

## Lecture 21A • 03/19/12

### Diels-Alder reaction

The Diels-Alder reaction is kinda in the same class [as] the conrotatory and disrotatory reactions; it's another form of pericyclic reaction, which means there is a cyclic mechanism. Unlike the [previous pericyclic reaction], instead of it just being one molecule that's closing up to become cyclic, there are two molecules involved in this case. This is a specific reaction between a diene – so it's some kind of conjugated system – and what's often called a dienophile – something that likes to react with dienes.

One of the simplest forms of Diels-Alder reaction involves the molecule cyclopentadiene. We'll discuss in a moment why this particular molecule is fairly reactive towards the Diels-Alder reaction – reactive enough, in fact, that when you buy the compound, it usually comes in the form of a dimer. Here's an example mechanism: we can imagine that one of the double bonds of the diene reacts with another molecule, which reacts back with the other end of the diene, which then pushes that double bond over to where the first double bond in the diene had been. Again, a cyclic style of mechanism. The product that results is a type of product that we haven't really seen in problems before: a bicyclic compound. Notice the way that I drew it: I drew the bottom part of the structure, which isn't exactly a cyclohexane ring but reminiscent of one, draw that first before you draw the little bridgehead carbon up top. We started with two double bonds in the diene, but you're going to end up with just one in the product; let me circle to show you which portion corresponds to which initial ring. We do only have one of the double bonds that reacted in the other molecule of cyclopentadiene, so we have one more double bond left over in that portion of the molecule as well. This is a dimer, which is when two of the same atom or molecule combine to form a larger structure. [It's related to the term oligomer,] when a few units are put together to make a larger molecule; oligo means a few, so another place you might have heard that term is oligarchy (rule by a few). Or, you might have heard the more common term polymer, which means when you bring a bunch of the same type of unit together to make a larger molecule. Dimer just happens to mean two.

Why does this reaction occur? Let's talk first a little bit about mechanics. This is a particularly good reaction. Why? Because of the way that the diene has its structure locked into a particular configuration. Let's imagine that we had a linear molecule like butadiene. Let me ask you: these two versions of butadiene I just wrote, are they different molecules? They're the same molecule. What is the only difference between these two? The lefthand molecule: is either of those double bonds classifiable as cis or trans? No. In the second molecule, is either of those double bonds classifiable as cis or trans? No. If you look at it, each of the double bonds in those compounds only has one substituent. You can't have cis and trans if the double bond itself only has one substituent. What you're accidentally looking at is what the single bond looks like. In the first way that I drew it, it has the appearance of being trans, even though it's a single bond. Remember that single bonds can rotate. But, it does turn out that the relative configuration of one double bond to the other is important for Diels-Alder reactions. Imagine this: we've got the diene. You could have the two arms of the diene that's almost as if it sits down on that double bond of the alkene that's going to react with it, the dienophile that's going to react with it. You could imagine that if you've got p orbitals from the diene and you've got p orbitals from that dienophile that, when those p orbitals have a head-to-head overlap, you form a sigma bond, just like we had in those [other] pericyclic reactions. These are rotomers, the difference between the two of them. Single bonds can actually rotate. The first one is called pseudo-trans, which for whatever reason is abbreviated s-trans, and then we have pseudo-cis or s-cis. If you had this diene that can sit down and react with the dienophile and you formed the new sigma bonds, then it matters that the two ends of the diene can actually connect to that dienophile. If you've got one double bond pointed one way and the other one trans and pointing the opposite way, then it can't get around to react with the dienophile. A diene must be in the pseudo-cis configuration in order for a Diels-Alder reaction to be successful.

In the case of this butadiene, it is reactive, but not as much so as the cyclopentadiene, because here we do have the possibility of making rotomers; that single bond can rotate, so any time it rotates and makes the [pseudo] trans configuration, that temporarily slows the reaction down cause it has to wait for that bond to rotate again. But if you have something that's locked into the [pseudo] cis configuration, like cyclopentadiene, then there is no steric factor in the sense that you don't have to wait for the bonds to get into the right orientation, so it makes it a much more reactive diene. Of course, the opposite possibility can occur. Here is a diene; it is conjugated, but there's not way this can ever become pseudo-cis. It's permanently locked into pseudo-trans, so it cannot undergo Diels-Alder. Another aspect we'll get into is the electron-withdrawing character of most ether the dienes or dienophiles – what you need really for the reaction to be successful is something that's got some extra electron density that can be provided and something that is lacking electron density to encourage the other molecule to attack it.

The other aspect I want to get into today is geometry. When you have a Diels-Alder reaction, there are often two different products that will form. Let me show you a very specific example of a Diels-Alder reaction. If we have something like this: this is a conjugated system, but it will be just the alkene portion of this that reacts. We could throw something like cyclopentadiene at that and have a Diels-Alder reaction. A reminder of the mechanism: it is one of these cyclic style mechanism, where one double bond attacks the next, attacks the next.

Here are the two products that result. One of the products looks as if the new bonds that were formed – not from one molecule to the next, but the position of the carbonyls that I'm getting at – the bonds connecting to those look like they're the equivalent of axial positions. The other possibility is to end up with a structure where it looks like those bonds are pointed more as if they were in the equatorial position. This is not a chair form of cyclohexane, so it's not really quite proper to be using those terms axial and equatorial, but close enough that they make sense enough that that's why I'm using them. Instead of using these terms axial and equatorial, notice that one of the forms of the molecule – if you have an imagination – it looks a little bit more like it's pointed towards the interior of the molecule, where the other one – this group that was added in – is pointed more towards the exterior of the molecule. Instead, we refer to these as the endo versus the exo forms.

In terms of sterics, if we could call these axial and equatorial positions, which one should be more thermodynamically stable would you guess, the endo or the exo? If it was a cyclohexane ring and we had substituents, do substituents prefer, in terms of sterics, to go axial or equatorial? Equatorial. If you have something axial, you have that diaxial strain that's possible. To avoid sterics, the exo form should be the one that's more favorable. But there are some Diels-Alder reactions where it turns out that, due to electronics, due to the way that orbitals interact, that you get preference for the endo form. Why is it that something might prefer the sterically more hindered endo form?

In order to explain why, for example in this specific reaction, the endo form is more preferred, to figure that out, we have to look at the molecular orbitals. We have two systems we have to look at the molecular orbitals of, because we have a six p-orbital molecule, the anhydride, that's reacting with a four p-orbital molecule, the butadiene. What kind of reaction's going to go on here? Remember that, for those conrotatory and disrotatory reactions, that's where we got our introduction to frontier orbital theory – the idea that there are these electrons in the highest occupied molecular orbital that are going to be the electrons that participate in the reaction. They have to go somewhere – they want to go to the lowest-energy spot available, which is the lowest unoccupied molecular orbital. Electrons from the HOMO of one of those molecules is going to go into the LUMO of the other. It turns out it doesn't matter which one we consider being the attacking molecule; we're going to get the same prediction for both of them. For this particular reaction, these types of Diels-Alder reactions that we have a diene and monoene reacting, they occur thermally. Why do I have to worry about whether something happens thermally or through light? If we had light, we could have something in its excited state. Remember that the highest occupied molecular orbital changes depending on whether you are in the ground or excited state.

[For the six-orbital system,] we don't need to write all of those out again, because what really just matters is which one is the HOMO, which one is the LUMO. For a six-orbital system, there are going to be six molecular orbitals. If we have six pi electrons – like we do – and this is the ground state, so this one is the orbital that we care about. Now look at the four-orbital system, where we have four pi electrons, and still we're going to be in the ground state, so it is the lower of the two antibonding orbitals that is going to be the LUMO. The theory is the reaction happens by these higher-energy electrons jumping into the lowest-available orbital. Just like we did for the other pericyclic reactions, let's look at the shape of the molecular orbital itself and see if there is the proper phase overlap that occurs between orbitals. What we need, then, is to write out the full orbital structure for the HOMO of the six-orbital system and the LUMO of the four-orbital system. In the six-orbital system, how many nodes are there in the lowest-energy orbital? Zero. How many in the first orbital above that? One. And how many in the orbital above that? Two. So if we had two nodes and they had to symmetrically break up the molecule, we know that the orbital that we need is this one. Remember, for linear systems, the [lowest-energy orbital] always has zero nodes, and every orbital above has one additional node in it. Instead of drawing all six different molecular orbitals, cause we don't need all six of them, we only need one, I just used a little logic: we need the third molecular orbital, which means it has two nodes, so I could jump to that drawing. We do the same thing with the other molecule. How many nodes are going to be in the LUMO of the four-orbital system? Two, because zero, one, and two nodes, so it's going to look like this.

Let's look at an interaction between these two molecules. Here is the diene portion, and here is the anhydride portion. Let's fill in the orbital diagram. We can see that we have the correct phase between the specific portions of the orbital that are going to be involved in this Diels-Alder reaction. If you look back at the mechanism, remember that the carbonyls don't get involved, and it's one end or the other of the diene that gets involved; those two ends have the correct phase overlap. If you notice the way that the anhydride is currently pointed, this is going to end up producing the exo product, which so far doesn't mean anything, just for the moment know, yes, we have correct orbital overlap, which justifies why this reaction can occur with heat. But, what if we take the anhydride and just turn it upside down, take the oxygen here and just physically turn the molecule upside down. Could that potentially change the reaction at all? Let's see. Let's put the orbitals in. We still have the correct kind of orbital overlap that's going to occur. This is the primary orbital overlap. But, notice that there's another portion of the molecule where the two orbitals can interact with the correct phase; they don't end up forming bonds, but because that is a possible favorable interaction, that's energetically more favorable, and so this product, even though it ends up more sterically hindered end up being the one formed in larger proportion, cause there's this additional electronic interaction. Due to the greater extent of orbital interaction, the endo form is produced in greater quantity, even though the product has more steric hinderance or steric interaction than the exo form.

Let me briefly summarize what we've done with the Diels-Alder reaction. We saw a classic example of cyclopentadiene dimerizing.

The cyclopentadiene is locked into correct configuration for a Diels-Alder reaction, which is why the reaction happens easily, even, effectively, at room temperature. When you buy cyclopentadiene, you have to do this process called cracking it, which is to heat it enough to dedimerize it. That was just our simple example of a Diels-Alder reaction, which led to a discussion of s-cis and s-trans. The whole point there is that if the ends of the diene are too far away from each other, they can't react with an alkene, so no Diels-Alder reaction occurs. There are other types of what are called cycloadditions. For this specific kind, you could also call it a [4 + 2] cycloaddition. It occurs thermally. The way we can argue why it should occur thermally is to write this type of orbital interaction diagram. I first identified the orbitals that are going to react – it has to be the HOMO from the one, the LUMO from the other. If you were to redo this problem and flop which one you choose – in this case I chose the LUMO for the diene and then I chose the HOMO for that conjugated alkene; I could have flipped it around and chose the LUMO for one and the HOMO for the other; it turns out that the orbital symmetry will be exactly the same. For answering the question, you can choose either possibility, but it has to be one of those two possibilities, cause it's going to be the highest-energy electrons that react, and it's going to be lowest-energy orbital that they can access that they're going to go into. From there, rather than drawing all of the orbitals out, I chose just to draw the one that corresponds to those frontier orbitals, the one that we care about. That's what the diagram on the right is that show how they interact.

The one warning I've got to give you for this is: if you write these two orbitals independently of each other, the way I did, I just said: ok, two nodes, I'll draw it like this; two nodes, I'll draw it like this. For either case, the diagrams, if I flipped which I shaded in and which I left unshaded, the p orbitals individually, if I flipped all of them, does it change the orbital? Another way of saying it: does the green represent plus or minus of the wavefunction? Don't know, and it doesn't matter, it just matters that the phase changes. From one molecule to another, it's alright if I had to do the following to make this answer work: if I had to flop around the green and white, but I did it for all of them, then that's an acceptable thing to do. That's because it's arbitrary how we shade it, as long as there is the right overall phase to the orbital. This diagram, in the mechanism, it's a cyclic mechanism where one end of the diene bumps into the other which bumps into the alkene which bumps back into where you started. This is exactly that situation I was talking about, where we imagine that the two ends of the diene sit down on top of that alkene; you're going to form new sigma bonds by head-to-head overlap. They don't look head-to-head, but that's because I drew one molecule off to the side so that I could draw it in a way that you could read it, but imagine that really they're just coming down like this. If you formed new sigma bonds here, there used to be pi bonds up above here, but they both had to break in order for this sigma bond to form. But if we had the two pi bonds left over, or the two p orbitals left over, we could imagine a new pi bond forming there. If we scoot this diagram and look at the exo form, that's exactly what we have. There's the new pi bond that's formed; here's where those two interactions occurred, and here's the bottom part of that conjugated alkene that reacted with the two carbonyls. Compare that to the orbital picture; you can see that, really, it's describing the same thing. The one thing that's kinda left out in this drawing is this little point which ends up getting pushed up by the two new bonds forming.

The reason I did that whole diagram one more time is I then said: what if this molecule had been upside down to begin with. In non-conjugated systems, we wouldn't have the carbonyls to worry about, so there wouldn't be this secondary orbital effect. But we do have the secondary orbital effect in a molecule like this, and what we can see is that other than the main bonding interaction, we have this [interaction] that doesn't produce bonds, but it's favorable. If it's favorable because the orbitals match phase, that's going to reduce the energy of the transition state, cause once you make the product, you don't have that orbital interaction any more, but because it's favorable before the reaction occurs, it lowers the activation energy, makes the reaction faster, makes it the more likely product. This is the whole Diels-Alder topic.

Recall the axial and equatorial positions on a cyclohexane ring. Look at the endo form; see how this is pointed straight up and down, the substituents written on the main ring; because they're straight up and down, it's as if they were axial positions, if that was a cyclohexane ring. They're called endo because, more than not, they're pointed towards the molecule, but not up into the interior. It's more that if you look at the exo form, those substituents really are pointed away from the molecule. Because they're pointed away, they avoid steric interactions; that's normally the favorable form.

There's always one less double bond on each molecule that you start with. The first example that I did had a diene, and it loses one of the double bonds, and it actually shifts over position as well. The other molecule happened to be a diene, and it lost one of its double bonds in addition. Both of the molecules each lose a double bond, and then on the diene, the positions move over. Ignoring whether you're forming the endo or exo product, draw the product of this reaction. It's the alkene portion of that first molecule that reacts. The answer is this. Notice that the bridge now has two carbons in it because there was two extra carbons, you could say, in the original molecule. Let me put numbers around all of these positions; that might help a little bit too. These are not nomenclature numbers, necessarily, just random numbers to help assign position. Notice that between 2 and 3, that used to be the bridging single bond between the two different double bonds; that's where the new double bond's going to open up, because if you look at the reaction mechanism, regardless of which way you push electrons, one way or another, the bond gets formed between positions 2 and 3. The other molecule used to be an alkene; once it reacts, it's not longer an alkene, but you still do have that nitrile that's hanging off of it. This is one product. Of course, you could also have its enantiomer if you put the CN on the other position, because those would be mirror image molecules, which means they're enantiomers. Of course, you could also have the two diastereomers, because I've failed to show whether this is endo or exo; if I made it endo versus exo, that makes the diastereomer of that molecule. [Here are the four products.]

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Diels-Alder – Diene + Dienophile → Cyclic product

Dimer – Two of the same atom or molecule combine to form larger structure.  
The diene must be in s-cis configuration to be reactive in Diels-Alder rxn.

[cyclopentadiene] Much more reactive since diene is “locked” into s-cis configuration.

[bicyclic] Cannot undergo Diels-Alder since the diene is permanently “locked” into s-trans.

[maleic anhydride] In this example, endo more preferred. Often preferred due to sterics (less hinderance @ “equatorial” position).

Due to the greater extent of orbital interaction, the endo form is produced in greater quantity, even though the product has more steric interaction than the exo form.

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Structures (remaining structures identical to lecture 22B)

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