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

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Lecture 21

Baldwin Rules

Hello welcome to this course on Structure Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-Solving Approach. Today, we will be talking about this stereoelectronic control that exists in a particular type of reaction which is very common in organic chemistry and that is intra molecular cyclization.

So, when you do cyclization you know that many of the natural products, many of organic compounds basically are cyclic in nature, so if you want to synthesize those compounds you have to devise strategies to induce cyclization and mostly that is intra molecular cyclization.

Now, all cyclizations by the way are not amenable to the stereoelectronic requirement which is, which is required, basically that requires the stereoelectronic requirement which is demanded by the reaction, remember the stereoelectronic effect for a reaction demands that the transition state that is involved in that particular reaction has maximum overlap of the orbitals, which will, of the interacting orbitals, orbitals which are involved in the reaction and that will induce stabilization to the transition state and if you can stabilize the transition state obviously you are lowering the activation barrier and that will cause the reaction to go faster.

Now, let us see that which type of intramolecular cyclizations are more facile and which are not, which are not so easy to do. Now, Sir Jack Baldwin in 1976 published a paper where he classified this intramolecular cyclizations into groups and then have framed certain rules which are called Baldwin rules and what is these rules are?

These rules actually basically predict whether a cyclization of a particular type is feasible or not, it is the word, the word that he used in his paper was favored and disfavored, remember there is a class of reactions which are pericyclic reactions, where we say allowed and forbidden, it is not those type of terminologies are not used here, the reactions which are more facile that is called the favored reactions and the reactions which are difficult to do are called disfavored reactions, it does not mean that the disfavored reactions cannot be done, it is not forbidden by the kind of rules that exist in case of pericyclic reactions.

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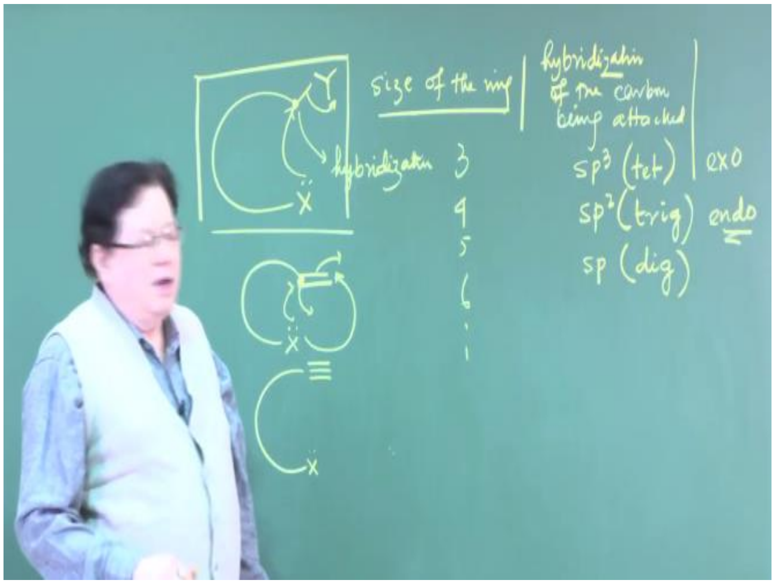

So, here the terminologies are basically some reactions are favored, some cyclizations are disfavored. Now, cyclization, the reactions that we are talking about, again I repeat is a cyclization reaction, so basically you are forming a cycle and in order to form a cycle you should have some functionality at one end and another functionality at the other end. So, that there is a reaction between the two ends and that will ultimately lead to the cyclic product.

Now, so basically when you classify this type of cyclization reaction, here just for simplicity, let us think that this X is a nucleophile and Y is a living group, so then the reaction that we can think of is that X attacks this carbon bearing the living group and Y leaves and that results in the formation of the cycle.

Now, the different classes of cyclization are framed according to, according to various parameters, first of all the size of the ring that you are making, size of the ring, so it could be starting from a 3 membered ring, then 4, 5, 6, 7, 8 etcetera. So, that is one parameter that decides which type of cyclization you are doing, whether you are making a 3 membered ring or a 5 membered ring and so on.

Then the other is that that the carbon that is involved, that is involved in the attack during the cyclization, what is the hybridization state of this carbon? The one that I have shown here, the hybridization state of the carbon is tetrahedral, it is sp3 hybridized but it could be of different types, you can have a double bond here and a nucleophile, that is also possible, the double bond you can add this X onto the double bond and but in that case you are attacking the carbon which is being attacked is sp2 hybridized, so and the third possibility is that it could be also sp hybridized.

So, depending on the type of hybridization of the atom that is being attacked during cyclization you have another parameter, so size of the ring is one, then you have the hybridization of the, hybridization, we are talking mostly about carbon here, so we will say the hybridization of the carbon being attacked, so there are now three types here, here size of the ring could be 3, 4, 5, 6 etcetera.

Hybridization, of the carbon could be sp3 and that will be called tetrahedral, abbreviated as tet and then you can have sp2 a double bond containing carbon, so that will be trigonal, so you can abbreviate that as trig and if it is acetylenic moiety, alkyne moiety then you have sp hybridization that is also called diagonal, so that will be dig in short.

So, basically you have cyclization involving a tetrahedral carbon, trigonal carbon or a diagonal carbon. So, now there is another parameter which needs to be considered during an intra molecular cyclization and that is the site of attack, it is like your Markovnikov type reaction that when you have a double bond or a triple bond you have a, you have a site selectivity which is also called regioselectivity.

So, the question is whether X attacks this carbon, or it can attack the other carbon also? So, everywhere there is a possibility that there are two sites where the incoming nucleophile can attack, we are actually talking about the nucleophilic nucleophile derived cyclization reactions, intra molecular cyclization reactions.

So, X is a nucleophile, so this attack can have 2 options, there are 2 centers and depending on where it attacks we have another parameter that is added to this to describe this cyclization is what is called exo and endo, what is exo and endo? That if the attack takes place in such a way that electron flows out of the ring, basically you are making a ring, so if the electron flows outside of the ring, then that is called exo ring closure, if the electron flows inside the ring that will be called endo, endo cyclization.

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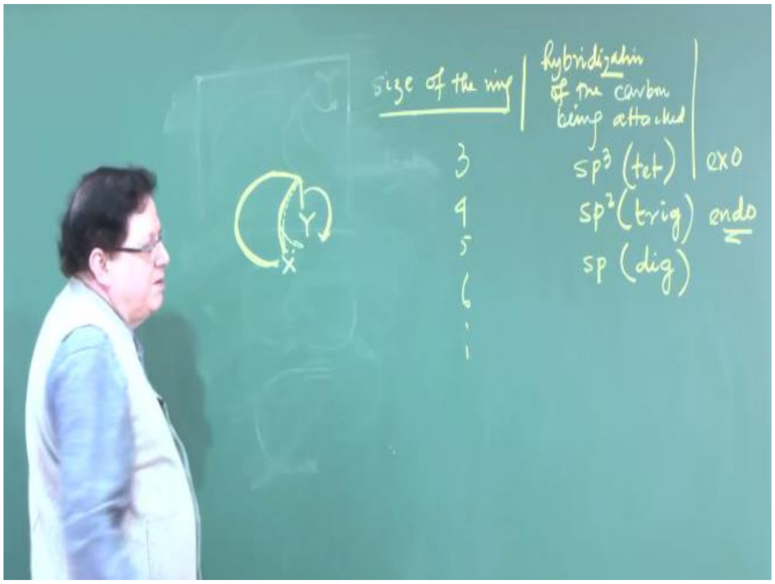

Let me make it little bit more clear by taking, if you take a tetrahedral center, suppose the cyclization is happening in a tetrahedral centre, then what happens that you have this X and you have this Y, so now X have two options, either it can attack here and the electron is flowing outside the ring, the ring that is formed is basically this, the ring that will be formed is this and the electron is flowing outside that ring, this is what is called exo cyclization.

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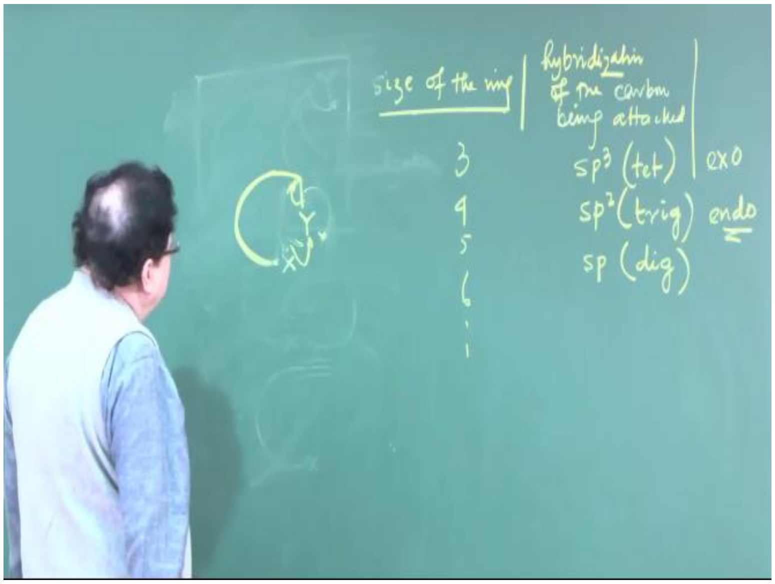

On the other hand if X attacks Y in this fashion and now the electron is going towards the that the transition state which is cyclic in nature because in this case what happens in tet cyclization, the endo cyclization does not lead to a ring rather the Y is basically transferred from this carbon to the X but the transition state is cyclic.

So, if you consider the transition state the electron flow is basically happening inside the ring, so this is nothing but an endo cyclization. Although you are not getting any cyclic product, remember in endo tet cyclization that means endo cyclization involving a tetrahedral center will not lead to a cyclic product ultimately, but it goes via a cyclic transition state, so that is why it is included under the cyclization rules.

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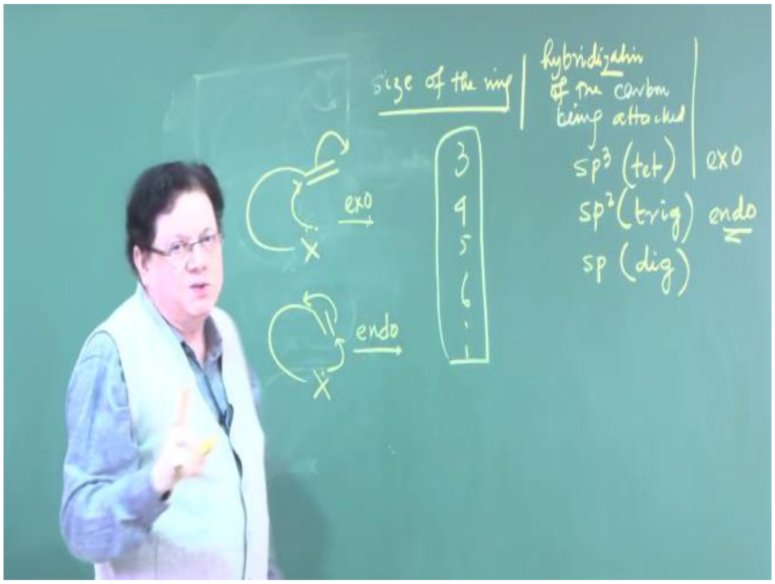

So, if you have a double bond now instead of this single bond if you have a double bond, so if you have a double bond and if you have this nucleophile, so double bond if it attacks here then the electron is flowing outside of the ring that is being formed, so this is what is called an exo cytization and on the other hand if you have this now X attacks here, so now the ring, now this the electron is flowing inside the ring, towards the ring that is what is being formed. So, this is what is called endo cyclization.

Sometimes, so basically now you have what I have said that there are three parameters, in order to describe an intramolecular cyclization your nomenclature should be such that it first should tell what is the size of the ring that is being formed, number one, what is the atom that is being attacked, what is the hybridization state of the atom which is being attacked by the nucleophile and third is whether it is an endo cyclic mode attack or it is an exo cyclic mod attack, so it is an endo attack or exo attack.

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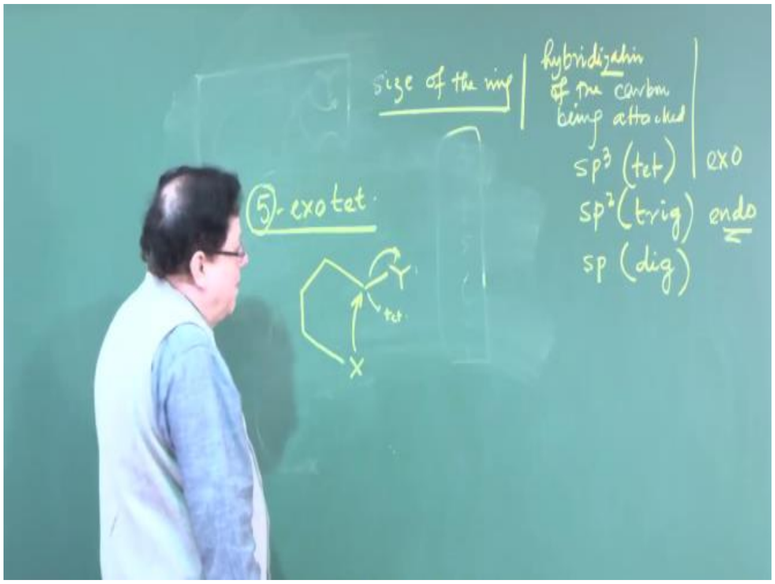

So, depending on that you have different nomenclature, that means if I say 5 exo tet, that means if I ask you to designate it 5 exo tet in terms of structure, then this is basically 5 exo tet, so you have suppose a Y and you are making a 5 membered ring because this is 5, then you are having an attack in an exo fashion, that means whatever is attacking this carbon it is the electron is flowing outside the ring that is being formed and so now this is if you put X here, so if I ask you to show what is 5 exo tet, so that will be 5, first of all this is the 5 member ring that is being formed, this is what is the tet and this is what is the exo cyclization. So, this is an example of 5 exo tet cyclization.

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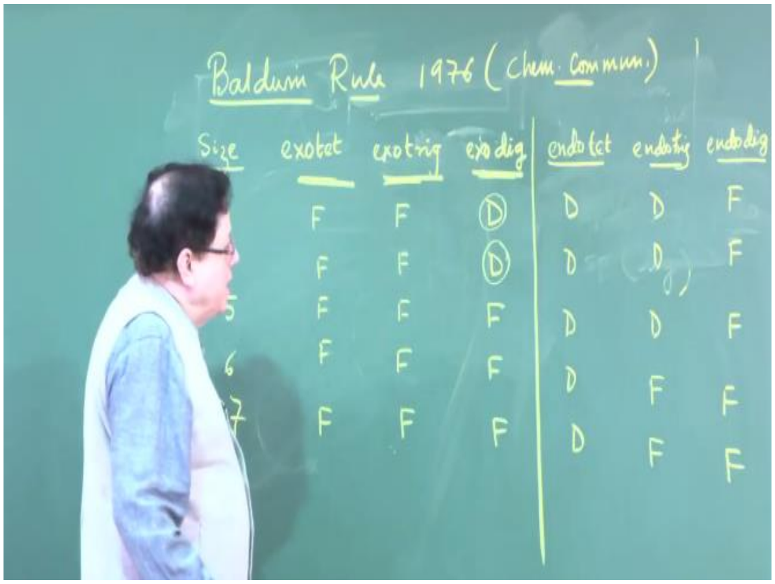

Baldwin Rule 1976 (Chem. Commun.)

Size	exotet	exotrig	exodig	endotet	endotrig	endodig
	F	F	Ⓓ	D	D	F
	F	F	Ⓓ	D	D	F
5	F	F	F	D	D	F
6	F	F	F	D	F	F
7	F	F	F	D	F	F

Now, the question is all these cyclization, so you have different varieties of now, if you have suppose, if I make a chart size of the ring and then you can have exotet cyclization, you can have exotrig cyclization and you can have exodig cyclization and suppose the ring sizes are 3, 4, 5, 6, 7 we will not go beyond that, so these are the common ring sizes that we generally consider but there are many molecules where there are macrocyclic rings.

However, those macrocyclic rings the rules for cyclization will not, is not valid. Simply, because these rules are valid for systems which are more rigid, more rigid, if the if the molecule is very flexible, then that can adopt any type of geometry which is demanded as per the stereoelectronic requirement. So, for large rings this is not applicable it is only for small size ring namely from 3 to 7.

Now, if you have a 3, question is whether 3 exotet is favorable or is a disfavored process? So, that is what is the basically the chart that I will be drawing, that what are the favored processes and what are the disfavored processes, then we will discuss that what is the although, these rules are a little bit empirical after studying many molecules, many cyclizations, Sir Baldwin came and derived and published his rules but and there are some logic behind these why something is favored and something is not, something is disfavored some cyclization that has some logic behind it.

We will discuss that but still these are, these are semi empirical rules, that means some logic is there, there are some violations also are there depending on the type of the reaction but let us not stray away, first consider where the rules are applicable, in majority of the cases fortunately the rules are applicable.

So, first of all ah if I take exotet cyclization, what it says that all exotet cyclizations are favorable, that means if you have 3 exotet, 4 exotet, 5 exotet all are favorable, we are not talking about the what happens to the endo, we will come back to that. Then exotrig also, all exotrig cyclization are favorable, whether irrespective of the size of the ring and in case of dig cyclization, the 3 exodig cyclization that means adding on to the triple bond, for the 3 exodig and 4 exodig they are disfavor, D means disfavored, again I repeat here disfavor does not mean disallowed, there may be conditions where the disfavored reactions can be possible, can be possible to operate.

And after the 3 and 4 then these are all favorable, so that is the set of rules that, so here there are only two disfavored processes and that is the exodig 3 exodig and 4 exodig, these are the disfavored processes, otherwise you can see that exo cyclizations are mostly favored processes. If you take tet systems or if you take trig systems, they are all favorable except these two cases dig.

Now, let us consider the endo ones, if you take the endotet, endotet, then endotrig and finally endodig. Let, us see what the rule says, endotet says these are all D, disfavored, that means endotet cyclizations from 3 to 7 membered rings are very difficult reactions, they are disfavored reactions and if there is other possibilities where, that there is exotet cyclizations possible, so that will the reaction will take the exotet pathway.

What about endotrig, endotrig is difficult, is disfavored up to 5 membered ring, that means 5 endotrig is a disfavored process, 4 endotrig is a disfavored process, so also 3 endotrig but beyond that, that means 6 endotrig and 7 endotrig are favored processes and in case of endodig processes, endodig processes now it is the all are favourable, so endodig processes whether it is 3 or 4 or 5 or 6 they are all favorable processes. So, this is the basic rules that Baldwin published in 1976 in a prestigious journal Royal Society Journal called Chemical Communication, so this is the rule.

Now, the question is there must be some logic because rules have although, they are they may not be having any mathematical background but there may be some other logic that you can propose and in fact Baldwin considered the stereoelectronic requirement of a cyclization and also looked at the different orbitals, their geometry, how they are situated in space and then see whether and then he analyzed whether the orbitals can be put into the right position, in the right geometry, in the right alignment at the right angle, right angle the requirement and then came out with these rules. So, we can now, so this is the rule, let us try to first give you some hint that what is the genesis of this rules.

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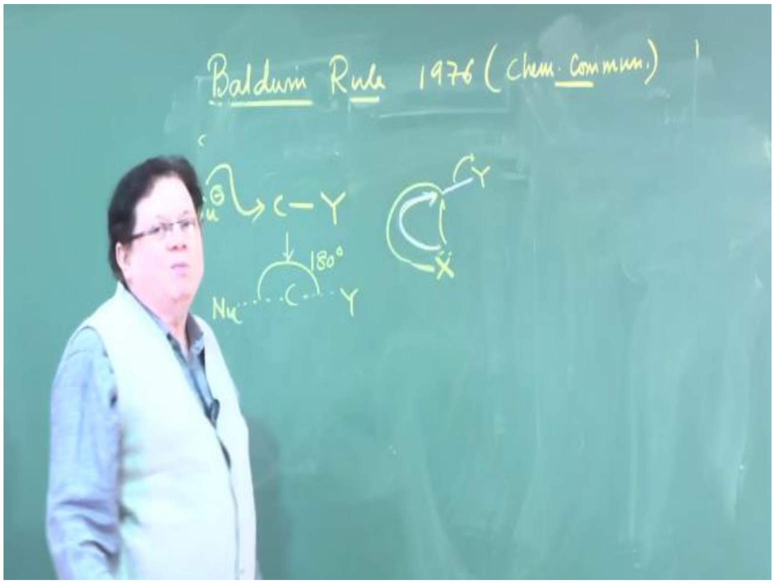

Now, the genesis is basically exterior electronic stereoelectronic requirement which is as I said which is demanded by their cyclizations, by intramolecular cyclization. Now, what is the stereoelectronic requirement? The stereo electronic requirement is basically that when you have a carbon with a living group and some nucleophile which will attack the carbon, you know that there is a distinct, distinct way that the nucleophile has to attack the carbon, there is a distinct path, distinct line of attack has to be there and what is that?

That the this is now breaking, and this is what is being formed, so this nucleophile approach just from the opposite side of Y but in line with the carbon Y bond, so the angle between the nucleophile and the bond which is now broken in case of a tetrahedral carbon is 180 degree, so that is the stereoelectronic requirement, this has to be true for an intramolecular reaction also.

Suppose, if you have an X here and if you have Y here and X you will attack this carbon and break the C Y bond it cannot attack in this way the way I have shown, it has to attack from the back side, exactly opposite to the C Y bond, exactly so it should attack exactly from this side, so then the question is whether you have sufficient flexibility in the molecule, so that the x lone pair which is occupying an orbital that can come to this side and make an angle of 180 degree with the C Y bond, if it can, then that cyclization will be possible, if it cannot then that will be a difficult one, that activation energy will be higher.

So, here basically to frame the rules Baldwin first considered that what is the trajectory of the attack by the nucleophile to the atom, where the connection is being made, so if it is a tetrahedral carbon, then your bond angle, the trajectory should make a an angle of 180 degree with the leaving group, so that is for tetrahedral carbon.

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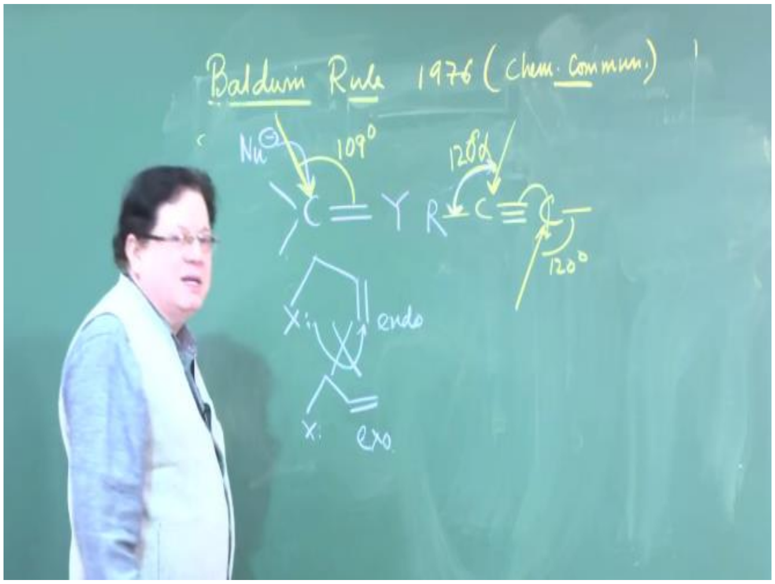

If you have trigonal carbon, then if you have trigonal carbon, then basically what happens, you have a double bond suppose, double bond Y and now you are attacking a nucleophile, it has been shown that this attack takes place in such a way, that this attack takes place in such a way that the angle between the departing group, that means Y although, Y is not fully departed, only the double bond is broken and forming a single bond. So, the angle between the incoming nucleophile and the Y will be 109 degree, this is what is called the Burgi Dunitz trajectory.

Now, these angles how you can arrive at these angles, if you consider that after the reaction, after the addition of the nucleophile onto the carbon, the carbon becomes tetrahedral, so the angle between these groups will be 109 degree 28 minutes, so it is closed, 109 degree so basically these reactions when Burgi Dunitz proposed this trajectory they are considering a late transition state, that means they are considering the product, the angle in the product and based on that they put their trajectory angle. So, in case of trigonal system this trajectory, the trajectory of the nucleophile should be such that it should be 109 degree, that is the stereoelectronic requirement for the attack.

And for diagonal ones, for diagonal ones, what happens? Now, you know that after the when the nucleophile attacks, the angle, ultimate angle between these two will be 120 degree because the carbon changes from sp to sp2. So, as I said that you always look at the angle what will be the angle when the addition has taken place, when the attack has taken place, the ultimate angle in the product will be 120 degree. So, the trajectory here should be such that this angle, this angle alpha should be 120 degree and if it goes here that the double, one of the bond goes here and takes up, adds to another group then that group also should be there at an angle of 120 degree.

So, just to summarize that in a tetrahedral system, the nucleophile should attack from the back side, so that it can make an angle of 180 degree with the leaving group. In case of a trigonal system, the Burgi Dunitz angle that is 109 degree, that means the nucleophile should approach in a trajectory that makes 109 degree with the departing group and in case of diagonal the trajectory of the nucleophile should be such that it makes an angle of 120 degree with the existing substituent, with the existing substituent that is R, so this is 120 degree.

So, this basic stereoelectronic requirement can be maintained in some of the cyclization processes while it is, it is not possible for others to be maintained, so because of this lack, of lack of maintaining the stereoelectronic requirement or fulfilling the stereoelectronic requirement some cyclizations become disfavored and cyclizations which are favored that means the stereoelectronic requirement as demanded by the hybridization state of the carbon which is being attacked is fulfilled. So, those become favored.

Like if I say that, suppose you have a double bond here and then you have a nucleophile here, now if you want to attack from this side it is now very difficult because it is only one carbon in between the double bond and the X, so because X has to approach at an angle of 109 degree 28 minutes from this side, from the top because the p orbitals are like this, which is not possible for X because the arm is too small.

On the other hand if you write it in this fashion, then it is for X to attain that 109-degree angle it is possible in the exo mode but it is not possible in the endo mode. So, that is why this is 4 endotrig cyclization is disfavored and because it can maintain the stereoelectronic requirement, so 3 exotrig cyclization is favored process and when there is a competition between the two obviously the 3 exo process will take place. So, that is the basic concept of Baldwin's rule.

Again, I just summarize what are Baldwin's rules, these are certain semi empirical rules which are, which have been proposed to explain that some of the cyclization reactions are favored processes and some of the cyclization processes are disfavored. The basis of the rules are basically the maintenance of stereoelectronic requirement in some of the processes and in some of the other processes this stereoelectronic requirement cannot be fulfilled.

And depending on the size of the ring, the type of hybridization, state of the carbon that is being attacked and the type of electron flow you have different types of nomenclature, you have the nomenclature system like, the nomenclature system says that first you should write what is the size of the ring that is being formed, then you should write whether it is an exo or endo cyclization and finally you should write what is the atom that is being attacked, what is the hybridization state, whether it is tet, trig or dig.

So, that is all of for Baldwin's rule, in the next lecture we will do the some problems, so its problems to clarify, to support the where the Baldwin rule are applicable that will be the next class. Thank you.