PERICYCLIC REACTIONS

PART-4, PPT-15, SEM-5, CC-12 Cycloaddition Reaction II Diels-Alder Reaction I

Dr. Kalyan Kumar Mandal Associate Professor St. Paul's C. M. College Kolkata

Cycloaddition Reaction II Diels-Alder Reaction I CONTENTS

- 1. The Diels-Alder Reaction: Introduction
- Energetics and Reversal (Retro Diels-Alder Reaction)
- Conformation of the Diene
- Cyclic vs Acyclic Diene
- Steric Effects
- Nature of Dienophiles
- 2. Frontier Orbital Control and Reactivity
- 3. Normal Electron Demand Diels-Alder Reaction
- 4. Inverse Electron Demand Diels-Alder Reaction

The Diels-Alder Reaction: Introduction

• The Diels-Alder cycloaddition of a diene with a dienophile is represented schematically in Figure 1.



The reaction involves the formation of two σ bonds at the expense of two π bonds. Besides all-carbon diene systems, heterodienes with one or more heteroatoms (commonly N, O) also participate in Diels-Alder reactions. The dienophiles are usually alkenes (C=C) or alkynes (C=C) but a variety of hetero-dienophiles such as C=O, N=O, N=N, O=O (singlet) and C ≡ N can also take part in Diels-Alder reactions. Such scope and versatility of the Diels-Alder reactions.





Otto Paul Hermann Diels 1876-1954

Kurt Alder 1902-1958

The Nobel Prize in Chemistry 1950 was awarded jointly to Otto Paul Hermann Diels and Kurt Alder "for their discovery and development of the diene synthesis."

The principle of Diels-Alder reaction was discovered in 1928 by Otto Diels and his student Kurt Alder. Both were honored with the Nobel Prize for Chemistry in 1950.

Energetics and Reversal of Diels-Alder Reaction

- Energetics of the reaction: As two σ bonds are formed at the expense of two π bonds, the reaction is exothermic. This is because the σ bonds are usually more stable than the π bonds. Hence, the formation of the cycloadduct is usually favoured energetically, i.e., $\Delta H = -ve$. On the contrary, this reaction is unfavourable entropically, i.e., $\Delta S = -ve$. This is due to the fact that two reactants combine to give one product, that is, there is decrease of number of particles in the system. Hence, the system becomes ordered as the reaction progresses.
- **Retro Diels-alder reaction:** It is, however, possible to reverse the course of the reaction on raising the reaction temperature as the free-energy change is related to the latter according to the equation: $\Delta G = \Delta H - T\Delta S$. In that case, $-T\Delta S > \Delta H$. As a consequence, cyclobutene, on passing over a heated nichrome wire (an alloy of Ni, Cr and Fe), decomposes to give a mixture of buta-1,3-diene and ethylene (Figure 2).



• The diene component of the Diels-Alder reaction cannot react in *s-trans* conformation as this introduces an impossibly strained *trans* double bond in the six-membered ring adduct (Figure 3). Therefore, the Diels-Alder reaction proceeds via a *s-cis* conformation, as a consequence of the formation of boat-like TS, which gives a stable *cis* double bond in the cycloadduct.



This Lecture is prepared by Dr. K. K. Mandal, SPCMC, Kolkata

- The diene component in the Diels-Alder reaction can be open-chain or cyclic and it can have many different kinds of substituents. However, the diene must have the *s*-*cis* conformation to participate in Diels-Alder cycloaddition reactions.
- Buta-1,3-diene normally prefers the *s*-trans conformation with the two double bonds as far away from each other as possible for steric reasons. The barrier to rotation about the central σ bond is small (about 30 kJ mol⁻¹ at room temperature) and rotation to the less favourable but more reactive *s*-*cis* conformation is rapid.
- The *s*-*trans* conformation of an acyclic diene has lower energy than *s*-*cis* conformation. Buta-1,3-diene which exists almost exclusively in the *s*-*trans* conformation (>99% at room temperature) must, therefore, take up the higher energy *s*-*cis* conformation to undergo the Diels-Alder reaction with a dienophile (**Figure 4**).

• On the other hand, cyclic dienes, such as cyclopentadiene, in which the double bonds are locked in *s*-*cis* conformation are usually highly reactive in Diels-alder reaction.



• Consequently, cyclopentadiene that exists in locked *s-cis* orientation straightway undergoes the Diels-Alder reaction. It is so reactive that on standing at room temperature, it slowly dimerizes (Figure 5).



The dienes with exocyclic double bonds which are fixed in *s-cis* conformation react readily with dienophiles in Diels-Alder reaction. Examples of such dienes include *ortho*-quinodimethanes and 1,2-dimethylenecyclohexane (Figure 6).



• *cis* Fused cyclic dienes are usually the most reactive, particularly if the ring size is such that the ends of the diene are a convenient distance apart for bonding to the dienophiles.

- Thus cyclopentadiene is somewhat more reactive than cyclohexadiene, both being more reactive than larger ring dienes, for example cycloocta-1,3-diene.
- The reactivity of the cyclic dienes decreases with increasing ring size and follows the order: cyclopentadiene >> cyclohexadiene >> cycloheptadiene >> cyclooctadiene. This is because the terminal carbons of the diene unit get further apart (Figure 7) with increase in ring size resulting in progressively less effective overlap with the dienophile in the transition structure.



This Lecture is prepared by Dr. K. K. Mandal, SPCMC, Kolkata

 Heterocyclic dienoid systems such as furan also take part in the Diels-Alder reaction but as expected the dienoid activity falls in the series furan < pyrrole < thiophene as the diene character is replaced by aromatic character (Figure 8).



Cyclic vs Acyclic Diene in Diels-Alder Reaction

• For the acyclic buta-1,3-diene, the free energy of activation is given by:

 $\Delta G^{\neq}_{\text{acyclic}} = G_{\text{TS}} - G_{\text{reactants}} = G_{\text{TS}} - G_{s\text{-trans diene}} - G_{\text{dienophile}}$

- The free energy of *ground state* buta-1,3-diene is a weighted average of free energies of *s*-*trans* and *s*-*cis* forms but *s*-*cis* form contributes negligibly (<1%). Therefore, the free energy of buta-1,3-diene is taken as that of *s*-*trans* diene.
- In the case of cyclic diene,

 $\Delta G^{\neq}_{\text{cyclic}} = G_{\text{TS}} - G_{\text{reactants}} = G_{\text{TS}} - G_{s\text{-}cis\text{ diene}} - G_{\text{dienophile}}$ • Comparing ΔG^{\neq} for acyclic and cyclic cases, it can be said that $\Delta G^{\neq}_{\text{cyclic}} < \Delta G^{\neq}_{\text{acyclic}}$ because $G_{s\text{-}cis\text{ diene}} > G_{s\text{-}trans\text{ diene}}$. Therefore, the free energy difference between *s*-*cis* and *s*-*trans* forms raises the free energy barrier for the acyclic case, and a cyclic diene would

react faster than acyclic diene in the Diels-Alder reaction.

- In the Diels-Alder reaction, the old *σ* bond in the centre of the diene becomes a *π* bond in the product and the conformation of that *σ* bond becomes the configuration of the new *π* bond in the product. For this reason, the cyclic dienes that are permanently locked in *s*-*trans* conformation and acyclic dienes which cannot adopt *s*-*cis* conformation due to steric reasons are unreactive in this reaction.
- For dienes with *s*-*trans* orientation at the double bond, the two ends of these dienes cannot get close enough to react with an alkene and, in any case, the product would have an impossible *trans* double bond (Figure 3) in the new six-membered ring.



This Lecture is prepared by Dr. K. K. Mandal, SPCMC, Kolkata

- The diene can only react in a *cisoid* configuration. Molecules in which the diene system is fused *transoid* do not react, and the rate of reaction with open chain dienes depends on the equilibrium proportions of *cisoid* conformer present. Thus, substituents in the diene can affect the rate not only by their electronic character but by their influence on conformer proportion.
- The Diels-Alder reaction is highly sensitive to steric effects due to the compact cyclic nature of the Diels-Alder transition state. Bulky substituents on the dienophile or on the terminal carbon atom, particularly in the *cis*-isomer, can resist the approach of the two components close to each other and decrease the rate of the reaction.
- *cis*-1-Substituted butadienes (A) are less reactive than their *trans*isomers (B) since a bulky R group disfavours the *cisoid* conformation.

• Large 2-substituents in the diene, however, favour the *cisoid* conformation and the diene is correspondingly more reactive. These are illustrated pictorially in Figure 10.



- When $R = CH_3$ group, the rate slightly increases from buta-1,3-diene itself. This is due to the electron releasing nature of the methyl group which raises the HOMO energy. The *trans*-isomer is, however, more reactive than the *cis*-isomer. For $R = -CMe_3$, the steric factor dominates in the rate, and the reaction becomes extremely slow (Figure 10A).
- However, when the *t*-butyl group is present at C-2 of buta-1,3-diene, the *s*-*cis* conformation of the diene is more stable than that of the *s*-*trans* diene (Figure 10B). Consequently, there is a large increase in the rate of the reaction.
- Presence of two large groups on both terminal carbon atoms of buta-1,3-diene in the (Z, Z)-configuration and -CMe₃ group both at C-2 and C-3 of buta-1,3-diene prevent the compound to take part in Diels-Alder cycloaddition reaction (Figure 11).



- Due to the severe repulsions between large groups in the *s*-*cis* and *s*-*trans* form, the buta-1,3-diene moiety in 2,3-di-*t*-butylbuta-1,3-diene do not remain in the same plane and *π*-*π* conjugation is lost. Consequently, it behaves as a stable non-conjugated diene.
- Buta-1,3-diyne has a linear structure. Unlike conjugated diene, it cannot assume bent *s*-*cis* conformation due to excessive strain involved in the process. So, it is also unreactive in this reaction.

Nature of Dienophiles in Diels-Alder Reaction

- The dienophiles with isolated double or triple bonds are usually unreactive. However, cyclic alkenes and alkynes with large angle strain are reactive dienophiles. For example, cyclopropene reacts as a dienophile with cyclopentadiene (Figure 12A).
- Cyclooctyne has a considerable ring strain and undergoes Diels-Alder reaction rapidly with diphenylisobenzofuran to give the cycloadduct (Figure 12B). The driving force for this reaction is due to the decrease in angle strain in the transition structure for the cycloaddition.
- The smaller cycloalkynes with increased angle strain can be trapped by Diels-Alder cycloaddition. Arynes are reactive intermediates and can act as powerful dienophiles. For example, benzyne reacts with a variety of dienes and even with benzene to give the cycloadducts (Figure 12C).

Nature of Dienophiles in Diels-Alder Reaction



- There are three types of frontier orbital control that can operate on the Diels-Alder reaction based on whether a single HOMO/LUMO pair or both HOMO/LUMO pairs are involved. These are
- 1. HOMO_{diene}/LUMO_{dienophile} control
- 2. $LUMO_{diene}/HOMO_{dienophile}$ control
- 3. $HOMO_{diene}/LUMO_{dienophile}$ and $LUMO_{diene}/HOMO_{dienophile}$ control
- The frontier orbital control is determined by the difference $\Delta E_{LUMO-HOMO}$ (= E_{LUMO} E_{HOMO}). The smaller the difference, the greater its contribution to ΔE_{FMO} . If the energy gaps for the two possible HOMO/LUMO interactions are closely balanced (~1 eV), both interactions become significant and the frontier orbital control is exercised by both HOMO/LUMO pairs.

- But, if the energy gap for one HOMO/LUMO pair is much smaller than the other complementary pair, the interaction with smaller energy separation becomes dominant and thereby determines the frontier orbital control. A HOMO/LUMO pair with a larger energy separation by 3 eV or more may practically be ignored. The estimated frontier orbital energies of unsubstituted and substituted ethylene and diene systems are shown in Figure 13.
- For prototype Diels-Alder reaction of butadiene with ethylene, $\Delta E_{LUMO-HOMO}$ is estimated as follows:
 - $E_{\text{LUMO(ethylene)}} E_{\text{HOMO(butadiene)}} = [1.5 (-9.1)] \text{ eV} = 10.6 \text{ eV}$ $E_{\text{LUMO(butadiene)}} E_{\text{HOMO(ethylene)}} = [1.0 (-10.5)] \text{ eV} = 11.5 \text{ eV}$
- The two energy gaps are almost 1 eV, and the frontier orbital control is operated by both $HOMO_{diene}/LUMO_{dienophile}$ and $LUMO_{diene}/HOMO_{dienophile}$ interactions.

Estimated Frontier Orbital Energies



• The prototype Diels-Alder reaction is found to be extremely slow and requires more forcing conditions (Figure 14A).



Let us now consider the Diels-Alder reactions when diene and dienophile are attached with a c-, z- or x-substituent where c, z and x stand for conjugating, electron-withdrawing, and electron-donating substituent, respectively. It is observed experimentally that the introduction of a z-substituent (e.g., CHO) on the dienophile speeds up a Diels-Alder reaction quite remarkably and the reaction occurs under much milder conditions (Figure 14B).

• The Diels-Alder reactions with electron-deficient z-substituted dienophiles are indeed most common. The frontier orbital control with a z-substituted dienophile is obtained from the estimate of HOMO/LUMO energy separation ($E_{LUMO} - E_{HOMO}$). $E_{LUMO(z-dienophile)} - E_{HOMO(butadiene)} = [0 - (-9.1)] eV = 9.1 eV$

 $E_{\text{LUMO(butadiene)}} - E_{\text{HOMO(z-dienophile)}} = [1.0 - (-10.9)] \text{ eV} = 11.9 \text{ eV}$

- The energy separation for HOMO_{diene}/LUMO_{dienophile} interaction is considerably smaller by 2.8 eV. The reaction is, therefore, mainly under HOMO_{diene}/LUMO_{dienophile} control with an energy separation of 9.1 eV.
- The reactivity pattern also follows from the HOMO/LUMO energy difference. The smaller the HOMO/LUMO energy difference the higher is the reactivity.

• For the prototype Diels-Alder reaction, both HOMO/LUMO pairs are important which give a weighted average value of 11 eV for $(E_{LUMO} - E_{HOMO})$ whereas the reaction with a z-substituted dienophile gives a smaller energy difference of 9.1 eV. Thus a z-substituent on the dienophile increases the rate of the Diels-Alder reaction.



- The rate of the Diels-Alder reaction is markedly influenced by the electronic effect of substituents. It is found to be promoted by electron-donating substituents in the diene and by electron-withdrawing substituents in the dienophile. The effect of such substituents is to lower the energy level of the LUMO in the dienophile and to raise the energy level of the HOMO in the diene, thus enhancing the degree of possible interaction between the them.
- The cycloaddition of buta-1,3-diene with a **z**-substituted dienophile reveals complementary electron demand involving electron-rich (donor) diene and electron-deficient (acceptor) dienophile. This type of Diels-Alder reaction is known as normal electron demand Diels-Alder (NEDDA) reaction.
- NEDDA reactions are HOMO_{diene}/LUMO_{dienophile} controlled, and proceed at reasonable rates. Most Diels-Alder reactions belong to such type.

- When the diene possesses a c- or x-substituent at C-1/C-2, it becomes even more electron rich and the reaction is expected to be more facile. The HOMO/LUMO energy separations (E_{LUMO} E_{HOMO}) for cycloadditions of the c- and x-substituted dienes with z-substituted dienophile are shown in Figure 16. The more important HOMO/LUMO interaction with a smaller energy separation in each case is indicated with the estimated value of (E_{LUMO} E_{HOMO}) using green coloured arrow.
- It is evident that the energy difference of the controlling HOMO_{diene}/LUMO_{dienophile} interaction for **c** and **x**-substituted dienes (as shown in Figure 16) ranges from 8.2 to 8.7 eV, which is less than that for the unsubstituted diene (9.1 eV). Therefore both **c** and **x**-substituted dienes react faster than the unsubstituted diene. This has been observed experimentally.



• For example, the reaction of 1-methoxybutadiene or 2-methoxybutadiene with acrolein is more facile and proceeds at lower temperature (Figure 17; Reactions B and C) than butadiene (Reaction A).



Inverse Electron Demand Diels-Alder Reaction

- If the electron demands of the diene and dienophile are reversed using acceptor diene (electron deficient) and donor dienophile (electron rich), the reaction is called inverse electron demand Diels-Alder (IEDDA) reaction. The frontier orbital control and reactivity trend for IEDDA reaction is illustrated with the combination of 1-z-substituted diene with x-substituted dienophile in **Figure 18**.
- Acceptor diene, i.e., diene with electronwithdrawing group has low energy LUMO, whereas donor dienophile has high-energy HOMO.



Inverse Electron Demand Diels-Alder Reaction

• Here the dominant interaction is LUMO_{diene}/HOMO_{dienophile} interaction with a smaller energy separation of 8.5 eV which is favoured over the other interaction by a margin of 4 eV. The IEDDA reaction is, therefore, under LUMO_{diene}/HOMO_{dienophile} control and has an energy separation similar to normal Diels-Alder reaction. The reaction with inverse electron demand is, thus, expected to be facile. However, IEDDA reactions are much less common, and performing a reaction with inverse electron demand is often less effective compared with normal Diels-Alder reaction.

Summary

• The frontier orbital control is principally decided by smaller frontier orbital energy separation. The HOMO/LUMO energy gap becomes smaller if HOMO energy is raised or LUMO energy is lowered. The smaller energy separation also increases the rate of the reaction. An electron-rich component has a high-energy HOMO and therefore, preferably uses its HOMO. An electron-deficient component on the other hand preferentially uses its low-energy LUMO. A normal electron demand Diels-Alder reaction is HOMO_{diene}/LUMO_{dienophile} controlled while an IEDDA reaction is under LUMO_{diene}/HOMO_{dienophile} control.