Pericyclic Reactions and Organic Photochemistry

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Pericyclic Reactions – Cycloaddition Reactions – Diels-Alder Reaction Woodward-Hoffmann rule – Regio-Chemistry and Stereochemistry aspects

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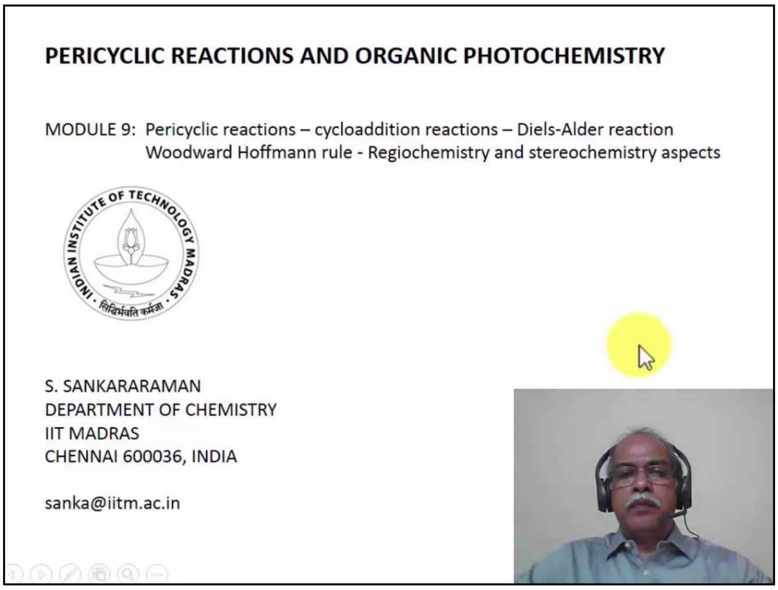

PERICYCLIC REACTIONS AND ORGANIC PHOTOCHEMISTRY

MODULE 9: Pericyclic reactions – cycloaddition reactions – Diels-Alder reaction
Woodward Hoffmann rule - Regiochemistry and stereochemistry aspects

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Hello, welcome to the course on Pericyclic Reactions and Organic Photochemistry. In this module, which is module number nine, for example, we will consider a very important Cycloaddition reaction, namely the Diels-Alder reaction. Diels-Alder reaction is an extremely important reaction, to learn in organic synthesis. And, it is very widely used in the synthesis of organic compounds, as a synthetic methodology, or a tool for organic synthesis. In this module, we will consider not only Diels-Alder reaction, we will also discuss the Woodward-Hoffmann rule, corresponded to the Diels-Alder reaction, the Regio-Chemistry and stereochemistry aspects of Diels-Alder reaction.

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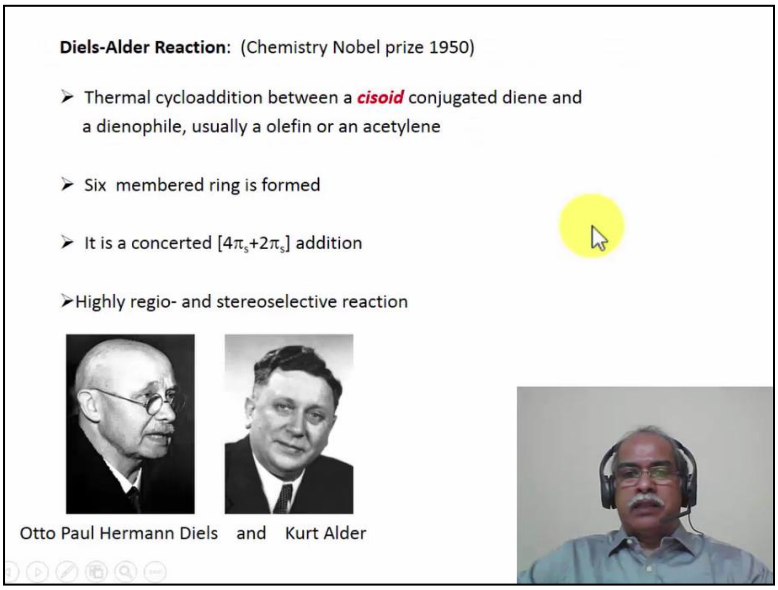

Diels-Alder Reaction: (Chemistry Nobel prize 1950)

- Thermal cycloaddition between a ***cisoid*** conjugated diene and a dienophile, usually a olefin or an acetylene
- Six membered ring is formed
- It is a concerted [$4\pi_s+2\pi_s$] addition
- Highly regio- and stereoselective reaction

Otto Paul Hermann Diels and Kurt Alder

Now, Diels-Alder reaction is a thermal Cycloaddition reaction, between a Cisoid conjugated Diene, which is known as the Diene component of the Diels-Alder reaction, with a Dienophile, which is the other component of the Diels-Alder reaction. Usually, an Olefin or an Acetylene is, what is used as a Dienophile. It is a 6-membered ring forming reaction. It is a concerted 4 PI Suprafacial-2 PI Suprafacial Cycloaddition reaction.

The most important aspect of Diels-Alder reaction is that, it is a highly regio, as well as stereoselective reaction. And, that is what makes this reaction, extremely useful in organic synthesis. This is Hermann Diels, and this is Kurt Alder. Kurt Alder was a student of Diels, for example. And, during 1950, both of them shared a Nobel prize, for the discovery of the Diels-Alder reaction.

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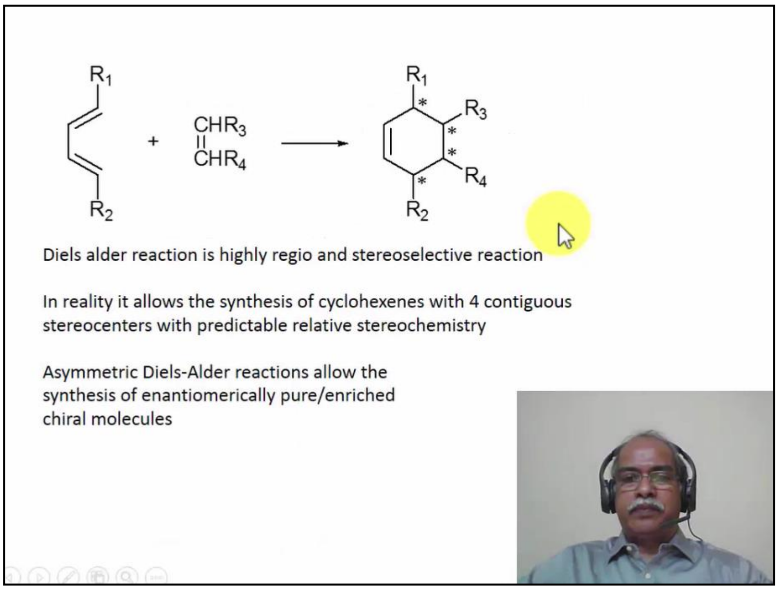

Diels alder reaction is highly regio and stereoselective reaction

In reality it allows the synthesis of cyclohexenes with 4 contiguous stereocenters with predictable relative stereochemistry

Asymmetric Diels-Alder reactions allow the synthesis of enantiomerically pure/enriched chiral molecules

Why is Diels-Alder reaction, such a useful reaction in organic synthesis? This is illustrated by a generic example, that is shown in this particular slide. If you consider a 1,4-Disubstituted Diene, and a 1,2-Disubstituted Dienophile, 2+4 Cycloaddition reaction essentially gives a Cyclohexene, where the R1, R2, R3, R4 are consecutively placed, are 4 contiguous stereochemistry center, is what is produced.

And, if the relative stereochemistry and the absolute stereochemistry of these four centers can be predictable, by means of the Diels-Alder reaction, then it becomes a, or if it is possible to control the relative and absolute stereochemistry of the R1, R2, R3, R4, during the course of the synthesis, then it becomes an extremely useful stereoselective synthesis of organic compound of this type, becomes easy using the Diels-Alder reaction.

Asymmetric Diels-Alder reactions allow the synthesis of enantiomerically pure, or enantiomerically enriched chiral molecule. We will see some examples of the Asymmetric Diels-Alder reaction, in the later modules.

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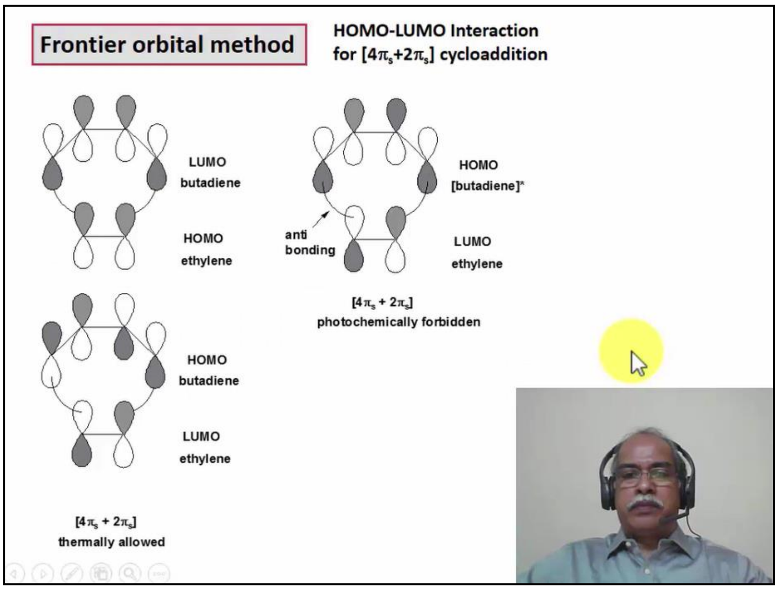

Frontier orbital method

HOMO-LUMO Interaction for [$4\pi_s+2\pi_s$] cycloaddition

LUMO butadiene

HOMO ethylene

HOMO butadiene

LUMO ethylene

[$4\pi_s + 2\pi_s$] thermally allowed

HOMO [butadiene]*

LUMO ethylene

anti bonding

[$4\pi_s + 2\pi_s$] photochemically forbidden

Now, let us first consider, the Frontier Molecular Orbital Method of the Diels-Alder reaction. The Homo-Lumo interaction for a 4 PI-2 PI Cycloaddition reaction is, what is shown in this particular slide, here. The Diene and the Dienophile interaction is, what is shown here. One can either consider, the Homo of the Butadiene and the Lumo of the Ethylene, or the Homo of the Ethylene and the Lumo of the Butadiene.

They are looking at the interaction between, the Homo-Lumo of the Carbon number-1 and Carbon number-4 of the Diene, with Carbon number-1 and Carbon number-2 of the Olefin. Clearly, the Suprafacial-Suprafacial interaction of this kind, we can see from here, this is a bonding type of an interaction. This is also a bonding type of interaction. Similarly, in the case of the Homo-Lumo interaction of this type, again these two are bonding type of an interaction.

So, these interactions are favorable interactions, towards the formation of the Sigma bond, between Carbon number-1 of the Diene, and the Carbon number-1 of the Dienophile, and Carbon number-4 of the Diene, and Carbon number-2 of the Dienophile, for example. Now, on the other hand, if you consider a photo chemical driven 4 PI-2 PI Cycloaddition reaction, this kind of a Suprafacial-Suprafacial interaction is a forbidden interaction.

Because, one of the interaction here is, an antibonding type of an interaction, which will have a much higher transition state energy, compared to the ground state reaction, which is a thermal reaction. So, the 4 PI-2 PI Suprafacial-Suprafacial mode of Cycloaddition of the type, that is shown here is thermally allowed, and photochemically it is forbidden.

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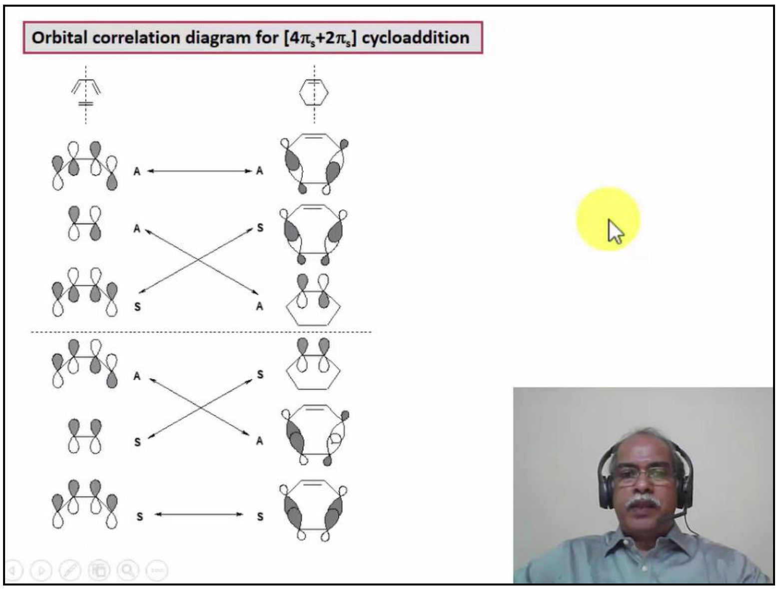
Orbital correlation diagram for [$4\pi_s+2\pi_s$] cycloaddition

One can also approach the Woodward-Hoffmann rule, by means of the Orbital Correlation Diagram Method. In other words, the conservation of symmetry of the orbitals, during the course of the Cycloaddition reaction. Here, the 4 PI-2 PI components are listed in the increasing order of energy, starting from SI-1 of Butadiene, PI of Ethylene, SI-2 of Butadiene, SI-3 of Butadiene, then PI star of the Ethylene, finally the SI-4 of the Butadiene. These are filled Molecular Orbitals. And, these are unfilled Molecular Orbitals.

Similarly, in the product state, what you have, is the formation of the 2-Sigma bond and 1-PI bond. So, Sigma-1, Sigma-2, PI, PI star, Sigma Star, Sigma-2 Star, is what is being represented in the increasing order of the energy of the Molecular Orbitals. Now, if you look at the symmetry element, that is present throughout the course of the reaction, it is this plane of symmetry, that is bisecting the Carbon number 2 and 3, and Carbon number 1 and 2, of the Olefin and the Butadiene, respectively.

So, that particular symmetry plane is present in the product state also. So, we will consider that plane of symmetry as the symmetry operator, for identifying the symmetry property of this Molecular Orbital. With respect to that symmetric plane, this is Symmetric, this is also Symmetric. Whereas, this is Antisymmetric clearly. Whereas, this is Symmetric, Antisymmetric, and Antisymmetric, with respect to that plane of symmetry, that is shown by the dotted line in the structure here.

You apply the same symmetry element, in the product stage also. Then, you identify this to be a Symmetric Molecular Orbital, Antisymmetric and Symmetric Molecular Orbital. Then, again Antisymmetric, this particular Molecular Orbital. Symmetric, this Molecular Orbital. Finally, Antisymmetric, this particular Molecular Orbital. If you look at this, this is a Sigma, which is a Symmetric Sigma combination.

This is also a Sigma, which is an Antisymmetric combination. This is PI and PI star of the Ethylene kind of a bond. This is an antibonding with a Symmetric combination. This is an antibonding with Antisymmetric combination. So, the most Symmetric one, is this one. The most anti-symmetric one, is this particular one, in terms of the overlap of the Molecular Orbital.

So, from this, you can clearly correlate the symmetry properties of the element. These two are symmetry, with respect to each other. So, that is correlated. The next one is Symmetric, that is correlated to this Symmetric Molecular Orbital. This Molecular Orbital is Symmetric correlated to this Molecular Orbital. So, essentially, all the Molecular Orbitals, which are filled are Symmetric correlated, with respect to each other.

There is no crossing of the nonbonded level at any stage, for the symmetry correlation. So, this implies that, this reaction is allowed in the ground state. 2 PI Suprafacial-4 PI Suprafacial overlap, of the 4 PI 2 PI components of the Diels-Alder reaction, are thermally allowed is a conclusion, that we arrive at, using the Molecular Orbital Correlation Diagram Method, also.

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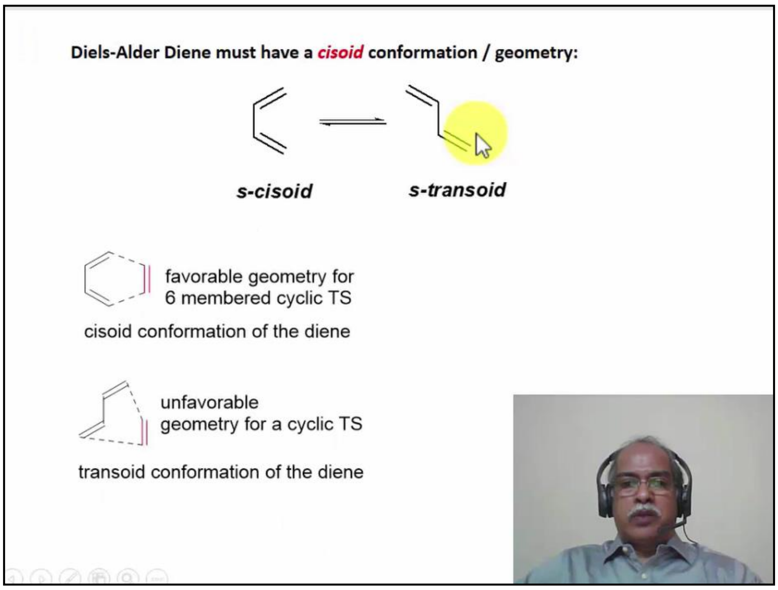

Diels-Alder Diene must have a *cisoid* conformation / geometry:

s-cisoid

s-transoid

favorable geometry for
6 membered cyclic TS

cisoid conformation of the diene

unfavorable
geometry for a cyclic TS

transoid conformation of the diene

Now, what do we mean by a Cisoid Diene, undergoing a Diels-Alder reaction. If we consider Butadiene, it can exist in two conformations, which are shown here, with respect to this Carbon-Carbon single bond. This is called the S-Cisoid. In other words, with respect to the single bond the two Olefins are Cis with respect to each other. But because, it is a single bond rotates, which is freely rotating, we call it as Cisoid.

On the other hand, the rotation around 180 degree, will result in the formation of the Transoid-Isomer. In fact, it is a Cisoid-Isomer, which has a favorable geometry for a nice overlap of the 4 PI-2 PI components of this kind, to give a six-membered cyclic transition state. The Cisoid conformation of the Diene, essentially is needed for the reaction to proceed. On the other hand, if you have a Transoid-Diene, the distance between Carbon number 1 and 4 are further away, and its ability to overlap with the Olefin becomes diminished.

So, this is an unfavorable geometry for a cyclic transition state. Moreover, this will result in the formation of a Trans-Olefin in a Cyclohexene, which is a Trans-Cyclohexene, which is an unfavorable system. So, the transoid conformation of the Diene, is an unfavorable kind of a conformation, for the Diels-Alder reaction.

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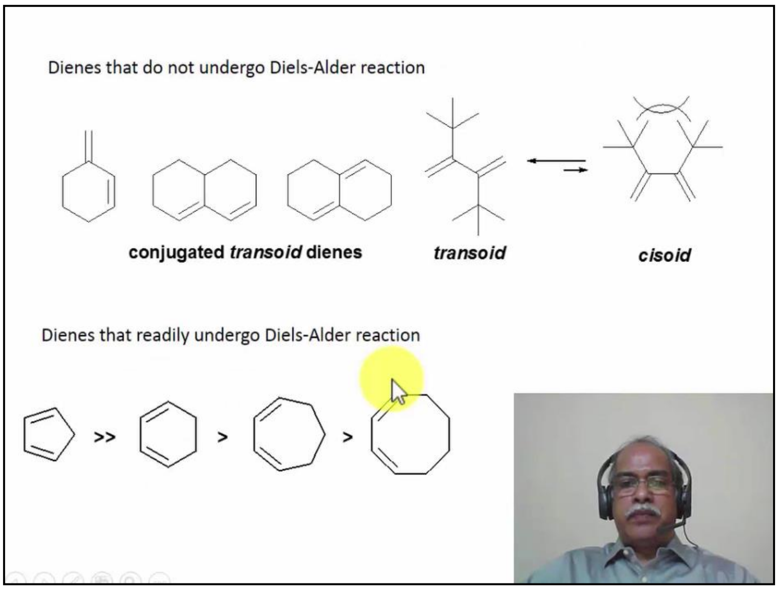

Dienes that do not undergo Diels-Alder reaction

conjugated *transoid* dienes

transoid

cisoid

Dienes that readily undergo Diels-Alder reaction

This is very clearly illustrated, in the inability of certain dienes, to undergo Diels-Alder reaction. These are inherently Trans-Geometry restricted dienes, for example. This is an Hexamethylene Cyclohexane. This is again, a transoid diene. This has a no way of adopting a Cisoid Geometry, because of the fact that, this is in a fused ring, bicyclic ring system.

This is also a transoid geometry. So, all these conjugated dienes, although they are conjugated, and they are also dienes, they are incapable of undergoing the Diels-Alder reaction, for the reason that, they are transoid in their geometry, with respect to the two Olefins being Trans, with respect to the single bond, here.

Alternatively, you can also have sterically restricting transoid molecule. This molecule, if it considers, the 2,3-Di-Tertiary Butyl Butadiene molecule in the transoid geometry, the two Tertiary Butyl groups are further away from each other, unlike the Cisoid geometry, where they will have severe steric interactions. So, this molecule prefers to be in the transoid form, rather than that, than in the Cisoid form.

So, this seldom undergoes Diels-Alder reaction, even with the most reactive Dienophile. So, this is essentially explained by the fact that, transoid geometry is essentially restricting the Diels-Alder reaction, from taking place in the molecule. On the other hand, if the molecule has inherently a Cisoid geometry, as in the case of cyclic conjugated systems of this kind, where the double bonds are Cisoid, with respect to each other.

Then, they undergo Diels-Alder reaction in a fissile manner. Cyclopentadiene, Cyclohexa-1,3-Diene, Cyclohepta-1,3-Diene, Cycloocta-1,3-Diene, all of them under go Diels-Alder reaction. However, the rate at which the Diels-Alder reaction takes place, with respect to a particular Dienophile diminishes, as we go from the Cyclopentadiene to Cyclooctadiene. This is essentially because, the distance between Carbon number-1 and Carbon number-4, is very crucial for the effective overlap with the Olefin.

In fact, in Cyclopentadiene, the distance is very optimum, for the 6-membered ring transition state to be formed. And, as you go to the higher and higher ring system, the distance between Carbon number-1 and Carbon number-4 becomes larger and larger, which makes the effect, overlap with the Dienophile ineffective, in relative to the Cyclopentadiene itself.

So much so, that Cyclopentadiene can undergo Diels-Alder reaction with itself, resulting in the formation of Dicyclopentadiene, which is this structure, we will see little later. Whereas, Cyclohexa-1,3-Diene, does not undergo Self-Diels-Alder reaction. This undergo Self-Diels-Alder reaction, quite readily.

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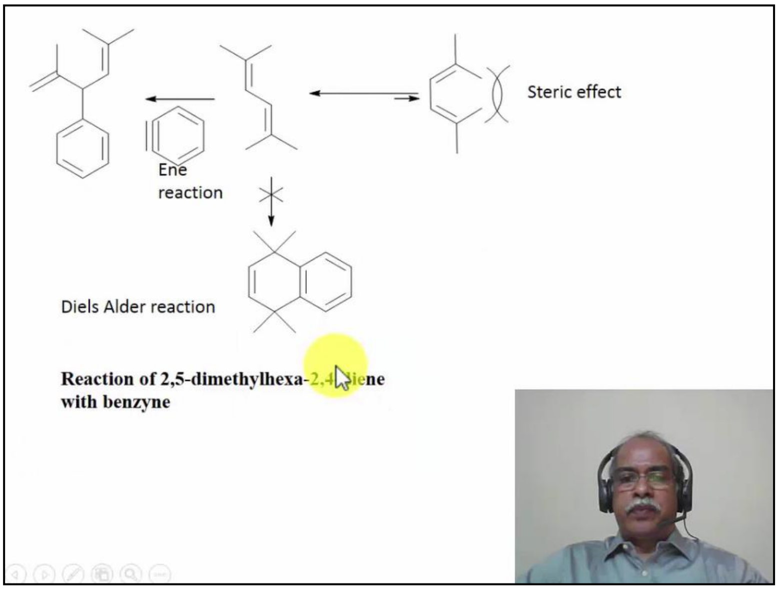

Reaction of 2,5-dimethylhexa-2,4-diene with benzyne

In explaining the reactivity of the tetra substituted derivative of this kind, this is 1,1,4,4-Tetra Methyl-Butadiene molecule. This has the steric effect in the Cisoid conformation. Whereas, in the transoid conformation, it does not have any kind of a steric effect. Even with the most reactive Dienophile, which is this benzyne, in this particular case. It undergoes a Ene kind of a reaction.

We will see, what is a Ene reaction, later. But, for the time being, we will discuss the inability of this molecule, to undergo Diels-Alder reaction. Because of the lack of the Cisoid geometry, as a contributor to the population of the equilibrium, of this particular conformational equilibrium, that is shown here. It exclusively exists, in this particular form, which is a transoid form.

Hence, it does not undergo Diels-Alder reaction, with even a reactive Dienophile like the Benzyne. It undergoes an Ene reaction inside, which is the Ene product is shown, in this particular slide, here.

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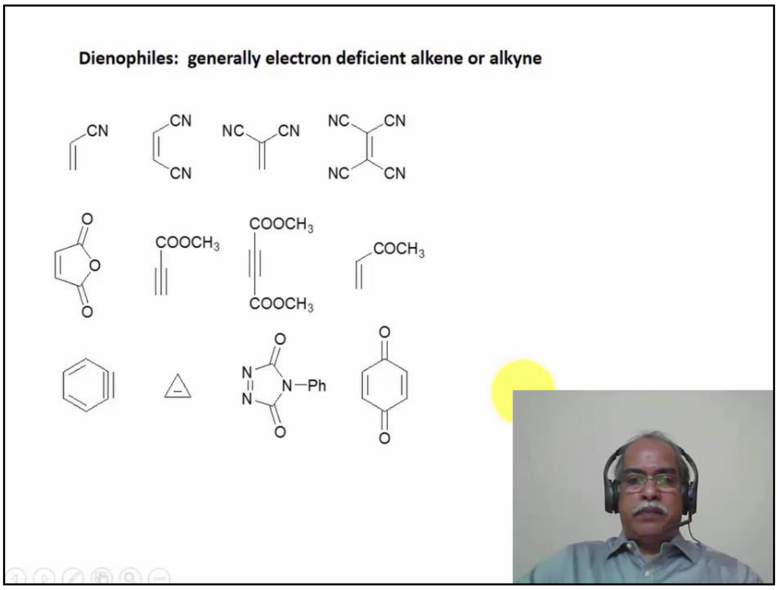

Dienophiles: generally electron deficient alkene or alkyne

Dienophiles are generally, either Alkenes, or Olefins. And, the Dienes are electron rich. And, the Dienophiles are generally electron poor. What is meant by electron poor? They have electron withdrawing substituents. So, the electron density of this double bond, is not as good as the electron density, in the case of Ethylene, for example. If you put more and more of electron withdrawing functional group, the Dienophile becomes extremely reactive, in a normal Diels-Alder reaction, where the two components namely, the Diene component is an electron rich component, and the Dienophile component is an electron poor component.

The more electron poor, it is the better, the reactivity. For example, Acerola Nitryl reacts with the Butadiene, at about, reflexing toluene kind of a solvent. Whereas, Tetracyanoethylene reacts with Butadiene, even at -10 degrees or so, to form the corresponding cyclo-adduct. So, that shows the reactivity pattern of this, multiply substituted electron withdrawing substituted dienophiles, for example. Acetylenes can be part of a Diels-Alder reaction. They can, in fact undergo, multiple Diels-Alder reaction. Because, they can undergo a Diels-Alder reaction, two times.

And, this will be illustrated in multiple Diels-Alder reaction topic, little later. Anhydrides of this kind, with this Maleic Anhydride, for example, is an excellent Dienophile. Benzyne can be a good Dienophile. If it is generated in-situ, it can be made to undergo Diels-Alder reaction. Cyclopropane by virtue of the ring strain, is an extremely reactive Dienophile. It undergoes Diels-Alder reaction. Diels-Alder reaction can also take place, with this kind of

Hetero Dienophiles. They are Nitrogen-Nitrogen double bond, is undergoing the Diels-Alder reaction. Quinone is also an excellent Diels-Alder Dienophile.

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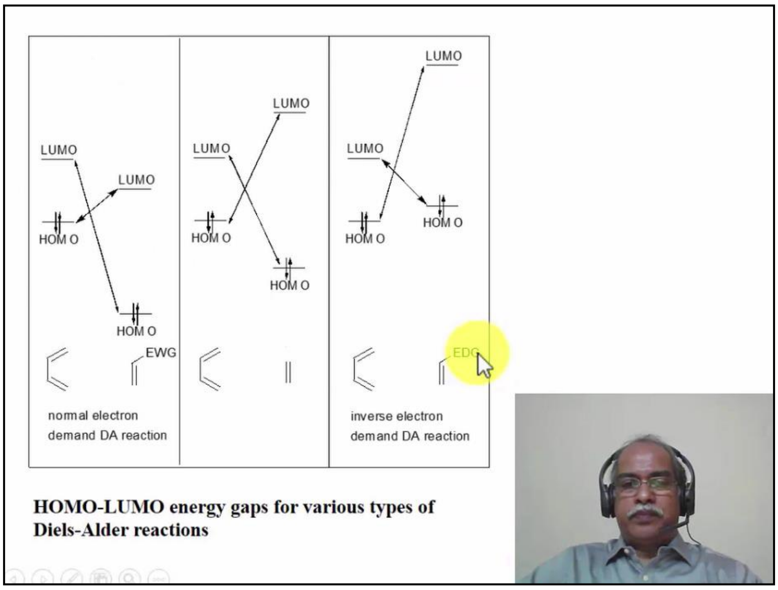

HOMO-LUMO energy gaps for various types of Diels-Alder reactions

This particular diagram, describes the Homo-Lumo energy gap, and explains, why complimentary nature of the Diene and the Dienophile, in terms of their electronic character is useful, in the Diels-Alder reaction. Let us assume that, initially, if we take a Diels-Alder reaction, where there are no substituents. In other words, the electronically unbiased Diene and Dienophile is taken. This is a relative energy of the Dienophile, and this the relative energy of the Diene. And, these are Symmetrical molecules.

So, their energy levels are essentially, whether you consider the Homo of the Diene and the Lumo of the Dienophile, or the Homo of the Dienophile and the Lumo of the Dienophile, the energy gap is essentially same, because of the Symmetric nature of the positioning of the Homo-Lumo gaps of these molecule. So, this Homo-Lumo gap is essentially same, as this particular Homo-Lumo gap.

So, overlap can be either from the Homo of the Diene, to the Lumo of the Dienophile, or vice versa, does not matter. Essentially, they are iso-energetic, with respect to each other. Suppose, if you put an electron donating substituent in the Diene, Dienophile moiety, and this is relatively retained as it is, as Butadiene. So, we are only varying the substituent on the Dienophile, to make it electron donating.

This is called an Inverse Electron Demand Diels-Alder action, where the Dienophile is electron rich, and the Diene is electron poor. When you put, an electron donating substituent of the Dienophile, the Dienophile energy levels are increased, for example. Because, the ionization potential gets reduced. So, the Homo gets increased.

The electron affinity becomes, decrease. So, as a result of that, the Lumo also gets increased. So, relative to the unsubstituted Olefin, the Homo-Lumo levels of the electron donating substituted Olefin, is increased. So, now if you look at the Homo-Lumo gap, this Homo-Lumo gap is much higher, than this Homo-Lumo gap. In fact, this interaction would be a more favorable interaction, now for the Diels-Alder reaction, where the Homo of the Dienophile, and the Lumo of the Diene, are closer together.

The closer the Homo-Lumo's energy levels are, the faster the reaction in the Diels-Alder reaction. That is essentially, the activation barrier, we are talking about, in these reactions. If we consider, the electron withdrawing functional group, the opposite effect takes place. This becomes ionization potential wise, much larger ionization potential, compared to the Olefin, itself. So, the Homo is energy, in terms of the energy, it is reduced, it is coming down in energy. The electron affinity increases.

So, the Lumo also brings down in energy, in terms of the relative positioning of this two energy levels, that we are talking about. So, both the Homo as well as the Lumo, are decreased in the energy, when the electron withdrawing substituent is placed on the Olefin. We are retaining the Butadiene, as it is, in all the three diagrams, if you look at. Here, the Homo-Lumo interaction is essentially between, the Diene and the Dienophile.

This is the preferred Homo-Lumo interaction. Because, this is of less energy, compared to this alternative option of the Dienophile Homo and the Diene Lumo, which is a much higher in energy, in terms of the (( )) (17:20). This is the reason, when you do a Diels-Alder reaction, if the Diene is electron rich, the Dienophile should be electron poor. Vice versa, if the Diene is electron poor, the Dienophile must be electron rich.

So that, the complementary nature, electronic nature of the Diene and the Dienophile, brings the Homo-Lumo gap, much closer together, so that the reaction can proceed, in a facile manner.

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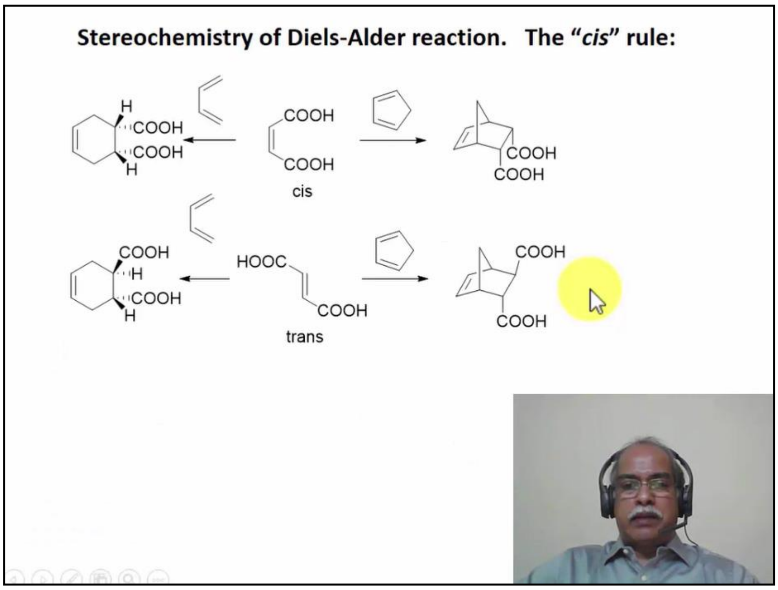

Stereochemistry of Diels-Alder reaction. The "*cis*" rule:

Now, let us come to the stereochemical aspects of the Diels-Alder reaction. Diels-Alder reaction is a highly Stereo Selective reaction. This is illustrated, by taking the Cis-Dicarboxylic acid and the Trans-Dicarboxylic acid as a Dienophile. With Butadiene, when the reaction takes place, the Cyclohexene product is formed, with the two Carboxylic acid, Cis with respect to each other, when the Cis-Isomer of the Dienophile is taken. When the Trans-Isomer reacts, the two Dicarboxylic acid, end up Trans with respect to each other.

In other words, because of the Suprafacial nature of the reaction, the stereochemistry, whatever was present originally in the Diene and the Dienophile, is essentially retained in the product. If you start with the Cis-Isomer of the Dienophile, and the product is Cis with respect to the two carboxylic acid groups. If it is a Trans-Isomer, then it results in the Trans-Isomer formation. With Cyclopentadiene, the Diels-Alder reaction produces a bridged Cyclopentadiene and the derivatives. Here again, the two-carboxylic acids are Cis. We are starting with the Cis acid with the Trans acid, the two carboxylic acids are Trans with respect to each other.

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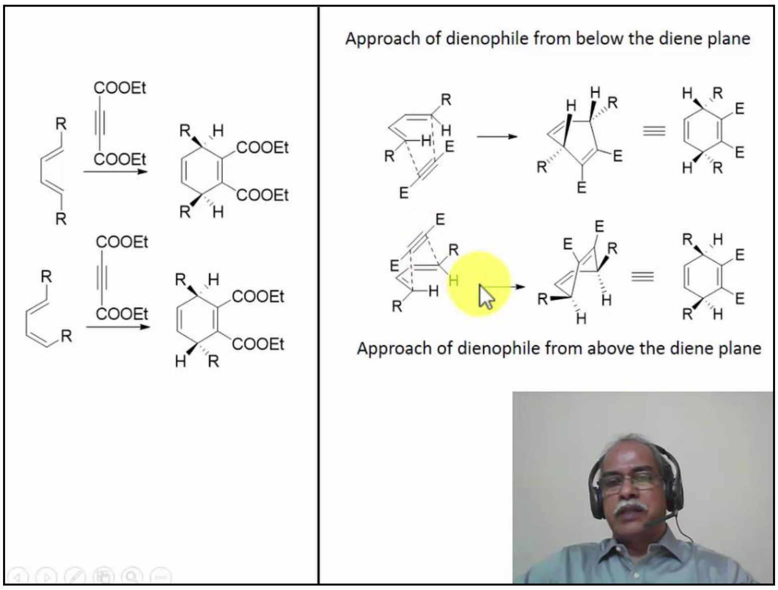

Now, here you are talking about the stereochemistry, with respect to the. In this particular example, we talked about the stereochemistry, with respect to the Dienophile. Here, we talk about the stereochemistry, with respect to the Diene itself. The Diene, you can have two isomers. This is the EE-Isomer of the Diene, whereas this is the ZE-Isomer of the Diene. This reacts with the Acetylene, to give the corresponding Cyclohexadiene. Acetylene is a Dienophile here, which will produce a Cyclohexadiene unit, rather than a Cyclohexene unit.

Now, what is important is, in doing so, the relative stereo chemistry of the two R groups in a position one and position four of the Cyclohexadiene. We can see, when it is the two R groups are outside of the PI framework, as in the case of the EE-Isomer, the two R groups result with respect to each other, in a Cis fashion. In other words, this two R groups are essentially pushed, both of them are pushed up, during the course of the Diels-Alder reaction, retaining the stereochemistry in a Cis manner, with respect to each other.

On the other hand, when one of the R group is in the interior of the PI framework, and the other R group is exterior, as in the case of the ZE-Isomer of the Diene, for example. The R group, which is interior is pushed down. The R group, which is the exterior of the PI framework is pushed up, resulting in the Trans-Isomer of the Diene. This is explained in a schematic manner, in this particular diagram. This is the EE-Isomer, where both the Olefin, the Acetylene is approaching from the bottom, for example, that pushes the two hydrogens up, and the two R groups down.

So, the two R groups end up, Cis with respect to each other. On the other hand, if the Dienophile approaches from the top face, the two Hydrogen will be pushed down, and the two R groups will be pushed up, resulting in the formation of the Cis-Isomer of the Diene. So, these are identical isomers, as far as the stereochemistry is concerned. Both the R groups are Cis with respect to each other. And, essentially this diagram explains, how the two R groups are pushed in the same direction, during the course of the reaction, depending upon, whether the Dienophile approaches from the bottom face, or from the top face of the Diene, with respect to the diene.

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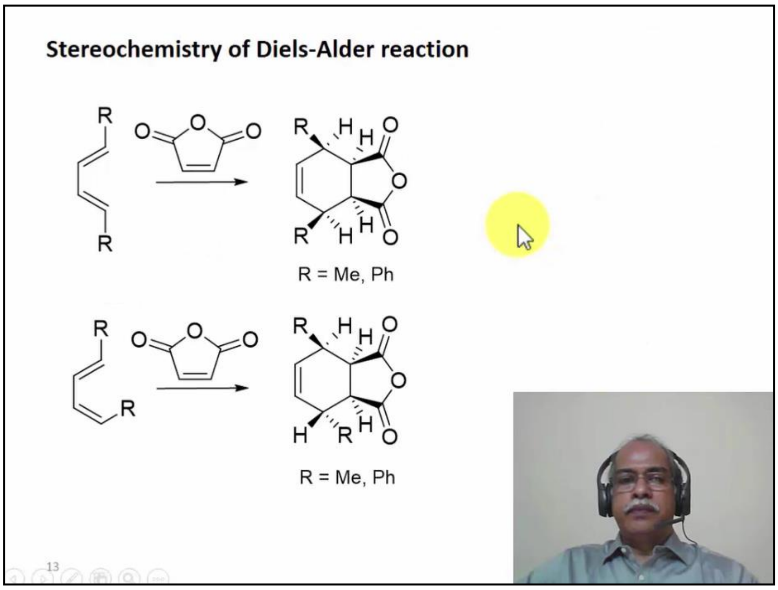

Stereochemistry of Diels-Alder reaction

R = Me, Ph

R = Me, Ph

Now, so we have four stereo chemistry centers, generated. The relative stereochemistry between these two centers, are generated from the stereochemistry of the Dienophile. In other words, between this Carbon, and if you follow the cursor, this Carbon here, and this Carbon here, the stereochemistry comes from the Dienophile. The relative stereochemistry between Carbon number-1 and the Carbon number-2, essentially comes from the Diene. So, now we know that, if you take the EE-Isomer, you will get the Cis-Isomer. If you take the ZE-Isomer of the Diene, you get the Trans-Isomer.

Similarly, if you take the Cis-Isomer of the Olefin Dienophile, you get the Cis-Isomer, here. If you take the Trans-Isomer of the Dienophile, you will get the Trans-Isomer, here. Now, what governs the relative stereochemistry, between these two Carbons. We know, what is governing the relative chemistry stereochemistry, between these two Carbons, and these two Carbons. Now, let us have a look at, what controls a relative stereochemistry, between Carbon number 1 and 2, or Carbon number 3 and four.

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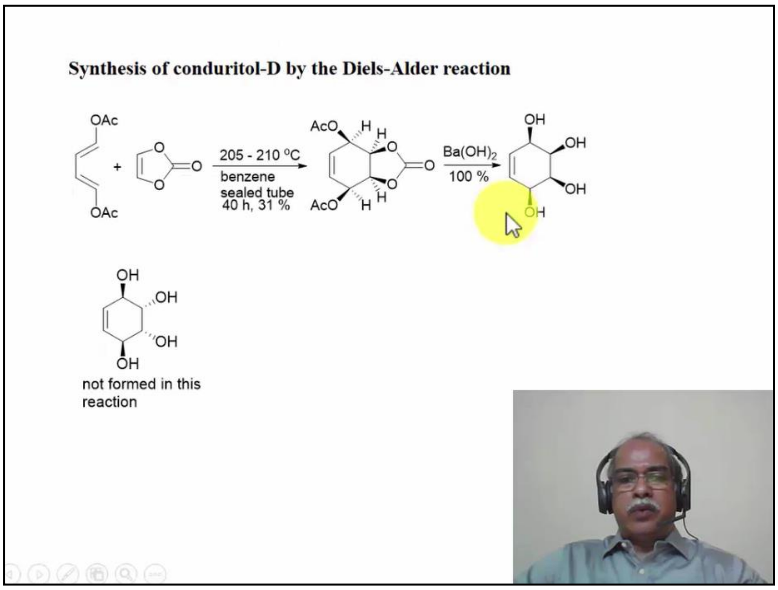

Synthesis of conduritol-D by the Diels-Alder reaction

205 - 210 °C
benzene
sealed tube
40 h, 31 %

$Ba(OH)_2$
100 %

not formed in this reaction

Now, this is an example of synthesis of Conduritol-D, by a Diels-Alder reaction. This is a Diels-Alder reaction, between this Di-Acetate and this Carbonate. This is Acetylene Carbonate, is what is shown as the Diels-Alder reaction. The Diels-Alder reaction is carried out at a high temperature, because both the Diene and the Dienophile are electron rich, because of the Oxygenated Diene and the Oxygenated Dienophile, in this particular case.

Now, this reaction proceeds exclusively with the Cis stereochemistry, in all the oxygenated functional group, essentially occurring from the overlap between the Diene and the Dienophile, in a Stereo Selective manner. And, upon hydrolysis of the Ester functional groups, in this molecule, you will get the Tetra Alcohol, where all the alcohol functional groups are Cis with respect to each other.

That is the beauty of the Diels-Alder reaction. One is able to control, for example, the stereochemistry of all the four isomers, to be Cis with respect to each other, in this case. This Isomer, which is also a possible Isomer, is not formed during the course of the reaction, for the simple reason, that the overlap between the Diene and Dienophile is highly Stereo Selective, in only one possible manner.

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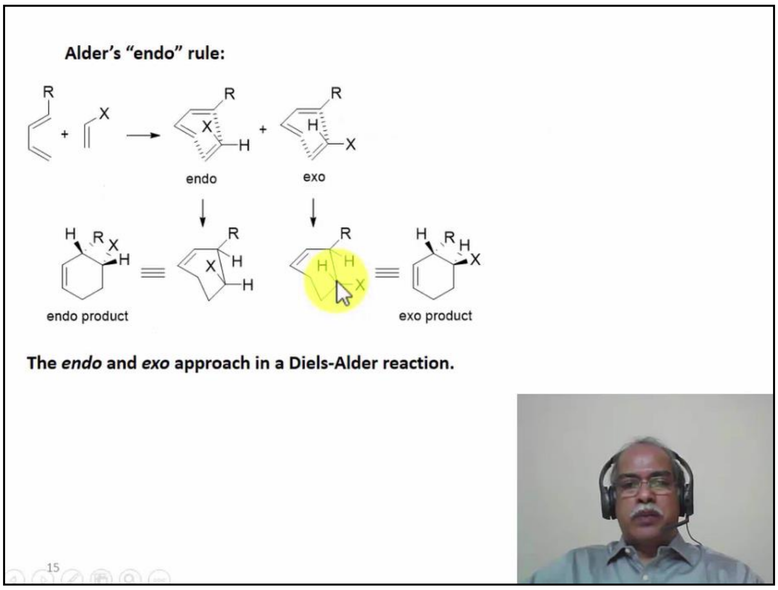

Alder's "endo" rule:

The *endo* and *exo* approach in a Diels-Alder reaction.

What are the possible manners in which, the Diene and the Dienophile can interact with each other? When you consider a mono substituted Dienophile, and one substituted Diene, for example, there are two possible overlaps, that one can think of, where both of them are Suprafacial-Suprafacial overlap. Except in this case, the X group is interior of the PI framework of the Diene, Whereas, this is X group, is exterior to the PI framework of the Hydrogen, is interior to the PI framework of the Diene. So, this is called the Endo approach.

Endo means inside. Exo means outside. Here, the X group is inside. And, the X group here is outside, for example. Now, the overlap between the Carbon number 1 and 4, essentially controlled by the Exo and the Endo approach. The relative stereochemistry is controlled, whether it is Exo or Endo. If it is a relative stereochemistry Endo, the X group and the R group essentially end up Cis with respect to each other. Because, this Hydrogen, there is a Hydrogen here, and this Hydrogen, they will be pointing in the same direction.

The X group and the R group also pointing inward, for example. So, that R and X end up Cis with respect to each other, in the Endo Isomer, Endo approach. The R and X group will be Trans with respect to each other. In other words, the two Hydrogen, one will be pointing out, the other one will be pointing in. So, these two hydrogens are Anti with Trans, with respect to each other, in the transition state.

So, that makes the two R and X group also, Trans with respect to each other, in the Exo product. So, the Endo approach gives the Cis product. Whereas, the Exo approach gives the Trans product, that explains the relative stereochemistry of the 1,2-Carbons, in the Diels-Alder adduct, in this particular case.

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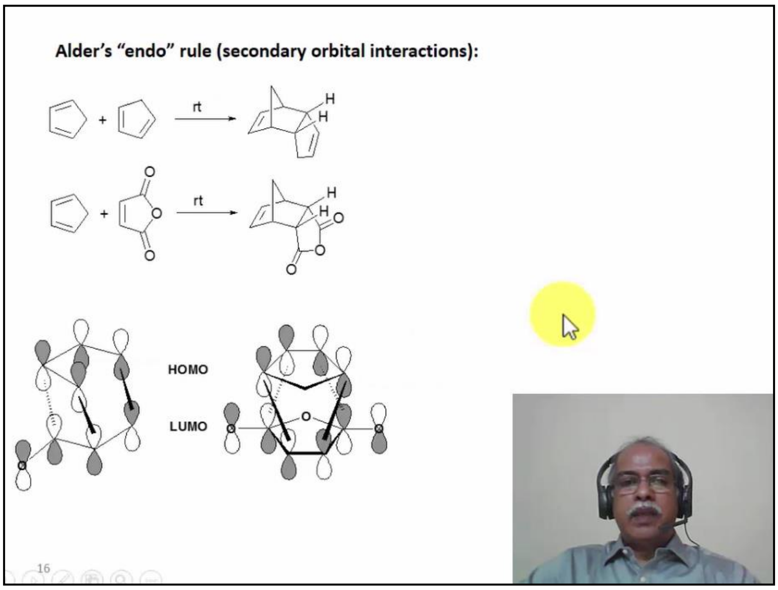

Alder's "endo" rule (secondary orbital interactions):

Predominantly, the Endo approach is a favorable approach, in the case of Diels-Alder reaction, as you can see in these two examples. With respect to the bridge. This bridge here, and the fusion here, this is up, and this is down. That means, this is an Endo approach, is what is taken place in this particular case. And, this is schematically explained by the orbital interaction diagram, where the secondary orbital interactions are shown very clearly. Let us consider this diagram carefully.

This is Butadiene Homo. And, this is the Acrolein, or the corresponding Carbonyl substituted Dienophile Lumo, of this. If you consider the Cyclopentadiene, the top portion is the Cyclopentadiene, the bottom portion is the Maleic Anhydride portion of the molecule. Now, the thick lines, which are the dark lines, indicates the primary orbital interaction, resulting in the formation of a Sigma bonds. So, you can see here, bonding interaction and bonding interaction. So, that will essentially form the Sigma bond.

In addition to that, in the Endo approach, you also have, what is known as a favorable bonding type of an interaction in the transition state, that reduces the energy of the transition state. So, the transition state energy becomes lower, in the case of the Endo approach. Remember, Endo approaches is a kinetic product, because of the transition state energy being lower, this will be the faster reaction, compared to a case, where if it is a substituent is in the Exo position.

Such a secondary orbital interaction is not possible. In the case of the Maleic Anhydride, in fact the secondary orbital interactions, are shown in the interior portion of the transition state. This stabilizes a transition state. In other words, the transition state energy becomes lower, activation energy becomes smaller. So, the reaction proceeds faster, when the Endo approach takes place. So, Diels-Alder reaction is predominantly, Endo selective in nature, because of the secondary orbital interaction, that are shown in this particular transparency.

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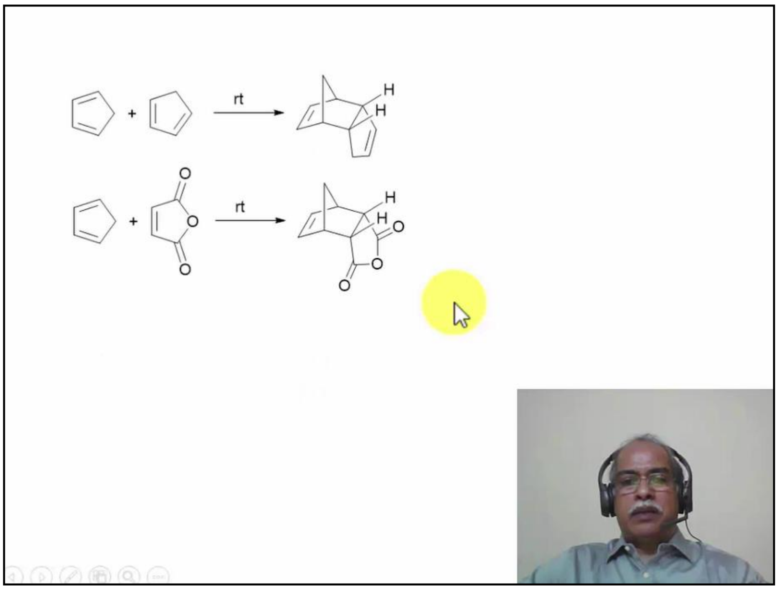

So, this is an example. The Cyclopentadiene reacts with itself, forming a dimer of the Cyclopentadiene namely, this Endo Isomer of the Cyclopentadiene. It is Endo, because this is in the interior, and this two hydrogens are exterior, with respect to this bridge, for example. The two hydrogens are in the same direction, as the bridge, in this case. So, it is an Endo, with respect to this approach. Similarly, the two hydrogens are Cis, with respect to the bridging methylene. So, this is also Endo approach, with respect to each other.

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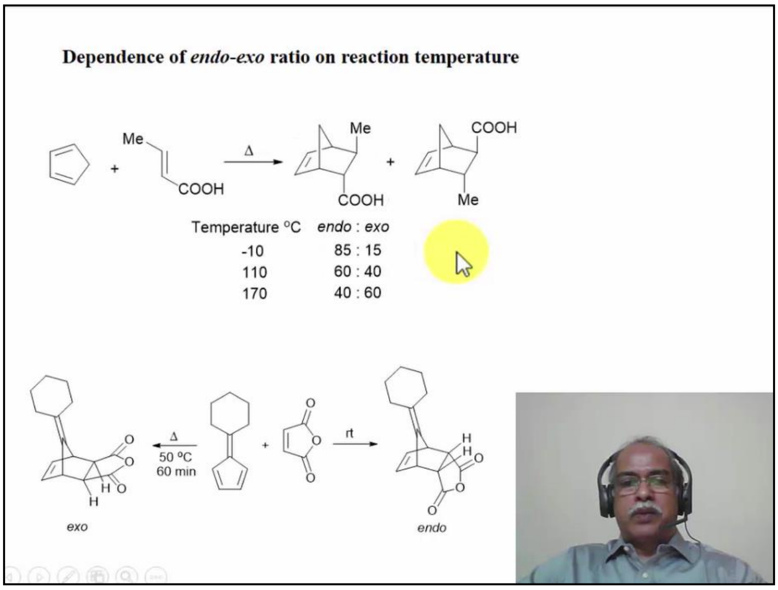

Dependence of *endo-exo* ratio on reaction temperature

Temperature °C	*endo* : *exo*
-10	85 : 15
110	60 : 40
170	40 : 60

Now, the Endo-Exo approach can be dependent on temperature. Because, the Exo approach, which is the least sterically hindered approach. For example, if you consider this approach, this is a sterically most hindered approach. Although, there is a secondary orbital interaction to stabilize the transition state, steric interactions can play a havoc, in terms of the Endo being not so favorable. So, Endo approach is actually a sterically hindered approach. It is the kinetic product. Because, it is driven by the lower transition state energy, and the lower activation barrier. The Exo product is a thermodynamically stable product, because it is divide of any sterically hindrance.

So, when the reaction is carried out at low temperature, you get predominantly the Endo product, because of the kinetic product, is what is formed under favorable conditions, which is this. On the other hand, if you reflex this, and heat it to high temperature, the Endo compound, that is initially formed, can undergo a Retro Diels-Alder reaction. And, at higher temperature, thermodynamically more stable, Exo product can be found.

For example, here, the carboxylic acid is Endo. It is Anti to the methylene, so it is Endo. Here, it is Cis to the methylene, so it is Exo, with respect to each other. That is also clearly shown, in the case of the Diels-Alder reaction of the Fulvalene, which is Penta-fulvene, that is shown here, which undergoes Diels-Alder reaction, with the Maleic Anhydride.

At room temperature, it just undergoes reaction, to give the Endo product, as the only product. Whereas, when it is heated to 50 degrees also, for sixty minutes, thermal equilibrium results in the reversal of this reaction, to give the starting material. And, Exo approach is now favorable at higher temperatures. Because, thermodynamically, more and more stable product is going to be formed, at the expense of the kinetic product, that is being formed in this reaction.

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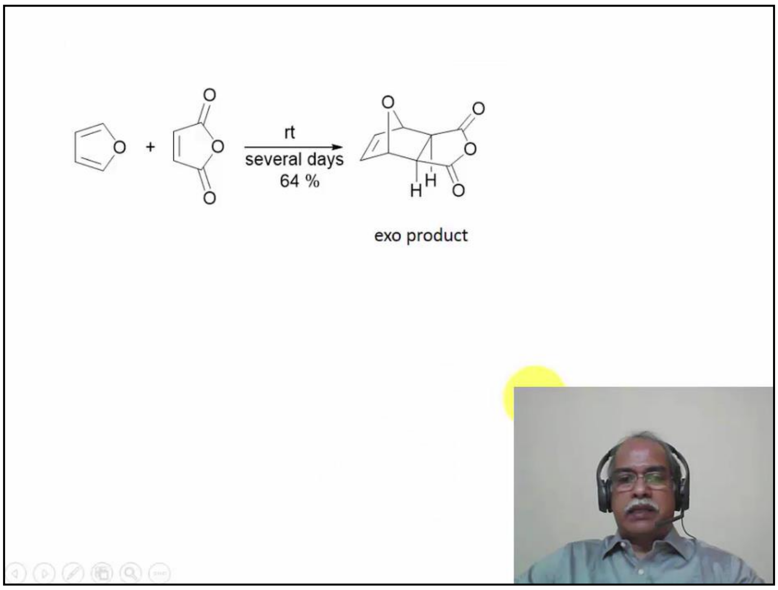

Furoin is not a very good Diene, because it is aromatic in nature. Nevertheless, it undergoes Diels-Alder reaction. When mixed with Maleic Anhydride, at room temperature for several days, the Exo product is formed as a selective product. Because, the initially formed Endo product, can be equilibrate to the Exo product, by the reversibility of the Diels-Alder reaction, in this particular case.

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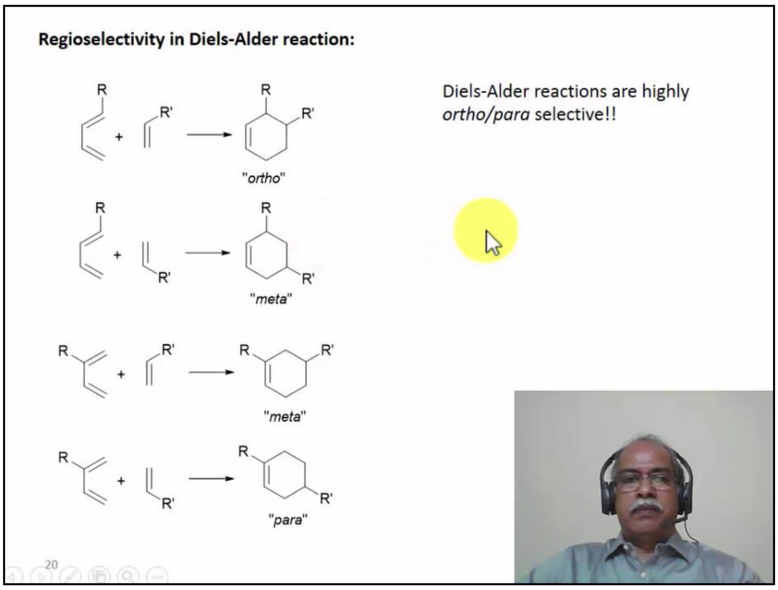

Regioselectivity in Diels-Alder reaction:

Diels-Alder reactions are highly *ortho/para* selective!!

Now, in addition to the stereoselectivity, there is also a regio chemical problem, associated with the Diels-Alder reaction. Now, let us consider the mono substituted, one substituted Diene, and a mono substituted Dienophile. There are two possible orientation, that can have two orientation. This is one orientation, where the two R groups are at the one, two position, for example. The Diels-Alder reaction, gives an Ortho type of a Diels-Alder reactions. One can have the orientation of the Dienophile, in this manner, with respect to the Diene, that will give a 1,3 type of a product.

This is an Ortho like product. And, this is Meta like product, for example. Whereas, if it is a two substituted Diene, and one substituted Dienophile, this is one possible orientation. This is another possible orientation. Relative orientation of the Diene and Dienophile are different. This gives the Regio-Isomer, which is the 1,3-Isomer.

Whereas, this gives the Regio-Isomer, which is a 1,4-Isomer, in this particular case. So, by enlarge, Diels-Alder reaction gives predominantly, the Ortho and the Para Isomer. The Meta Isomer, Meta like Isomer, for example, is the least preferred product, in this particular case.

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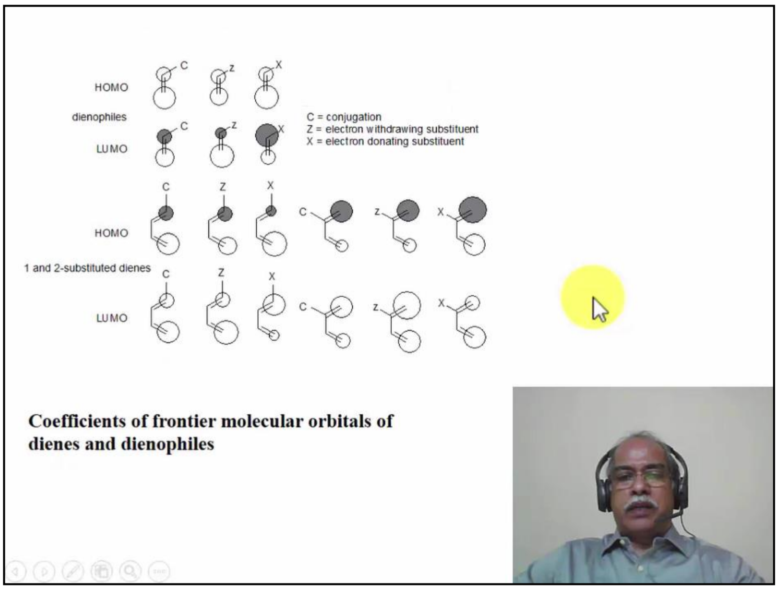

C = conjugation
Z = electron withdrawing substituent
X = electron donating substituent

Coefficients of frontier molecular orbitals of dienes and dienophiles

This can be explained, on the basis of the size of the Molecular Orbital. In other words, the coefficient of the Molecular Orbital, if it is higher, then the size of that particular lobe will be higher. And, the larger the lobe, then the large-large lobe will interact much faster, compared to a smaller-smaller lobe.

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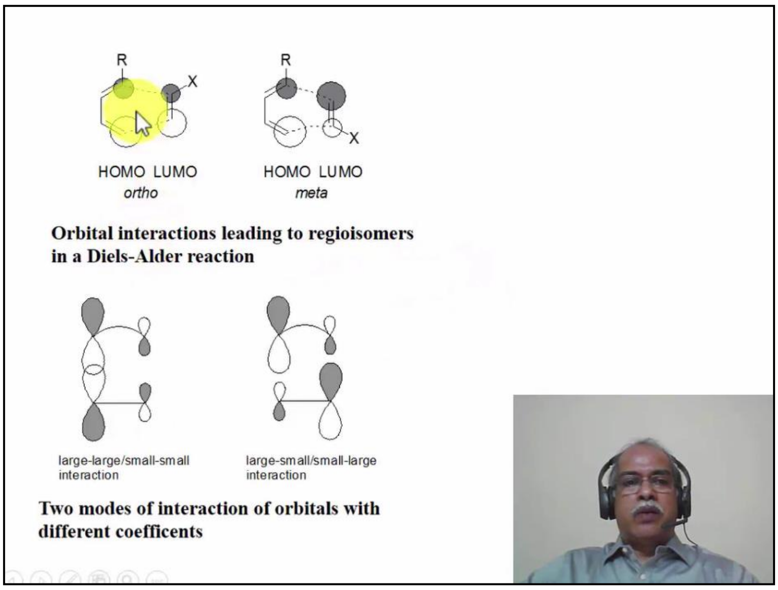

Orbital interactions leading to regioisomers in a Diels-Alder reaction

Two modes of interaction of orbitals with different coefficents

What i mean is, suppose, you have an orientation, which is this orientation, where these two large lobes are interacting with each other, in this manner. This is another way of interacting. This is an Ortho like interaction. This is a Meta like interaction. Here, the large lobe is interacting with the smaller lobe. Similarly, the smaller lobe is interacting with a large lobe. So, this is a large-large, small-small interaction, whereas, this is a large-small, large-small kind of an interaction.

Orbital interaction of this kind, is much more favorable, because the large-large interaction essentially brings the two molecules closer together, and forces the other end to react in a manner, that it is Suprafacial-Suprafacial overlap is effective, in this kind of a geometry. Rather than, this kind of a geometry, whether the Suprafacial-Suprafacial overlap is not as effective, as in this particular case, for example.

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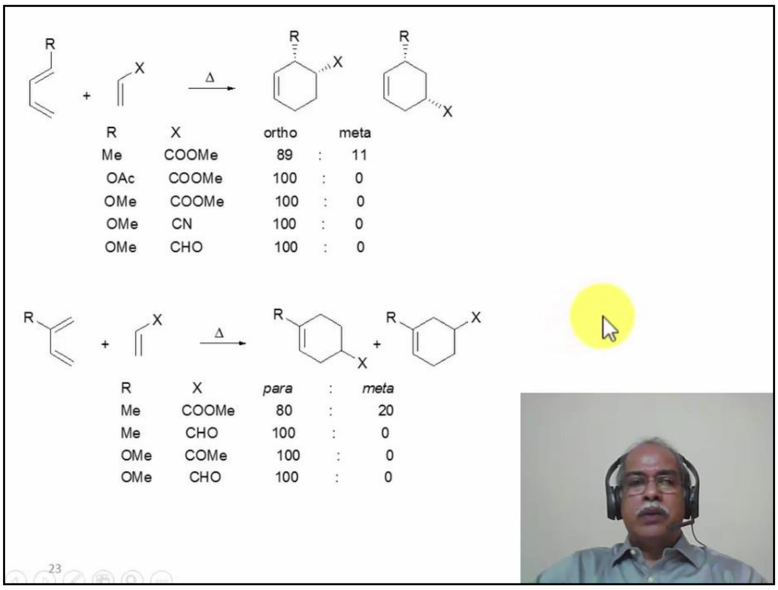

R	X	ortho		meta
Me	COOMe	89	:	11
OAc	COOMe	100	:	0
OMe	COOMe	100	:	0
OMe	CN	100	:	0
OMe	CHO	100	:	0

R	X	*para*	:	*meta*
Me	COOMe	80	:	20
Me	CHO	100	:	0
OMe	COMe	100	:	0
OMe	CHO	100	:	0

Now, the Diels-Alder reaction, Regio Selectivity is illustrated in these examples here. If you take a mono substituted Diene and the Dienophile, it is the Ortho, either predominantly or exclusively formed, under these reaction conditions similarly, when you take a two substituted Diene and a Dienophile, it is the Para, which is exclusively or predominantly formed in the course of the Diels-Alder reaction, in this particular case.

So, what we have seen in this module is, the introduction to Diels-Alder reaction. The derivation of the Woodward-Hoffmann rule, as 4 PI superficial-2 PI Suprafacial reaction of the Diels-Alder reaction, using both Frontier Molecular Orbital Method, as well as the Orbital Symmetry Correlation Method. Conservation of Orbital Symmetry method, we have seen. Then, we have seen, the Stereo Selectivities and the Regio Selectivities, involved in the Diels-Alder reaction.

The Cis rule, which predicts the Stereochemistry, at the ring junctions of the Diels-Alder reaction. And, the Exo, Endo, which predicts the Stereochemistry at the adjacent Carbon centers, that are generated in the Diels-Alder reaction. Finally, the Regio-Chemistry, Ortho, Para selectivity is also explained, on the basis of the size of the Molecular Orbital lobes, that is being present in the substituents, are present in the Diels-Alder reaction. So, hope you enjoyed, this particular module. Thank you very much, for your kind attention.