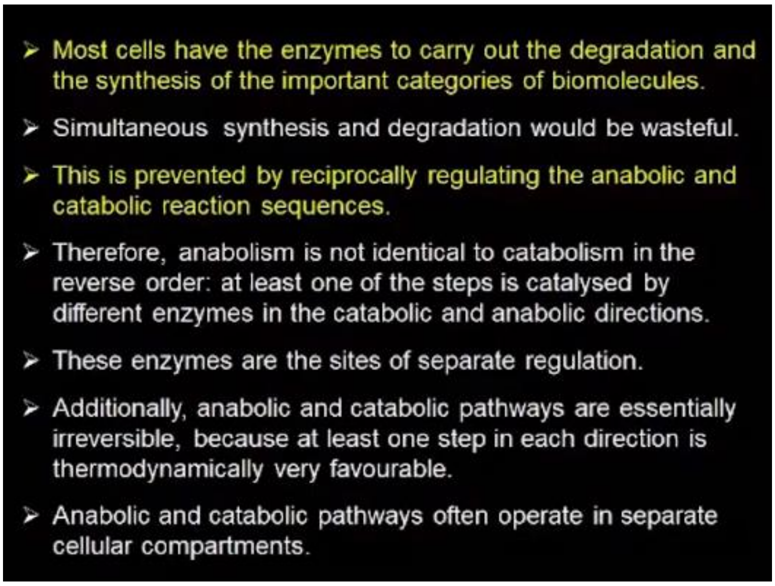
Introduction to Biomolecules
Prof. K. Subramaniam
Department of Biotechnology
Indian Institute of Technology - Madras

Lecture – 15
Introduction to Metabolism (Part 2/2)

(Refer Slide Time: 00:14)



- Most cells have the enzymes to carry out the degradation and the synthesis of the important categories of biomolecules.
- Simultaneous synthesis and degradation would be wasteful.
- This is prevented by reciprocally regulating the anabolic and catabolic reaction sequences.
- Therefore, anabolism is not identical to catabolism in the reverse order: at least one of the steps is catalysed by different enzymes in the catabolic and anabolic directions.
- These enzymes are the sites of separate regulation.
- Additionally, anabolic and catabolic pathways are essentially irreversible, because at least one step in each direction is thermodynamically very favourable.
- Anabolic and catabolic pathways often operate in separate cellular compartments.

Yesterday we began our discussion on metabolism. So primarily I was telling you that metabolism means it comprises all the biochemical reactions in our cells and then I listed the major functions like obtaining energy either from other nutrients or from the sunlight, then building cell specific molecules, then making macromolecules, polymers out of monomers and so on. Then we looked at what are autotrophs, what are heterotrophs.

And then we looked at the way the carbon, oxygen and the water cycle in the biological system and then we looked at the nitrogen cycle as well. So today we will go from there. So, let us look at some of the characteristics of metabolism as a whole and then we will get into more specific aspects. Then of course we discussed about what is anabolism the synthetic pathways and then catabolism the breakdown pathways primarily to obtain energy from the energy rich molecules.

So, the one important aspect we need to consider here is that most cells have enzymes for both anabolism and catabolism. So that means in most cells synthesis degradation both can happen and if they really happened without any specific regulation like you make and break all the time then it would be a wasteful in an expenditure of energy. And that is prevented by a reciprocal regulation.

Like for example in a particular cell synthesis of certain molecules are required at a given context, then in that cell the catabolism is negatively regulated, it is inhibited and this is achieved by having certain steps that are unique to anabolism and as well as certain other steps you need catabolism. So, in other words anabolism and catabolism are not exactly perfect reverse sequence of the other one.

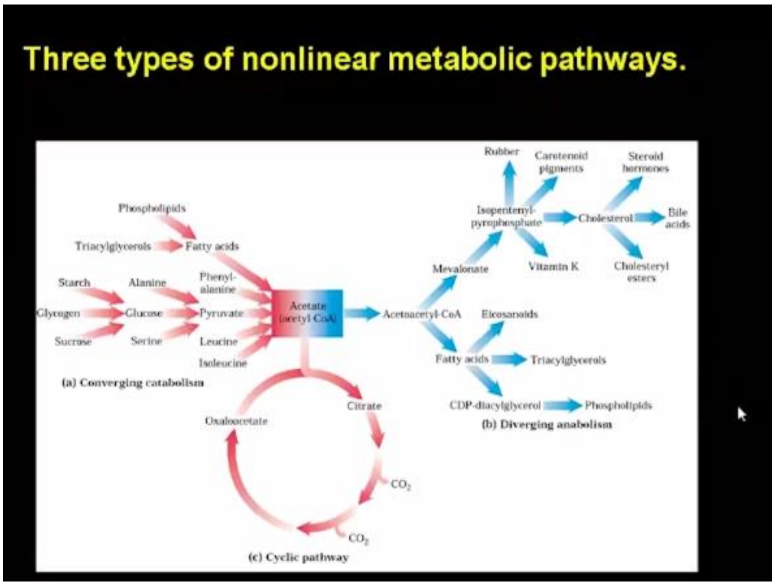
If there are 10 steps involved in the biosynthesis of one molecule, it does not mean exactly the same 10 steps in the reverse direction is breakdown of that molecule. One or two steps will be different and therefore the net sequence is going to be reciprocally regulated. So, they are not identical in the reverse order. And such end steps which is unique to anabolism are unique to catabolism they are usually subject to regulation.

So that is where the enzyme regulations that we have learned come into picture. And that is one and second at least one step in either one of the two directions is thermodynamically very favorable. Means the net synthetic reaction the whole pathway or the catabolic pathway the opposite, the net pathway is thermodynamically is a reversible sequence. One is more energetically favored than the other one.

So, therefore you are going to have a kinetic control over the total pathway. Individual reactions may be reversible, but at the end a whole pathway is going to be unidirectional that is one, second. And the third aspect is that these pathways, the biosynthetic pathway and the degradation pathways, may operate in separate compartments. For example, if you take fatty acids the biosynthesis happens in the cytoplasm on endoplasmic reticulum.

While the breakdown of fatty acids to derive energy out of them that happens in the mitochondria. So, these are the ways by which the anabolism and catabolism are separated and therefore they are not all the time happening in a futile cycle. So, this is one important feature of metabolism that we need to remember.

(Refer Slide Time: 05:19)



Three types of nonlinear metabolic pathways.

And another characteristic of metabolic pathways is the branching pattern or linear sequence or operating in cycles, here you see a cycle. So, in cycle what happens is a certain molecule cycles through the pathway again and again. For example, in this particular cycle the only cycle shown in this cartoon oxaloacetate N combines with Acetyl-CoA every time at the start of the pathway and then it gets regenerated and that is the reason it is a cycle, one molecule gets regenerated every time.

And so you can see here branches and then you can also see some linearity, so these are characteristics. So, in this there is a pattern in terms of the linearity as well as branching you see patterns. If you look at all the red color, these are breakdown pathways catabolism. So, they usually converge, so they are convergent pathways. So, the different branches finally come to one certain molecule.

In this particular case what you are seeing is phospholipids, triacylglycerols you understand how fatty acid comes from both, right. So, this has glycerol image you have 2 fatty acids in ester linkage, here you have glycerol in 3 fatty acids. So, if you hydrolyze those ester bonds you get the fatty acid and glycerol. And this fatty acid is broken down to acetyl-CoA. Similarly, here you have amino acids, alanine, phenylalanine. So again, when the amino group is removed, they can be converted into Acetyl-CoA.

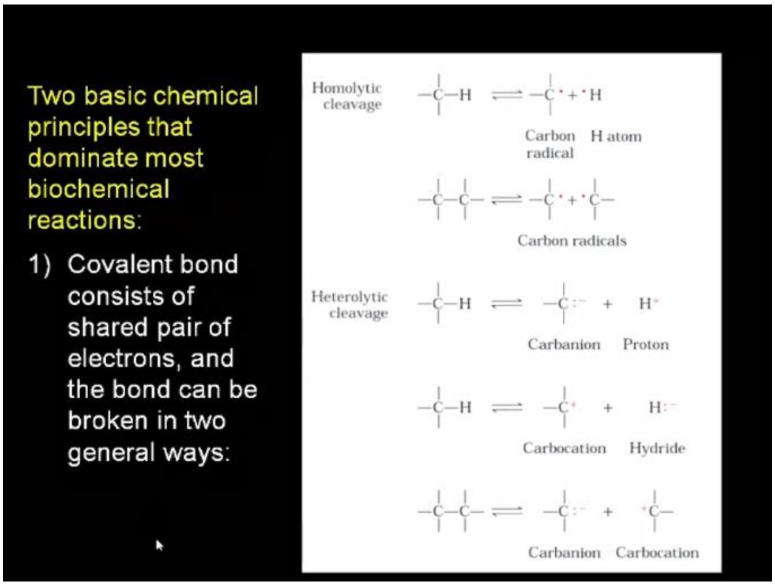
Similarly starch, glycogen, sucrose you hydrolyze them you get glucose and that again gets Acetyl-CoA. So, from different sources, we have looked at three different sources lipids, proteins and carbohydrates breakdown of all of them leads to acetyl-CoA. So, the breakdown pathways are usually convergent. And the synthetic pathways on the other hand are divergent. So, you start with a common precursor and then you build different kinds of molecules.

So here acetyl-CoA is the precursor for fatty acid biosynthesis converting within lipids to eicosanoid our favorite prostaglandin, thromboxane, leukotriene, etc., triacylglycerol the storage fat, we remember the sperm whale's head, then you have the membrane phospholipids. So, within fatty acids you have these many diverging pathways, so all start from acetyl-CoA.

And not just that they can go ahead to make carotenoid pigments, vitamin K, cholesterol, steroid hormones. Bile acids is a derivative from cholesterol that I think I briefly mentioned, this is involved in emulsifying and digesting fat in our intestine. So, within this you have so much diversity all starting from acetate, acetyl-CoA. So, actually this can go even in reverse order by one couple of steps different from this breakdown to make glucose and glycogen as well.

And from this pyruvic acid by having transamination you can make alanine too. So degradative pathways are convergent, meaning from multiple different macromolecules you obtain a common breakdown small molecule product and synthetic pathways are divergent meaning diverse group of macromolecules are built from a common simpler precursor. So, these are certain characteristics of metabolic pathways.

(Refer Slide Time: 09:51)



Two basic chemical principles that dominate most biochemical reactions:

1) Covalent bond consists of shared pair of electrons, and the bond can be broken in two general ways:

So, we are now poised to look at the individual pathways and if you really look at them if any of you can go to google and images and search for metabolic network, you will find a really maze like network and you will be intimidated by this. Do I need to remember all of them does anyone understand all of them? So, like that you will really get threatened by the complexity of these pathways and their interconnections.

But fortunately, there are certain common patterns and that helps us to make sense of the individual reactions. And that is the way we are going to look at it and before we get into that let us refresh couple of chemistry concepts and then we look at the common patterns and probably that is all we will achieve in today's class. So, this is like really high school chemistry, but let us quickly refresh our memory.

So, I am sure that helps us to proceed further into the metabolic common patterns. So, all of us know what is a covalent bond. So here you have an atom carbon and another atom hydrogen and these two share a pair of electrons meaning that pair of electron goes around hydrogen nucleus as well as carbon nucleus. So, this is what is a covalent bond, a pair of electrons are shared between two atomic nuclei.

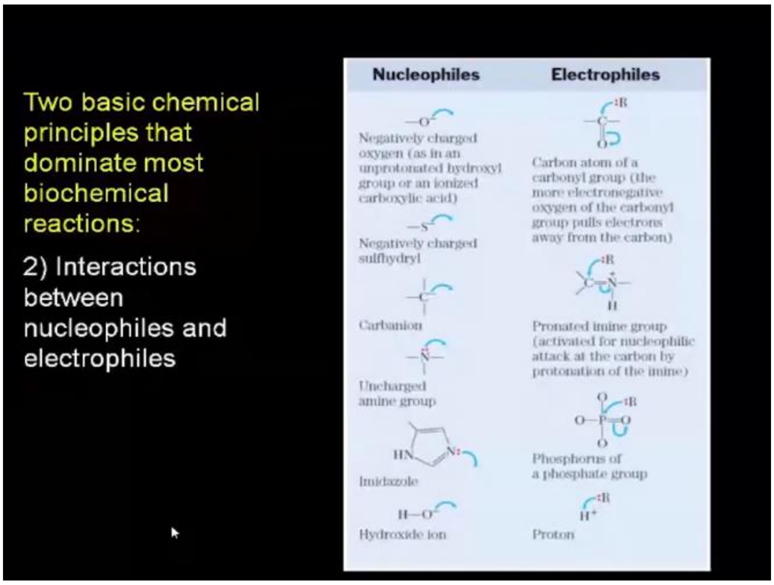
And this can be broken down such that each one takes one electron with them as you see in the top thing where my cursor is and that kind of a cleavage would be called a homolytic cleavage. And here you have another example where it is carbon-carbon covalent bond breaking down into two carbon radicals. So, these unpaired electron containing atoms these are the radicals that can readily react.

Then you have a heterolytic cleavage where one pulls both electrons and the other one loses that shard electron. So, in this particular example you generate a carbanion meaning this has one extra electron and therefore it is negatively charged. And this last one electron and as a result it is positively charged if it happens to be hydrogen then it is proton. And you can have another type of heterolytic cleavage where hydrogen takes both electrons, so you get hydride.

So here you have 2 electrons 1 proton that situation is hydride. And this has one less electron and therefore it is carbocation. So, carbon can be both carbanion as well as carbocation. This matters a lot in biochemistry. So, try to remember the difference between the two. And you can have a similar situation with this carbon-carbon double bond also, one becoming carbanion, another becoming carbocation.

So, these are the ionic species generated when you have heterolytic cleavage. So, we understand what is the covalent bond and how the covalent bond can be cleaved. There are two ways of cleaving, one is homolytic where both the atoms separate with one electron each and heterolytic cleavage where one atom gets both the electrons and the other one loses an electron. So, this is one feature, it is very simple right, you learned this long time ago.

(Refer Slide Time: 14:10)



Two basic chemical principles that dominate most biochemical reactions:

2) Interactions between nucleophiles and electrophiles

Nucleophiles

Negatively charged oxygen (as in an unprotonated hydroxyl group or an ionized carboxylic acid)

Negatively charged sulfhydryl

Carbanion

Uncharged amine group

Imidazole

Hydroxide ion

Electrophiles

Carbon atom of a carbonyl group (the more electronegative oxygen of the carbonyl group pulls electrons away from the carbon)

Pronated imine group (activated for nucleophilic attack at the carbon by protonation of the imine)

Phosphorus of a phosphate group

Proton

Here are examples of the second concept rather. So that concept is the idea of nucleophiles and electrophiles. So, what is a nucleophile? Something that has high electron density and will readily interact with an atom that has less electrons and therefore positively charged. Like for example in our previous case itself so this has more electrons, so this is a nucleophile, meaning nucleus loving. Hydrophilic means water loving, it likes water.

So, like that this likes nucleus because it has more electrons and therefore it is negatively charged and it is the opposite with the cations. You know these are less electrons and therefore they are electrophiles, they are attracted towards atoms having more electrons. So, these are electron rich and these are electron poor. So, this is what gets us to these two terms nucleophiles and electrophiles.

And the most of the biochemical reactions are reactions between nucleophiles and electrophiles. So, the inset in the right lists some examples of nucleophiles and electrophiles.

So, you have a hydroxyl group having lost the proton so that is a nucleophile. Same with thiol group, instead of oxygen here you have sulfhydryl group having lost the proton. Carbanion, we just saw how carbanion can form.

Then uncharged amine groups, imidazole group so this is there in the side chain of histidine and hydroxide ions. And similarly, you have examples of electrophiles. So, a couple of them are important for us and all of them are common in biology, but in the interest of time I am going to focus on two of them. So this carbonyl carbon is something it is going to come in couple of slides from now again.

And this is the most important chemistry concept for understanding many of the biochemical reactions. The unique feature of carbonyl carbon like the way we learned elaborately about water if you recall, the strong electronegativity of the oxygen is the cause for all the properties that we see about water. Remember water has high specific heat capacity you need lot more heat to raise one liter water's temperature by one degree than doing it for other solvents.

That is because lot of it goes into breaking down the hydrogen bonds. And the hydrogen bonds are because oxygen is electronegative and as a result the shared electrons spend more time with oxygen nucleus, therefore it is partially negatively charged and the covalently bonded hydrogen is partially positively charged. And that subtle difference in the charge is the cause for hydrogen bond and everything about water the specific heat capacity, surface tension.

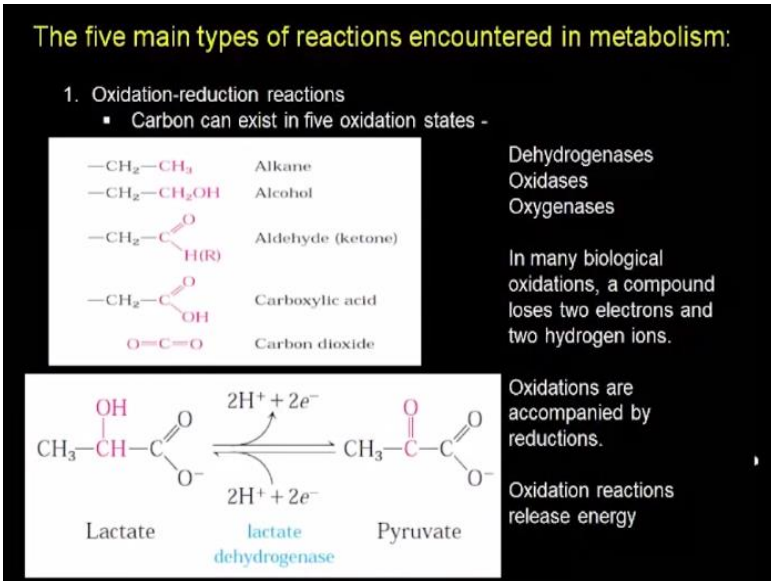
And that surface tension helping water to cohesive among themselves and adhere to hydrophilic surfaces and move to grade heights in plants all of that comes from that one feature, right, the oxygen’s strong electronegativity. Very similarly you need to focus here again on oxygen’s strong electronegativity in this carbonyl group and this will be a very crucial for our understanding of much of biochemistry.

So, this carbonyl group oxygen being strongly electronegative in relation to carbon, so this is going to be partially negatively charged and this is going to be partially positively charged. So therefore, it is leading to an electrophilic substitution here. So, the same with phosphoric acid so we are going to see this again and again, we have already seen enough of it. We have seen it as part of the phosphodiester bond.

We have seen it in the polar lipids like glycerophospholipids and this phosphoric acid we saw. So, the interesting thing about phosphoric acid which we will discuss a little later is although we draw double bond with one oxygen. So this is actually in resonance with all of them. And here again this is going to be partially positively charged just like this carbon due to the strong electronegativity of oxygen.

So, these two groups come again and again, of course imines and protons also are important as electrophiles in biochemistry. So, the two concepts again to revise what is a covalent bond and how a covalent bond can break? That is one and covalent bond breaking can either generate radicals or can generate nucleophiles or electrophiles, carbocation, carbanion. And now the second point is nucleophiles and electrophiles and some examples of that. So remember these two basic chemistry concepts, these are important for us.

(Refer Slide Time: 20:23)



The five main types of reactions encountered in metabolism:

1. Oxidation-reduction reactions
    - Carbon can exist in five oxidation states -

Dehydrogenases
Oxidases
Oxygenases

In many biological oxidations, a compound loses two electrons and two hydrogen ions.

Oxidations are accompanied by reductions.

Oxidation reactions release energy

So now among the myriad biochemical pathways, what are those common patterns that I mentioned? So, there are 5 common types of chemical reactions that happen. So, the first one we are going to look at them are the oxidation-reduction reactions. So, before we get into oxidation-reduction reactions, the molecules listed here on the top box where you see my cursor moving you see the pink carbon.

The whole thing is pink but just focus on the carbon there; this carbon has different oxidation states. So here this is the most reduced state, so this oxidation level is the lowest and this is the highest as you can see. So here it is highly oxidized because its electrons are pulled towards two oxygen atoms and this is strongly positively charged. And here that is slightly less because one of them is single bond with oxygen.

And this is not as this hydroxyl group is not as electron pulling as an oxygen atom. And here you do not even have that oxygen and it is just hydrogen, so one more level low. So here you have that oxygen is replaced with a hydroxyl group and here there is no oxygen it is fully reduced. So, you have 5 states of oxidation for carbon and this again helps in oxidation-reduction reactions in biochemistry.

So, we will see these in specific cases as we go through the metabolism later. So, this is just to make us remember these basic points. This makes you to right away think what is an oxidation state and the fact that carbon can exist in five different states. So, usually the oxidation reactions are coupled always with a reduction reaction, meaning if electrons are being taken away from one atom or in one reaction it is absorbed by another one.

So, one donates and another one accepts, both happen in a coupled way and that is why we call this as oxidation reduction. For example if you look at here, lactate lactic acid present in milk can lose 2 protons and 2 electrons that is 2 hydrogen atoms simultaneously. This is characteristic again of oxidation reduction-reactions in biology. Usually, the oxidation reactions in biology are losing a pair of electrons and protons simultaneously.

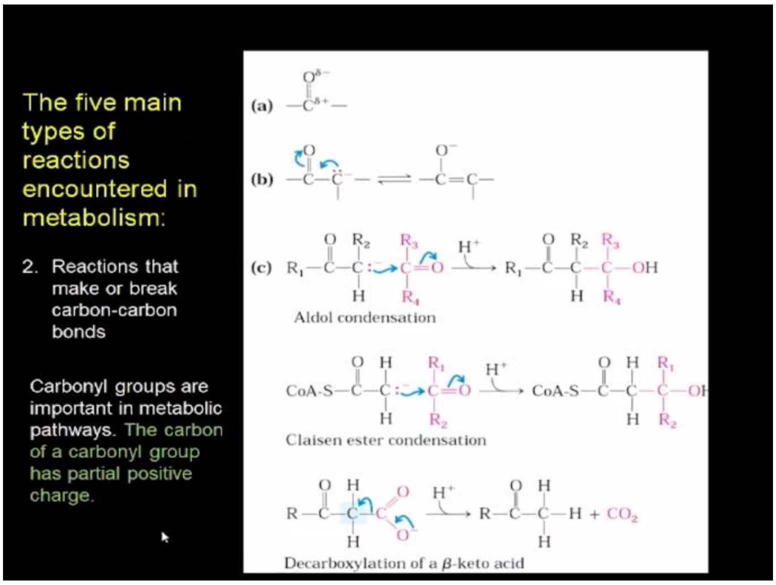
Meaning 2 hydrogen atoms are simultaneously lost as shown here, 2 protons and 2 electrons. And these are usually catalyzed by enzymes called dehydrogenases because you are removing hydrogen and that results in an oxidize, this carbon is now oxidized so from this state to this. So, it has essentially moved from here to this. So that is a lactate to pyruvate. And these are usually used to reduce other molecules.

In this particular case what is not written here is the co-enzymes that we learned earlier little bit but we learn in detail later when we go to oxidative phosphorylation, so they take up this for example a coenzyme called NAD gets reduced to NAD H+ H+. So that detail will come later but that is the reduction that is simultaneously happening here while this oxidation happens that molecule gets reduced.

And sometimes an oxygen is directly added to a carbon and when then that happens these are called oxidases the enzymes that catalyze that kind of reaction and if that oxygen comes directly from molecular oxygen those enzymes are called oxygenases. Oxidase adds an oxygen to a carbon like covalent bond with oxygen carbon and if the oxygen actually comes from molecular oxygen O 2 then those enzymes are oxygenases.

So, examples will come when we go through the individual reactions. And so these points already I told you and usually oxidation reactions release energy. So why do they release energy will come again in for detailed discussion when we are going to look at electrochemical potentials, so that is where we are going to get a conceptual clarity on why oxidation releases energy. So, actually here our goal is to get energy to do other reactions and that is why we do oxidation.

(Refer Slide Time: 26:13)



The five main types of reactions encountered in metabolism:

2. Reactions that make or break carbon-carbon bonds

Carbonyl groups are important in metabolic pathways. The carbon of a carbonyl group has partial positive charge.

So, the second major types of chemical reactions that we find in biochemistry are a carbon-carbon covalent bond formation or breakdown of the carbon-carbon bonds. So, the reactions that make or break a carbon-carbon bonds. So this is the second major thing and this is very common in many synthetic reactions as well as breakdown reactions. And in this the main group that we want to focus, a few minutes ago I just emphasized this already.

And here is where we are going to really thoroughly focus on this that is this carbonyl groups’ special feature. So here is a carbonyl group. Carbonyl group means carbon double bonded to oxygen. So, I just explained to you that why this carbon will be partially positively charged and this oxygen will be partially negatively charged. So, this already poises this carbon for reactions with other molecules.

In addition, the electron delocalization within this double bond can actually make hydrogens bound to this carbon to readily ionize, meaning the hydrogens bonded to carbon adjacent to a carbonyl group is sort of weakly acidic compared to any other carbon. Now you see if you have a long chain of aliphatic chain like what you see in fatty acid. So, the carbon somewhere in the middle the hydrogens bonded to it is not acidic, it is not going to readily lose hydrogen.

Whereas the one that is adjacent to carbonyl group can readily lose because its electron can be taken and delocalized within this carbonyl double bond. As a result, it generates a carbanion in that adjacent carbon. So, two important features that; we are looking at it and they are sort of independent but at the same time connected. One is that carbonyl groups carbon and oxygen are partially charged that is one.

And second electron delocalization with this carbonyl group can make the adjacent carbon to be carbanion and these can exist in this keto-enol tautomerism, hydroxyl group and double bond here. So this is enol, so this is a double bond and then alcohol group and that is why it is called enol and this is ketone, so this is keto-enol tautomerism. This exists even in our nucleotides, the nitrogenous base has double bond O or OH.

And that was a big deal in discovering the Watson and Crick base pairing rule the base stack in the middle and not outside. So that you can read if you go through the history of solving the structure of DNA double helix. So here these are the two main things. One is carbonyl group’s unique feature and its ability to make an anion in the adjacent carbon and that makes reactions possible.

And this is so much important that many biochemical pathways actually are arranged to generate a carbonyl group at the vicinity of a carbon where you need a bond cleavage or bond formation. So, we will see this in our first biochemical pathway we will learn which is glycolysis. There again if you take a glucose structure, the first carbon has an aldehyde group, so the carbonyl group is in the first carbon.

And when it is converted from glucose 6-phosphate to fructose 6-phosphate we move the carbonyl group one carbon down from first to second and that helps later in breaking the bond between the three and fourth carbons to make two trioses. So, we will see that when we go to glycolysis. So, like this there are many examples where the biochemical pathways are arranged such that the carbonyl group is brought or generated adjacent to the carbon where you want a bond to form or break.

So, this features in these three kinds of reactions listed in under c. One is aldol condensation so where you have an aldehyde group reacting with a carbonyl carbon. So here you see this can actually react, so this is partially positively charged and from this you understand why this would have a negative charge and as a result it favors this reaction. So here who is silently helping this reaction possible? This carbonyl group adjacent.

So, this is aldol condensation. We will see this in the reverse direction when fructose 6-phosphate breaks down to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate. So those two are the trioses generated by cleaving the carbon-carbon bond in fructose 1, 6-bisphosphate. So that is a reverse direction in glycolysis. So, aldol condensation is in that particular example it is the glyceraldehyde 3-phosphate and dihydroxyacetone phosphate joining to make fructose 1, 6-bisphosphate.

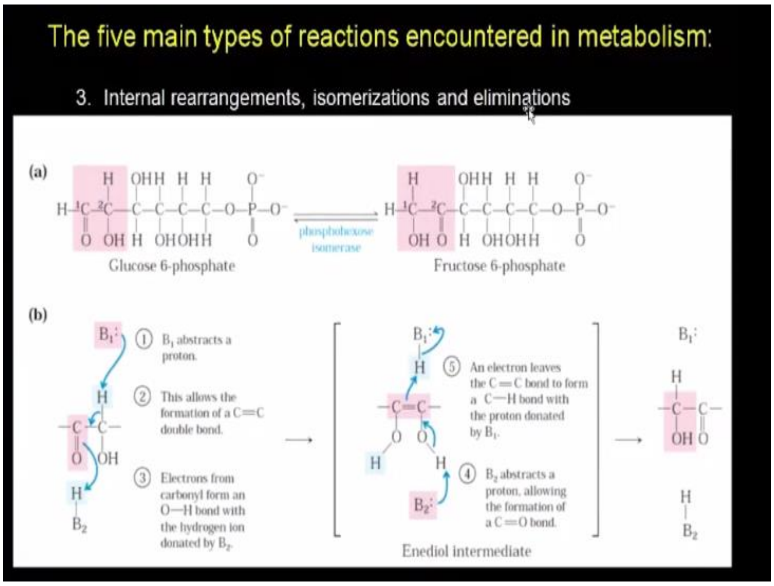
So, we will see that when we go to that pathway but that pathway is the biochemical example for this variety aldol condensation. And so in a proper chemistry sense this usually results in loss of water and that is what they call aldol condensation, this just the addition itself the carbon-carbon bond formation itself they call it as aldol reaction, but in biochemistry we call this itself as aldol condensation.

And a very similar thing the only difference is instead of this R group here it is and this carbonyl group is part of an ester. Here it is a thiol ester with coenzyme A, do not worry about what co-enzyme A, we will learn in great detail its structure later. This is very common in biochemistry like for example fatty acids participate in reactions only when they are esterified with the coenzyme A.

So, coenzyme A’s functional group here is the SH, fatty acid’s functional group would be the carboxylic acid. So that sort of an ester when it has this condensation reaction that is called glycine condensation, glycine ester condensation. So there again this carbonyl group aids this reaction. And a third variety is a loss of carbon dioxide. Here again this carbonyl group aids the shift of electron here and releasing carbon dioxide.

So, this becomes a double bond and this takes up that extra electron. So, this is decarboxylation of a beta-keto acid. So, this is like alpha carbon and this is the beta and that is why it is called beta keto acid. So, these are the 3 types of reactions in which we see the importance of carbonyl group and how this carbonyl groups specific electronic configuration nature enables these carbon-carbon bond formation as well as this one example where we see cleavage R.

(Refer Slide Time: 35:43)



The five main types of reactions encountered in metabolism:

3. Internal rearrangements, isomerizations and eliminations

(a)

Glucose 6-phosphate

Fructose 6-phosphate

(b)

① B_1 abstracts a proton.

② This allows the formation of a C=C double bond.

③ Electrons from carbonyl form an O—H bond with the hydrogen ion donated by B_2.

④ B_2 abstracts a proton, allowing the formation of a C=O bond.

⑤ An electron leaves the C=C bond to form a C—H bond with the proton donated by B_1.

Enediol intermediate

So, the third type of common reactions that we see are internal rearrangements. So, the one that I was constantly telling you the structure is here glucose 6-phosphate to fructose 6-phosphate. You see this for the previous discussion the carbonyl group is transferred from first carbon to second carbon in fructose. This stays in the cleavage here, so between the third and fourth.

So, before that there would have been a phosphorylation here as well; so it would have become fructose 1, 6-bis phosphate. So, in first carbon sixth carbon and that is why it is bis. So that is for the carbonyl group discussion but here we are looking at internal rearrangement.

So here what actually happens is the electrons are redistributed within a molecule such that the bonds are rearranged.

And here the shaded in pink shows that kind of a rearrangement generating another isomer and such reactions are catalyzed by enzymes called isomerases, here you have phosphohexose isomerase. So, meaning this is to any hexose, need not be glucose and here you go the reaction mechanism. So, I am sure all of you know basic chemistry so these may be already very familiar to you.

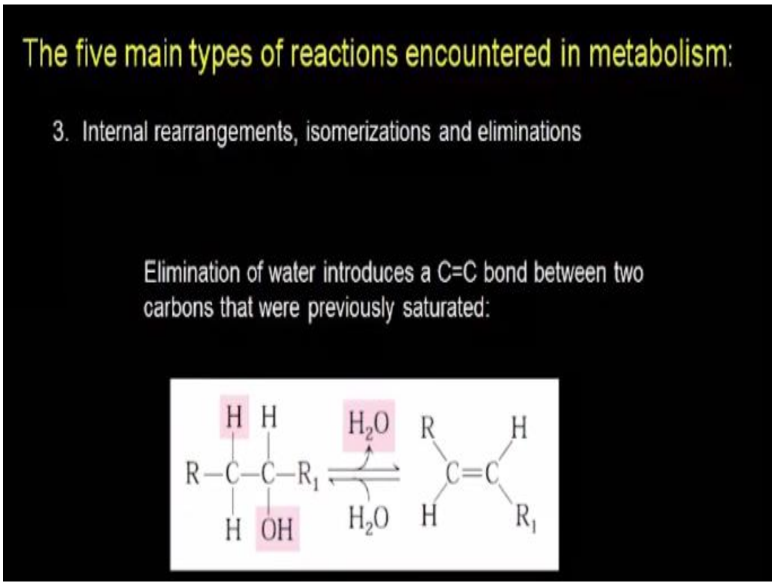
So, the arrow indicates the electron flow in a reaction where you are going to have a bond formation or breakage. And we usually shade pink the one that is going to donate a proton and we are going to shade this blue for the one that is going to accept. So, remember the general acid-base catalysis and recall that here. So this is a side chain group in the enzymes active site base one and this is going to abstract a proton from this.

And this one is going to donate a proton and that is what it helps in getting to this enediol intermediate. So, accepting this proton and electron coming here is what allows a transient double bond formation and that in addition enabled by this taking up an electron and donating a proton leads to a transient hydroxyl bond formation here. And when that happens you have two alcohol groups it is diol and it is enol because of the double bond here.

So, this is an enediol intermediate that is made possible by one acting as base and another, acting as acid catalysis. So, this is an acid-base catalysis mechanism in this enzyme isomerase. And then this enediol intermediate reverts back by the opposite direction generating double bond here and hydroxyl group retaining here. So that is how these two get swapped and this whole thing is done purely to bring that carbonyl group adjacent to the carbon where you need the breakage.

And this is going to aid like what we saw in the previous examples in breakdown of the bond here. So, this is an isomerization reaction and some of the internal rearrangements lead to transposition of double bonds. I do not have a picture for that here, we will see that kind of examples when we go into cholesterol biosynthesis. There we readily see shift of double bonds from one carbon to another carbon and in some molecules they move quite a distance that way. So those transpositions are another kind of internal rearrangements.

(Refer Slide Time: 40:26)



The five main types of reactions encountered in metabolism:

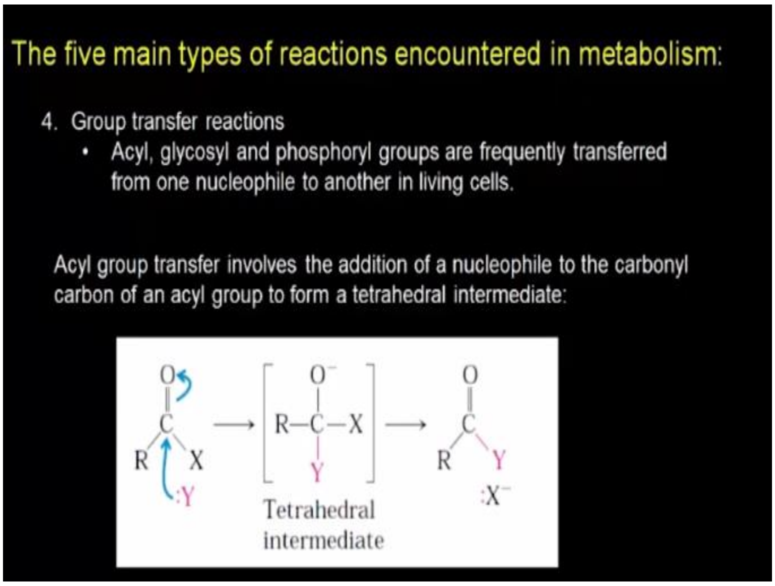
3. Internal rearrangements, isomerizations and eliminations

Elimination of water introduces a C=C bond between two carbons that were previously saturated:

And the third variety that comes from internal rearrangement usually is elimination and that elimination is shown here in this particular thing. We will see the elimination reactions; a good example is enolase that is going to be involved in phosphoenolpyruvate reaction, so that we will see when we go to glycolysis. So, when we go with glycolysis most of these mechanisms will become thoroughly grounded in our minds.

So here you have a water molecule elimination leads to a double bond formation. So, this is another common type of internal rearrangement. So, we have seen oxidation-reduction reactions, then we have seen carbon-carbon breaking and joining, the aldol condensation the primary thing that we need to remember there and now we have the rearrangements leading to isomerization and we saw in that an example of how carbonyl group is brought to a place where we want a cleavage to happen.

(Refer Slide Time: 41:35)



The five main types of reactions encountered in metabolism:

4. Group transfer reactions
    - Acyl, glycosyl and phosphoryl groups are frequently transferred from one nucleophile to another in living cells.

Acyl group transfer involves the addition of a nucleophile to the carbonyl carbon of an acyl group to form a tetrahedral intermediate:

So now the fourth one we are going to see are the group transfer reactions. So, group transfers are very common and quite often they are required to activate certain molecules for reaction to make them poised for a reaction. We saw that with the dolichols, you know how dolichols join with glucose or other carbohydrates and they help in the biosynthesis of glycolipids and glycoproteins.

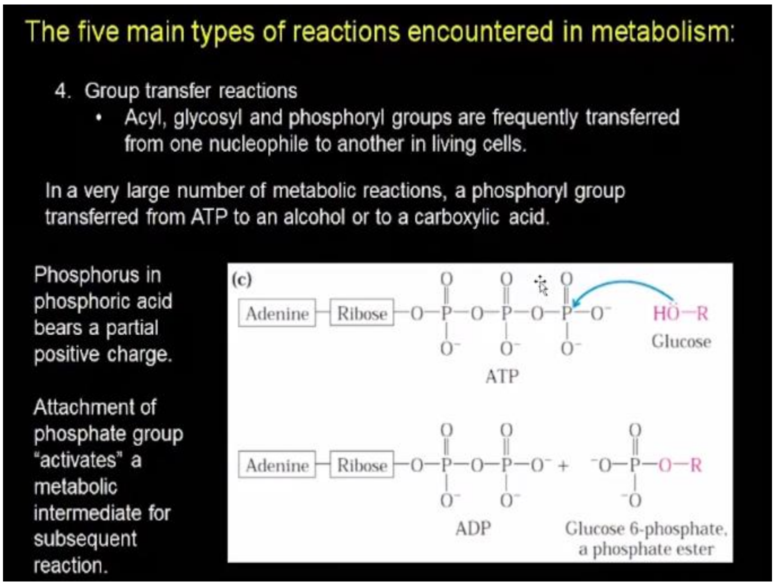
Dolichols bind to these molecules and since they are hydrophobic anchored in the membrane in addition to activation, they bring them to the right place that is on the membrane. But there are other situations for example for many glycosylation the carbohydrate moiety is going to be covalently linked to one of the nucleotides. It is usually like glucose UDP you know that kind of activation. So there the UDP moiety’s group is transferred.

So quite often we encounter group transfers of these three types. One I just told you glycosyl. The other one is acyl group like fatty acid acyl group one good example. And the other one the most common energizing kind of group transfer is this phosphoryl group. So, we will have a long discussion on this phosphoryl group at multiple points. We have already had some discussions and we will have some more discussions under the current context, then we will also talk about it later.

So, these are the three groups that are frequently transferred and the transfer is usually from one nucleophile to another nucleophile. So, when you have acyl groups it is usually addition of a nucleophile to the carbonyl carbon. So, you see here you have an R group with the carbonyl group and you have one nucleophile this is X and there this carbonyl group may be attacked by another nucleophile ending of this tetrahedral structure formation by the electron shift the way shown by here.

So, this this is a nucleophile and this is positively charged partially because of this electronegativity and therefore this reaction readily is favored and this becomes hydroxide. And now you can have a double bond here of breaking this, so essentially these two changes place, so that is a group transfer. So, essentially this entire group is transferred from X to Y.

(Refer Slide Time: 44:40)



The five main types of reactions encountered in metabolism:

4. Group transfer reactions
    - Acyl, glycosyl and phosphoryl groups are frequently transferred from one nucleophile to another in living cells.

In a very large number of metabolic reactions, a phosphoryl group transferred from ATP to an alcohol or to a carboxylic acid.

Phosphorus in phosphoric acid bears a partial positive charge.

Attachment of phosphate group "activates" a metabolic intermediate for subsequent reaction.

So, the other major group that we want to discuss is the phosphoryl group transfer. So, I just told you UDP glucose, a similar thing. So here you have if you look at phosphoric acid, phosphorus in phosphoric acid bears a partial positive charge that is again because the electronegativity. And due to that partial positive charge, it can readily react with a molecule like this alcohol group in glucose and that will lead to an ester linkage, acid alcohol.

A similar thing can happen with a carboxyl group as well. For example, fatty acids are carboxyl group and that would have a mixed anhydride. Mixed anhydride because this is inorganic acid and that is organic acid, acid-acid is anhydride but here one is mineral, another is organic, so we call mixed anhydrides. So, the phosphate group transfer usually leads to an ester formation or a mixed anhydride bond formation.

So, what we see here is an example of the ester bond with glucose. So, this being a nucleophile and this is like partially positively charged, so these two readily form covalent bond leading to glucose 6-phosphate. And this sort of addition is what I was referring to as energized molecule. So, this bond is now activated for chemical reactions compared to this. So, what you actually are doing is this is a poor leaving group in a reaction where you are going to have a bond formation.

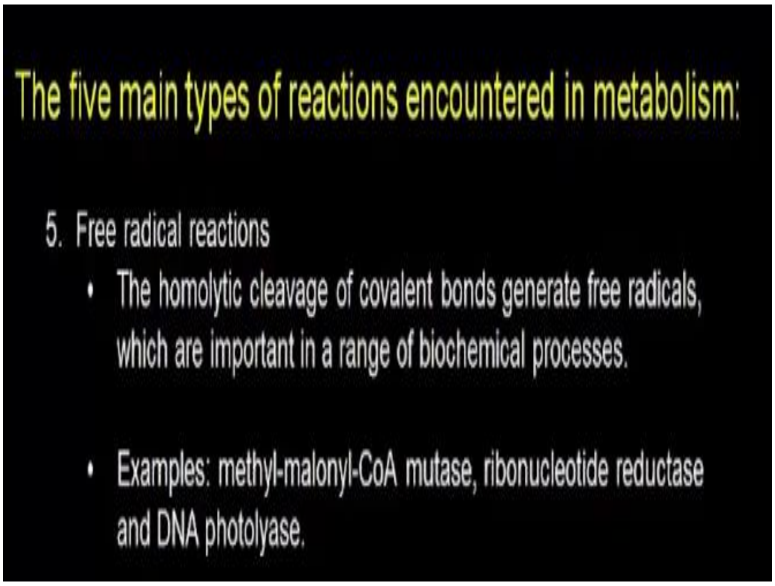
And that poor leaving group is replaced with a good leaving group. So, the phosphate is a good leaving group and that is what is done in this sort of an activation; in this sort of a phosphoryl group transfer. So, attachment of phosphate group activates a metabolic intermediate for subsequent reaction and that is one. And second these are phosphorylated carbohydrates.

Because they are highly hydrophilic and the membranes do not have transporters for these, these carbohydrates are now trapped inside the cell they do not really get out of the membrane whereas glucose can. There is a transporter for glucose and glucose can really get out of the plasma membrane whereas glucose 6-phosphate will not and usually this phosphorylation the donor is some ATP, adenosine triphosphate.

Tri because the carbohydrates a particular carbon, carbon 5 in ribose has 3 phosphates in tandem so that we call triphosphate. On the other hand, this is for nomenclature not in our current context. Here this particular carbon will have one phosphate and this has another phosphate and when fructose one single carbohydrate having two phosphates in two different carbons you, call that as bisphosphate.

So, remember the difference between bis and the bi or tris and tri. So, I kind of emphasized on that when we learned 1, 4, 5-inositol trisphosphate. So that is about the group transfer reactions the fourth variety.

(Refer Slide Time: 48:49)


The five main types of reactions encountered in metabolism:

5. Free radical reactions
   - The homolytic cleavage of covalent bonds generate free radicals, which are important in a range of biochemical processes.
   - Examples: methyl-malonyl-CoA mutase, ribonucleotide reductase and DNA photolyase.

So, the fifth one is free radical reactions. So far whatever we have seen these are all requiring heterolytic cleavage of covalent bond generating carbocation or carbanion if it is carbon. There are situations where homolytic cleavage happens and the free radicals are generated and they are important for reactions and so we will see them when we go to this, we will not be learning about ribonucleotide reductase.

We will not have time and we will not learn this, but we will learn about this methyl-malonyl-CoA mutase. So, there we will see how free radical helps that reaction. So, these are the 5 types of reactions that we need to keep in mind and these will keep reoccurring in all through. Yes, I am stopping right now.