Medicinal Chemistry
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Module 02 Lecture 8
Enzyme Catalysis Part-2

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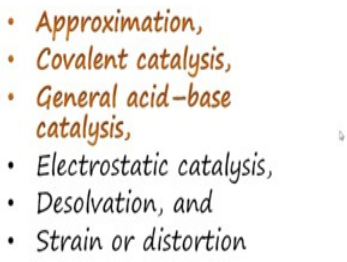

We have looked at various mechanisms of catalysis by enzymes. So we first looked at approximation in which the substrates the two reacting molecules were brought close to one another and in a very preferential manner so that reaction can occur and then we looked at covalent catalysis where an intermediate a highly reactive covalent intermediate is produced during the reaction which results in acceleration and subsequently we looked at acid-base catalysis, where there is transfer of a proton or a hydroxide ion and that results in generation of reactive intermediates or acceleration. There are broadly three other ways in which enzymes are able to catalyze reactions next mechanism by it does it is electrostatic catalysis ok.

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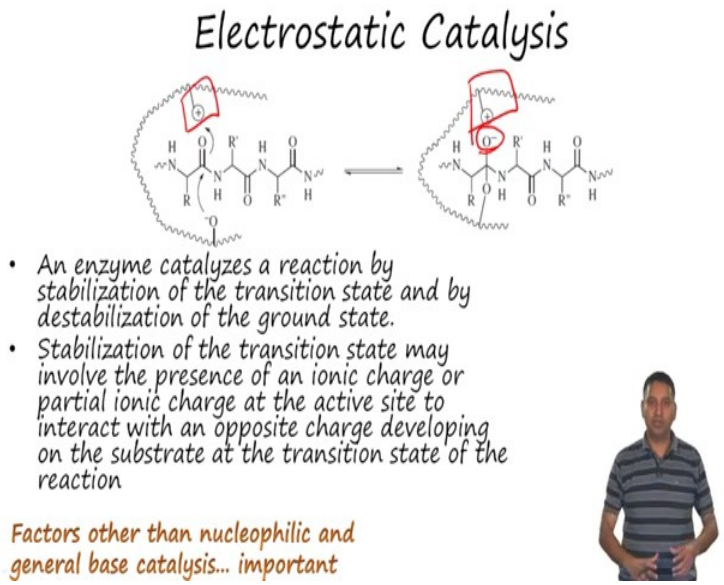

So, in electrostatic catalysis what happens is that the transition state that is produced during a reaction is actually stabilized by residues in the active site ok. So here the transition state will most likely involve the generation of an ionic charge or a partial ionic charge. So for an example when you have a negative charge that is being produced here the incipient negative charge can be stabilized by a residue that is positively charged ok. So fundamentally this form of catalysis involves electrostatic and stabilization of the transition state an oppositely charged species ok.

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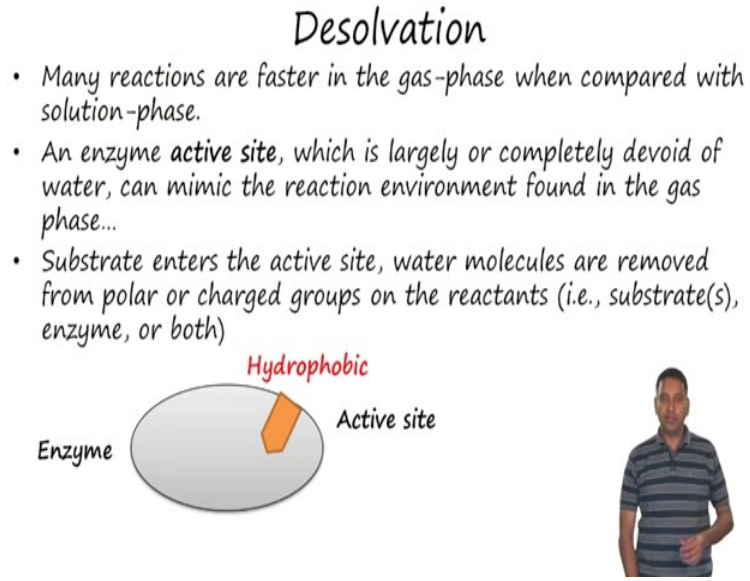

Next we look at a mechanism called as Desolvation, so desolvation basically the concept of desolvation is that many reactions are much faster in the gas phase when compared to the solution phase. So as a concept if you want to understand this if there are two molecules that have to collide to react when there is a solvent surrounding it, it has to displace the solvent and then collide whereas the gas phase it still has to displace a gas but because of the easy fluid nature of the gas you don't have that level of resistance.

So in enzyme active site is more or less devoid of water so in this it is usually a hydrophobic cavity and therefore there is very limited amount of water. So in this situation when the molecules are getting into the active site it is almost like a gas phase situation ok. So this concept is known as desolvation wherein the solvent molecules in this case water are removed from the active site and that facilitates the reaction ok.

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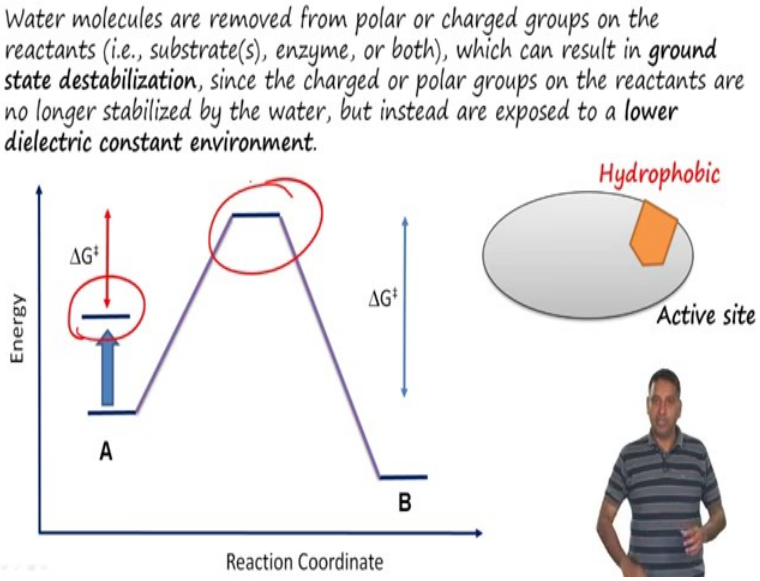

But conceptually if you want to look at it, what essentially happens is that once the molecules are getting in and if the molecules are polar or charged, when water molecules are removed from these polar or charged groups that are getting into the active site, what happens is that there is an increase in the ground state energy ok.

So you may recall that rate acceleration occurs when the transition state goes down or the ground state goes up and offcourse when both of them happen there is going to be a large increase in the reaction rate. So here ground state de-stabilization largely contributes to an increased rate ok. Now to understand this we also need to understand di-electric constant, and di-electric constant is nothing but the ability of the medium to separate charges.

So water which has a very high di-electric constant if you remove it from the active site then it is likely that the molecule that are getting in are going to experienced a completely different di-electric environment. So together this contributes to ground state de-stabilization.

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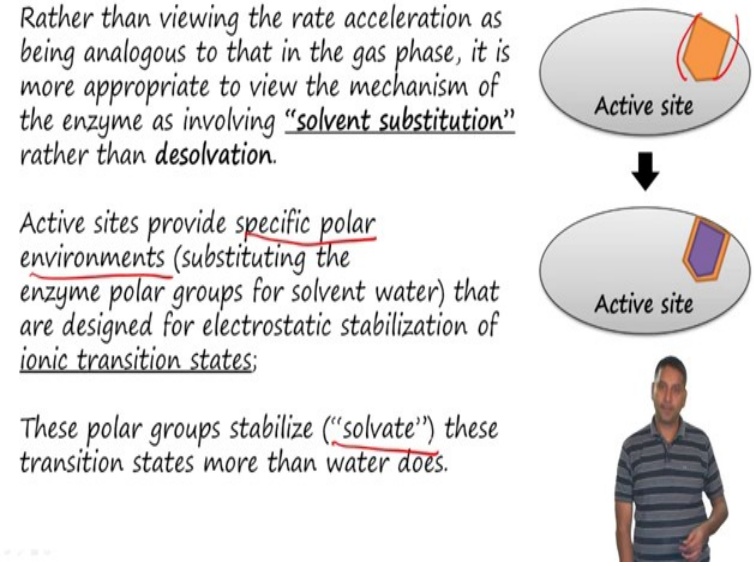

Now another view of this is that instead of thinking about it like as being a gas phase it is perhaps more appropriate to view this mechanism as solvent substitution ok. So when you have an active site and inside the active site there are groups that are around in the active site which can sort of solvate the substrate ok.

So this provide specific polar environments in the area and so instead of thinking about a gas phase you can instead think about solvent substitution in this case substitution by a polar environment created by the active site residues. So it's perhaps more appropriate to think about this as solvent substitution rather than desolvation ok. Now let's move on to the last in way in which enzymes catalysis can be understood which is strain or distortion.

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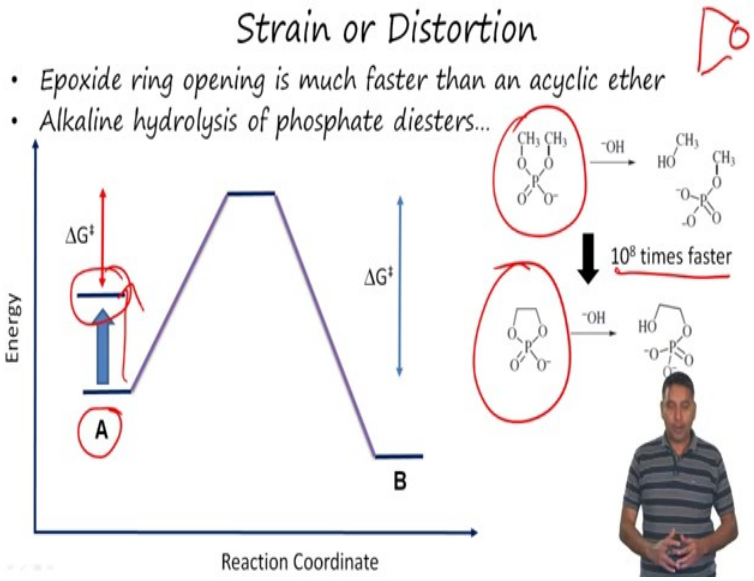

So we all know that epoxide ring opening is much faster when compared to its acyclic ether counterpart. So the way we understand this is that the oxygen is present in a ring which is highly unstable, once the ring is opened it results in increased stability ok. So therefore this opening of the ring contributes to some instability in the reaction and so one could understand this in terms of ground state de-stabilization right. So to look at another example from a biological context Alkaline hydrolysis of phosphates ok phosphates diesters is significantly faster when you restrict it into a cyclic system ok and the rate acceleration is about 10 power 8 ok.

So this suggests that once you increase the energy of the ground state it can result in a dramatic acceleration right. So what does an enzyme do?

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Ok, enzyme creates a situation where you can have, enzymes create a situation wherein you can have stream or distortion that promotes or increases the rate of the reaction ok. Now in a nutshell, catalysis is typically achieved by ground state de-stabilization or transition state stabilization and both of this will result in acceleration of rate.

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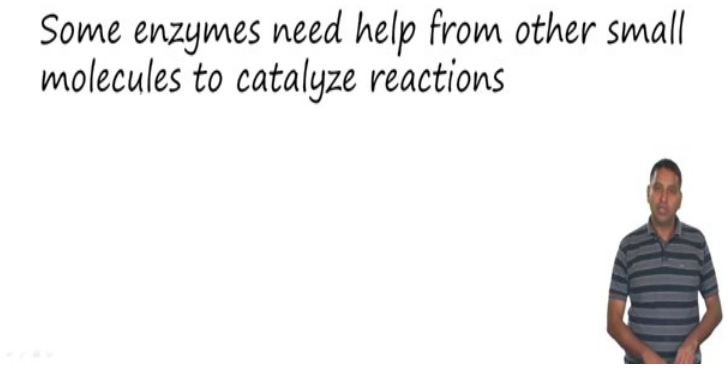

Now some enzymes need the help of small molecules to catalyze reactions.

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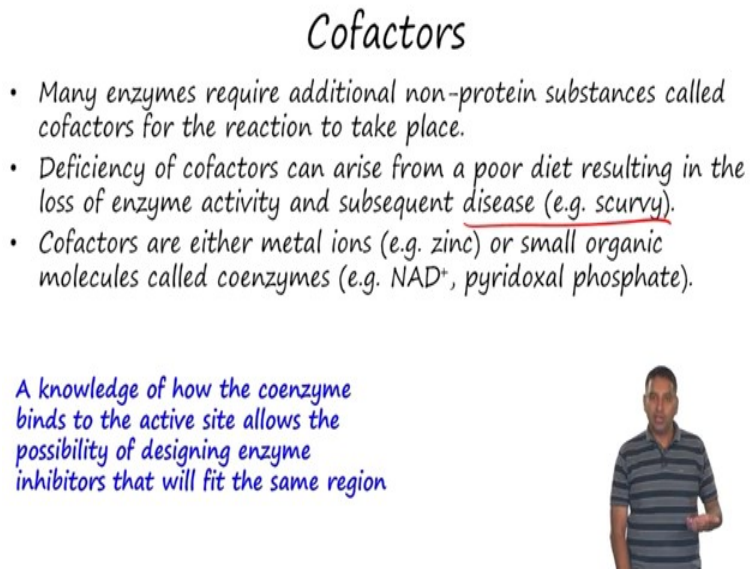

So these small molecules are known as co-factors ok, so co-factors are nothing but small molecules or non-protein substances which are required for reactions to take place ok. Deficiency of some co-factors typically because of malnutrition or poor diet can result in the loss of enzyme activity and subsequently even one could fall sick. The example is scurvy which is where vitamin C is required ok.

Now the knowledge of how the enzyme, how the coenzymes binds to the active site or how it enables the reaction is very important because if we want to develop inhibitors of these enzymes let's say in a bacterium we want to inhibit a coenzyme then it would be useful for us to understand how this coenzymes works ok. Co-factors as I mentioned earlier are either small metal ions or the small organic molecules. Now let us look at some examples of these ok.

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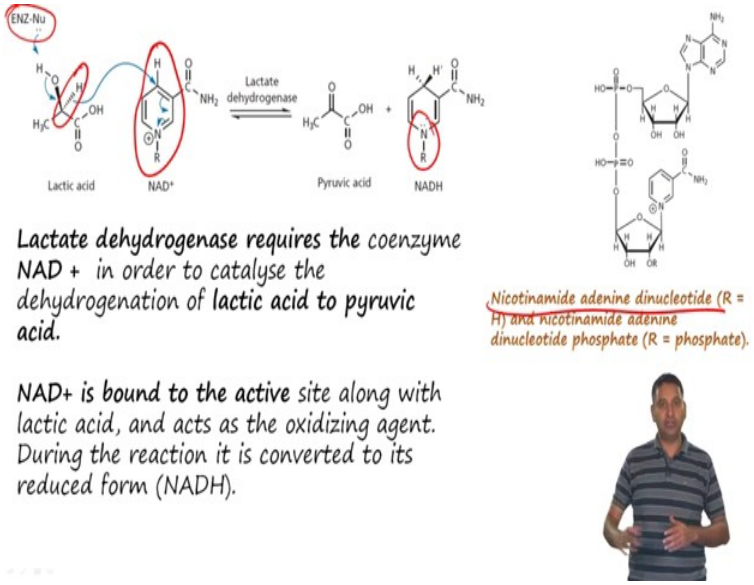

The first example that we would wish to look we could look at is NAD which is Nicotinamide adenine dinucleotide ok or its phosphate analog which is called NADP ok.

NAD is a very important co-factor and you can see that it has a pyridinium ion as the main functional group. Now this pyridinium ion functional group is an excellent acceptor of electrons especially when you look at hydrate, so here you have an example of a enzyme which has nucleophilic active site which is reacting with an alcohol, pulls the proton from hydroxyl group which results in migration of the electrons between O-H into the to form a carbonyl and the hydride is, then transferred to the pyridinium ion.

So here NAD plus becomes a neutral NADH ok, this enzyme that we are talking about here is lactate dehydrogenase and the substrate for this is lactic acid ok. Now NAD plus has to be bound at the active site along with lactic acid, so in this enzyme of lactate dehydrogenase we would have as it is expected that you would have a binding site for lactic acid and a binding site for NAD plus. Once the binding occurs oxidation is facilitated and you form pyruvic acid which is then dissociates.

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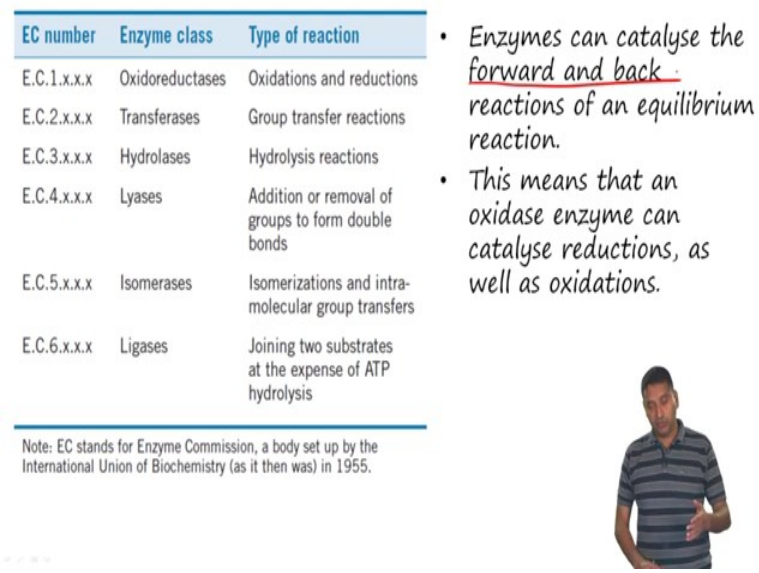

Now if we were to look at various classes of enzymes there are found you can find them in this table and they are typically enzymes which carry out oxidation or reductions which are known as oxidoreductases or they can transfer groups for example glutathione and they are called transferases and in the case of glutathione, it would be called glutathione transferases or gluthathione S transferases and then there are once that can hydrolyze functional groups and these are known as Hydrolases and you can also have enzymes which are Lyases which basically form double bond which results in loss of group to form a double bond and then there are ones which are basically Isomerases they convert one isomer to another and lastly there are ligases which help in forming a bond between two different substrates and typically these are dependent on ATP which means you need energy to do this.

So these are the major classification of enzyme and keep in mind that enzymes that can catalyze the forward reaction can also catalyze the reverse reaction because it is in an equilibrium ok. So an oxidase which can oxidize enzymes can also do reductions ok.

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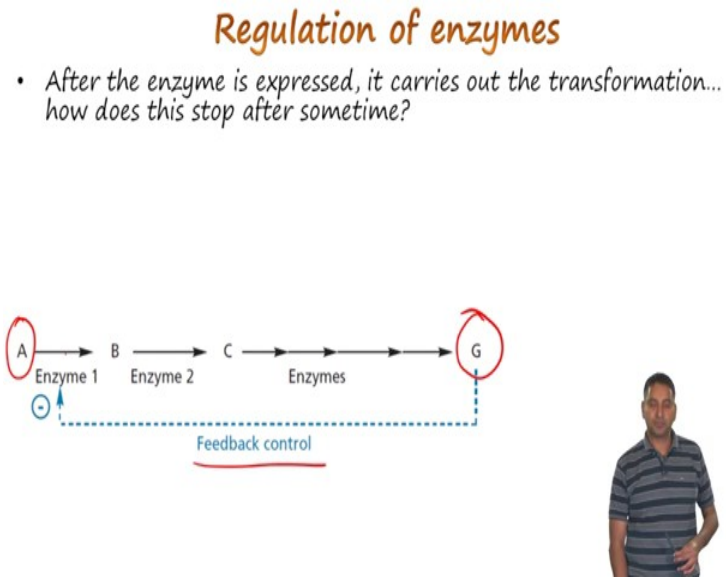

Now once the enzyme has done its job you would need for the enzyme to stop working after sometime otherwise it will just keep on consuming the substrate and giving you the product.

So enzymes have to be regulated inside the cell. One of the mechanisms by which an enzyme is regulated in the cell is called as feedback control. So imagine that there is a biosynthetic scheme that is happening. So you want to synthesize a or there is biosynthesis of a molecule which involves n number of steps ok. Now as long as a substrate A is available an enzyme 1 is available then enzyme 1 is going to turn over A to produce B which is then the substrate for enzyme 2 and that forms C and so on and so forth.

Now this final substrate product G can be an inhibitor of enzyme 1 ok, so once levels of A go down and levels of G go up G starts to compete with A for the same enzyme and it prevents the reaction from occurring ok. So this is one of the ways in which enzymes are regulated, so this is called as feedback control.

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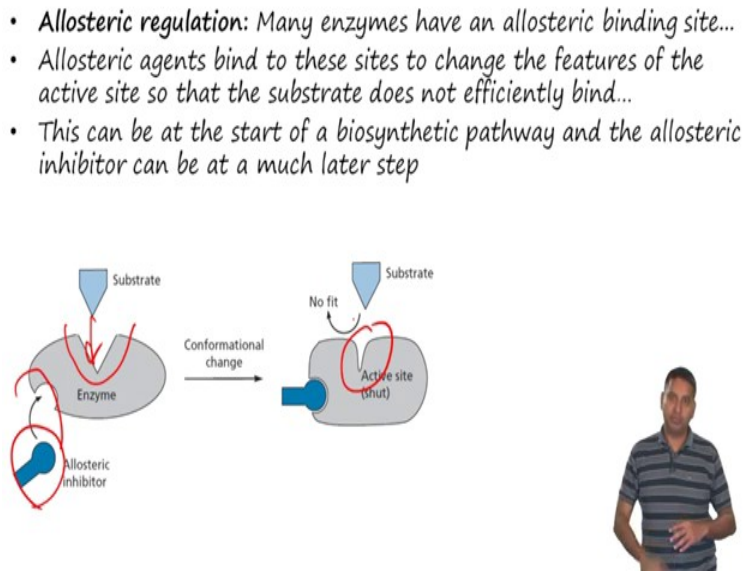

The other way in which enzymes can be regulated is through Allosteric regulation ok. Allosteric regulation sites are nothing but site which are not at the active sites but are in a remote location.

So here is the schematic representation so imagine that this is the active site of the enzyme and here is where the substrate binds. You could have another site on the site which is allosteric site and if you want to regulate the activity of this enzyme what would need to be done is to is for this substrate which is an allosteric inhibitor to go and bind to the enzyme, once the enzyme binds you have a conformational change and the active site is blocked. So previously when the substrate used to bind to the enzyme active site since the confirmation changes occur the substrate does not bind anymore, there is no fit and therefore the enzyme can be inhibited or regulated ok.

This type of regulation can be at the start of a biosynthetic pathway and the allosteric inhibitor can be much later in the pathway.