Biological Inorganic Chemistry
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Lecture 41
Coordination Chemistry and Function of Zinc Ions

Hello students, welcome back. So, we will now today start the new module, which is your module number 9, and lecture number 41. So, now we will move to the third most important metal ion, which is your zinc. So, after iron, we have reached to copper, then we have reached to zinc.

So, iron, copper, zinc is also easy to remember in terms of your position in the periodic table. So, in just in this particular class, quickly we will see some recapitulation also what we have seen earlier in your other days that you can have the coordination chemistry as well as the function of the different zinc ions.

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So, I have deliberately made this list a big one, because you are talking about the copper bio coordination chemistry, and the very basic nature of the copper we should know as a metal ion which we put within the list of the transition metal ions but truly speaking, they are not transition metal ions. So, they can function only like your calcium or magnesium as strong this acid or a little bit, we stronger sometime.

They are not showing electron transfer, so they are redox inactive, spectroscopically silent because you do not have any DD transition and not even the corresponding charge transfer

transitions also but they are very much suitable and they can function very useful roles for many metalloproteins and metallo enzymes where they can show the regulatory and structural roles. They can go for the hydrolysis reaction. They can go for the condensation reactions. And the thing where we can have the genetic code and all these things and that can also be modulated by the structure forming metal ion like zinc two plus.

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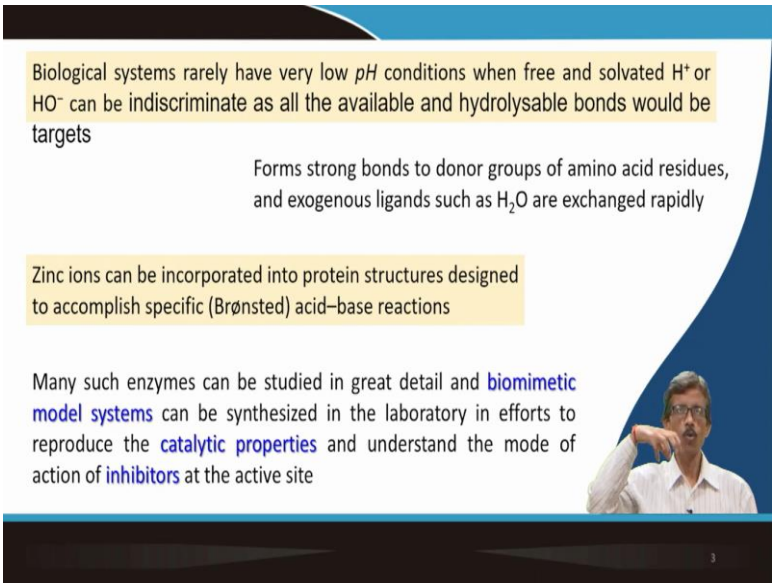

So, what we know that the biological systems, which basically what we have seen, very low pH conditions we can have when free or solvated H plus or HO minus can be indiscriminate, as all the available, and hydrolysable bonds would be the targets. So, if you have the targets, and if you do not have the control of the pH, so abruptly, what we see instead of going, or depending on your zinc ion, you can bring the hydrogen ion only the proton itself.

So, if there is no need for talking about the bio coordination chemistry, only the proton is sufficient for the hydrolysis but you do not have that much change in the pH values, but we see the important property of the zinc ions and that we can use nicely for the corresponding activity because these ions basically form strong bonds with the amino acid residues, the amino acid donor points like nitrogen, like oxygen, and sulfur, and some exogenous ligands, which is your active site or the labile site what we call as the corresponding coordination for the water molecule.

So, if we have, that one site if you have the corresponding binding like this, so this is your protein envelop from the bottom, basically. So, this protein envelop is coming and on it your

zinc is sitting, but you are not covering it up with the another protein envelop from the top. So, it is on the bottom only.

So, what can happen that if you have the corresponding coordinations again, that particular huge protein site, many amino acids residues are there, peptide bonds are there, and peptides, short peptides, long peptides and the polypeptides are there? But you only look at this particular tripod. So, basically the protein can function as a tripod, where you can pick up these three amino acid residues and you bring the zinc over here. So, what will happen?

So, these three amino acid residues basically can function as a facial coordination to your zinc site. And that facial coordination to the zinc site is basically helping because you have the huge protein chain, and you have the corresponding hydrophobicity of the protein is also important. So, you are basically stabilizing from this particular site, but your fourth site is available. Fourth site, why is this fourth site?

Because you have already three, we have seen in case of copper that you can have a coordination geometry 3 plus 1. So, if you bring the fourth one, like that of your water molecule, you can have a regular tetrahedral geometry, but it will not be a regular tetrahedral geometry because your protein part binding the nitrogens from the protein or the sulfur or the oxygen from the protein part give you the strong bonds.

This bond from the zinc site will be strong, unlike your copper because you can copper you can have much more distortion. But if you have little bit of distortion your hydrogen attached to that of your water molecule will give you some weaker bond with it because it is the water molecule itself. And that exogenous ligand, that particular one, can exchange rapidly. And then it is incorporated in the protein structure so it can accomplish some very useful interactions, or acid-based reactions in terms of bronze state acid-based reactions. That means the proton donor and the proton acceptor, but it can also function as your lewis acid, or the corresponding attraction to your lone pair of electrons.

So, proton transfer as well as the attraction for the lone pair is also there in built within these zinc ions, so in some very important reactions. So, large number of enzymes, several hundred enzymes are well known, because they can be studied nicely with that of your biomimetic model systems for their catalytic properties for showing something, for understanding something because we know that overactivity of these enzymes can can give you some diseased condition. You will face some problem.

If you are overactive, these metal enzymes are there. That means, once we have seen that your concentration is dependent, whether you are loaded with more zinc or you are loaded with less zinc that is important, because the minimal concentration, the optimum concentration of zinc level is important. That is why that particular zinc site, if it is overactive, you will have the problem. It is less activity, you will have again the problem.

But the overall activity, you can check some time because in most of the cases overactivity gives you that corresponding disease state. And that over activity of those particular cases can be minimized by putting some inhibitor molecules such that you can stop the binding of these water molecules from the fourth coordination site from the top. So, if some other group can go for your competitive binding to that particular zinc site, you will be blocking that zinc site for its catalytic activity.

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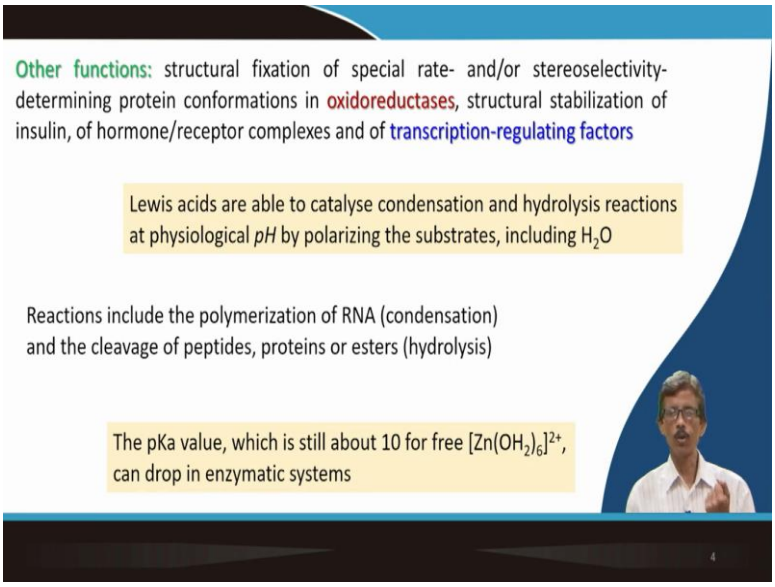

So, it can so many other reactions or other functions, so they can also go for the special rate, as well as the stereo specific reactions or stereoselective reactions, and we can change the different protein confirmations by doing so. There will be a structural change in some one type of these enzymes which are oxidoreduct phases. It can go for structural stabilization because the binding, giving you new bonds, coordination bonds, like that of your insulin stabilization, giving you the new complexes or interaction with the hormone, and other receptor molecules and of transcription-regulating factors where the zinc binding is important.

Is not so strong binding like your iron or copper, but it will be a harder type sometime that it can have sometimes strong binding than that of your copper binding. So, that way, you have to manipulate the weak binding, strong binding, or the change in the structure and all these. So, after bronsted, you can also have some activity due to its lewis acidic corrector, which we all know that can be useful for catalyzing the condensation reaction, as well as the hydrolysis reaction at a physiological pH of 6.8. So, always try to remember whenever some statement comes to you, whenever the question comes to you what is your physiological pH. It is definitely have some range, but it is around pH 6.8. So, 6.8 plus minus 0.1, say.

So, at that particular pH, you can polarize the water molecule, can give you many complex reactions like the RNA condensation reaction where we can know all the polymerization reactions, and sometimes the cutting of the peptide bond, or the star bond of the protein molecules, where we can use these as the corresponding hydrolyzing agent.

So, if we just simply compare the most standard model species or model coordination compound for zinc is the exact hexaaqua zinc space, which is readily found when you dissolve some zinc salt, zinc chloride or zinc acetate in your testube, we will end up with that of hexaaqua zinc two plus like your iron.

But if you side by side compare that with your iron center to that of your zinc center because iron is in the ferric state that is why always when you go for the dissolution of ferric ion in ferric chloride dissolution, we will end up with that particular precipitation of ferric oxide or Fe two O three initially through FeOH whole three or ferric hydroxide.

So, here when all of them are the water molecules, you will have the corresponding binding of that six water molecules is not giving you a drastic change in the pKa value, which is at 10 only. So, if it is 10, is not acidic, you will not go for the decoordination. So, what to do then? So, what you should bring then, and how to bring down the corresponding pKa value of the zinc center such that it can basically activate the water molecule and go for that deprotonation?

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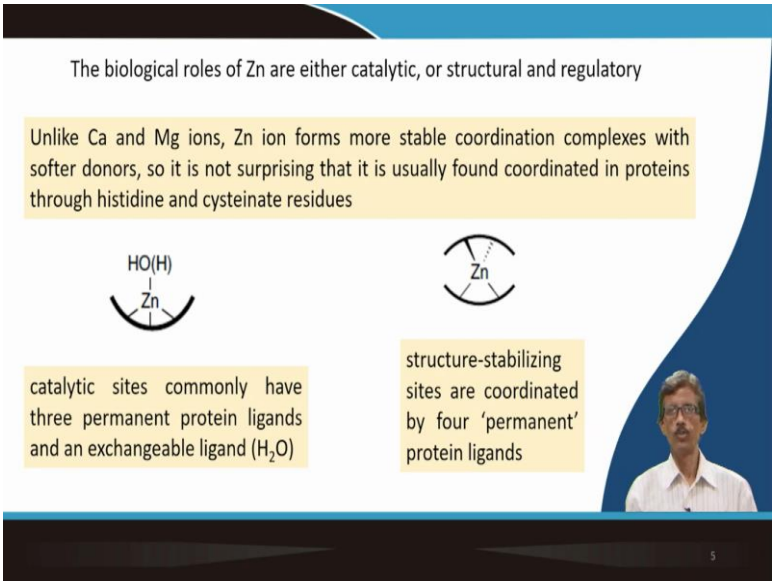

So, the roles basically, the biological roles of these zinc ions are very important. Not zinc, zinc ions or can be catalytic means you can go for the hydrolysis reaction, can be structural, you can go for the bonds also, and sometimes the regularatory, that means the assimilation, not only for other important biomolecules, but also the assimilation processes for the storage and the corresponding result of the zinc ions also.

So, if we compare, I just I told you that okay zinc is very much similar to that of your calcium and magnesium ions also, but unlike it is not that of similarity. It forms more stable coordination complexes with softer donors, that means it can form bonds with the ions also, the cysteine residuals also. And it is not surprising that it is usually found coordinated to the proteins through histidine and that is why the cysteine residues.

So, NS coordination is very useful, like that of your copper for your zinc ions which you do not see for calcium 2 plus, as well as magnesium 2 plus. So, out of these three properties that means the catalytic site, the structural site, and the regulatory function, why we see that the for the catalytic site can have three permanent protein ligand. Just now I told you that the facial thing that means you can have 3 nitrogen.

So, to start with, we bring 3 nitrogens only. So, these three nitrogens basically like this, so is the bowl, basically. So, bowl you can have and three nitrogens you bring, so it can either bind to the water molecule or it can bind to the hydroxide group. So, its basically this thing where

you can have the catalytic site so you get these to this particular drawing that you have the catalytic site so you should be able to remember it that. What is your catalytic zinc site?

The catalytic zinc site will be like this. So, you will have one bowl, but you go for the structure, so you'll have the two bowls. So, one you have the bottom and another at the top. Why it is not like this? Why it is this?

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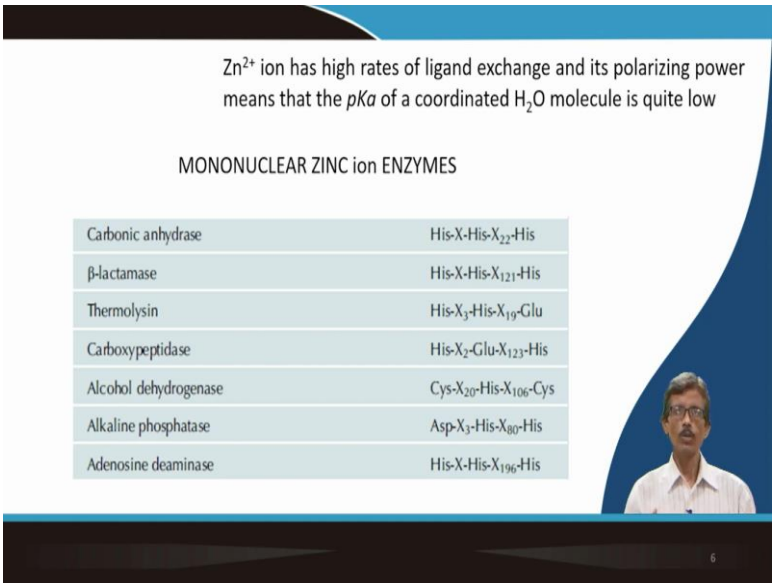

Because the two of the bonds which is coming from the lower bowl is giving this direction and another one is giving because the king is basically looking for a tetrahedral geometry. So, that you can have before permanent protein coordination to the zinc center in tetrahedral geometry. And it can also show for very high rate of ligand exchange, and its polarizing power means that the pKa of the coordinated water molecule can go down now from 10.

So, what happens now if you have many examples of these mononuclear zinc ion enzymes? So, I prefer to write in that way because all of the merging ions, there is no zinc center, which is zinc 0. So, the zinc ion enzymes are there is a huge list, do not worry about all these names and all these things, but you should know about because these are showing some fundamental reactions.

That is why it is the language or biochemistry which we should understand little bit such that you can understand nicely about these molecules, where you can have the parent metal ions center in all these cases are zinc ion because as a coordination chemist or as inorganic

chemist, you know better than anybody else about the corresponding behavior of zinc ion within these molecules.

But those people are bound to the a biochemist is bound to learn all these things because they have to study these as the biomedical functions and all these things. But if we come forward, and we can understand a little bit about their zinc coordination chemistry, we can also contribute many things in understanding the full picture because it is our collective effort, not that you are inorganic chemist or a coordination chemist, and another one is a biochemist, or a doctor, or a biochemist, is a collective effort basically to understand all these molecules to its complete potential such that we can utilize its potential for many other useful purposes also, to make the medicines, to get rid of the disease conditions and all these things.

So, what we now find that we will just have the three amino acid residues because already I told you that if you have the bowl, and having three donor centers for the facial coordination. So, what you get? You get, straight away you write three amino acids, his his his for the carbonic anhydrous molecule. So, his his his is there. So, three amino acid residues are coming, then how they are connected?

So, the connected by x, that means one amino acids residue or connected by 22 amino acid residues, sometimes more. So, is the basically the chain length, x 22 is basically the chain length, how this chain length is connecting the second and the third histidine residues.

So, by looking at all these things and the three letter abbreviations, I am not making your life a little bit complicated because I can make your life little bit complicated but you should read it nicely. Take the challenge basically. I will replace all these amino acid residues by single letter abbreviations.

You should have immediately close your eyes and think in that way that what are the donor atoms. So, the first two cases, you have the all three nitrogen, but the third case for the thermolysine, in case of thermolysine, you are bringing instead of bringing one, you are bringing the glutamate residue.

If no the glutamate residue which is dangling on the pendant from the polypeptide chain which particular group will be available for donation to the metal ion that you should know whether you will have a nitrogen donor or a oxygen donor because all we know that the sulfur donors will be coming from your cysteine residues.

Similarly, for carboxypeptidase also the glutamate residues is not at the end but it is at the center. Alcohol dehydrogen is what you see now is that now you bring the cysteine residue that sulfur you bring and nitrogen histidine and then another sulfur. So, it is basically idented physically caping Ns 2 type of ligand. It is a very useful ligand.

People go for the modeling of all these things. If you have a ligand, tridented facially caping ligand, you can think, you can design, you can imagine that particular ligand and make in the laboratory. You can go for the modelling reaction binding to that particular zinc and go for reactions which the alcohol dehygrogen S can replicate.

Then for alkaline phosphates and adenosine deaminase, so these basically 3, 4, 5, 6, 7 molecules will be very important, but we do not have that much time to cover all these mononuclear systems, but slowly, we will give those examples, we will take those examples where we can understand all these things very nicely because the story of this carbonic anhydrase, the C capital A, we abbreviate that CA. The story of carbonic anhydrase is almost 80 years, more than 80 years.

It has been discovered in 1940 and structurally characterized also not at that time but later on, but first time it was identified is that very useful molecule for our system, our body also because it can go for the corresponding hydration of the carbon monoxide molecule or dioxide molecule or dehydration of the carbonic acid.

Similarly, the latest one basically can be your adenosine deaminase, but in detail we will go for carbonic anhydrase and carboxypeptidase molecules, because after 14 years of that 1940, the carboxypeptidase has also been nicely identified there.

So, it is the only metal, not metal, its the only metal ion to have the representatives of all these 6 fundamental classes of enzyme. So, we have we are talking about 7 such.So, you see that these are the 7 mononuclear zinc enzymes. So, you have the six numbers. So, you can immediately give the examples of 6 mononuclear zinc enzymes, at least you should know about. Okay, obviously, we will talk about the structure, we will talk about the functions, but at least you should know that alcohol dehydrogenase. What is the basic reaction attached to that alcohol dehydrogenase? Zinc is there, and where is alcohol is your substrate.

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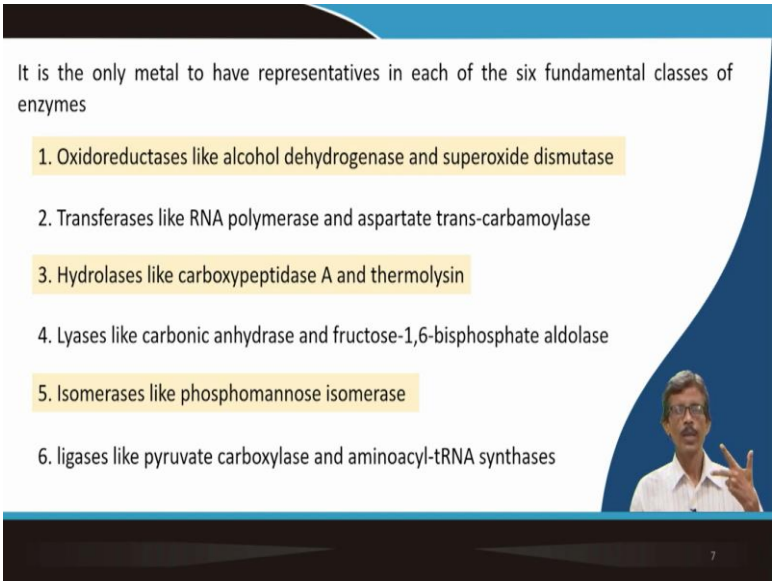

So, you can have the very basic fundamental classes of enzymes is well known, so if you study only the zinc enzymes, you are master in yourself in understanding, in knowing all the different six classes of all these enzymes. So, these are only available 6 classes of enzymes, the first class belongs to your oxidoreductases is the turn or level of all these molecules which are responsible for alcohol dehydrogenase reactions and the superoxide dismutase reactions.

Then transferases is the very sophisticated molecule, what people want to know for RNA polymerase and as per the transcarbamoylase reaction. So, this is one type of reaction so that the molecules can consider. Then the other category, the carboxypeptidase, that means the clipping of the peptide bond is nothing but your hydrolysis. So, those enzymes are known as hydrolysis. And thermolysine is also another lysine is the cleavage, nothing else. Peptidase is the peptide bond cleavage. Lysine is also another corresponding cleavage reaction due to that of your attack of the water molecule.

Then lyases, the lyases or lyases, whatever you say, like carbonic anhydrase, is the most well known and well studied example during the last 81 years, but it is coming under the category number 4. And another most recent advancement in this area is aldoses, this phosphate aldoses. Aldoses is there and that aldolase reaction or the corresponding similarity can be correlated with that of your carbonic anhydrase.

So, once you know about CA, the activity function and all these about the CA, you will be knowing about the other molecule also or the other enzymatic activity. Then isomerase is for

phospho mannose isomers reactions and ligases is L is capital L-I-G-A-S-E-S. So, ligases, like pyruvate carboxylase, and amino SIL T-RNA synthesis. So, these are the whole list I am giving you. I am presenting a whole list in front of you, but we will be talking about only mostly we will be talking about in our next one class or two classes that we will be talking about the carbonic anhydrase first and then the carboxy peptidase.

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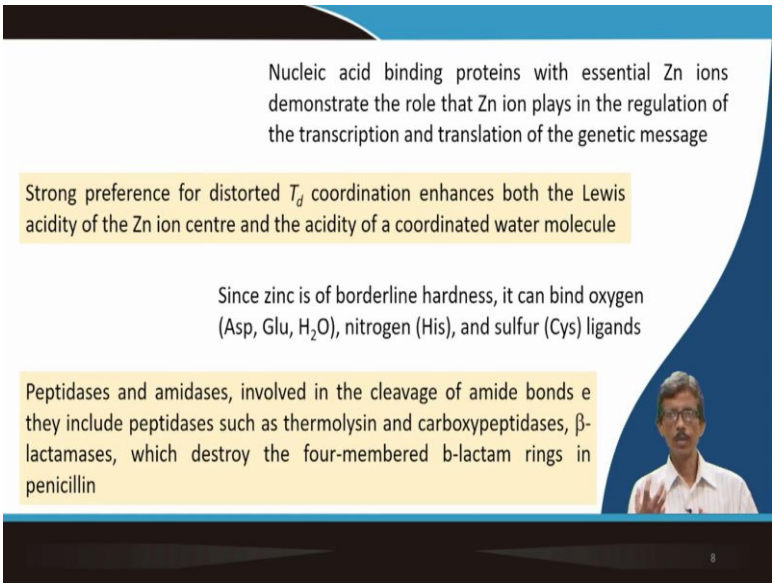

Then if you just make your life little bit complicated but bringing the (nuclear acids) nucleic acids, and the nucleic acid binding proteins, which are also essential for Zinc ions that demonstrating that the role of zinc ions are important. And those zinc ions will be there and we will be approaching there, and the nucleic acid binding proteins zinc will go and bind all these cases, and the regulation of the transcription and translation of genetic messages.

So, if you say, if you see that somebody is talking about the genetic engineering, they are talking about the zinc, or the genetic modifications, or the mutation people are talking about the COVID virus and all these things. So, what message you will transfer, the genetic information, or the genetic messages, the message and informations we losely call so that information, the genetic message basically.

The zinc can also plays some important role, the signaling thing. The zinc, if it is available and the coordination or the D coordination or the removal of the zinc ion can give you some or can manipulate the signaling processes, you see that the zinc can have some important role.

They are having some strong preference for a distorted tetrahedral geometry, which can enhance its lewis acidity, that is the goal, basically. You can manipulate. So, if you distort the tetrahedral geometry, you can either enhance the corresponding lewis acid in a particular direction but if you go to the regular geometry, which is the basic lewis acidity of the zinc center attached to that particular geometry.

So, the coordination geometry will be important to change the corresponding acidity of that particular center which is a very important thing to understand. So, we will be able to manipulate the acidity of the coordinated water molecules to that particular zinc center through the fourth coordination site. Since zinc is a metal ion having a borderline hardness that's why it is attracting sulfur. That is why it is attracting oxygen, that is it is attracting or going bind to your histadine centre.

So, if you now see that your peptidases and the amidases, so amide you have to clip, the peptide you have to clip. The cleavage of the amide bonds, they include the peptidases is are there definitely. So, such as thermolysine and carboxypeptidase is beta lactamases which which destroy also the four member, not b, the beta lactam ring in penicillin.

So, closely how you see that how much you have learned so far, we will be learning then the zinc activity or zinc hydrolyzing capacity for some very simple molecule like carbon dioxide, or the hydrolysis of the corresponding peptide bond CO-NH or the star bond. We also see that no zinc is also important for clipping or breaking the penicillin, which is a medicine to us. So, that penicillin can also be destroyed by zinc.

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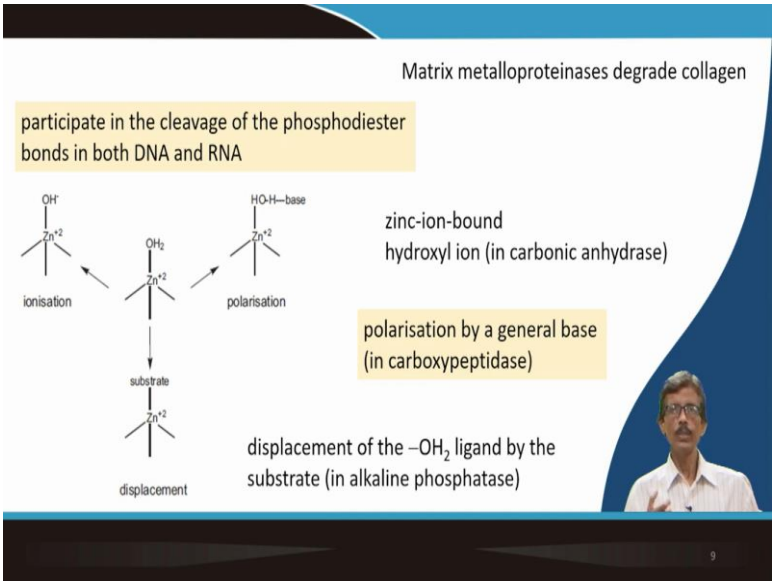

So, there will be direct correlation between the zinc centre as well as the corresponding beta lactamase activity of that corresponding molecules will immediately destroy the molecules what we take as the medicine. So, if a person, the doctor has prescribed penicillin and the patient is consuming that penicillin also but he does not know, he or she does not know that her body is active in that particular beta lactamase activity, zinc center is there.

So, zinc, and the protein is available so it can cut immediately without targeting to that particular site where it should go and do the effective reaction. Then, most importantly, the latest information. These are all latest information, but we will not read all in detail but for the introductory zinc enzyme class, you should know about the corresponding metalloproteins, which are matrix metalloproteinases, which can degrade the collagen.

So, do not confuse about the metalloprotein, proteins, which we already discussed, we discovered and we are finding out and we are classified, these are metalloproteinases. So, read up to the end only. So, do not do any mistake over here that these are not metalloproteins. These are metalloproteinases, which can again go for the cleavage or the destruction of the collagen molecules, which are also sometime can be beneficial, sometime can be harmful also.

So, they can participate in the cleavage of phosphodiester bonds in both DNA and RNA, because it is also one kind of ester bond involving phosphoric acid, phosphoester bonds, involving phosphoric acid. So, the zinc ions can also be effective in trimming those. So, what

do you see now that you can have the ionization? You can have the polarization and you can have the displacement around the zinc centre in that particular simple tetrahedral geometry.

So, you can have, if you want to see the carbonic anhydrase activity, what do you need? You need a zinc ion bond OH molecule. If you require to have the polarization, if you require to have the polarization by a general base, you can see that you can have that particular as a general base. You can see that in the carboxypeptidase molecule also.

So, look at the geometry, look at the species, and look at the corresponding catalytic activities, what you can see, in terms of the different important molecules because the first two we will discuss and if time permits, if we have some enough time, we will just go for the alkaline phosphatase. There, the third category of reaction is important, that means the displacement of the OH two ligand, the water bound to that zinc center is that you have to displace it, not for deprotonation, not for any other interaction or stabilization with the way that of your water molecule. So, by the substrate molecule and it can be given to you in alkaline phosphatase chemistry.

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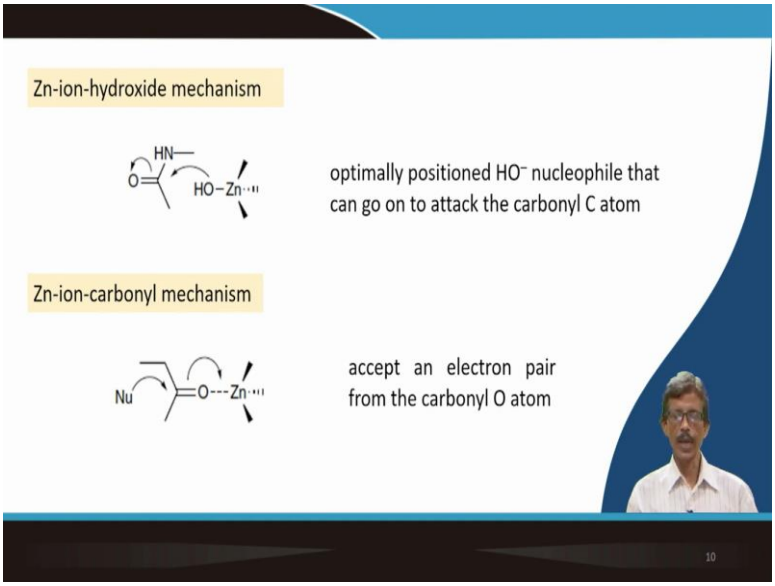

So, zinc ion hydroxide mechanism, how it happens? That we see quickly now that you have activated hydroxide ion is not that you externally you add some bare hydroxide ions, like sodium hydroxide, potassium hydroxide, lithium hydroxide, even the organic hydroxide is like tetrabutylammonium hydroxide, but that reaction will not take place.

You have to have a zinc activated OH ion because the reactivity pattern of that zinc bound hydroxide ion is different, and is basically optimally positioned hydroxide ion as a nucleophile that can attack the carbonyl carbon center. So, you have the zinc center sitting nicely at a particular point, where you have the carbonyl function of the amide bond is available.

Then, the second category is zinc ion carbonyl mechanism that it will attack, or it will show some reactivity on the carbonyl function. So, you see now that in one case, we are talking about the loss of water molecule that means the bronsted acidity, and then you have a base, the corresponding bronsted base you generate and the base is attacking, the hydroxide ion is attacking that particular amide bond, CO bond of the amide function.

But now, you have the corresponding lewis acid. So, lewis acid is will attract a lone pair from the carbonyl function. The CO is your carbonyl function, and that carbonyl function is giving or donate the lone pair to the zinc site. And that is why you will have a different reaction. So, it accepts. So, there you have the bronsted acidity, here you have the lewis acidity of the zinc center. It is accepting the electron pair and (form) perform the carbonyl oxygen atom.

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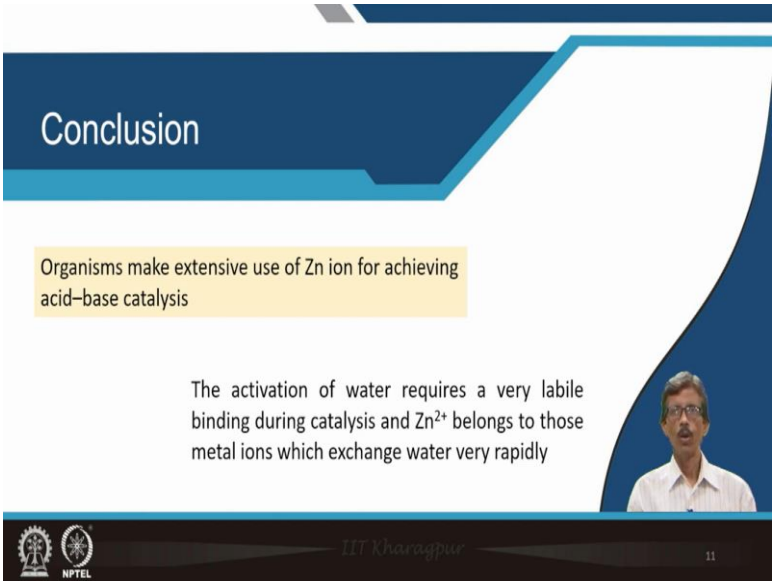

So, we have reached to the end. And that's why we can summarize a little bit in that way, that there are many organisms, which can make extensive use of zinc ions for achieving the very first case is acid base catalysis only. An acid base catalyst can be correlated to the hydrolysis reaction, and that can be classified in very complex, different types of enzymes. So, if you study nicely this particular class or this particular lectures on zinc center, you'll be mastering

yourself in the area of enzymatic catalysts because it is covering all the enzymes. You have the specific examples, but they are zinc bearing enzymes, and also the activation of water that we require all the time, and the labile binding during the catalysis of these zinc two plus belongs to those metal ions with exchange of water, very rapidly.

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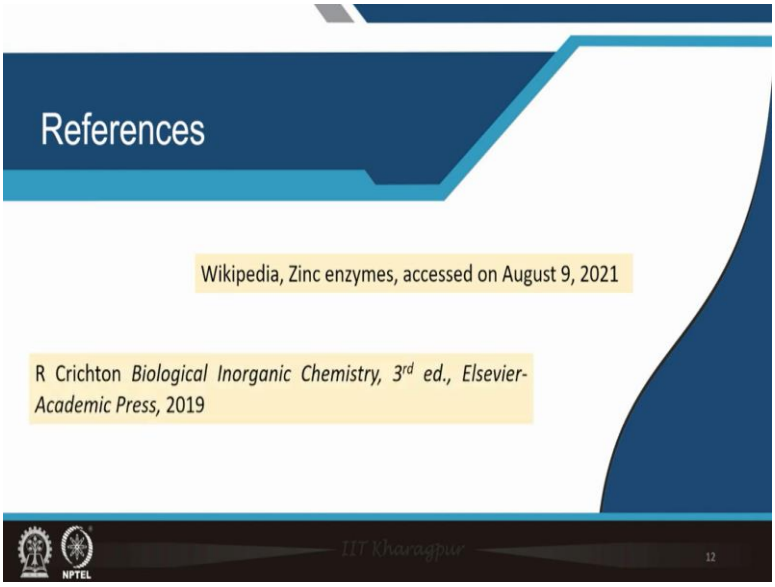

So, the references what we can have the zinc enzymes, which you can talk about, can think about, and you can read nicely, and the corresponding book of Crichton. So, thank you very much for your attention and for your presence.