Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-Solving Approach
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Lecture 23
Problem Solving on Baldwin Rules

Hello everyone welcome to this course on Structure Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem Solving Approach. In the last session we have discussed the cyclization rules which are commonly known as or popularly known as Baldwin rules, these rules are basically employed to predict the outcome of an intramolecular cyclization reaction involving a nucleophile attacking a carbon with a living group or attached by a multiple bond like a double bond or triple bond.

So, we have seen different types of cyclization possibilities like exo cyclization or endo cyclization and then we have seen the how the rules predict that certain cyclizations are not favored, that is disfavored and certain cyclizations are favored, these are not forbidden or disallowed or allowed by any symmetry rules that is not the case, it is basically a favored process and a disfavored process.

Today this session I will do some problems based on where Baldwin's rule have been applied we will see that and then move on to other topics. The first problem, first of all let me try to point out that when you talk about Baldwin's rule there are different types of ring sizes 3 to 7 that is the normal ring size, then this exo and endo possibilities and then the hybridization of the carbon. So, it is a exotet or exotrig or exodig all these possibilities are there.

So, sometimes ah students become confused that about how to remember these rules, so what I suggest is basically you concentrate on the disfavored processes, if you know which processes are disfavored, then automatically you know which processes are favored, so better concentrate on the or try to find out what is disfavored.

Now, if you, if you see that, see there are two types of again rules I have pointed out that is one is basically the say the ring size, then exo or endo, then tet or trig or dig, that is one type of cyclizations and the other one is where an enolate is involved in the cyclization.

So, the nucleophile is coming in the form of an enolate where there are ambient nucleophiles center, nucleophilic centers possible.

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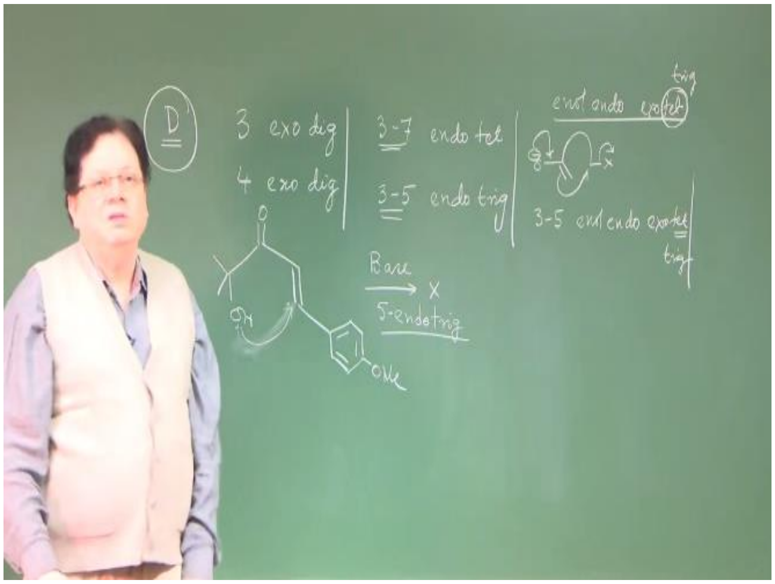

So, the first one is that the disfavored ones are, this so if I say D means disfavored, so 3 exodig, usually exo cyclizations are favorable but for diagonal system, that means sp hybridized carbon the rules are little different, 3 exodig and 4 exodig these two are disfavored and the other ones, the endo ones, the endo ones that means here the endo ones are favorable, like 3 endodig or 4 endodig and that is why I am saying just concentrate on one, that is what is disfavored.

So, that is one type that involving cyclization at a sp hybridized carbon and the other one is 3 to 7 endotet cyclizations, endo cyclizations are usually difficult at tetrahedral carbon and trigonal carbon, so what is really disfavor is 3 to 8 endotet cyclization and 3 to 5 endotrig cyclization. So, there is a difference here, both are endo, so when it is happening at a tetrahedral carbon then all sizes are disfavored because I told you in my previous lecture that until you reach a ring size of 9, the nucleophile cannot approach, is geometrically not possible for the nucleophile to approach exactly from the back side of the living group.

So, that is why it should be 3 to 8 but as per Baldwin's rule because he mentioned the ring sizes of 3 to 7, so we are restricting to that size and for trigonal cyclization 3 to 5 endotrig is disfavored, that means when you say 6 endotrig that should be favored, that is possible. So, these things you should remember and for the other type that enol, that is the enol, endo and then you have exotet that is another type of cyclization, remember that is basically that you have a something like this o minus, so now this is what is enol, endo, exotet, so if you think of that type of cyclization then what happens 3 to 5 ring size involving enol, endo, exotet is disfavored.

So, 3 to 5 enol endo, exotet that is disfavored and so also enol, endo, exotrig that means if you have instead of tet if you have trig that is also you can say that this is also disfavored if it is 3 to 5 enol, endo exotrig. So, that means when you have the enolate double bond attacking in an endo fashion then 3 to 5 ring side is disfavored, beyond that it is possible that is favored and that immediately tells that enol, endo, enol, exo and exotet or enol, exo, exotrig these are actually favored processes because we are not mentioning that, we are just picking out the disfavored processes.

So, again I repeat disfavored processes involving non enolate systems, that is 3 exodig and 4 exotet, so we can combine 3 to 4 exodig cyclizations are disfavored and then 3 to 7 endotet and 3 to 5 endotrig are disfavored. In case of enol, endo systems then enol, endo exotet and enol, endo, exotrig here 3 to 5, if you are making 3 to 5 is the ring size then these are disfavored beyond that things become favorable.

So, let us now start doing the problem session. So, this is the basic rules that I remember, so let us do the first problem and that is, that is this one. this is an alpha beta paramethoxy, paramethoxy then this double bond, this is not cinnamoyl, this is paramethoxy substituted, paramethoxyphenyl substituted alpha beta unsaturated carbonyl system.

So, if you want to attempt a cyclization like this in a Michael fashion, now you have to make a powerful nucleophile and that is by the use of a base, so if you use a base like potassium tertiary butoxide, so that will make the o minus. However, there was no reaction, so the anticipated type of addition to give a 5 membered ring is not possible actually this is forbidden by the, this is not forbidden, sorry, this is disfavored as per the Baldwin's rule, again I repeat it is not a forbidden by any symmetry that is why we are not using the word forbidden or allowed, it is basically we are saying favored and disfavored.

Now, this cyclization if it had happened, then that classify that cyclization, this cyclization will be first of all the ring size will be 5 and this is an endo cyclic double bond, so 5 endo and this is a trigonal carbon, so 5 endotrig and we have the rules here, 5, 3 to 5 endotrig is disfavored and that is why this reaction is not going. So, as simple as that.

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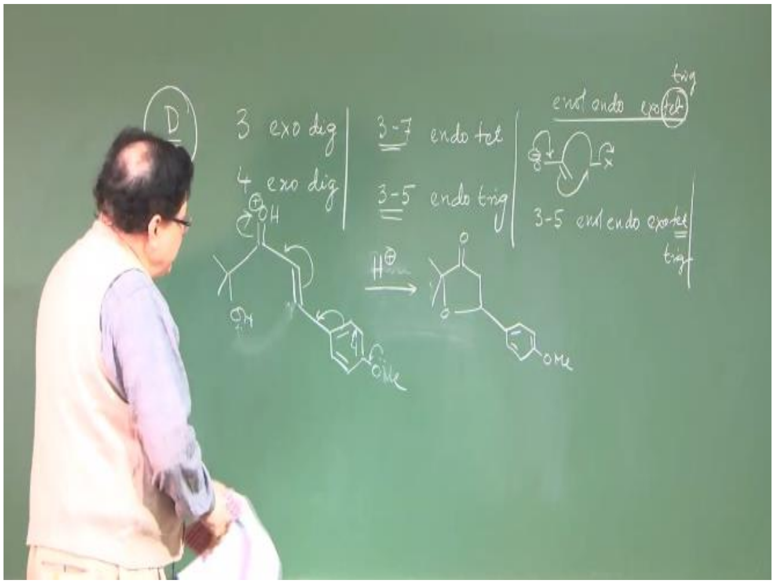

However, if you now add acid, in presence, if you want to do this you can do this cyclization or attempt this cyclization in two different ways, either increase the nucleophilicity of the attacking nucleophile that is the weight, so you want to make o minus that is one way, the other way is to ah increase the electrophilicity of the double bond that you can do by adding acid.

So, if you add acid then that will protonate this carbonyl and this protonated alpha beta unsaturated carbonyl system is even a better Michael acceptor. So, more electron deficiency is created at the beta carbon, now in this case you get the product, so the product, the anticipated product is formed here, so what is the difference between the acid and base and how it is possible to whether this reaction, this product it has been formed as per the Baldwin's rule or following the Baldwin's rule let us see.

So, actually what happens here that before these which attacks, this OMe because of this it is a donor, so this type of delocalization will take place, so that creates a new structure, so that creates a new structure.

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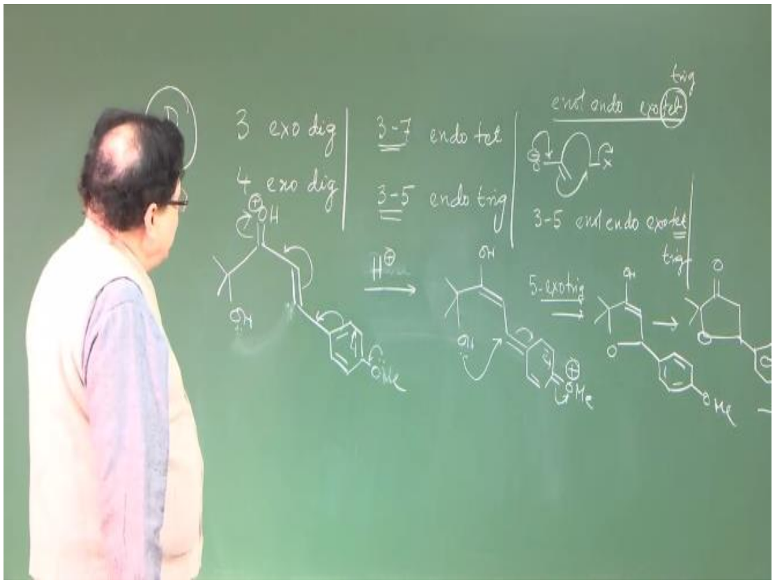

Let me try to write that, so this is OH, so this is the other resonance form double bond, then a double bond and you have the aromatic ring OMe plus, so this is the other resonating form, now what will happen? Now, this wedge, now this wants to again gain back the aromaticity, so this wedge can now attack this carbon, the same carbon but now the electron flows in the opposite direction, this is a double bond which is exo cyclic, as per these 5 membered rings.

So, that goes there, this goes there and the methoxy which was the oxygen was positive now it has satisfied the charge and the ring becomes aromatic. So, this will generate the anticipated 5 membered ring and then OMe and this cyclization now you can classify this cyclization as 5 exotrig, now which is now favored, which is a favorite process because this is the rule, 5 endotrig is not favored but 5 exotrig is favorite process. So, that is why this is now possible, this type of cyclization is possible.

So, now only thing is that you have to tautomerize the enol into the carbonyl and that is the final product, sorry, so nothing is violated this product is following the Baldwin's rule, the only difference is that because of this resonating structure now you can have an attack by a 5 allowed, by a favorable 5 exotrig process, so this is one example.

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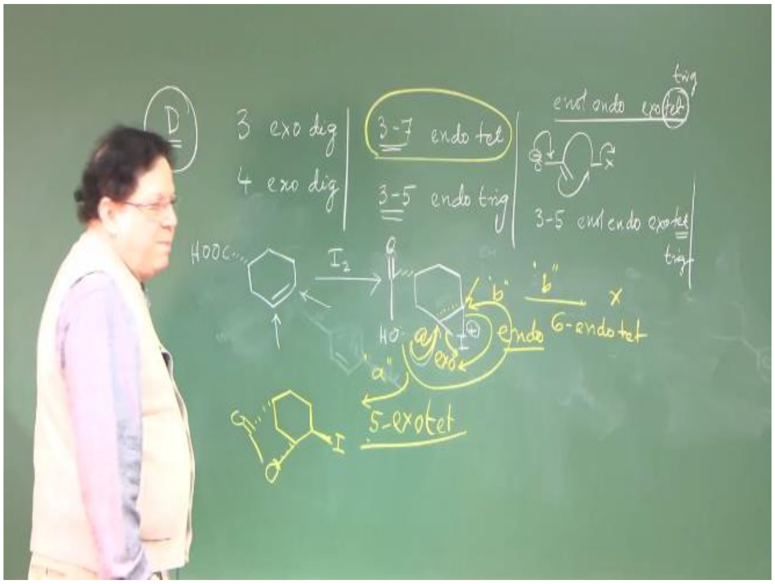

Then you have, suppose there is a system like this that you have a unsaturated carboxylic acid but it is not a conjugated carboxylic acid, the double bond is somewhere else, now this is very common reaction that if you add iodine here then what happens it forms a lactone, that means the carboxy adds to the double bond. Now, there are two possible positions of attack by the carboxy, so the mechanism is that it forms an iodonium ion and then CO, OH, so either the OH attacks at this position or it can attack the or it can attack this carbon and opens up that one.

Now, which one is possible, actually which one will happen as per Baldwin's rule? Now, remember, if you have this 3 membered ring opening like the epoxide ring opening, then you have some problem to define the reaction as exo or endo, so what I suggested that when it attacks this carbon and opens up these, think this as a, it has originally a double bond, so your double bond carbon is actually the double bond and is basically exo to the ring that is formed, that is being formed, on the other hand if this attacks the second carbon, this one, then if you think this as nothing but ah originating from a double bond so if you consider the double bond as a proxy, then that bond is going in this direction and that is basically an endo, endo cyclic attack.

So, when this breaks that is the exo, when this bond breaks that is the endo, so now you define these two processes, suppose this process is process a and attack at this carbon is the process b. So, the process a is, the size of the ring is 1, 2, 3, 4, 5 so that is 5 exo because I have told you that that is actually exo, 5 exotet, that is the pathway a and pathway b is 6 endotet, 6 endotet.

So, obviously 6 endotet falls under this, so which is a disfavored process and if it is disfavored so that product will not be formed, so the product that will be formed you can write that is this one, carbonyl oxygen this and there will be an iodine here, if it is coming from the alpha side because the carboxy was originally alpha, so the iodine should be beta. So, that is the, that is another example of where the Baldwin's rule ah can be applied and you get the iodolactone, this is the iodolactone as per the 5 exotet, so this is the second one.

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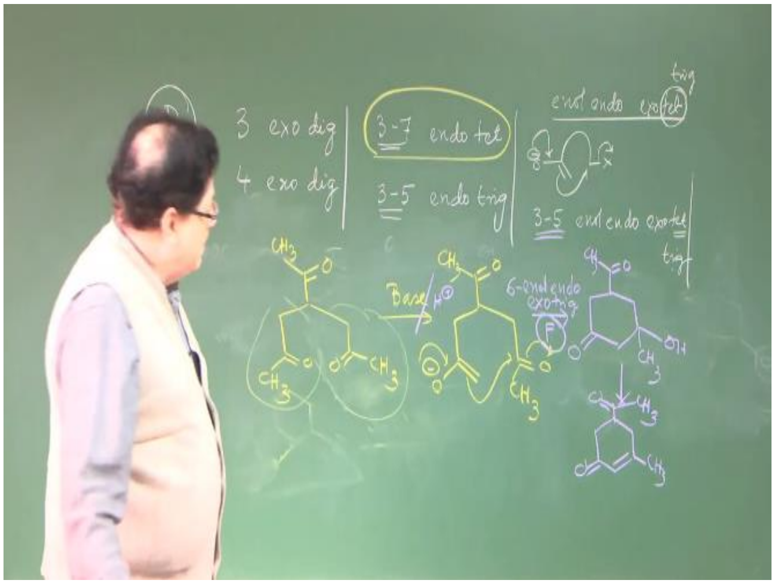

Now, let us see what other problems we have. Now, this is an interesting example that you have a triketone like this and you are trying to do an intra molecular aldol reaction, intra molecular aldol reaction by employing say a base, now because there are so many carbonyls the possibility of different enolates and possibility of different types of cyclization are there, so which product will be formed? Now let us see, see these two hands are basically same, so you can form enolate of one hand and the enolate attacking the carbonyl of the other, this is nothing but the aldol condensation, intra molecular aldol condensation.

So, let us see, first let us try to draw the enolate from one of the carbonyl from these this hand, so that will be say O minus, this is the double bond, so that is the enolate and on this side you have CO, CH3, so this is one possibility and if you now do the cyclization, so this will be the flow of electrons and what you will get is CO CH3 here and so that will become OH and then there is a methyl and this will be ketone, this is not the final product this is the aldol and then it will undergo dehydration you can actually do this reaction in presence of base or acid, if you want to do in base then you have to heat it a little to induce the dehydration otherwise under acid medium this will be protonated and dehydration will be spontaneous.

So, this is CO, CH3, so this is one possibility, now let us try to define this reaction as per Baldwin's classification, so this will be enol, first of all the size, this is 1, 2, 3, 4, 5, 6 so this is 6 enol, endo, exotrig, 6 enol, endo, exotrig what the rule says, the rule says that 3 to 5, that means up to 5 enol, endo, exotrig is disfavored but not this one, so this one will be favored, so that is a favored process. Let us try to see other, so at least this product will be found for sure but what are the other possibilities?

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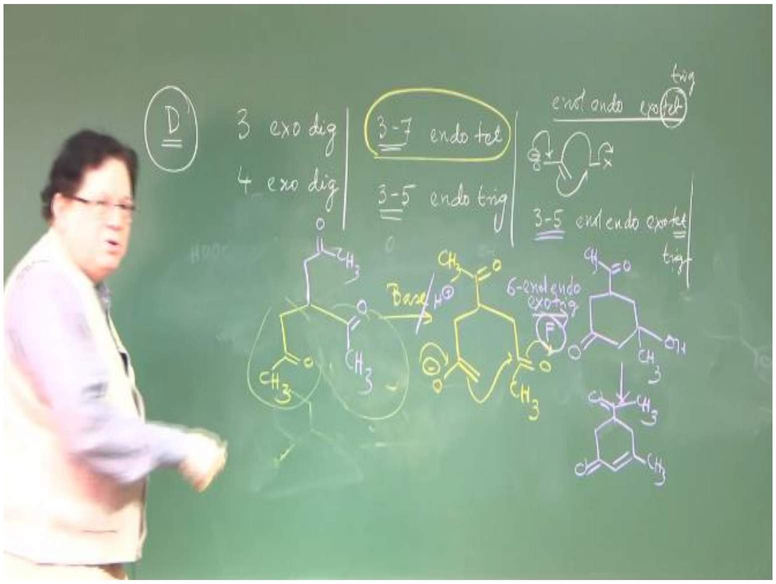

The other possibility is that I can just change the two hands like other possibilities that you have CO CH3 here that means the top group I am writing on this side and here CH2 CO CH3, earlier the aldol condensation was happening between, between this and that now the aldol condensation I am trying to do between this hand and the enolate generated from the same.

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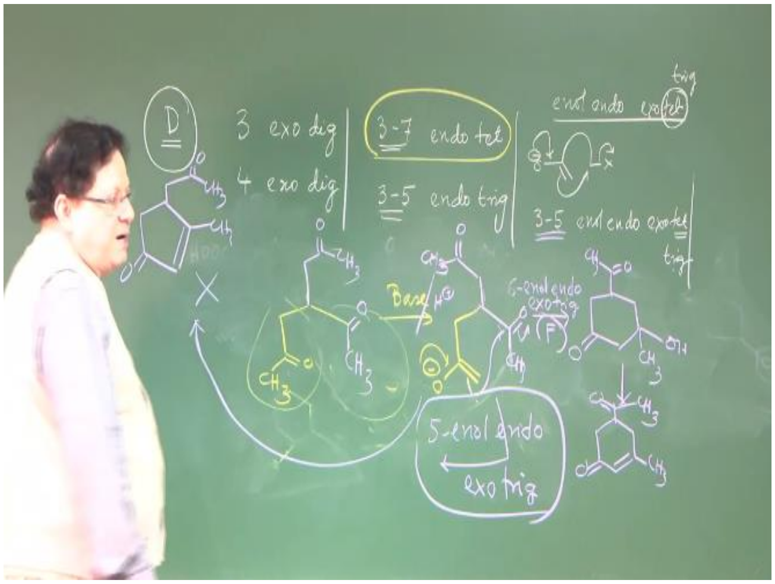

So, you basically, you change the two hands, so here it will be CO, CH3 and this will be CH2 CO CH3. Now, if you want to do this reaction now there is a possibility of an aldol condensation like this and then followed by dehydration, you will be getting a 5 membered ring and very similar type of system alpha beta unsaturated carbonyl system but that is imposed on a 5 membered ring.

Now, let us see that what is the process, the process is basically again it is now a 5 enol, endo, 5 enol, endo, exotrig is that allowed, is that favored or disfavored, what it says? It says that 3 to 5 enol, endo exotrig, so this is 5 enol, endo, exotrig that is not a favored process. So, this process whatever product actually the product that will come out of this I can write that the product will be double bond o, here there will be a double bond, this is a methyl and here there will be this CH2 CO CH3, so this product will not be obtained because it is violating the Baldwin's rule, this is a very good example that we have.

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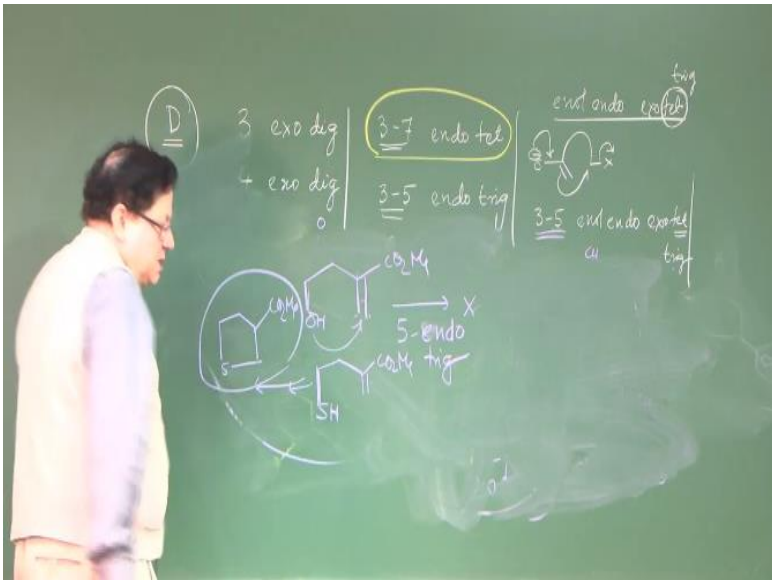

Other problems or other important points about Baldwin's rule that when the nucleophile, nucleophilic atom, usually we are dealing with oxygen or carbon or we are dealing with nitrogen that is the second row of elements in the periodic table but if you go beyond that, suppose you are having this type of cyclization or attempting this type of cyclization, like CO2 Me double bond and then you have, say OH here, if you try to do this cyclization again in presence of base or acid, both are possible agents but this reaction does not happen because it is nothing but a 5 exo, sorry, 5 endotrig process which is not allowed.

On the other hand if you have, now instead of oxygen, if you have sulphur here a thiol, if you have a thiol then this reaction, then this reaction takes place because of this as you go to the third row of elements, then your bond length increases, if the bond length increases then the type of restrictions that you are having when the bond length was smaller, this oxygen could not attain, could not make the trajectory that is imposed by the Burgi Dunitz trajectory of 109 degree, that is not possible when you have a small bond which is a smaller length but as you put sulphur, the bond length increases so that gives more approachability and the sulphur now can adopt the Burgi Dunitz trajectory of 109 degree and then form the product.

So, in this case you have, you will form this thiofin, the reduced thiofin product like this that means this is, so if somebody says that if 5 endotrig, this is nothing but 5 endotrig process is whether it is possible or not at all, you will say that yes, it can be, it is possible if you have a longer, longer bond length involving the nucleophile attached to the carbon and that happens when you go beyond the second row of elements in the periodic table like in case of sulphur, so obviously, this if sulphur is replaced by selenium that reaction will definitely happen, so that is another important point to note here regarding Baldwin's rule, so this is applicable for second row of elements, second row.

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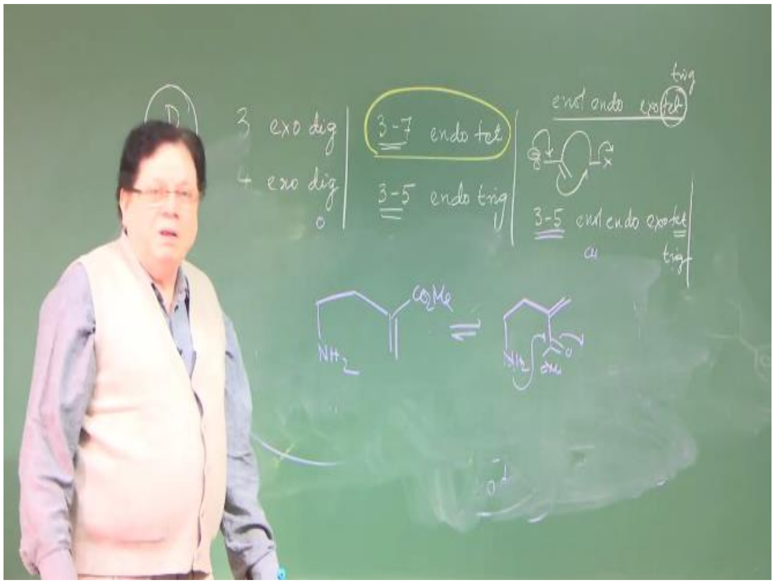

Now, let us go back to the problem which, let me see what is this, I told you about this oxygen sulphur that system but if you have the nitrogen now, NH2 and then double bond and CO2 Me here the nitrogen again the CN bond is a short, is relatively shorter than the carbon sulfur, so here also this 5 endotrig cyclization does not take place, so what happens here, that this takes the other conformation NH2 OMe and then the double bond here, so now the nitrogen attacks here, in a 5 exotrig process, that is allowed, that is an allowed reaction, so it forms an amide instead of that nitrogen adding to the double bond.

Now, this could have happened with oxygen provided you have much more forcing condition, nitrogen is a better nucleophile, so this happens at a much, much less stringent condition, so people isolated the amide, the cyclic amide and but for oxygen definitely that reaction will happen, but you have to raise the temperature.

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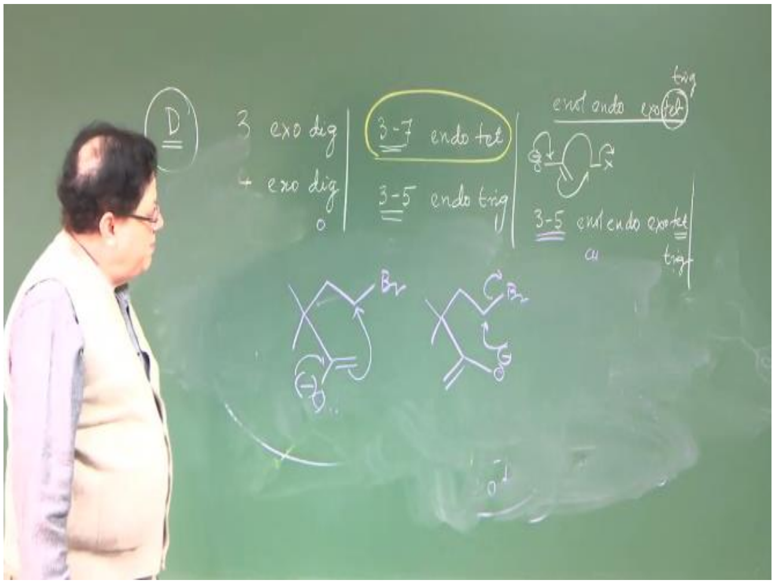

The other type of example that I have is, yes, this one, this is an, want to show the, this is also I think we have discussed this last time, that if I try to do this cyclization, this is nothing but enol, 5 enol, endo, exotet, what was written here? 5 enol, endo, exotet is not an allowed process.

So, this will not take place, here it will just the o minus will act as the act as a nucleophile and then will displace the bromine and that will make it a, so if you have the double bond on this side O minus, so now the o minus will act as the nucleophile, so that will form 1, 2, 3, 4, 5 again the 5 membered ring but it is 5 exotet which is allowed, 5 exotet is allowed, so you get the ether.

Let us try to visualize this, the cyclization processes, some are allowed, some are favored some are disfavored, I told you that because some stereoelectronic requirement cannot be met as that depends on the structure that you are handling, so I want to show you a model and then you will realize that why Baldwin came out with his rules and what is the rationality, why certain stereoelectronic requirements cannot be met.

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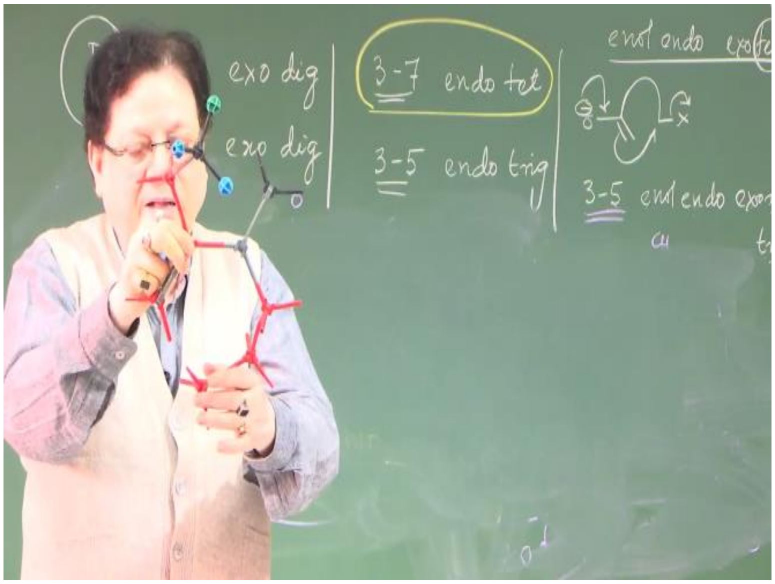

So, the example I have here this is my model, this is basically, this is a carbonyl that means an ester so this is my CO C double bond O, this is oxygen and this is the methyl, so it is a CO2 Me group and then you have the next carbon has a double bond and the next carbon has a double bond, then you have a CH2 and then you have another CH2 and think that this is a nucleophile like NH2. So, the question is there are two types of possibilities.

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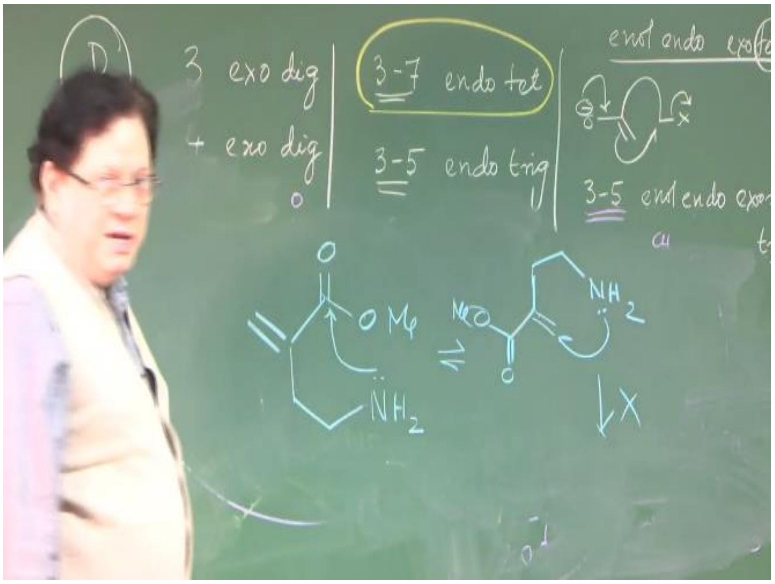

Let me write the molecule first, the molecule is C double bond O MEe and then a double bond and then CH2 CH2 NH2, so there are two types of cyclization, this problem just now we have done, that here one possibility is that this attacks this carbonyl and finally the methoxy leaves, that gives the amide, that is the lactam, the gamma, the gamma lactam because it is a 5 membered ring, the other possibility is that it can take up another conformation where you have the double bond on this side and this is the CO2 Me and then you have CH2 CH2 NH2, so this is the other possibility where the nitrogen attacks in a Michael fashion to the double bond.

So, obviously we know that this is not going to take place because it is a 5 endotrig cyclization which is disfavored, whereas this is a 5 exotrig process because that is it is attacking the carbonyl, so 5 exotrig process and that is the one which will be, which will be allowed.

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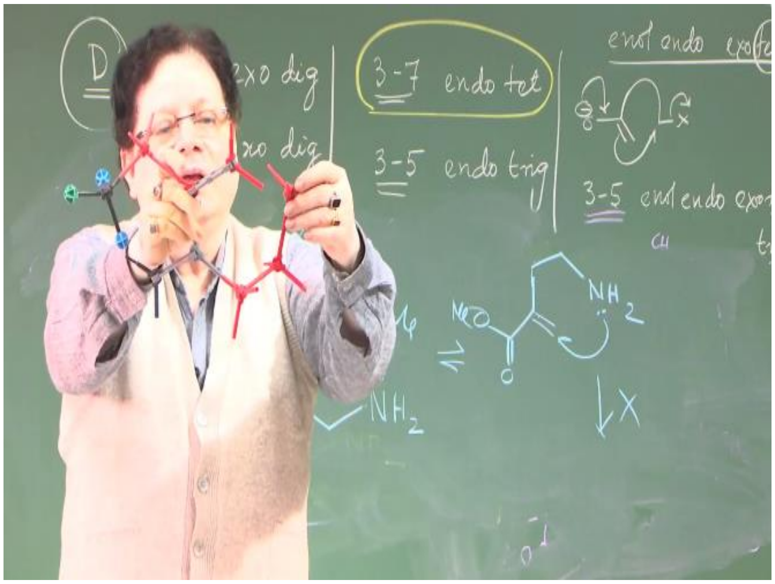

So, let us see the model again just to fix the atoms, so this is the carbonyl, again I repeat this is the carbonyl, this is the ester group, that oxygen and CH3 and this is the double bond, this is the double bond and here you have the CH2 CH2 NH2, now if you want to do the attack at the double bond that means this is the double bond if you want to attack the attack the double bond by the nitrogen with the help of the nitrogen, so this is my nitrogen, so the nitrogen has to attack it at an angle at a trajectory of 109 degree.

So, basically it has to come on this side and then attack from here at this carbon which is not possible because it is the length is too short, had there been another carbon and then the nitrogen, then possibly it would reach and I told you also that if it is not nitrogen, if it is sulphur, then the bond length will be more, so then the sulfur is able to reach this carbon and follow the trajectory that is demanded by the stereoelectronic requirement.

So, this reaction, the nitrogen is not able to because if you want to do it then there is lot of strain, if you want to do that trajectory, you see the strain that is imposed in the molecule on the other hand if you, now switch it in this way that this is my carbonyl, that ester carbonyl, that is the ester and CO and MEe now what we are saying that this is now allowed, now you see the nitrogen is basically you can bring it right at the top of the carbonyl, so now this type of trajectory that 109 degree and is possible because the nitrogen is right on the top of the carbonyl, you can bring that in a conformation without inducing any strain in the molecule.

So, it is basically that trying to satisfy the stereoelectronic requirement, if you think that lot of strain is developing because you are forcing that the center should reach each other and then satisfy the electronic, stereoelectronic requirement then that is basically disfavored, on the other hand if you see that if the trajectory can be made without much deformation then that will be favored.

So, that is exactly, that is very clear from this model, the carbonyl nitrogen can reach very easily on the other hand, the double bond it is ah not possible because it is endo cyclic, if you see that the it is now difficult for the nitrogen to adopt this 109 degree, so that is the basis and I wanted to show you through a model like this.

So, I think that ends up the this cyclization rules and the related problems, related issues and next we will move on to another new topic, so that finishes up the topic which is basically broadly under the heading of stereoelectronic effects on confirmation and reactivity of organic molecules. Thank you.