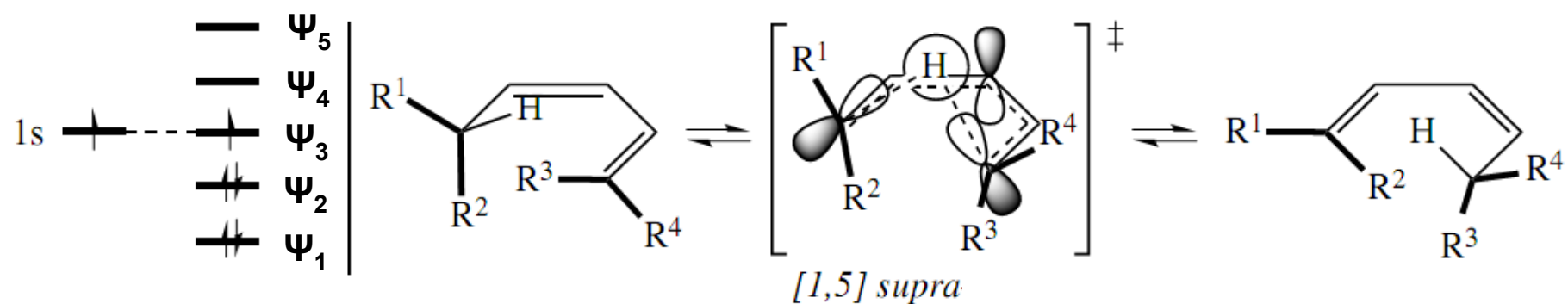
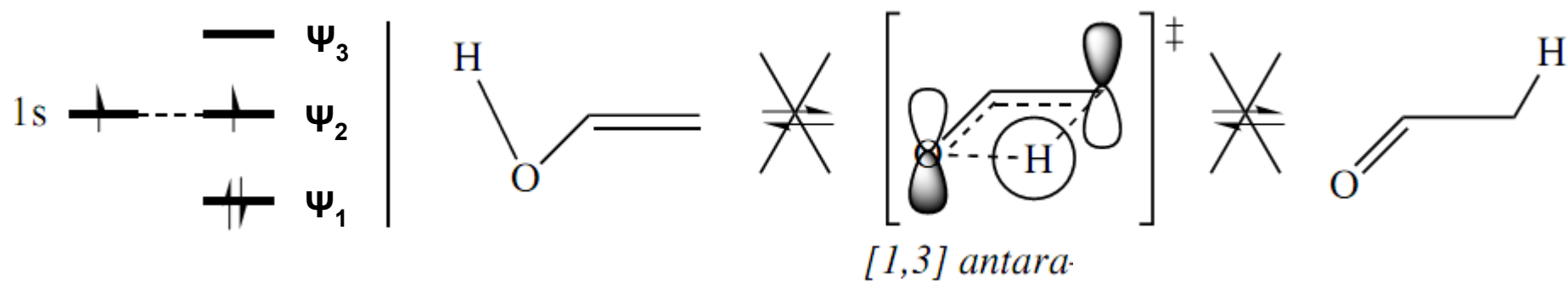
Sigmatropic Rearrangements

Migration of Hydrogen

- The phase relationships between the HOMOs of the two “radicals” then determine whether the reaction is suprafacial or antarafacial.²
- Whether a sigmatropic reaction actually take places, depends not only on the **symmetry requirements** but also on the **geometry** of the system.¹
- [1,3] and [1,5] antara shifts should be **extremely difficult**, since they would require the pi framework **to be twisted** far from the planarity that it requires for delocalization of electrons.¹
- For larger pi frameworks, both *supra* and *antara* shifts should be **possible** on geometric grounds.¹

Sigmatropic Rearrangements

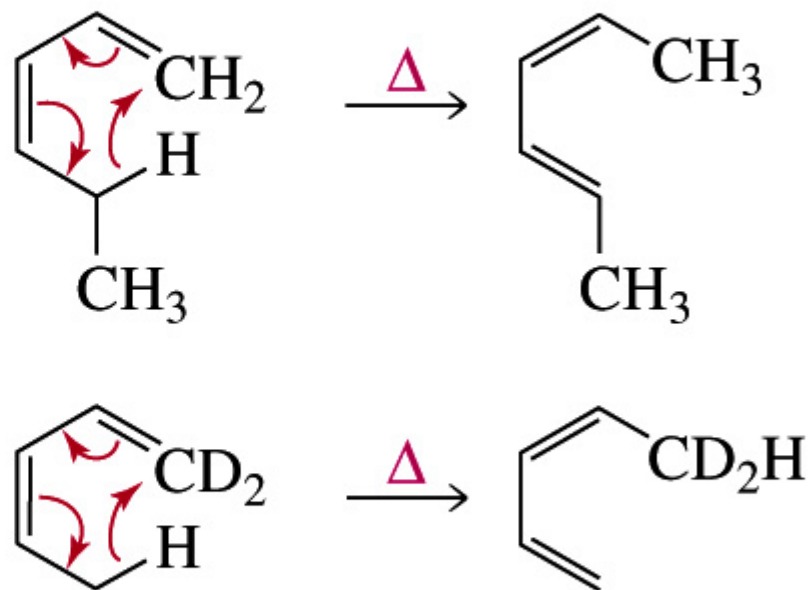
Migration of Hydrogen¹



Sigmatropic Rearrangements

Migration of Hydrogen

- [1,3] sigmatropic shifts of hydrogen are not known, whereas [1,5] shifts are well known. For example:¹



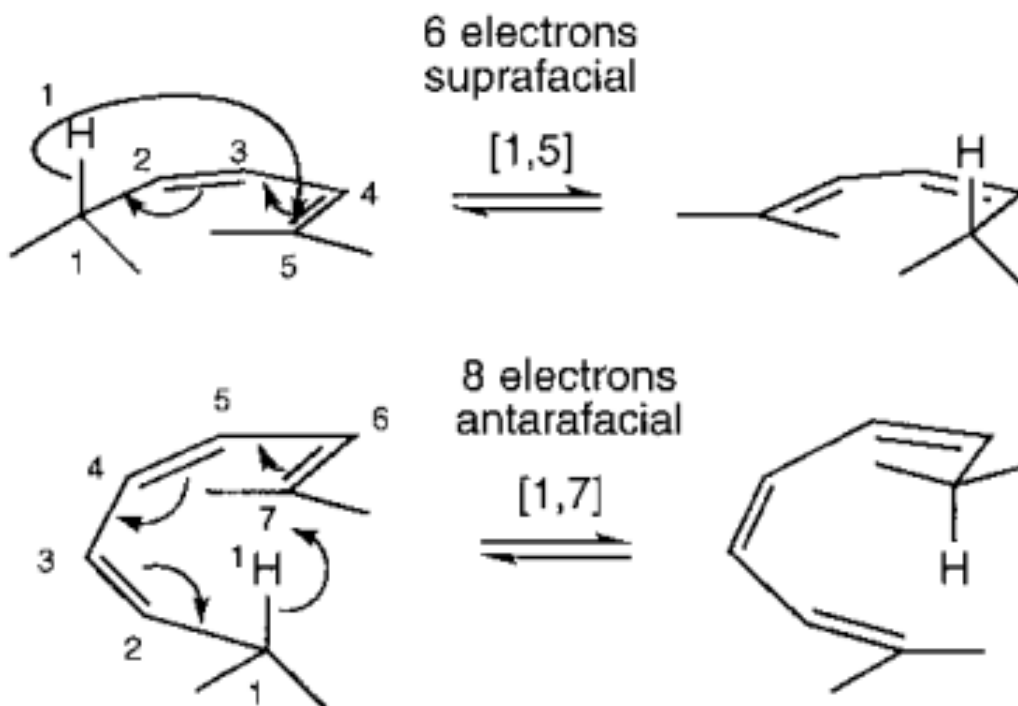
Sigmatropic Rearrangements

Migration of Hydrogen¹

➤ As a general rule: for [1,x] hydrogen shift, where $x = 2, 3, 4, 5, 6, 7, \dots$

When the total number of electrons = $4n + 2$ **→** Suprafacial

When the total number of electrons = $4n$ **→** Antarafacial

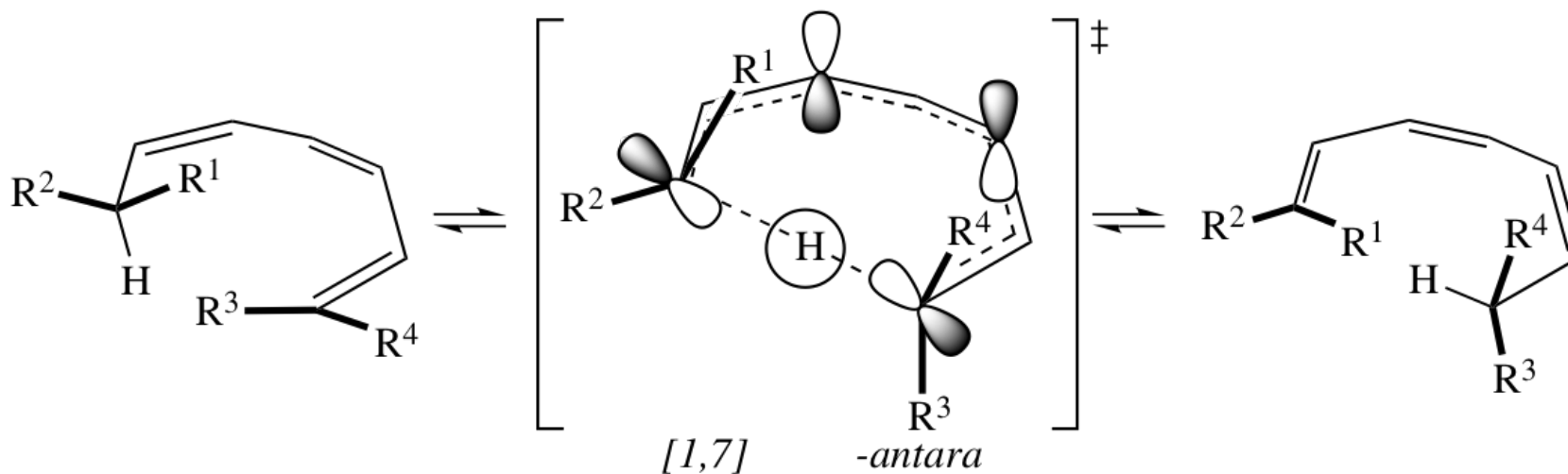


Sigmatropic Rearrangements

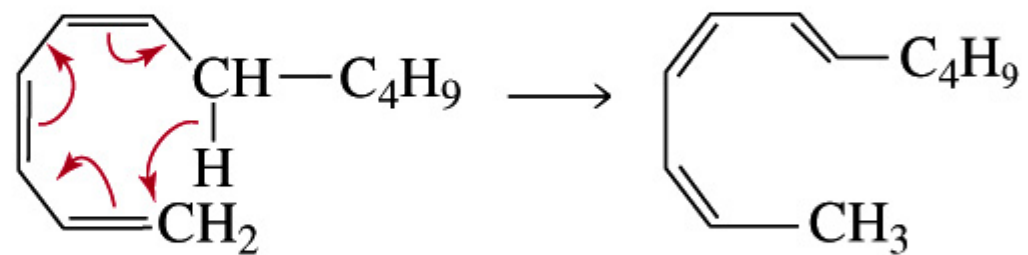
Migration of Hydrogen¹

For [1,7] hydrogen shift:

- A thermal, concerted [1,7]-H shift is sometimes observed in acyclic systems because the 1,3,5-triene system is **floppy enough** to allow the H to migrate from the top face to the bottom face (making the triene the antarafacial component).



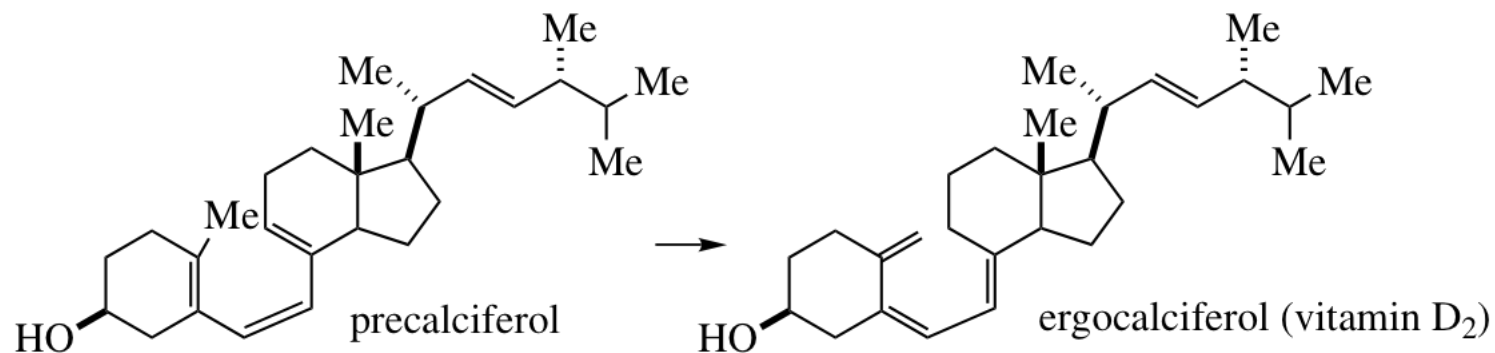
1,7-hydrogen shift



Sigmatropic Rearrangements

Migration of Hydrogen¹

- A very important [1,7] sigmatropic rearrangement occurs in the human body. Precalciferol (provitamin D₂) is converted to ergocalciferol (vitamin D₂) by a thermal [1,7] sigmatropic H shift. This shift must be antarafacial.^{1,2}



- In **cyclic compounds** like cycloheptatriene, **geometric constraints prevent** the H from migrating from the top to the bottom face of the seven-carbon pi system, and **the shift does not occur**.¹

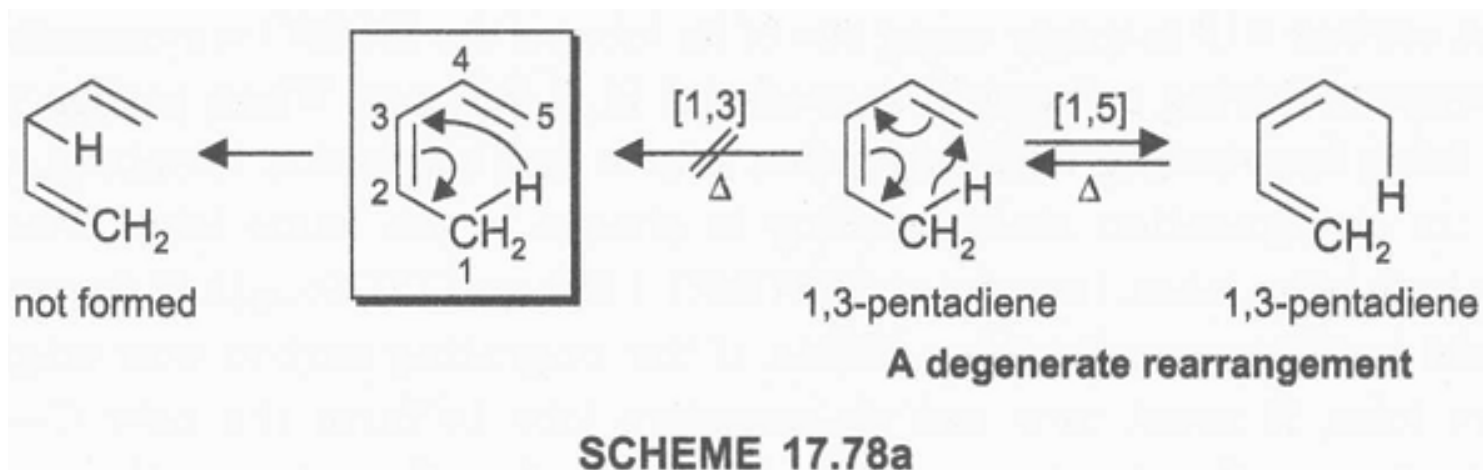
Sigmatropic Rearrangements

Summary of thermal sigmatropic hydrogen shifts

	[1,3]H shift	[1,5]H shift	[1,7]H shift
stereochemistry	antarafacial	suprafacial	antarafacial
feasibility	impossible	easy	possible

Sigmatropic Rearrangements

Degenerate rearrangements¹

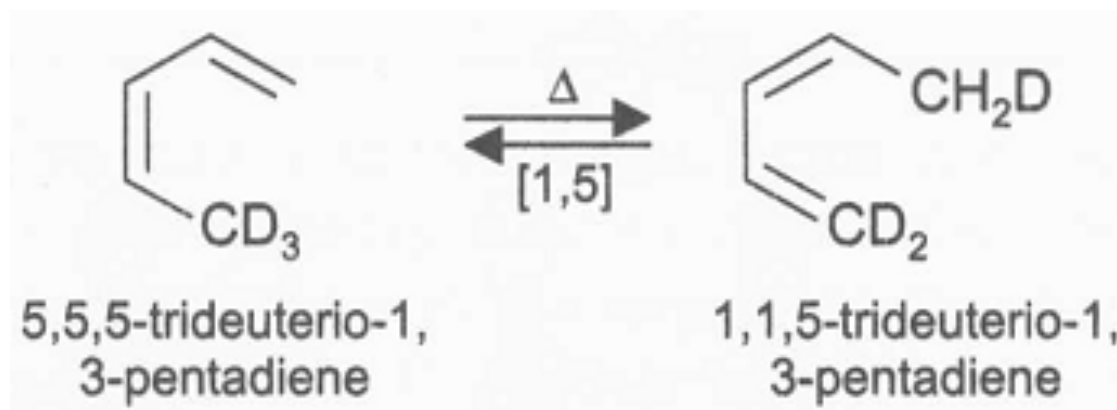


- On heating, 1,3-pentadiene rearranges to itself via a [1,5]-H shift.
- **Degenerate rearrangements:** It is a process in which a reactant rearranges to itself.

Sigmatropic Rearrangements

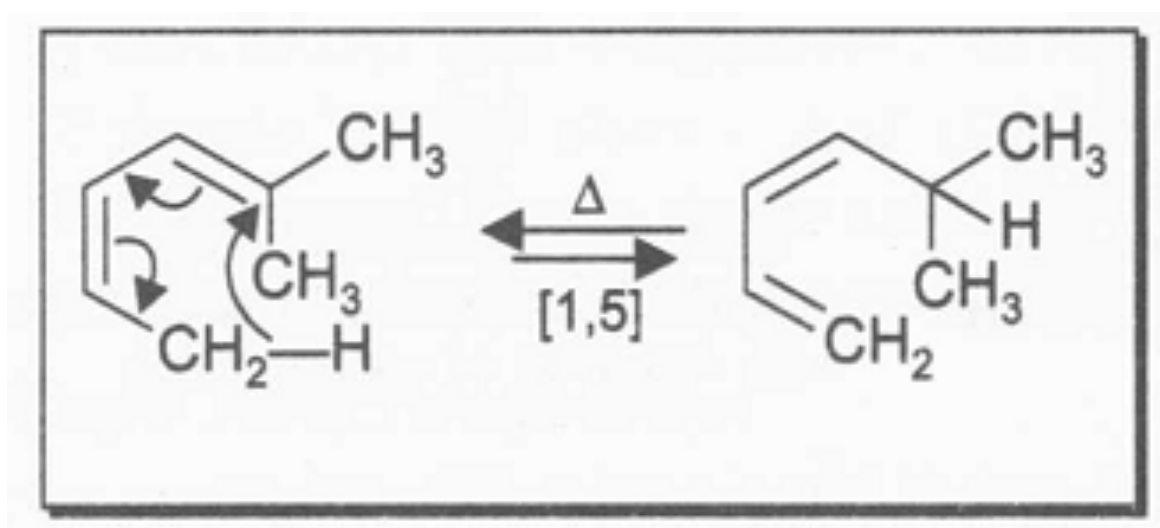
Degenerate rearrangements¹

- How can we establish the **degenerate rearrangements**?
- This can be confirmed by using **isotopically labeled** molecules or **suitably substituted** molecules.



Sigmatropic Rearrangements

Degenerate rearrangements¹



Sigmatropic Rearrangements

Migration of Hydrogen

- The preference for [1,5]-H shifts over [1,3]-H shifts has been demonstrated many times. For example:¹

