Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-Solving Approach

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Lecture 22

Cyclization in Enolic Systems

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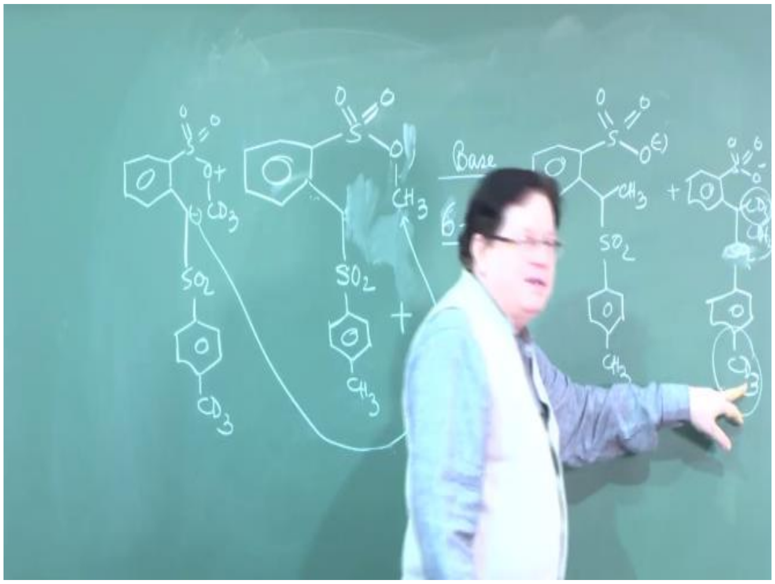

So, the question is whether this process, this product has been generated by a 6 endotet process or something else is going on because if it is formed by this process, then Baldwin's rule will be called into question, now in order to solve this dichotomy, so what was done that there was another molecule which was which was combined with this because there was a debate that whether this methyl is transferred in an intramolecular fashion or whether another molecule where there is a negative charge here that attracts the methyl of another molecule and not the same molecule.

So, that will be intermolecular, so that debate cropped up that, whether the methyl transfer is going on in an intra molecular fashion or intermolecular fashion. So, in order to distinguish between that, you know you have to do crossover experiments, you take another system, very similar but with different groups and that is SO2 so you change these into CD3 and then SO2 and then make it CD3.

If you do that, if it is intramolecular, then you will expect only two products this and when you are doing the reaction or a mixture CD3, sorry, SO2 and then CD3, so these are the two products that you expect provided the transfer is intra molecular but if it is inter molecular, then what will happen? Then this negative charge can attack another molecule and that molecule may happen to have the methyl group and not the CD3 group, so that means you can get a product where this CD3 is replaced by a CH3 but at the para position of this aromatic ring this is CD3.

So, that immediately tells, in fact that products was isolated, two types of crossover products, one is CH3 here, CD3 there, another is CD3 here CH3 there these are the crossover products, those were isolated and that immediately proved that this is an entire molecular process that means Baldwin's rule is not violated, inter molecular process it was forced to adopt an inter molecular pathway just to avoid this 6 endotet cyclization which is not allowed as per Baldwin’s rule. So, that is a nice example of that some reactions are not favored and then the course of the reaction takes a different route, so that is the first example.

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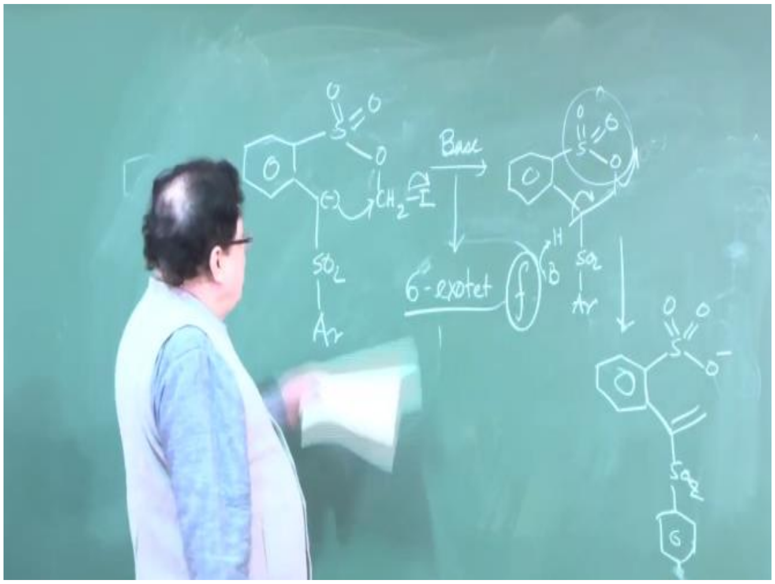

Let us take another example to support Baldwin's. Let me see, just one second, a very similar one if you take the very similar molecule O but say CH2 I, so instead of CH3 you take CH2 I and then SO2 and the aromatic ring and then add base, so what will happen now? Now, there is another possibility of reaction, another type of reaction that is possible instead of that the transfer breakage of this bond, now this carbon has a good leaving group, so what can happen that this negative charge which is formed carbon ion that attacks this carbon and it is now perfectly it can adopt and the geometry which satisfies the stereoelectronic requirement for an SN2 displacement, this is nothing but an intra molecular SN2 displacement, so that can adapt what is required by the stereoelectronic rule and then it can remove the iodine, the iodine leaves and you will get SO2 O and then CH2 and then you have SO2 Ar.

However, the reaction does not stop here because again this is another good living group, first it was iodine, iodide is one of the best living group you know, so first it was the iodide which is which is kicked out, there are two reasons for that iodide is a good living group that is number one and number two is also that this reaction is allowed by Baldwin's rule because this will be now a 6 1, 2, 3, 4, 5, 6 so 6 exotet cyclization, the electrons are flowing outside the ring that is being formed.

So, it is a 6 exotet which is favored, so that is why that reaction took place and now there is an another intra molecular reaction, another elimination that will take place because the base abstract this hydrogen this is one two elimination, so ultimate product will be, this happens because this is still another, this is also a good living group. So, the reaction will not stop there, ultimately you get this type of product, SO2 Ar.

So, you see the behavior, the differential behavior for the two processes, when you have iodine you have a different course of reaction, when you have a methyl you have a transfer but that transfer is via an intermolecular fashion but in both the cases Baldwin's rule is applicable, the reaction is going as per the Baldwin's rule if something is disfavored then it will not go that pathway and in the second case it is allowed, it is a 6 exotet process so that process happened.

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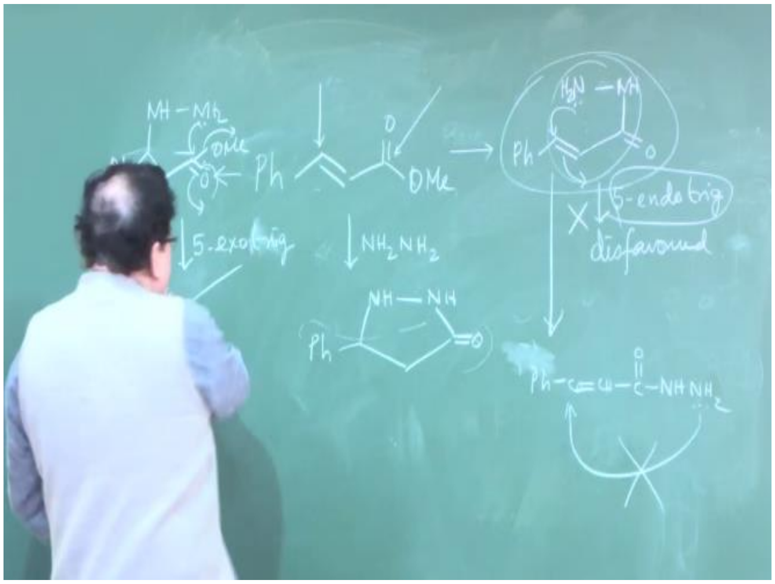

The next one is quite interesting, very simple reaction Ph it is a cinnamyl type molecule, it is a cinnamic acid not fully acid it is an ester, methyl cinnamate, methyl cinnamate and you are adding hydrazine onto it to make 5 membered heterocycles, 5 membered pirazine type of heterocycles where the 2 nitrogens are occupy a 5 membered ring.

Now, you can draw 2 mechanisms for the reaction product, first let me write what is the reaction product, the reaction product is Ph and then you have a 5 membered ring NH, NH, then CO and you have this, so this is CO, NH, NH so that comes from the cinnamic acid with the removal of the methoxy and the other nitrogen adds to the double bond, here there are two centers where nucleophile can attack, it is the double bond beta carbon in a Michael fashion, the nucleophile can attack or the nucleophile can attack the carbonyl carbon, actually both are happening, both have happened, so that you ultimately got the heterocyclic ring.

Now, question is which one has happened first? Let me see, if suppose the reaction has taken place at the carbonyl carbon first, then the intermediate will be something like this CO, NH, NH2 and if the first reaction is a Michael addition then it will be Ph, NH, NH2 and then CO OMe so these are the two intermediates.

Now, for the cyclization to happen the intra molecular cyclization where Baldwin's role is applicable, this one if it adds in this fashion, so that gives a product no doubt but it is a violation of the Baldwin rule because this will be called a 5 endo because now the ring, the electron is flowing inside the ring that is being formed, so that is 5 endotrig which is disfavored process, on the other hand here if the attack has first taken place here, then it will be the nitrogen attacking here, first this goes up and then it goes back and the OMe leaves.

So, basically this is nothing but a 5 exotet process, so one is 5, sorry, not tet, trig, extremely sorry, this is a trigonal carbon, so one is 5 exotrig, another is five endotrig, so obviously, this is not the, should not be the process, the mechanism, the mechanism should be this one because this is allowed by Baldwin’s rule.

Now, you can actually have a proof for this, for this mechanism, that one actually, one can make this intermediate by treating, by treating cinnamic acid with hydrazine, cinnamic acid salt or cinnamoyl chloride with hydrazine, so you will get this type of intermediate and this was attempted, this on attempted cyclization even at high temperature did not work.

So, that says that this is not the mechanism, you understood what I said? That you can make this intermediate starting from, there are many ways you can do that, one way that you can take cinnamoyl chloride and then add hydrazine, so you get this molecule, the hydrazide and if you want to now cyclize an intramolecular cyclization with this hydrazide it never worked, so that means that it never work because 5 endotrig cyclization is not a favored process as per Baldwin’s rule, so you see the success of the rules in explaining certain reactions and also explaining the mechanistic possibilities of many reactions.

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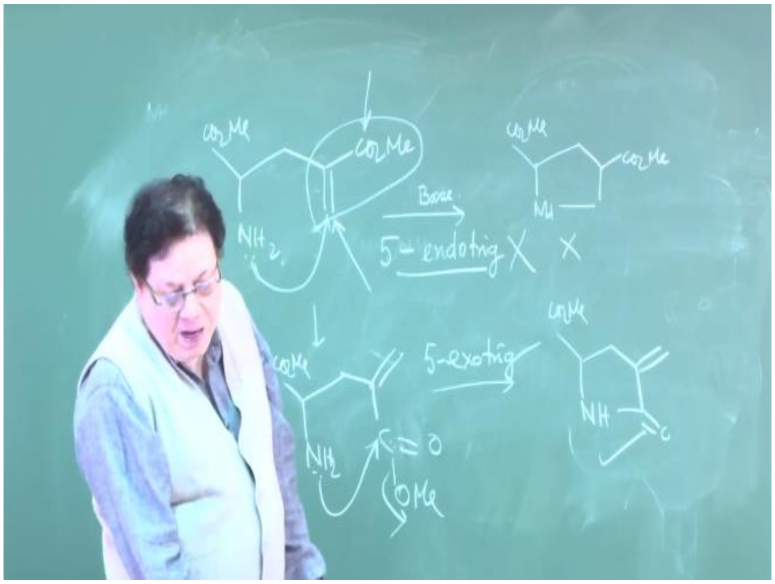

Then this is the second example that I give that involve the trigonal carbon, let us stick to that the trigonal aspect, there was another reaction which is also fairly interesting, that is CO2 Me, then NH2, then a double bond, CO2 Me now let me, let me tell you one story, real story that if somebody does not, is not aware of Baldwin's rule suppose, then if this problem is given, that what will be the product if you treat with a base, the base is basically abstracting the hydrogen from nitrogen and the nitrogen will add to the double bond.

Now, usually students know Michael Addition very well, what is Michael Addition? It is basically the addition to the double bond carbon, beta carbon in a alpha beta unsaturated system, it is a 1, 4 addition. So, if you do not know the Baldwin’s rule you will see that okay there is this Michael acceptor and so this NH can add in a Michael fashion to this double bond, however, if you know Baldwin's rule, then first of all try to classify this reaction this NH2 adding to the double bond that will be then, that will form a 5 membered ring 5, the double bond is basically a part of the ring that means electron is flowing inside the ring, so it is an endo cyclization, so 5 endotrig cyclization.

Now, if you look into the rules that is not favored process, so in fact it never gave this molecule, this product was never obtained from this reaction although, we know Michael reaction is very facile, reaction can be very facile but as long as the stereoelectronic requirement is satisfied, if stereoelectronic requirement cannot be fulfilled then an apparently facile reaction may not happen, that is given by this example.

So, what is the product here? The product actually is CO2 Me, then NH2 and it is not adding to the double bond at all, it is adding to the, it is actually attacking the ester functionality, that is the other way because as I said there are two sides of electrophilic attack, there are two sides of electrophile, electrophilic centers, two sides of electrophilic centers, so the nucleophile can attack any one of them but usually Michael reaction is very facile but here Michael reaction is not possible because of Baldwin's rule it is a 5 endotrig. So, you write it in another fashion like this and then the nitrogen attacks this carbon and finally this OMe leaves.

Now, this is the reaction which is what? Which is 5 exotrig which is allowed, 5 exotrig is allowed is a facile process, so this product will be obtained and in fact that was obtained, NH, CO so this is the product and this is not obtained at all, so you see the success of Baldwin's rule in explaining why reaction takes place in one fashion and not the other way, so there are many, many examples of this, let me try to find out some, some relevant examples which are also interesting and later on we will also do problem solving classes, then we can bring more problems at that time.

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Now, let me one interesting point as well as very important, that is opening of the epoxide carbon, epoxide ring. Suppose, you have this because that is where students face problem, if you have an epoxy alcohol like this and if you want to do a cyclization chemistry adding acid, so this will be protonated now, now this H has 2 options either it can attack here, so that will be broken or it can attack here, then this will be broken, here the problem is how to define the exo and endo of this reaction, of this type of mechanistic aspect because in both the cases when it attacks this carbon, the electron is flowing outside the ring and when it attacks this carbon, the again the electron is flowing outside the ring. So, whether both are exo processes then or one is exo or indo, means how to define that.

I think the best way to do that think epoxide as a kind of, if it is a double one instead of an epoxide, then what you would have done or how you do define those processes, if it attacks this carbon then that is obviously an exo process, an exo process and if it attacks this carbon that will be an endo process.

Now, here basically the double bond is being substituted by epoxide but if you think epoxide in this term that if there was no epoxide, if there was a double bond then attack at this carbon would constitute an exo process and attack at this carbon would constitute an endo process. So, I think by that analogy you can give a terminology for this reaction.

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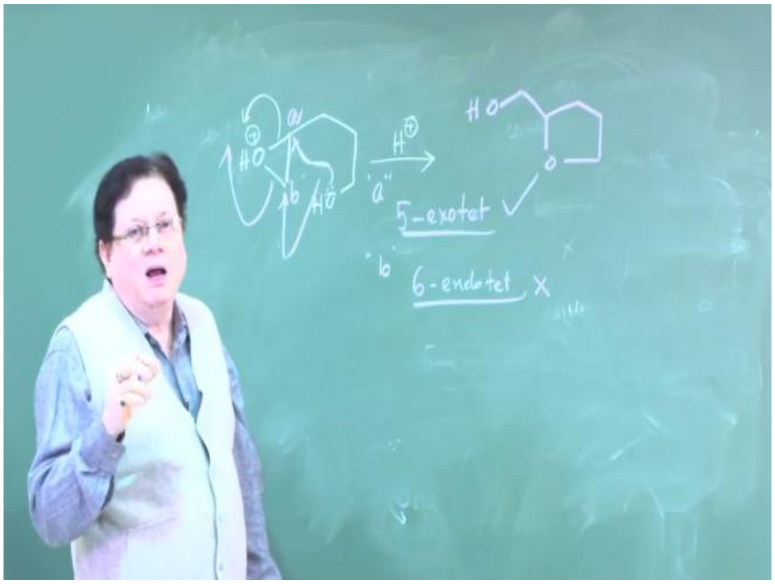

So, when it is attacking a carbon, carbon a so that will be called, so you are making 1, 2, 3, 4, 5 that will be 5 exotet and when it attacks the b carbon so that will be called 6 endotet. So, once you define those now you know that 6 endotet as I said 3 to 8 basically, that endotet cyclizations are not possible, so this is not the favored one, so this is the favored one, so the major product that you will get is this is the product which is obtained from 5 exotets.

So, remember this opening of 3 membered ring and how to assign the exo and endo in this cases, think of that 3 membered ring as kind of originating from a double bond and what would be the nomenclature if the one of the double bond carbon is attacked by the nucleophile, how do you define it whether it is exo or endo versus the attack at the other carbon, then you go back to the epoxide or it could be an aziridine ring also, then you define it as the exo or endo, only difference is that in the when you see as a double bond it will be a trig cyclization, as you make an epoxide or an aziridine that will be a tet cyclization.

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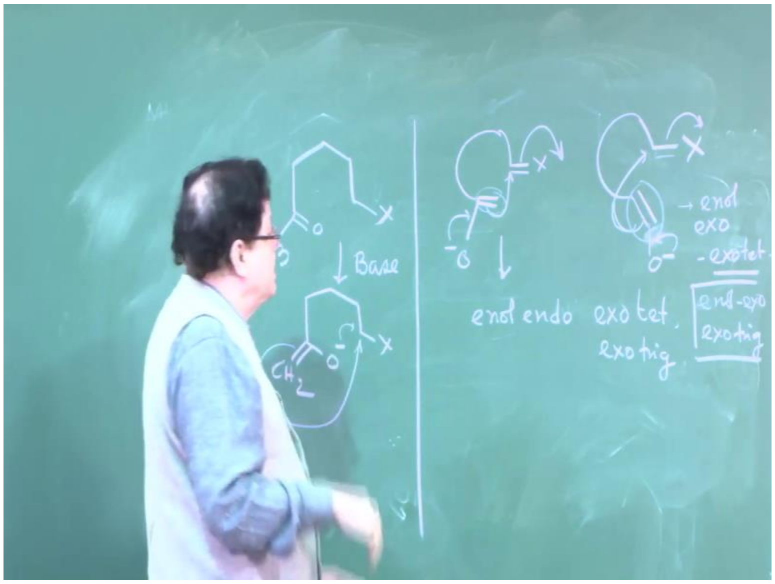

Let me ah try to find out some other some other cases where the rules, you have to adopt new rules and that is for the enolate cyclization, see many of the cyclizations are basically cyclizations involving enolates, like if you have X and then if you have COCH3 suppose and you add a base, then what will happen?

This molecule will form an enolate o minus double bond CH2, o minus double bond CH2 and then what will happen? Now, you have basically these are ambident nucleophiles, there are two nucleophilic centers, so either this can attack or this carbon can attack, so these are the two possibilities, these are the two possible way of attacking and forming the cyclic, in that forming the cycle.

So, there are again rules that are framed for that, see there are like if you have, first of all you have to define the exo endo, suppose you have a system like this and enol which looks like this, if that be the case then the, then if this is the cyclization mode that will be called, that will be called enol endo, that means the enol double bond is actually endo cyclic because that is becoming part of the ring.

This part the enol part, the 2 carbons of the enol part becoming the part of the ring, that means electron is flowing inside the ring, that is being formed and on the other hand where it is attacking that electron flow is outside the, outside the ring that is being formed, that flow is outside the ring, exo to that ring, so this type of cyclization will be called enol endo and then exo, if it is a carbon, tetrahedral carbon then it will be exotet, so enol endo exotet. If it is a double bond, then that will be exotrig, if it is triple bond that will be exodig.

On the other hand there is another type of possibilities that is you have o minus here, sorry, you have o minus here, the enolate is like this and this is the carbon where the attacking, attack takes place, the carbon bearing the either the leaving group or the double bond or triple bond, now in this case if the cyclization happens like this, that o minus comes here and then that attacks this carbon and X leaves, now what happens?

These two carbons is not, both the carbons are not becoming the part of the ring, so this is enol, enol endo, this is enol exo because both the carbons are not forming the part of the ring, so that is enol exo and then exo this is exo cyclization exotet, enol exo exotet and if it is a double bond then that will be called enol exo exotrig like that.

So, basically when you have a cyclization involving an enolate, then you have to define the reaction not only like the exotet or endotet that is one side, but you have to also your nomenclature system should also tell what is the geometry of the enolate, how the enolate is reacting whether it is reacting in an endo fashion or it is reacting in an exo fashion. So, that is the different another set of rules that were, that were devised and let me write that Enolate, the rule for the enolate.

Again, I repeat here if there is any doubt this is an endo cyclization, enol endo because both the carbons of the enol are becoming part of the ring and this is in enol exo because the enol only this carbon is becoming part of the ring but not the other carbon, so that is exo cyclization.

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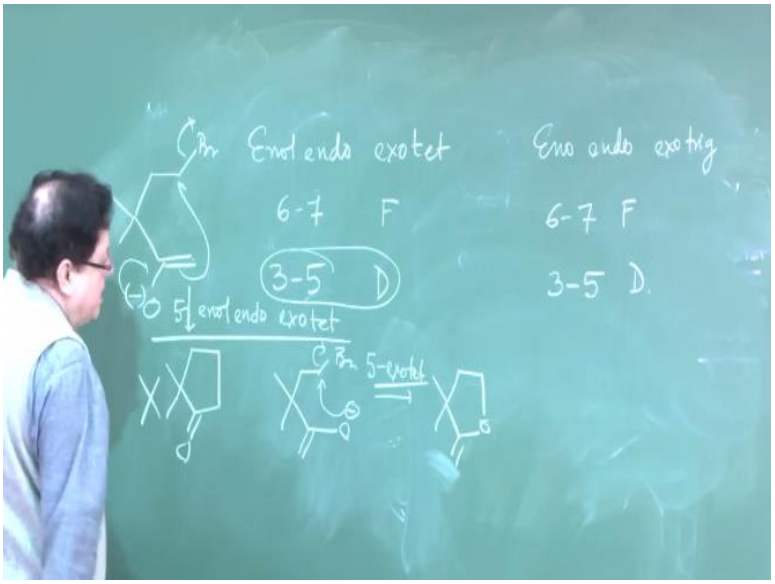

Now, the rule for which one is favored and which one is disfavored, let me write the rule, so if it is enol endo cyclization, enol endo exotet, we are talking about now first consider enol endo and then exotet and enol endo, then exotrig, two types we are considering, enol, endo, exotrig. If it is 6 to 7 membered ring means it is a 6 enol, endo, exotet, then that is favored and the same is here 6 to 7 that will be favored and for lower size of ring 3 to 5 involving enol, endo, exotet that is disfavored and the same thing is here 3 to 5 is disfavored.

Now, let me give you an example that will immediately because this is little bit more complicated than the earlier one let me give one example quick example which will clarify your doubt. Suppose I have this molecule a bromine and then an enolate like this, in fact this is one of the example which prompted Sir Jack Baldwin to propose his rules. So, this is the enolate with a living group here, so it will be definitely involving a tet cyclization.

Now, there are two possible products, one is this one, so that will give double bond o, so this is one possible product and if you want to define this reaction, this reaction will be called enol, both the carbons are forming the part of the ring, so enol endo and the size of the ring is 5, so 5 enol, endo, exotet, 5 enol, endo, exotet.

Let us see whether this is allowed or not, what it says enol, endo, exotet, so it comes under this and it says that 3 to 5 is disfavored, that means this is a disfavored reaction, so this product will not be formed. So, then which product is formed? The product that is formed is basically a straight cut, that means the earlier rule that we were adopting that this is an ambident nucleophile.

So, o minus is also the nucleophile, so rather than involving the enolate double bond, so o minus comes directly attacks the carbon having the bromide and displace the bromide, so that will form this, sorry, not double bond o, this is only double bond, so this will be formed and this reaction is nothing but 5 exotet which is a favorite process. So, instead of 5 enol, endo, exotet you have 5 exotet process that predominates.

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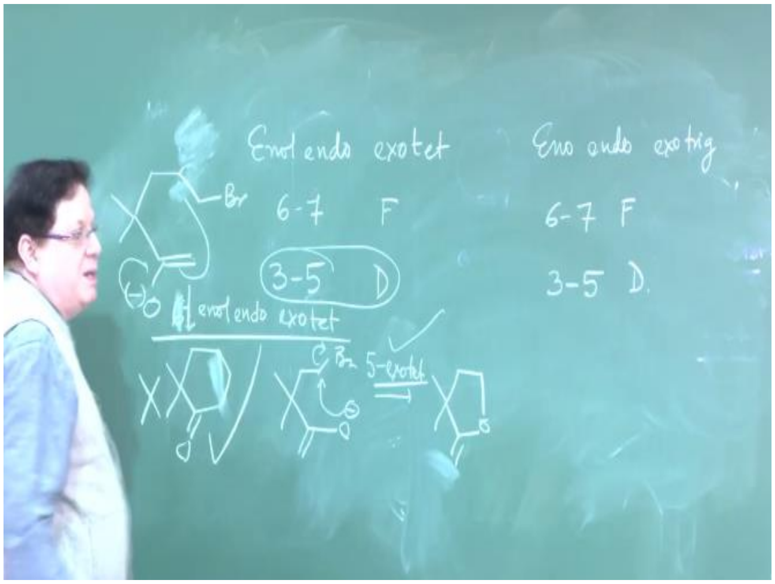

If you can increase the number of carbon atoms, suppose I now increase here by 1 carbon, if that be the case then this becomes 6 enol, endo, exotet, 6 enol, endo, exotet which is allowed by the way, which is favored, so in that case you will be able to get the product, in that case this will be the product because it is going through 6 enol, endo, exotet.

I think we will do more problems in the next class where we will clarify this enol, exo that thing as well as other problems and there are reactions where multiple cyclization reactions, consecutive cyclization reactions take place, we will take up those examples in our next class which will be basically a problem solving, only problem-solving class and that will finish up this stereoelectronic effects in organic chemistry that topic. Thank you very much.