Medicinal Chemistry
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Department of Chemistry
Indian Institute of Science Education and Research Pune
Lecture No 31
Mechanisms in Biological Chemistry Part III

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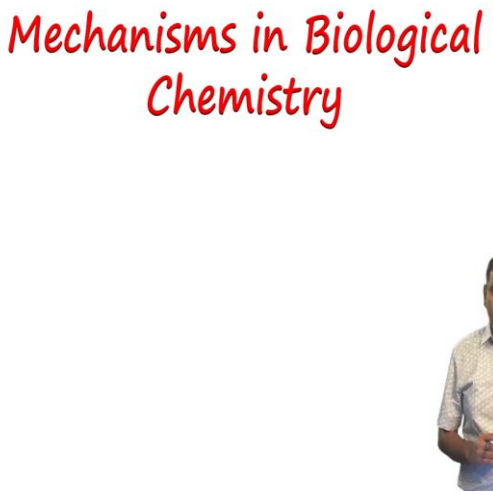

Welcome back. So we looked at in the last lecture some of the important mechanisms in biological chemistry. So we are going to continue with the same theme and look further into some of the mechanisms that are very interesting and relevant to, in biological chemistry.

So just to put

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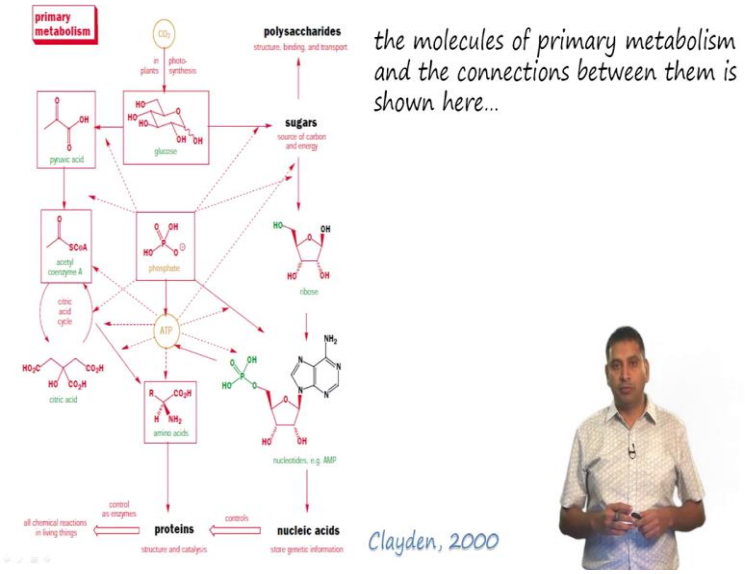

this in perspective, we looked at this very large picture of how metabolism occurs and we looked at some key molecules such as pyruvic acid and how

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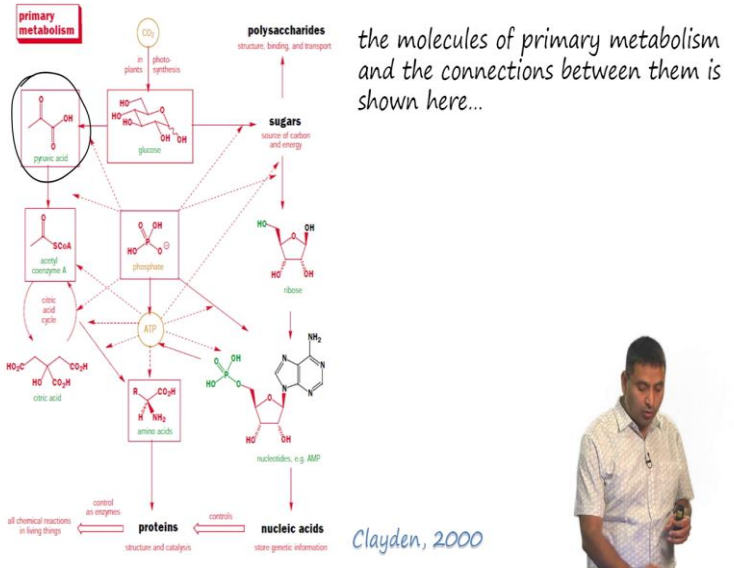

pyruvic acid actually can, you know plays a very important roles in transferring groups.

And we looked at how alpha-keto-acids are actually, such as pyruvic acid is actually in equilibrium with the corresponding amino acid and this transfer that can occur is catalyzed by aminotransferases.

And we also looked at enol equivalents and, because it is not possible to generate an enolate or it is unlikely that an enolate will be generated inside the cell. And so the cell, nature takes care of this by making very interesting enol equivalents, so one of the enol equivalents that we looked at was phosphoenolpyruvate and so on.

So now, in today's class

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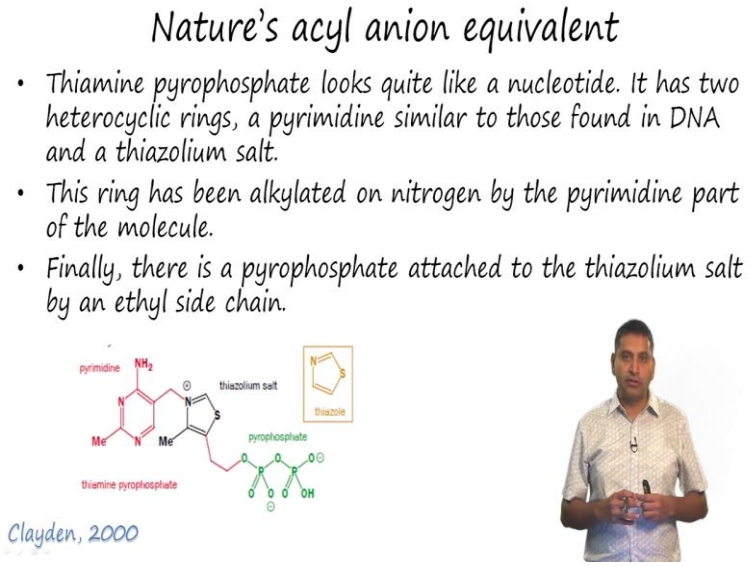

we look at acyl anion equivalents. So acyl anions are very important in many reactions that we will, that we conduct in the organic chemistry lab.

And the way it happens in nature is through thiamine pyrophosphate. So the structure of thiamine pyrophosphate is shown here. And what, the interesting part of the structure is that it contains a thiazole ring,

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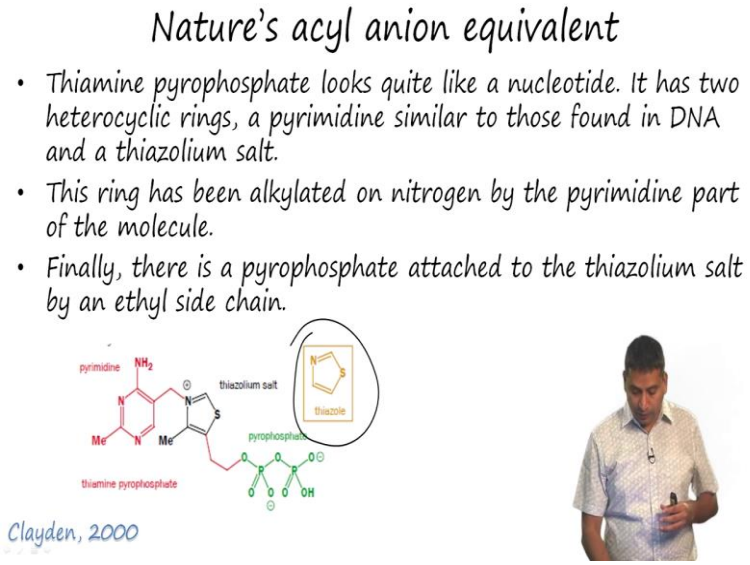

Ok.

And this thiazole ring is actually positively charged because this nitrogen has

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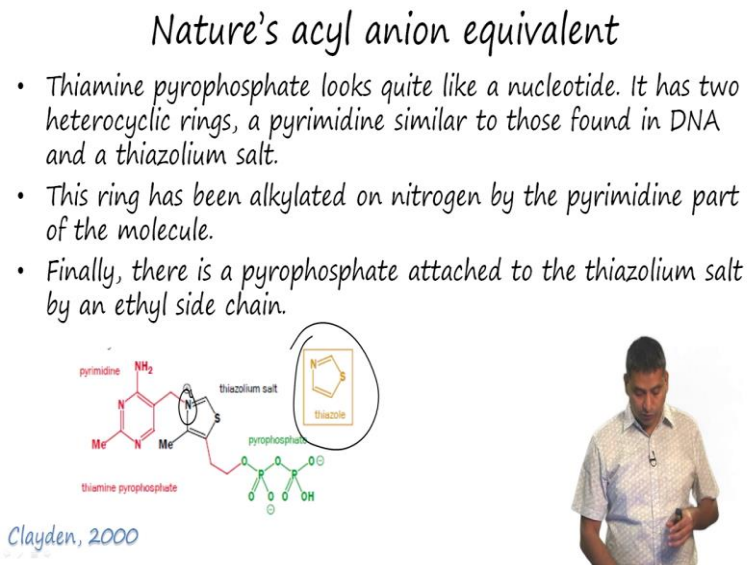

four bonds to it. And so this provides a very interesting chemistry that we will look at soon. But this thiamine pyrophosphate as the name suggests, contains pyrophosphate here

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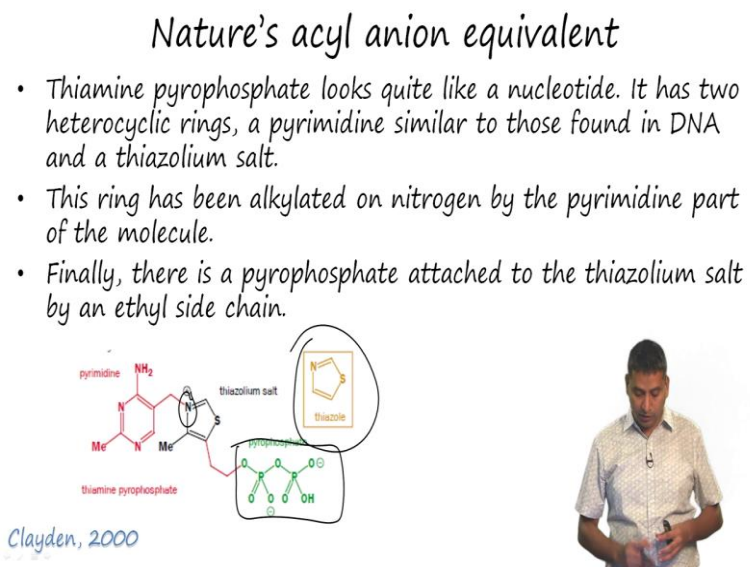

as shown here and it also contains the pyrimidine

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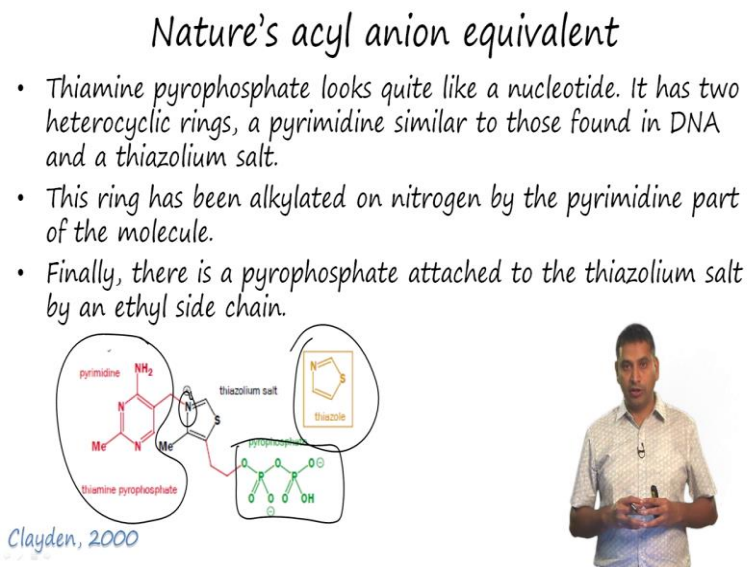

ring over here.

And, so this together this molecule plays a very important role in nature.

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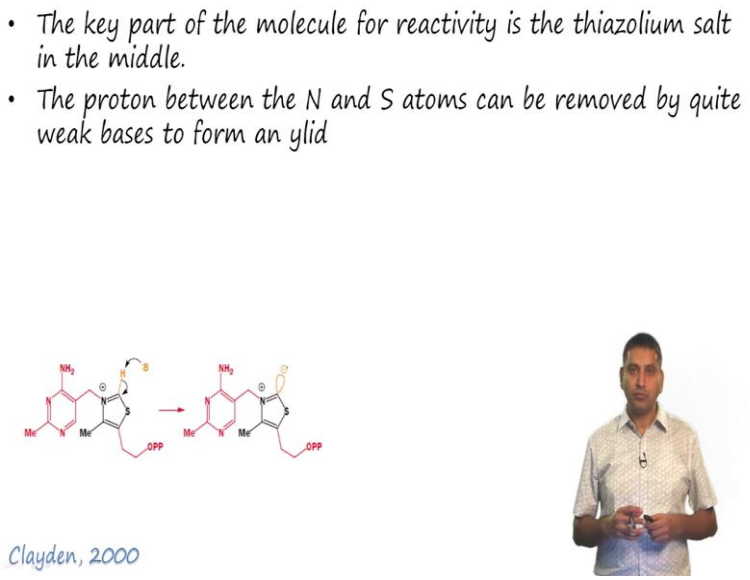

So the key part of this molecule is the thiazolium salt which is shown here in the middle. So here is

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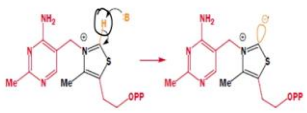
- The key part of the molecule for reactivity is the thiazolium salt in the middle.
- The proton between the N and S atoms can be removed by quite weak bases to form an ylid



Clayden, 2000

a proton or a hydrogen which is next to this positively charged nitrogen species which can be deprotonated and form

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- The key part of the molecule for reactivity is the thiazolium salt in the middle.
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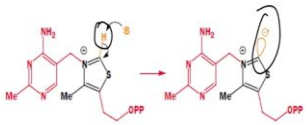

Clayden, 2000

a carbanion.

So to put this in perspective if you imagine a ketone which has an alpha hydrogen next to it, if you add a strong base,

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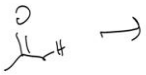
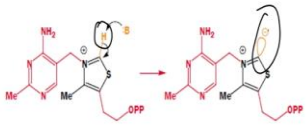
- The key part of the molecule for reactivity is the thiazolium salt in the middle.
- The proton between the N and S atoms can be removed by quite weak bases to form an ylid





Clayden, 2000

then you would expect that a carbanion is

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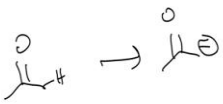
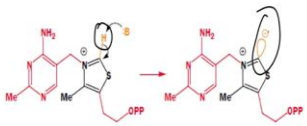
- The key part of the molecule for reactivity is the thiazolium salt in the middle.
- The proton between the N and S atoms can be removed by quite weak bases to form an ylid





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produced, Ok. This carbanion is in resonance with the

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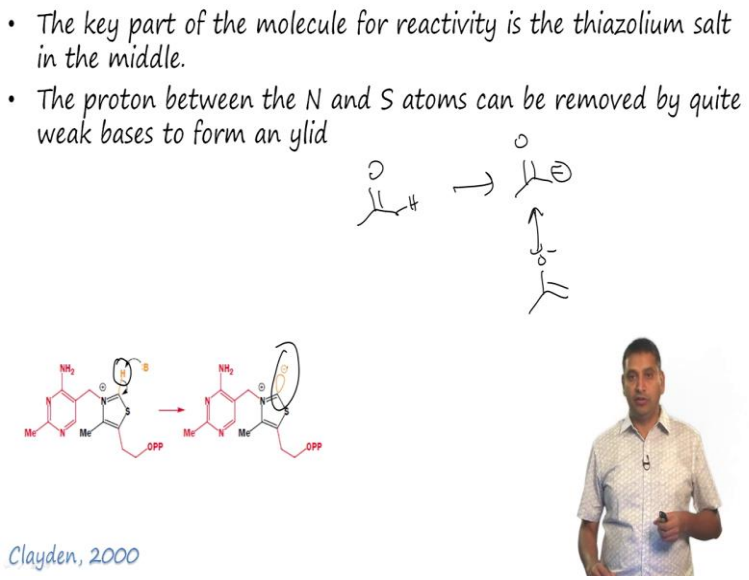

enolate form. So here the proton between the nitrogen sulphur atoms and it can be removed and it forms what is known as an ylid.

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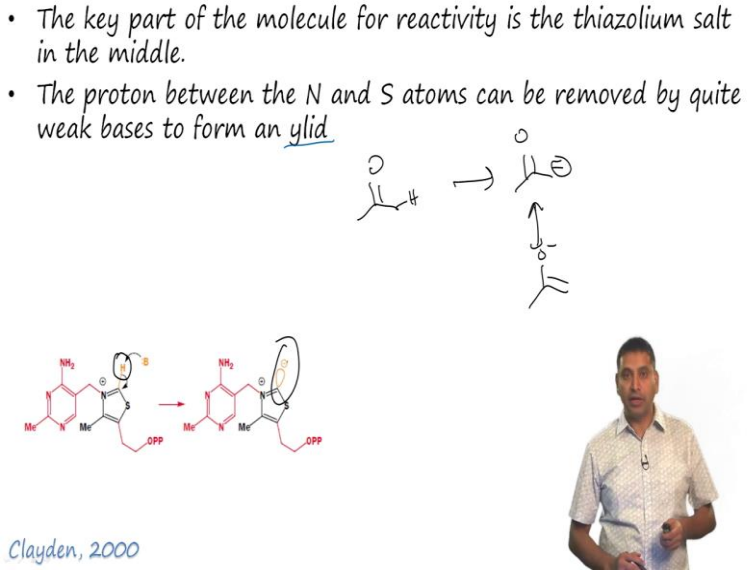

Ok.

So ylid is something that we have encountered previously in organic chemistry courses when we are looking at a Wittig reaction.

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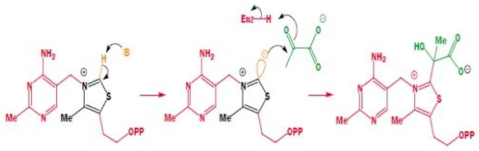
- The anion is in an sp^2 orbital, and it adds to the reactive carbonyl group of pyruvate.



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So this ylid is basically an anion which is in the sp^2 orbital and it adds to the reactive carbonyl group of pyruvate. So once you produce this carbanion,

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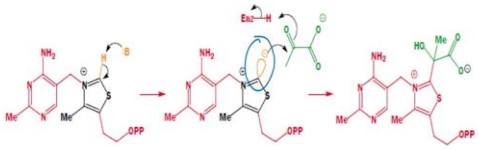
- The anion is in an sp^2 orbital, and it adds to the reactive carbonyl group of pyruvate.



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this carbanion can then react with the carbonyl

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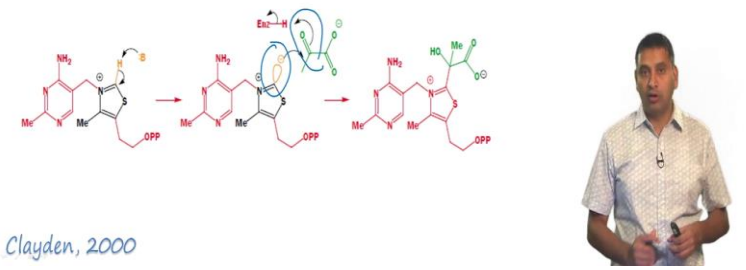

of pyruvate to form a carbon carbon bond.

And

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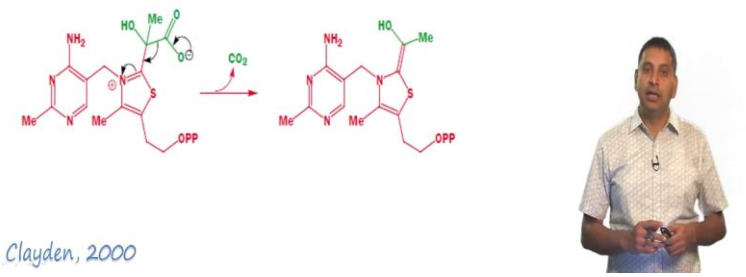

now the carboxylate ion can be lost from the former pyruvate as positively charged imine in the thiamine molecule which provides a perfect electron sink to take away the electrons. So recall we had a very similar situation in the positively charged NAD plus, right where you had positively charged nitrogen which was the electron sink.

So similarly here you can push electrons from the O minus to produce carbon dioxide.

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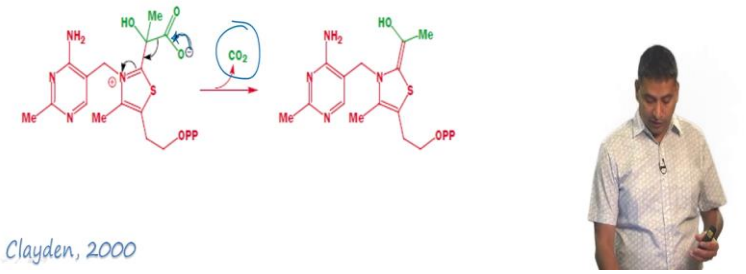

This carbon carbon bond is broken and you end up with this nitrogen as the electron

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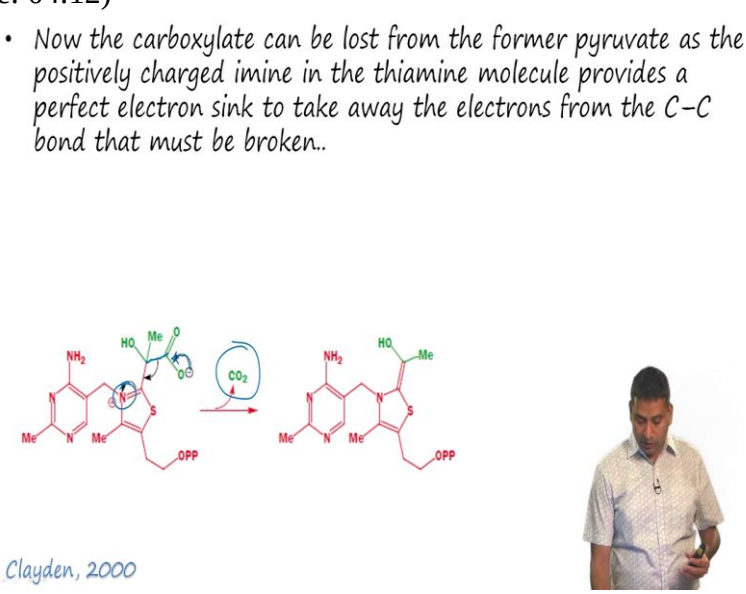

sink and you produce nitrogen with three bonds which is neutral, Ok. So therefore the formation of carbon dioxide forms a very important driving force in this reaction.

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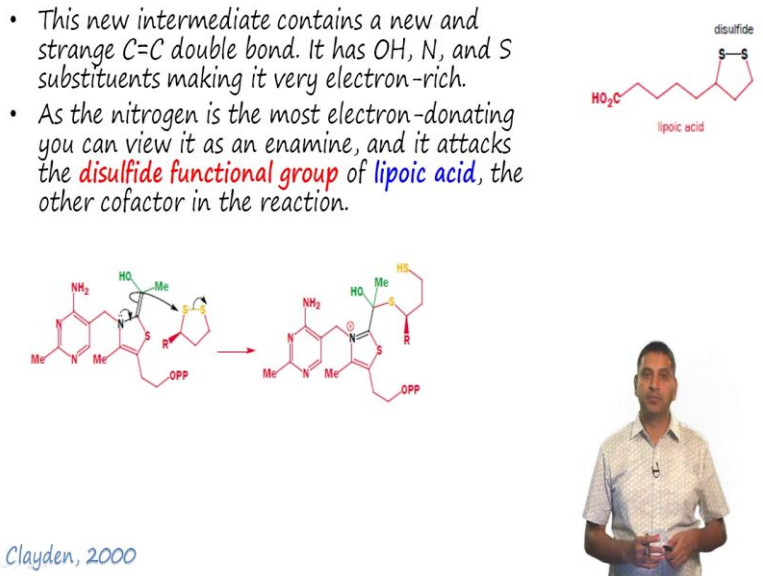

This new intermediate contains a new and strange carbon carbon double bond, Ok. So this carbon carbon double bond has on it an oxygen,

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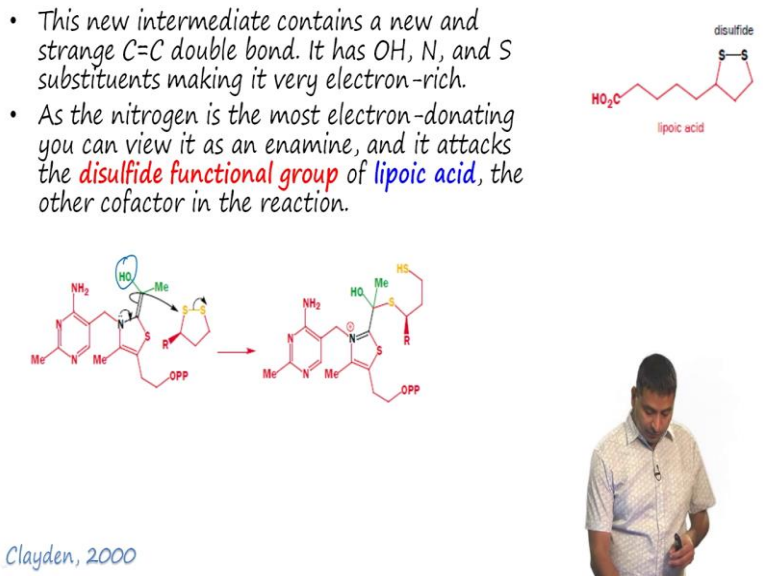

a nitrogen and

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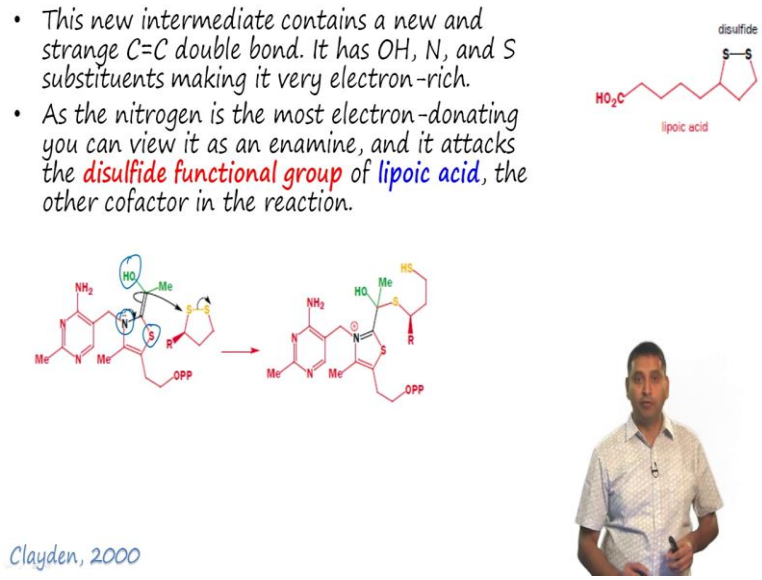

a sulphur, three electronegative atoms sitting on it, Ok. So this makes this double bond quite electron-rich and at this point this electron-rich double bond can react with disulphide functionality of lipoic acid, Ok.

So to just recall or to understand what lipoic acid, lipoic acid structure is

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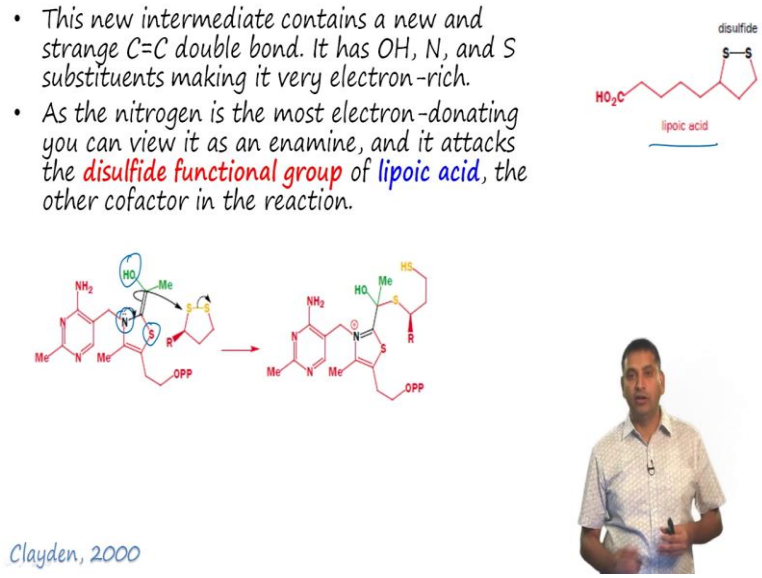

shown here which has this disulfide bond. And so this C double bond C which is electron-rich can react with the disulfide and produce a carbon sulphur

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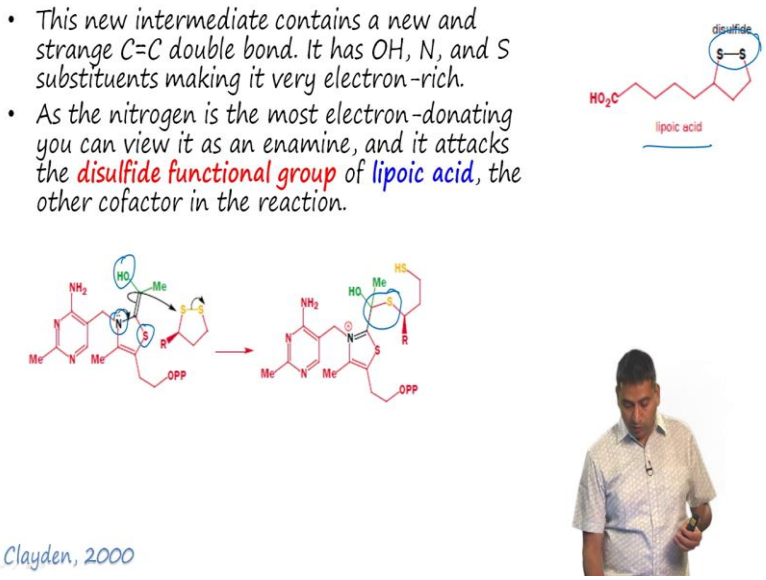

bond and it breaks the disulfide to produce a

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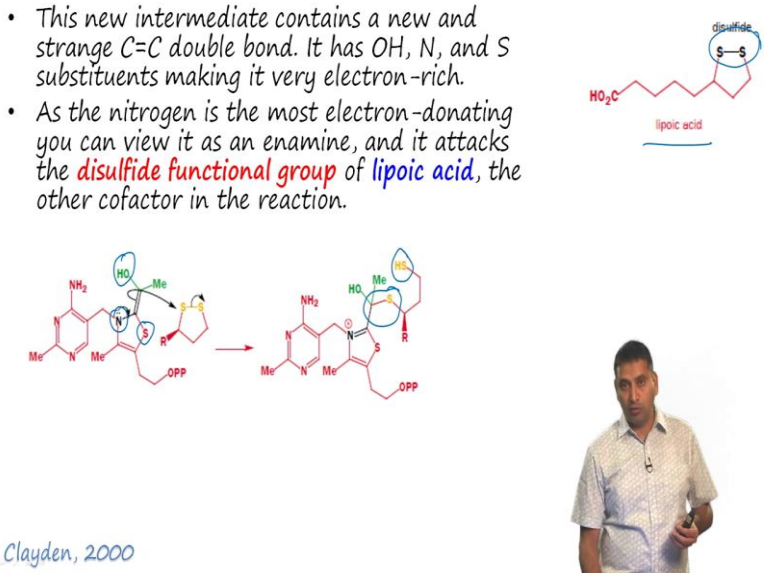

thiol.

Now if you see here, this thiamine

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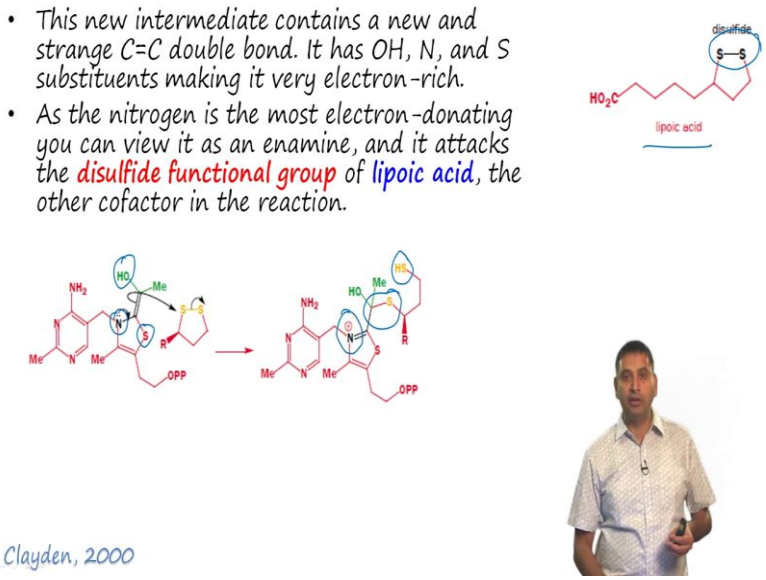

regained its positive charge.

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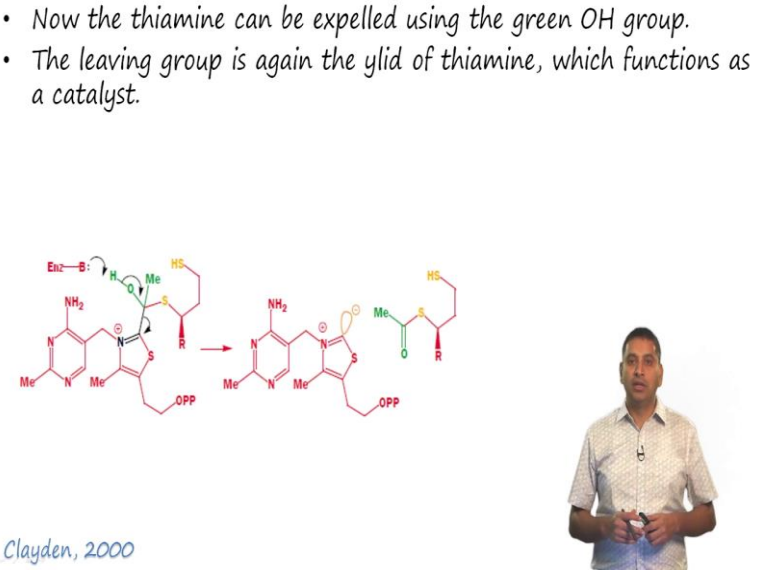

So now this thiamine which has a positive charge on it can again react to produce the carbanion which is originally reacting with pyruvic acid. So here is how that mechanism happens. So you can have a

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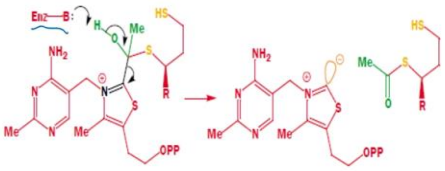
- Now the thiamine can be expelled using the green OH group.
- The leaving group is again the ylid of thiamine, which functions as a catalyst.



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basic residue in an amino acid to come and pick up this proton

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- Now the thiamine can be expelled using the green OH group.
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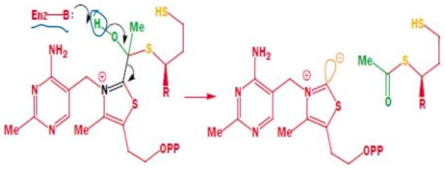

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from this alcohol which then generates the ketone as shown here.

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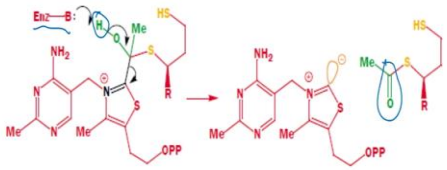
- Now the thiamine can be expelled using the green OH group.
- The leaving group is again the ylid of thiamine, which functions as a catalyst.



Clayden, 2000

And this carbon carbon bond breaks and regenerates the carbanion.

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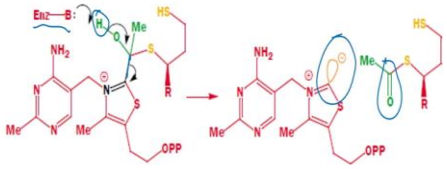
- Now the thiamine can be expelled using the green OH group.
- The leaving group is again the ylid of thiamine, which functions as a catalyst.



Clayden, 2000

So this is the ylid of thiamine which functions in very crucial way to transfer an acetyl group.

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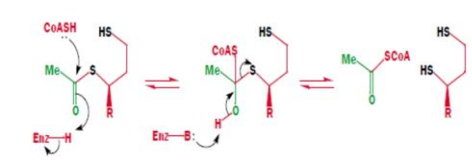
- The product is a thiol ester and so can exchange with CoASH in a simple ester exchange reaction.
- This is a nucleophilic attack on the carbonyl group and will release the reduced form of lipoic acid.



Clayden, 2000

So the product is a thiol ester and so it can exchange with a CoASH in the simple ester exchange reaction.

So you see here that CoASH

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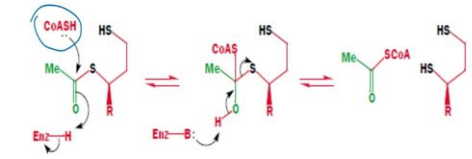
- The product is a thiol ester and so can exchange with CoASH in a simple ester exchange reaction.
- This is a nucleophilic attack on the carbonyl group and will release the reduced form of lipoic acid.



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as we have looked at previously can come and react with this acetyl group and then regenerate this

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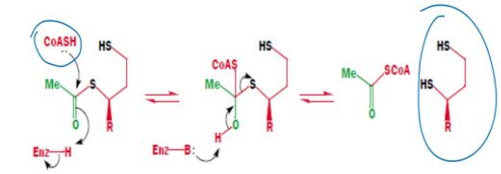
- The product is a thiol ester and so can exchange with CoASH in a simple ester exchange reaction.
- This is a nucleophilic attack on the carbonyl group and will release the reduced form of lipoic acid.



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dithiol intermediate which is basically the reduced form of lipoic acid. Now this acetyl CoA

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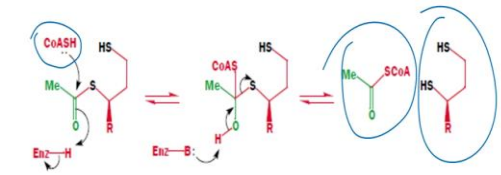
- The product is a thiol ester and so can exchange with CoASH in a simple ester exchange reaction.
- This is a nucleophilic attack on the carbonyl group and will release the reduced form of lipoic acid.



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species is produced and the dithiol can be oxidized to produce the disulfide,

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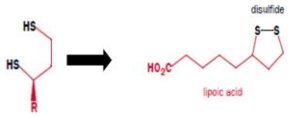
- All that is necessary to complete the cycle is the oxidation of the dithiol back to the disulfide.
- This is such an easy reaction to do that it would occur in air anyway but it is carried out in nature by FAD, a close relative of NAD+.



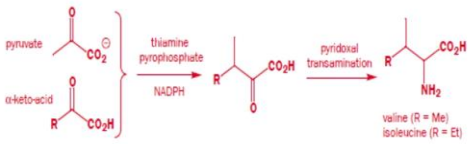
Clayden, 2000

Ok and which basically regenerates the lipoic acid.

And this oxidation can, is very facile and it would occur in air but in nature it is carried out by another cofactor known as FAD which is flavin adenine dinucleotide which is a very close relative of NAD plus.

(Refer Slide Time: 06:54)

- Thiamine pyrophosphate also catalyses reactions of α-keto-acids other than pyruvic acid.
- One such sequence leads through some remarkable chemistry to the biosynthesis of the branched chain amino acids valine and isoleucine.



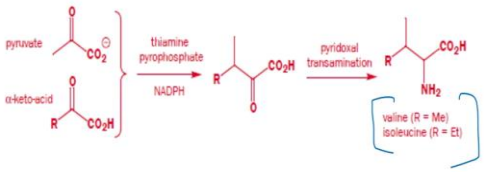
Clayden, 2000

So thiamine pyrophosphate also catalyzes reaction of alpha-keto-acids other than pyruvic acid.

So if you take pyruvate and react it in the presence of thiamine pyrophosphate and NADPH you can actually form valine and isoleucine.

(Refer Slide Time: 07:12)

- Thiamine pyrophosphate also catalyses reactions of α-keto-acids other than pyruvic acid.
- One such sequence leads through some remarkable chemistry to the biosynthesis of the branched chain amino acids valine and isoleucine.

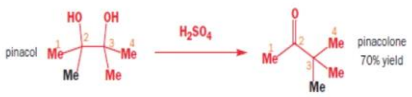


Clayden, 2000

Now let us look at this remarkable chemistry in the biosynthesis of branched chain amino acids valine and isoleucine.

(Refer Slide Time: 07:19)

- The remarkable aspect of this chemistry is that it involves 1,2-alkyl shifts in pinacol-like rearrangements
- Let us briefly look at the pinacol rearrangement...



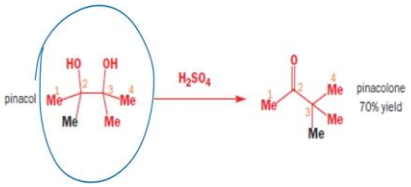
Clayden, 2000

So the remarkable aspect of this chemistry is that it involves, it involves a 1,2- alkyl shift which is resembling a pinacol like rearrangement. So in order for us to understand pinacol like rearrangement let us go back and look a little bit in detail what this rearrangement is.

So pinacol is basically this group here

(Refer Slide Time: 07:44)

- The remarkable aspect of this chemistry is that it involves 1,2-alkyl shifts in pinacol-like rearrangements
- Let us briefly look at the pinacol rearrangement...

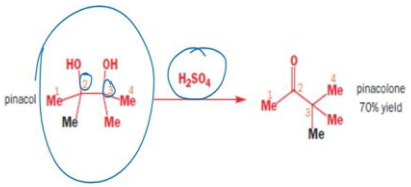


Clayden, 2000

which is shown here where there is a hydroxyl group on the 2 and 3 positions. So there are flanking hydroxyl groups which in the presence of

(Refer Slide Time: 07:53)

- The remarkable aspect of this chemistry is that it involves 1,2-alkyl shifts in pinacol-like rearrangements
- Let us briefly look at the pinacol rearrangement...

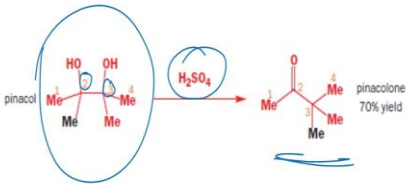


Clayden, 2000

an acid such as sulphuric acid gives you what is known as a

(Refer Slide Time: 07:57)

- The remarkable aspect of this chemistry is that it involves 1,2-alkyl shifts in pinacol-like rearrangements
- Let us briefly look at the pinacol rearrangement...



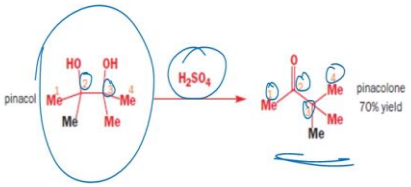
Clayden, 2000

pinacolone, Ok which is basically a ketone.

So where, if you number the carbons here, here is 1, 2, 3 and 4,

(Refer Slide Time: 08:04)

- The remarkable aspect of this chemistry is that it involves 1,2-alkyl shifts in pinacol-like rearrangements
- Let us briefly look at the pinacol rearrangement...

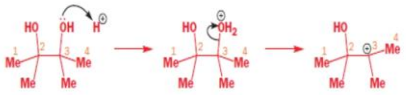


Clayden, 2000

so the carbon here is 1, 2, 3 and 4 and so you form a ketone on carbon 2 and the original alcohol that was present in carbon 2 has now gone and carbon 3 which has an alcohol is also now going to be occupied by a methyl group. So this is known as the pinacol pinacolone rearrangement. And now we shall look at the mechanism of this reaction.

(Refer Slide Time: 08:31)

- Under acidic conditions, the protonation of the hydroxyl group is likely, which can lead to the formation of a carbocation...

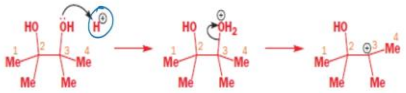


Clayden, 2000

So in the presence of acid it is quite likely that this alcohol will undergo

(Refer Slide Time: 08:35)

- Under acidic conditions, the protonation of the hydroxyl group is likely, which can lead to the formation of a carbocation...



Clayden, 2000

protonation. So once it undergoes protonation

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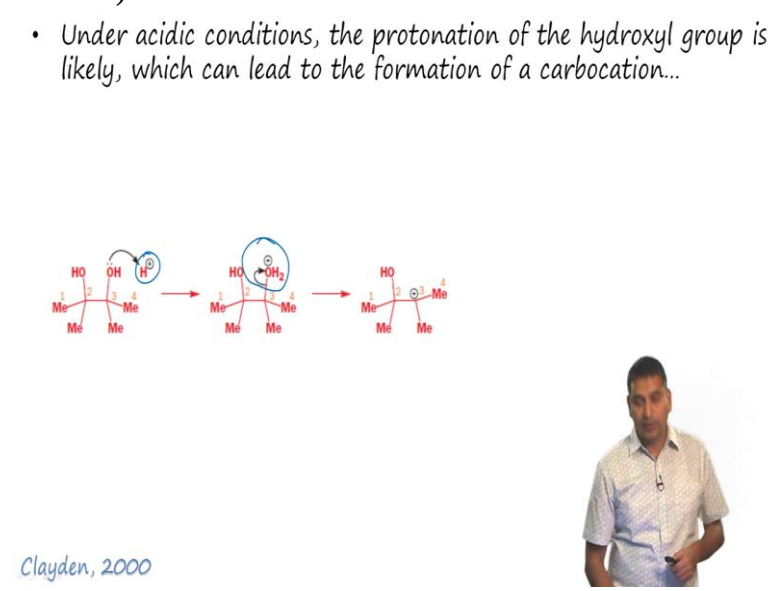
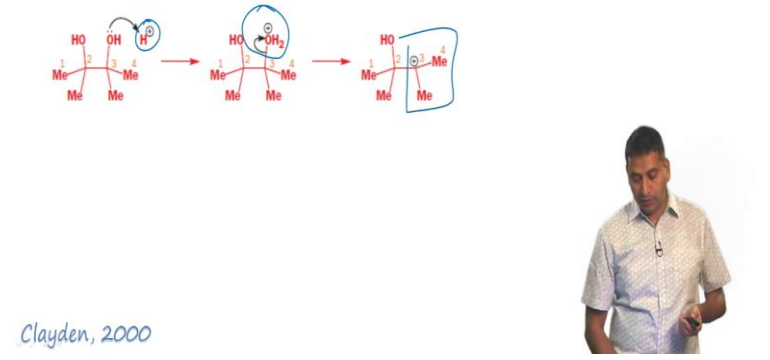


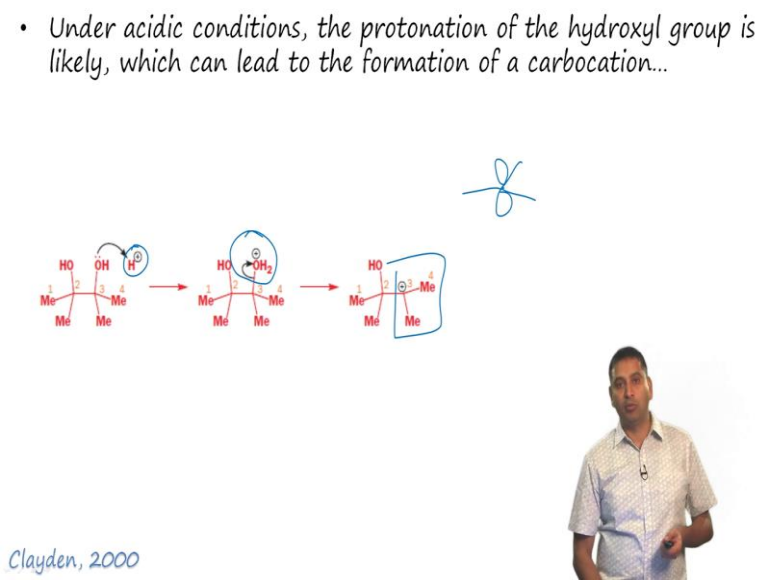
it is going to perhaps loose water to generate a carbocation,

(Refer Slide Time: 08:44)



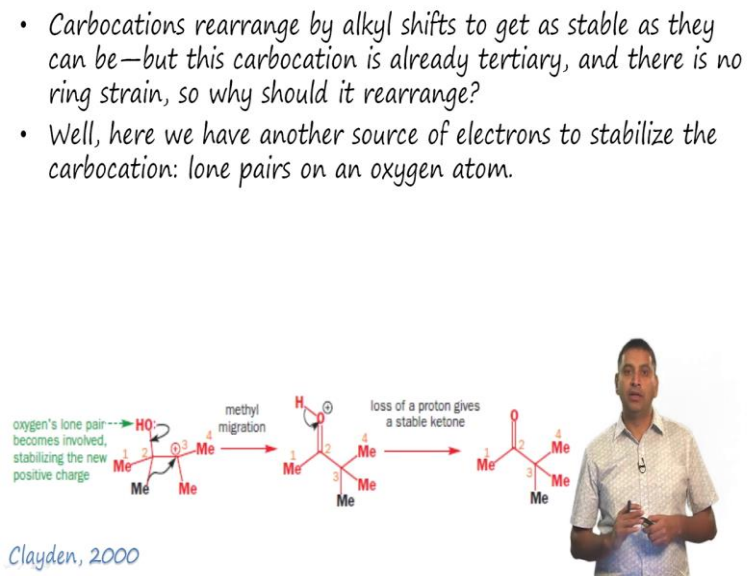
Ok. So this carbocation as we know is going to have an empty

(Refer Slide Time: 08:49)



p orbital which can facilitate this rearrangement or which can act as a place where this new carbon carbon bond is going to

(Refer Slide Time: 09:00)

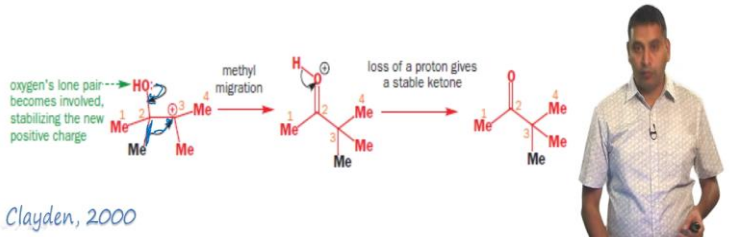


form.

So what happens is that the lone pair on the oxygen then comes in and this carbon methyl bond breaks

(Refer Slide Time: 09:10)

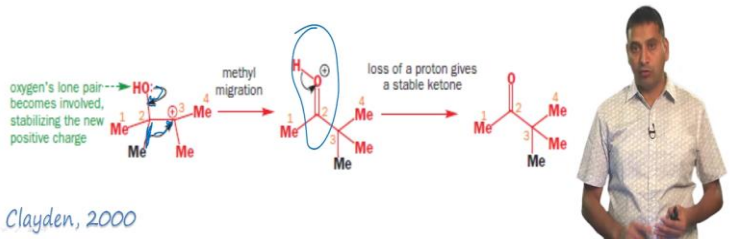
- Carbocations rearrange by alkyl shifts to get as stable as they can be—but this carbocation is already tertiary, and there is no ring strain, so why should it rearrange?
- Well, here we have another source of electrons to stabilize the carbocation: lone pairs on an oxygen atom.



and forms a new carbon carbon bond with the adjacent carbon and you form a protonated carbonyl

(Refer Slide Time: 09:17)

- Carbocations rearrange by alkyl shifts to get as stable as they can be—but this carbocation is already tertiary, and there is no ring strain, so why should it rearrange?
- Well, here we have another source of electrons to stabilize the carbocation: lone pairs on an oxygen atom.

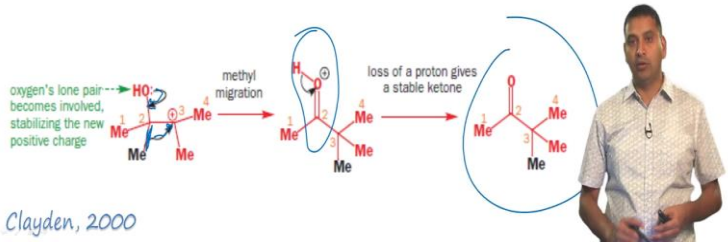


species as shown here.

And loss of this proton gives you the ketone

(Refer Slide Time: 09:22)

- Carbocations rearrange by alkyl shifts to get as stable as they can be—but this carbocation is already tertiary, and there is no ring strain, so why should it rearrange?
- Well, here we have another source of electrons to stabilize the carbocation: lone pairs on an oxygen atom.

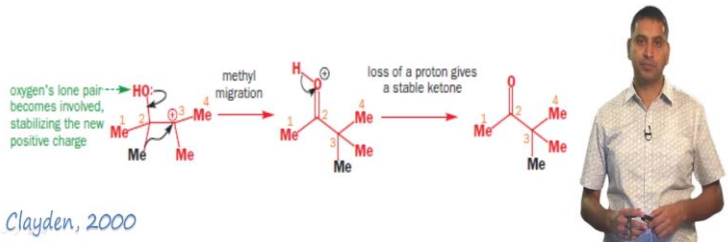


which is pinacolone. So carbocations are typically rearranged by alkyl shifts. But this carbocation is already in the tertiary form and so there is no need for it to rearrange.

So the reason why this rearranges is that the lone pair on oxygen plays an important role. So since the lone pair on oxygen can now move in and form a stable ketone, this is a, this constitutes a driving force for this reaction.

(Refer Slide Time: 09:49)

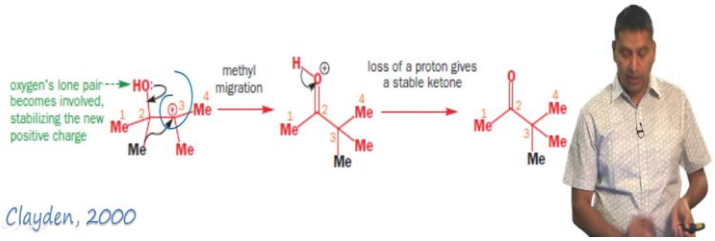
- Oxygen is very good at stabilizing a positive charge on an adjacent atom, and somewhat less good at stabilizing a positive charge two atoms away.
- By rearranging, the first-formed carbocation gets the positive charge into a position where the oxygen can stabilize it, and loss of a proton from oxygen then gives a stable ketone.



Also oxygen is very good at stabilizing a positive charge on an adjacent atom, and somewhat less good at stabilizing a positive charge two carbons away. So by rearranging the first formed carbocation which is here

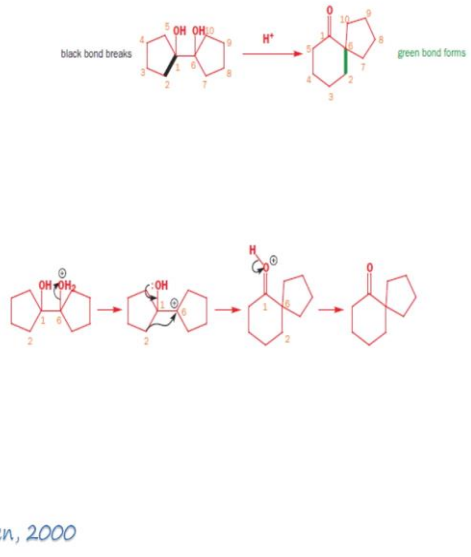
(Refer Slide Time: 10:05)

- Oxygen is very good at stabilizing a positive charge on an adjacent atom, and somewhat less good at stabilizing a positive charge two atoms away.
- By rearranging, the first-formed carbocation gets the positive charge into a position where the oxygen can stabilize it, and loss of a proton from oxygen then gives a stable ketone.



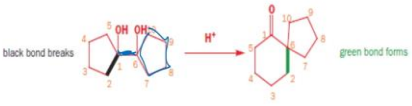
Ok gets the positive charge into a position where oxygen can stabilize it and loss of a proton from oxygen then gives a stable ketone.

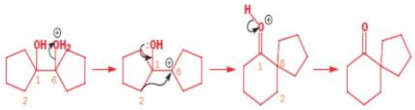
(Refer Slide Time: 10:14)



So let us look at an example here of this pinacol pinacolone rearrangement and here is a, the pinacol type

(Refer Slide Time: 10:24)

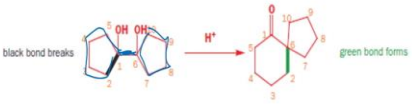


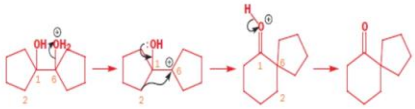


Clayden, 2000

structure with two 5-membered

(Refer Slide Time: 10:26)

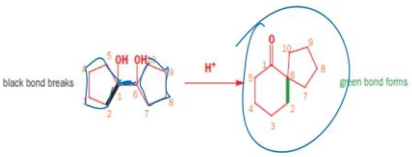


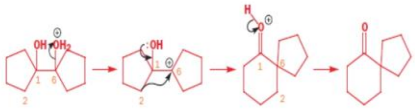


Clayden, 2000

rings and this rearranges and gives you

(Refer Slide Time: 10:28)

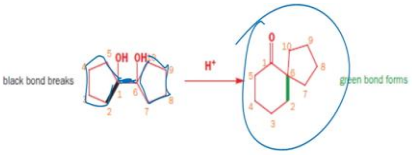


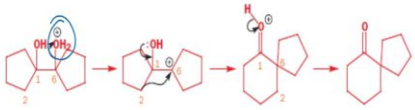


Clayden, 2000

this product here. So the mechanism that we would propose would be protonation of this OH to give

(Refer Slide Time: 10:35)



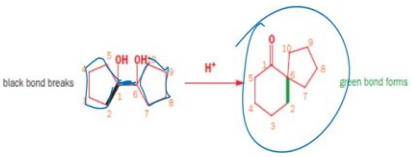


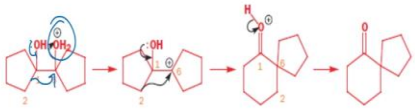
Clayden, 2000

you OH_2 plus.

And subsequently the rearrangement or the shift of this carbon carbon

(Refer Slide Time: 10:43)



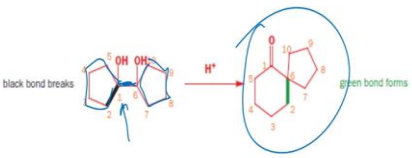


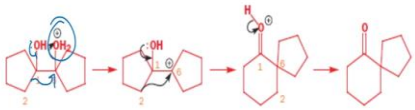
Clayden, 2000

bond here will give you a spirocyclic system. So a very useful tip in solving such rearrangement mechanisms is to number the carbons. So if we are able to number the carbons correctly then we can keep track of which carbon ends up where.

So if you number, if you see that

(Refer Slide Time: 11:02)

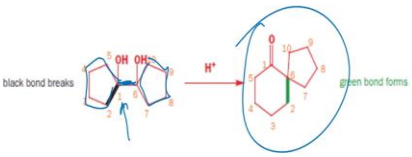


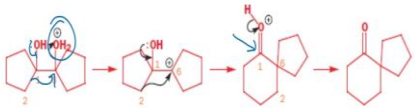


Clayden, 2000

this is carbon number 1 and this

(Refer Slide Time: 11:04)

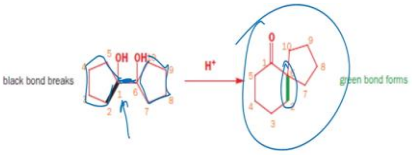


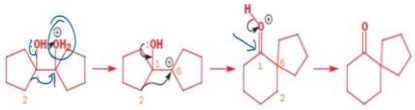


Clayden, 2000

is carbon number 1, if you keep track of it then you know that the carbon number 1 which has an alcohol initially ends up with a ketone. And the bond

(Refer Slide Time: 11:14)

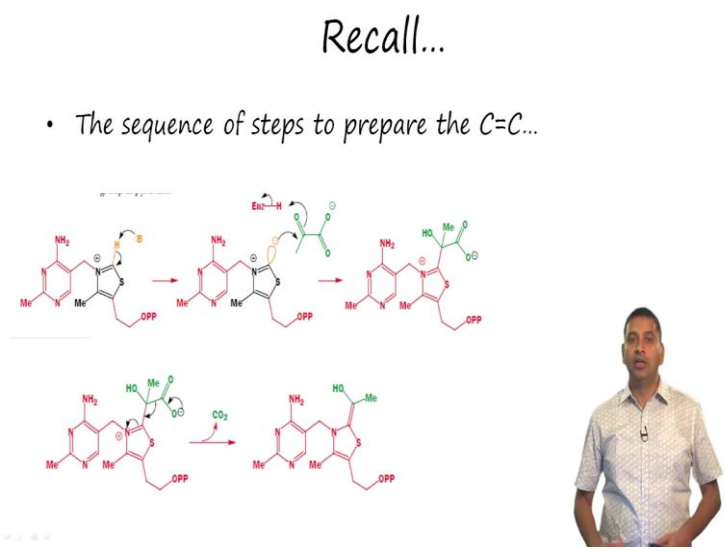




Clayden, 2000

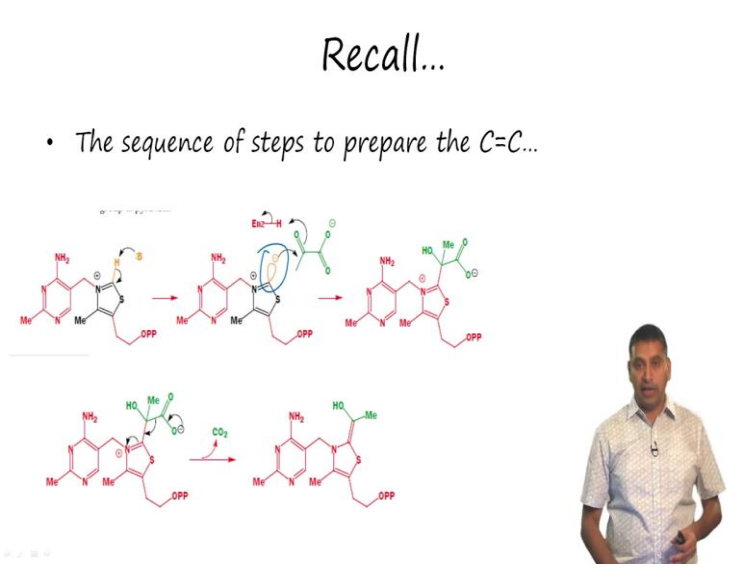
that forms is between carbon 2 and carbon 6 which is shown here, Ok.

(Refer Slide Time: 11:19)



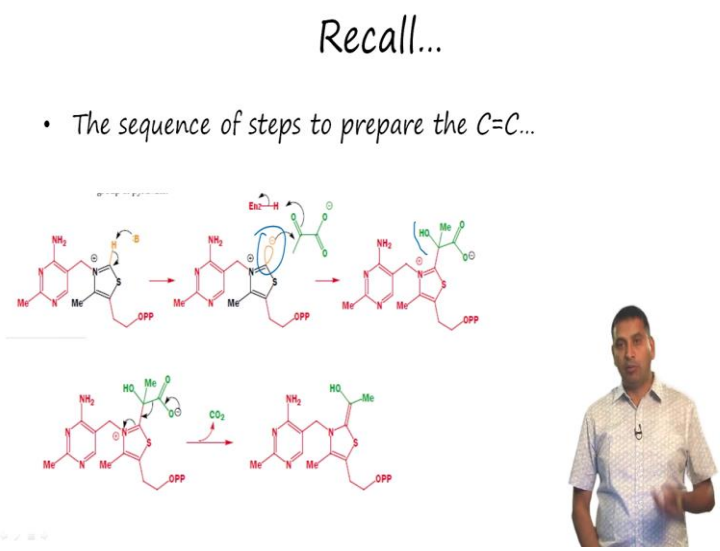
So now just to recall or put it in perspective of what we are looking at in thiamine, so thiamine forms a carbanion which is shown here

(Refer Slide Time: 11:29)



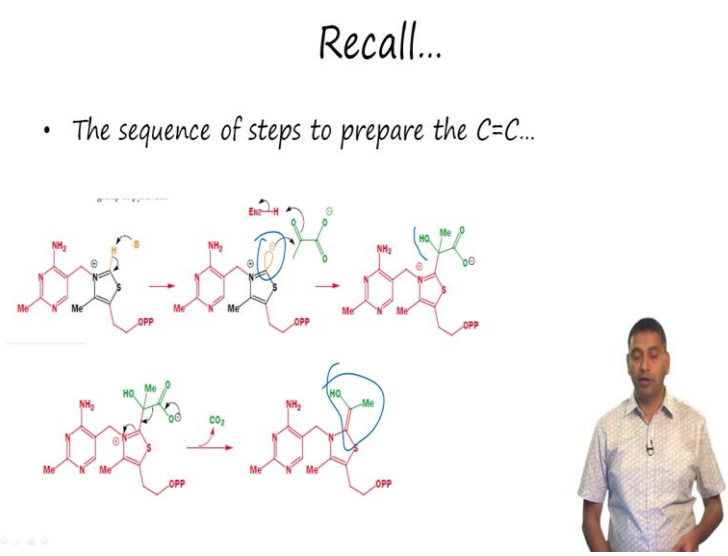
and this carbanion reacts with pyruvate to give you this alcohol here.

(Refer Slide Time: 11:35)



The carboxylate then undergoes decarboxylation to produce this enol shown here.

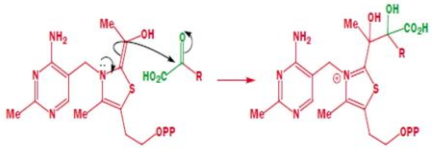
(Refer Slide Time: 11:40)



And as we discussed this enol is a very interesting enol because it has 3 electronegative atoms on it. And it can then serve to do very interesting

(Refer Slide Time: 11:53)

- The sequence starts as before and we will pick it up after the addition and decarboxylation of pyruvate...



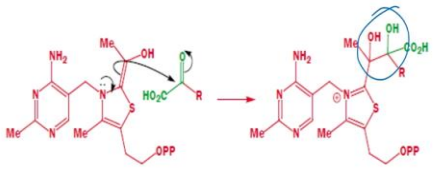
Clayden, 2000

reactions. So the sequence of reactions starts now.

So this enol reacts with the ketone or the alpha-keto-carboxylic acid and then it forms an intermediate which is exactly

(Refer Slide Time: 12:08)

- The sequence starts as before and we will pick it up after the addition and decarboxylation of pyruvate...

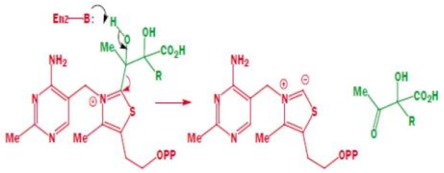


Clayden, 2000

identical to the pinacol type reaction. So

(Refer Slide Time: 12:13)

- Decomposition of this product with the release of the thiazolium ylid also releases the product of coupling between the two keto-acids: a 1-hydroxy-2-keto-acid
- Thiazolium ylid is free to catalyse the next round of the reaction.



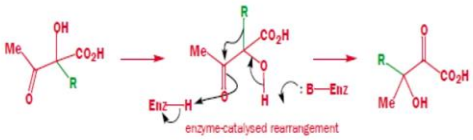
Clayden, 2000

here the decomposition of this product with the release of thiazolium ylid can occur.

It also releases the product of a coupling reaction between two keto acids, that is it forms a 1-hydroxyl-2-keto acid. So the thiazolium ylid is now free to catalyze the next round of reactions.

(Refer Slide Time: 12:33)

- The hydroxy-keto-acid is now primed for rearrangement.
- The migration of the group R is pushed by the removal of a proton from the OH group and pulled by the electron-accepting power of the keto group.
- Notice that the group R (Me or Et) migrates in preference to CO_2H.



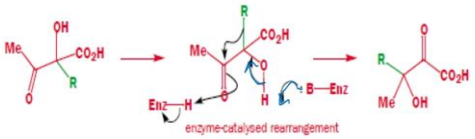
Clayden, 2000

So the hydroxy keto acid is now primed for the rearrangement.

So the migration of the R group is pushed by the removal of a proton from hydroxyl group, Ok. So you can think about this enzyme with the basic residue here coming and picking up

(Refer Slide Time: 12:50)

- The hydroxy-keto-acid is now primed for rearrangement.
- The migration of the group R is pushed by the removal of a proton from the OH group and pulled by the electron-accepting power of the keto group.
- Notice that the group R (Me or Et) migrates in preference to CO_2H.

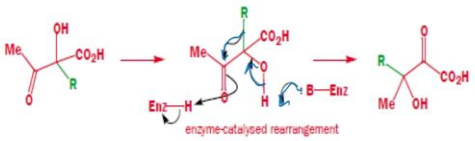


Clayden, 2000

this proton and then this R moves here

(Refer Slide Time: 12:53)

- The hydroxy-keto-acid is now primed for rearrangement.
- The migration of the group R is pushed by the removal of a proton from the OH group and pulled by the electron-accepting power of the keto group.
- Notice that the group R (Me or Et) migrates in preference to CO_2H.



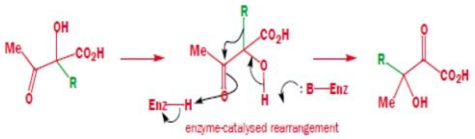
Clayden, 2000

to, and reacts with the ketone and gives you the product.

Notice that the R group which is methyl or ethyl migrates in preference to the carboxylic acid.

(Refer Slide Time: 13:05)

- Usually, the group that is better able to accommodate the positive charge migrates...
- Here, the enzyme plays a major role in determining migration

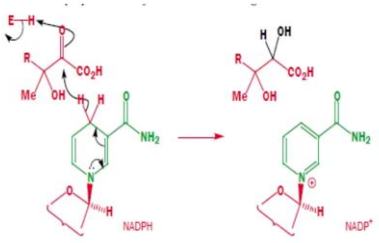


Clayden, 2000

So usually the group that is better able to accommodate the positive charge migrates. So here again the enzyme plays a major role in determining migration.

(Refer Slide Time: 13:17)

- Control in this reaction is likely to be exerted stereoelectronically by the enzyme as it was in the pyridoxal reactions above.
- Since the C–R bond is held parallel to the p orbitals of the ketone, R migration occurs, but if the CO_2H group were to be held parallel to the p orbitals of the ketone, decarboxylation would occur.



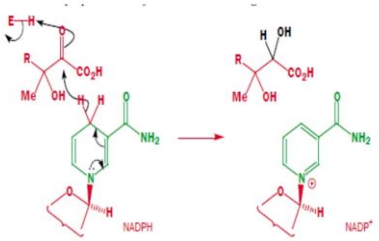
Clayden, 2000

So control in this reaction is likely exerted stereoelectronically by the enzyme as it was done in the pyridoxal reactions which we discussed previously. Since the carbon R bond is held parallel to the p orbitals of the ketone R migration occurs. But if the carboxylic acid were to be held parallel to the p orbital then decarboxylation would occur.

So, which is what we saw in the previous case, in the case of the NAD reaction.

(Refer Slide Time: 13:48)

- A simple reduction with NADPH converts the ketone into an alcohol and prepares the way for a second rearrangement.

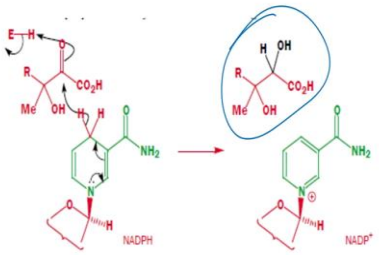


Clayden, 2000

So simple reduction with NADPH converts the ketone to an alcohol and prepares the way for a second rearrangement. So when this reduction occurs then you end up with the

(Refer Slide Time: 14:01)

- A simple reduction with NADPH converts the ketone into an alcohol and prepares the way for a second rearrangement.

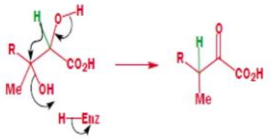


Clayden, 2000

dihydroxy compound as shown here.

(Refer Slide Time: 14:04)

- The second rearrangement is even more like a pinacol rearrangement because the starting material is a 1,2-diol.
- The tertiary alcohol is protonated and leaves, and again the CO_2H group does not migrate even though the alternative is merely hydride.



Clayden, 2000

The second rearrangement is even more like a pinacol rearrangement because the starting material is a 1,2-diol. So the tertiary alcohol is protonated and leaves and again the carboxylic acid does not migrate even though the alternative is merely hydride, Ok. So here you again have

(Refer Slide Time: 14:23)

- The second rearrangement is even more like a pinacol rearrangement because the starting material is a 1,2-diol.
- The tertiary alcohol is protonated and leaves, and again the CO_2H group does not migrate even though the alternative is merely hydride.

Clayden, 2000

a shift of this

(Refer Slide Time: 14:25)

- The second rearrangement is even more like a pinacol rearrangement because the starting material is a 1,2-diol.
- The tertiary alcohol is protonated and leaves, and again the CO_2H group does not migrate even though the alternative is merely hydride.

Clayden, 2000

carbon hydrogen hydride here to kick out

(Refer Slide Time: 14:27)

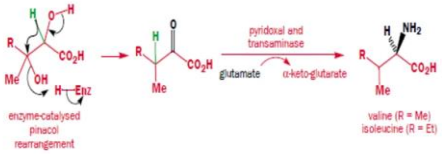
- The second rearrangement is even more like a pinacol rearrangement because the starting material is a 1,2-diol.
- The tertiary alcohol is protonated and leaves, and again the CO_2H group does not migrate even though the alternative is merely hydride.

Clayden, 2000

hydroxide ion to give you the product as shown here.

(Refer Slide Time: 14:31)

- Finally, a pyridoxal transamination converts the two keto-acids stereospecifically to the corresponding amino acids, valine (R = Me) and isoleucine (R = Et).
- The donor amino acid is probably glutamate—it usually is in amino acid synthesis.

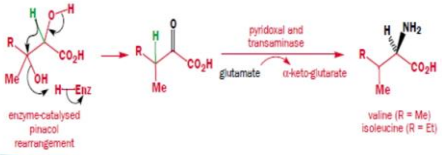


Clayden, 2000

Finally a pyridoxal transamination converts the two keto acids stereospecifically to the corresponding amino acids. So where R is methyl it becomes valine, and when R is ethyl it becomes isoleucine. So the donor amino acid is probably glutamate and it usually is in the amino acid synthesis. So this

(Refer Slide Time: 14:54)

- Finally, a pyridoxal transamination converts the two keto-acids stereospecifically to the corresponding amino acids, valine (R = Me) and isoleucine (R = Et).
- The donor amino acid is probably glutamate—it usually is in amino acid synthesis.

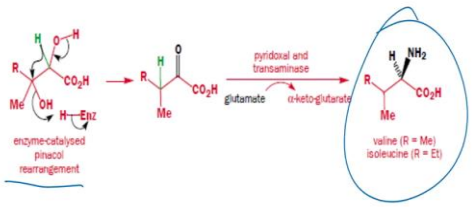


Clayden, 2000

enzyme catalysed pinacol rearrangement gives you the final product

(Refer Slide Time: 14:59)

- Finally, a pyridoxal transamination converts the two keto-acids stereospecifically to the corresponding amino acids, valine (R = Me) and isoleucine (R = Et).
- The donor amino acid is probably glutamate—it usually is in amino acid synthesis.



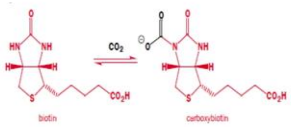
Clayden, 2000

which is valine or isoleucine.

(Refer Slide Time: 15:03)

Carrying carbon dioxide

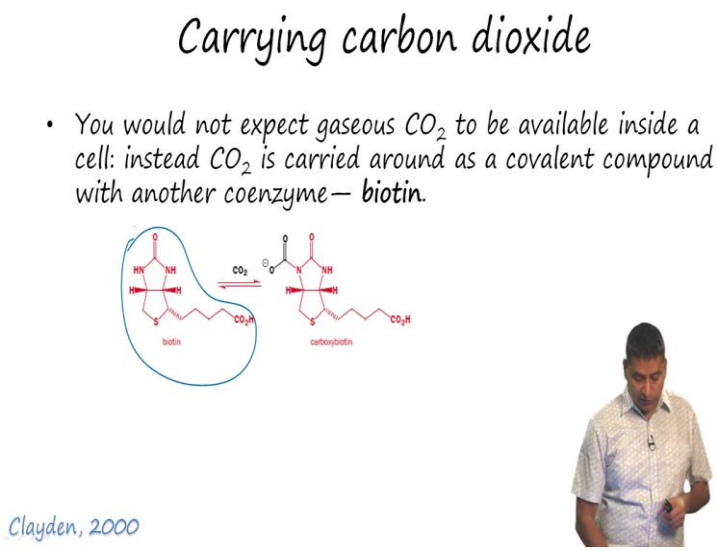
- You would not expect gaseous CO_2 to be available inside a cell: instead CO_2 is carried around as a covalent compound with another coenzyme— **biotin**.



Clayden, 2000

The next topic that we will look at is carrying carbon dioxide. So we would not expect gaseous carbon dioxide to be available inside a cell. Instead CO_2 is carried out as a covalent molecule by another coenzyme known as biotin. So here is a structure of biotin and

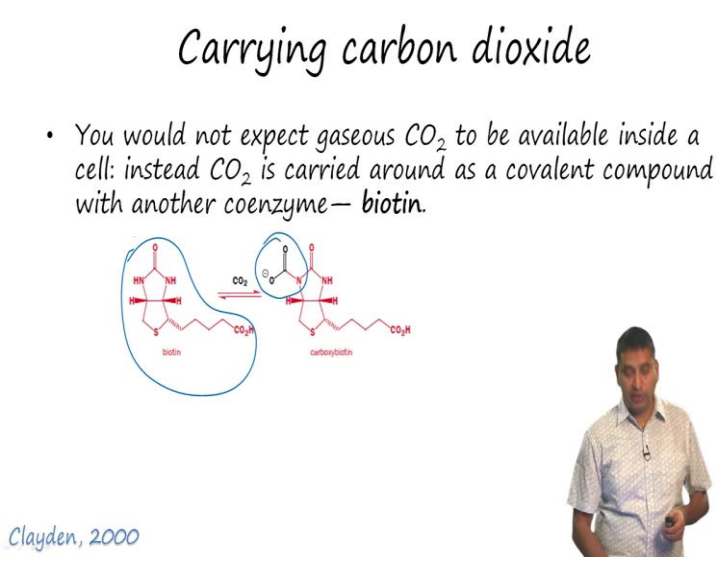
(Refer Slide Time: 15:21)



it has this thioether which is in a 5-membered ring and it also has a urea functional group on it.

And this can react with carbon dioxide to produce

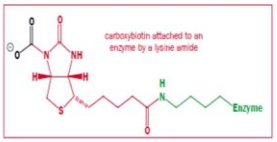
(Refer Slide Time: 15:35)



a species such as this.

(Refer Slide Time: 15:37)

- Biotin has two fused five-membered heterocyclic rings.
- The lower is a cyclic sulfide and has a long side chain ending in a carboxylic acid for attachment to a lysine residue of a protein
- The upper ring is a urea—it has a carbonyl group flanked by two nitrogen atoms.
- It is this ring that reversibly captures CO_2, on the nitrogen atom opposite the long side chain.
- The attachment to the enzyme as a lysine amide gives it an exceptionally long flexible chain and allows it to deliver CO_2 wherever it's needed.



Clayden, 2000

So biotin has two fused 5-member rings, heterocyclic rings. The lower is a cyclic sulfide and has a long side chain ending up in a carboxylic acid. And so this helps with

(Refer Slide Time: 15:50)

- Biotin has two fused five-membered heterocyclic rings.
- The lower is a cyclic sulfide and has a long side chain ending in a carboxylic acid for attachment to a lysine residue of a protein
- The upper ring is a urea—it has a carbonyl group flanked by two nitrogen atoms.
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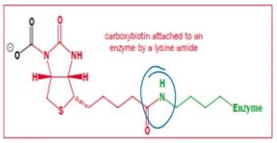
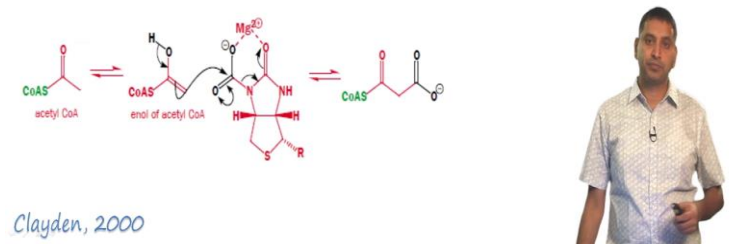


Clayden, 2000

attaching itself to lysine residues of a protein.

The upper ring is a urea and it has a carbonyl group that is flanked by two nitrogens. It is this ring that reversibly captures CO_2 on the nitrogen atom opposite the long side chain. The attachment of the enzyme as a lysine amide gives it an exceptionally long flexible chain and allows it to deliver CO_2 whenever it is needed.

(Refer Slide Time: 16:14)



One of the important points at which CO_2 enters as a reagent carried by biotin is in the fatty acid biosynthesis where CO_2 is transferred from a, to the enol of acetyl CoA. We have already looked at the major aspects of the structure and reaction of acetyl CoA.

But here a magnesium ion is also required and one can imagine the reaction as a nucleophilic attack of the enol on the magnesium salt of carboxybiotin.

So what we would expect is that magnesium would form

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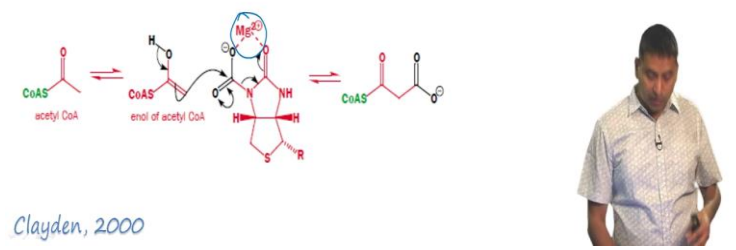
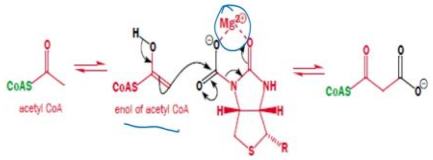


some sort of a chelating arrangement as shown here and then we just looked at acetyl CoA being an excellent enol transferring group and so you can form, this is the enol

(Refer Slide Time: 16:58)

- One of the important points at which CO_2 enters as a reagent carried by biotin is in fatty acid biosynthesis where CO_2 is transferred to the enol of acetyl CoA.
- A magnesium(II) ion is also required and we may imagine the reaction as a nucleophilic attack of the enol on the magnesium salt of carboxybiotin.

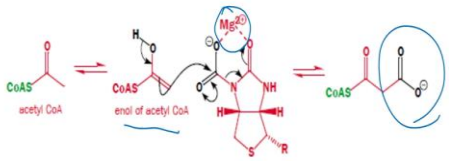


Clayden, 2000

of acetyl Co A which then reacts with this carbon dioxide and produces

(Refer Slide Time: 17:03)

- One of the important points at which CO_2 enters as a reagent carried by biotin is in fatty acid biosynthesis where CO_2 is transferred to the enol of acetyl CoA.
- A magnesium(II) ion is also required and we may imagine the reaction as a nucleophilic attack of the enol on the magnesium salt of carboxybiotin.



Clayden, 2000

this type of a product.

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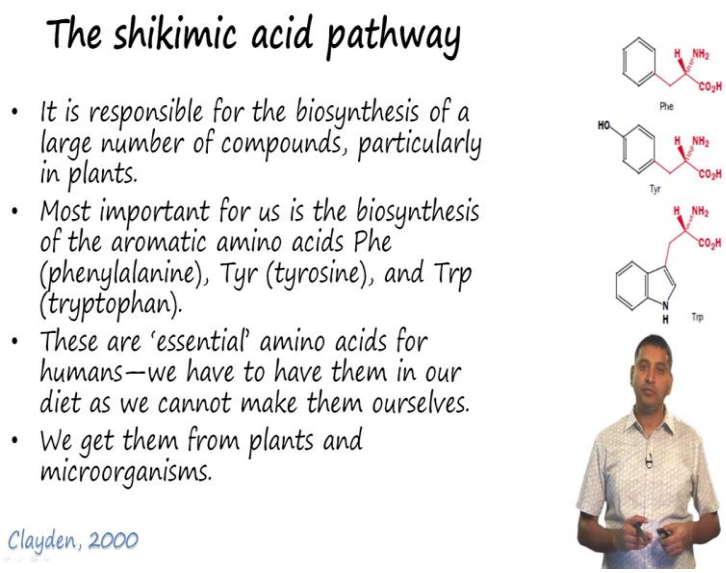
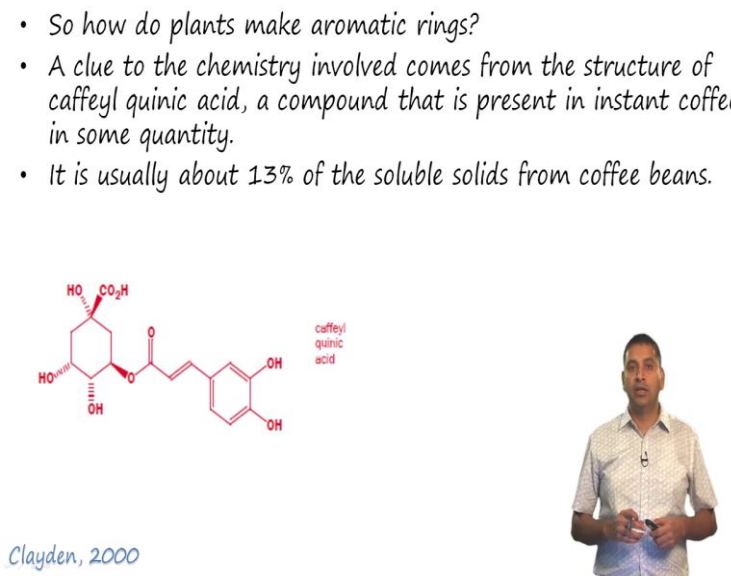


Now let us look at a very important pathway which is the shikimic acid pathway. This pathway is responsible for the biosynthesis of a large number of compounds. And it is very important in plants. Most importantly for us is the biosynthesis of aromatic amino acids which are phenylalanine, tyrosine and tryptophan whose structures are shown here.

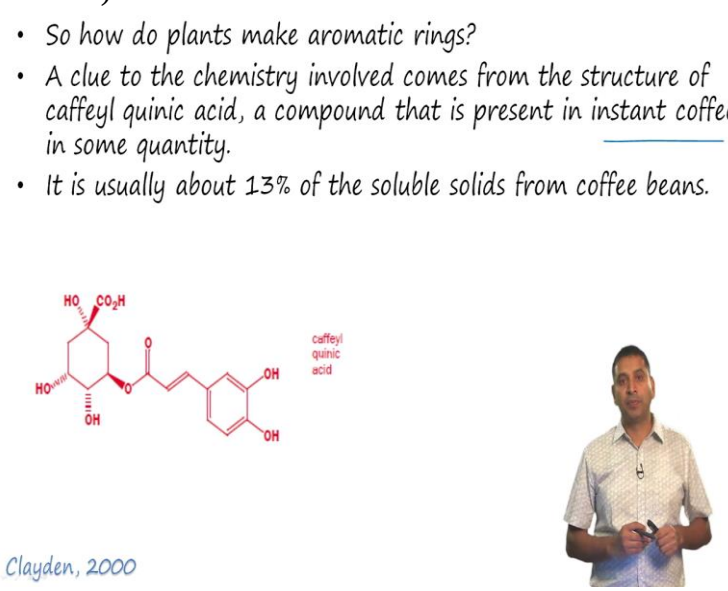
These are classified as essential amino acids and we have to have them in our diet as we cannot make them ourselves. So we get them from plants and microorganisms.

(Refer Slide Time: 17:39)



So how do plant, plants make these aromatic rings? So clue to this structure, to this chemistry comes from the structure of caffeyl quinic acid which is a compound that is present in instant coffee in some quantity.

(Refer Slide Time: 17:54)



It is about 13 percent of soluble

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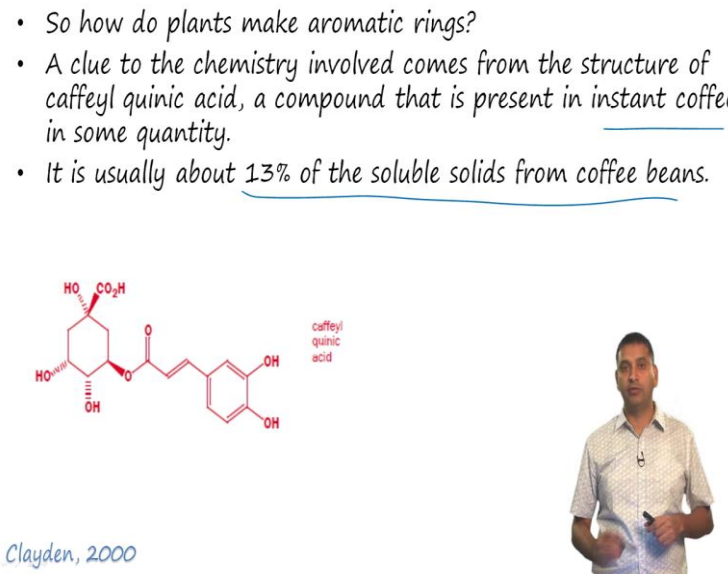
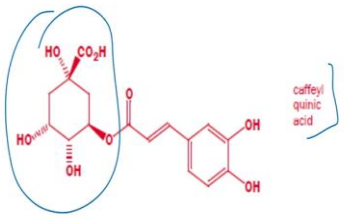


solids from coffee beans. So here is a structure of caffeyl quinic acid. It is have this very nice

(Refer Slide Time: 18:03)

- So how do plants make aromatic rings?
- A clue to the chemistry involved comes from the structure of caffeyl quinic acid, a compound that is present in instant coffee in some quantity.
- It is usually about 13% of the soluble solids from coffee beans.

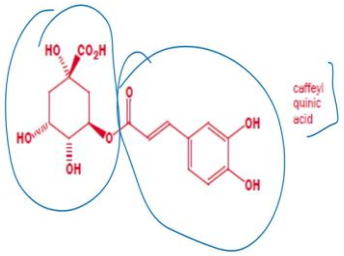


Clayden, 2000

sugar unit here or a carbosugar unit here and it has this

(Refer Slide Time: 18:09)

- So how do plants make aromatic rings?
- A clue to the chemistry involved comes from the structure of caffeyl quinic acid, a compound that is present in instant coffee in some quantity.
- It is usually about 13% of the soluble solids from coffee beans.



Clayden, 2000

dihydroxy benzene ring which is attached to alpha beta unsaturated ester.

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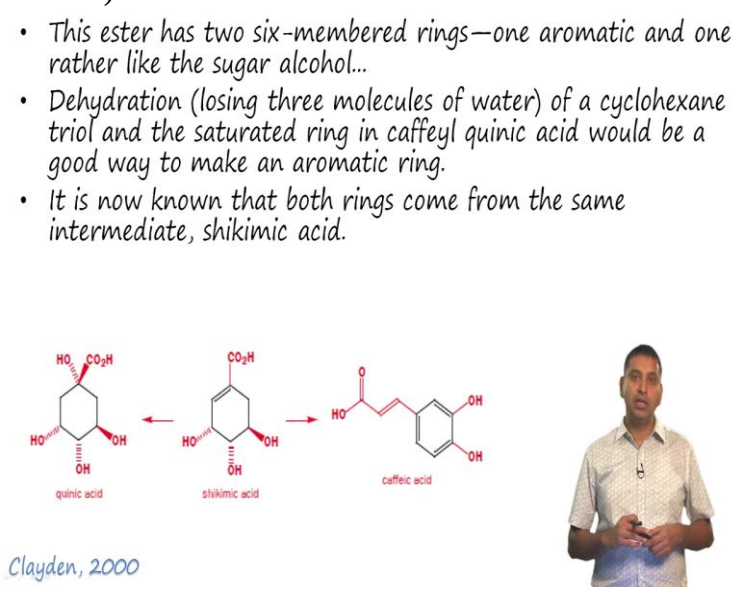
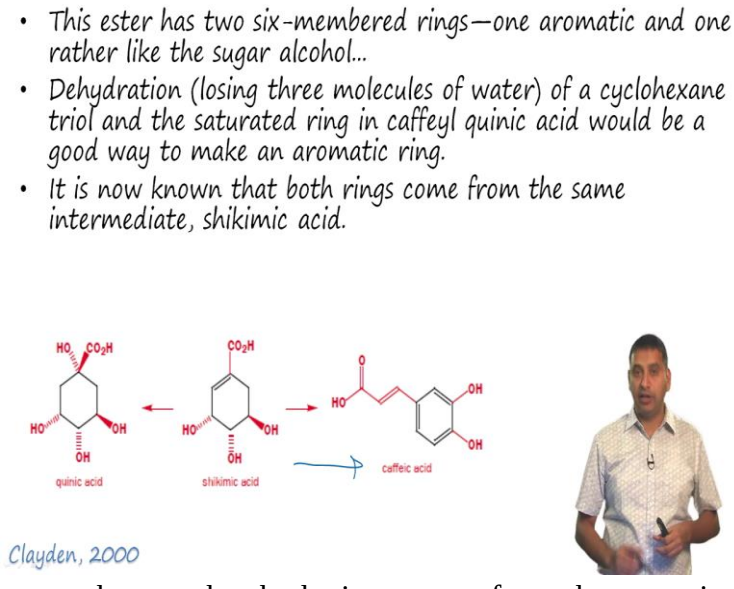


So this ester has two six-membered rings, one aromatic and one rather like a sugar alcohol.

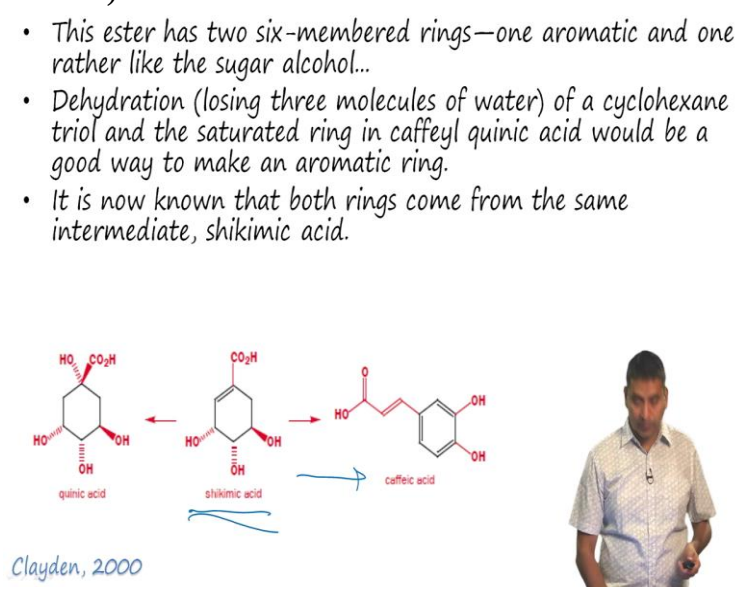
So you can imagine that dehydration, that is losing 3 molecules of water from this species is going to give you a

(Refer Slide Time: 18:30)



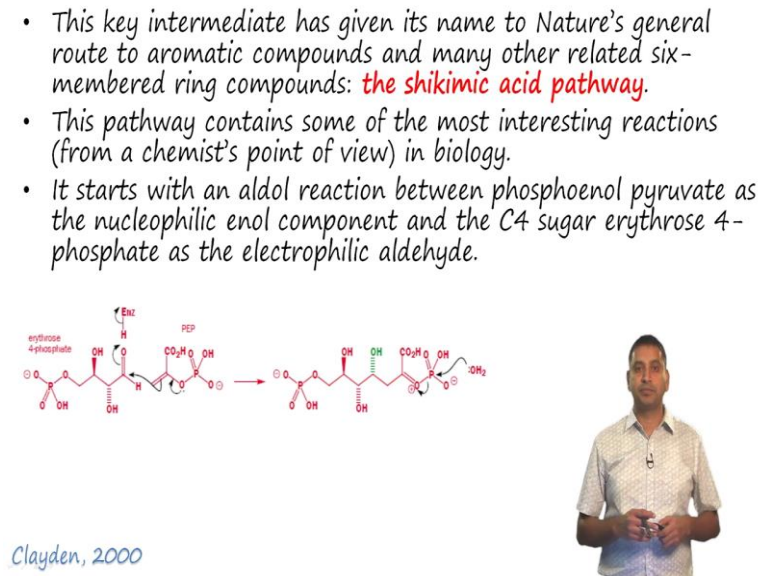
caffeic acid. It is now known that both rings come from the same intermediate which is shikimic acid whose structure is shown here.

(Refer Slide Time: 18:38)



So we shall now look at the biosynthesis of shikimic acid or conversion of shikimic acid to an aromatic ring.

(Refer Slide Time: 18:45)

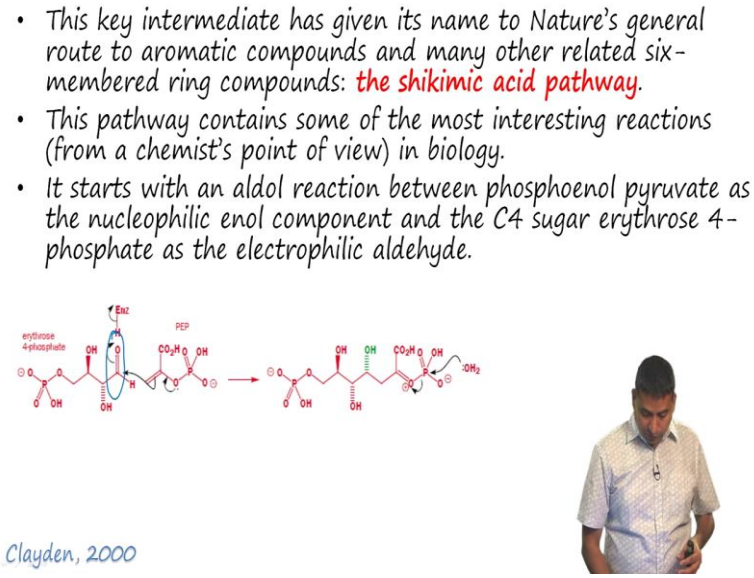


So the key intermediate has given its name to nature's general route to aromatic compounds and many others related six-membered rings which is called the shikimic acid pathway. This pathway contains some of the most interesting reactions especially from a chemist's standpoint in biology.

It starts with a very interesting aldol reaction between a phoshoenolpyruvate which we have looked at previously as the nucleophilic enol component and a C4 sugar, erythrose-4-phosphate as the electrophilic aldehyde.

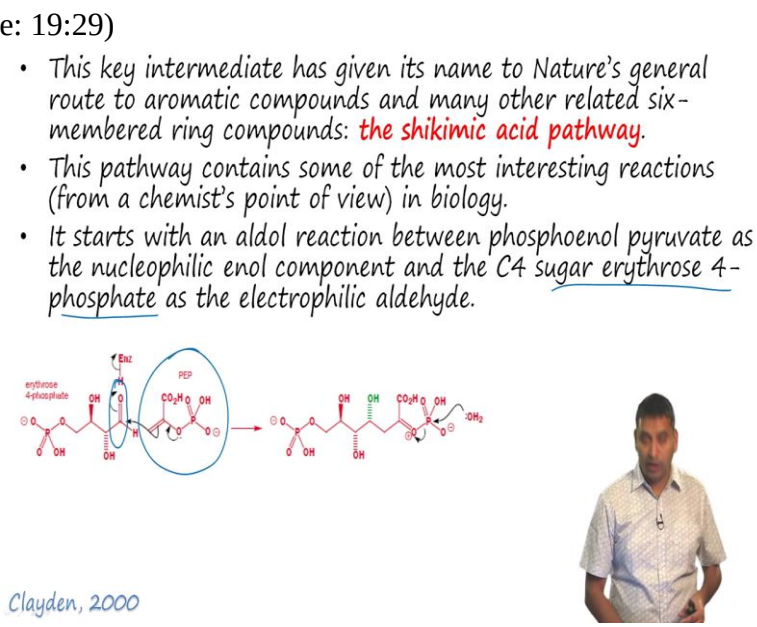
So here is the electrophilic aldehyde

(Refer Slide Time: 19:24)



which comes from erythrose-4-phosphate and here is the

(Refer Slide Time: 19:29)

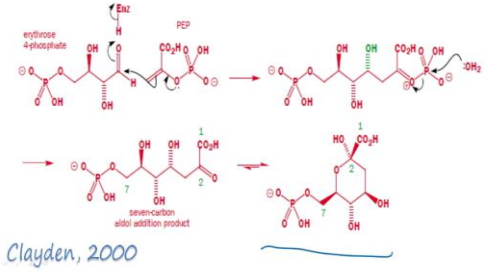


phoshoenolpyruvate equivalent. And now you can imagine an aldol reaction that can, that occurs which gives you this product.

And now this can subsequently break to give, or can be hydrolyzed by water to give you inorganic phosphate and give you the ketone. So once it gives you this ketone this intermediate has the right number of carbons for shikimic acid and the next stage is a cyclization reaction. So here the cyclization reaction gives you this

(Refer Slide Time: 19:59)

- Hydrolysis of the phosphate releases the aldol product, a C7 α-keto-acid with one new stereogenic centre, which is in equilibrium with a hemiacetal, just like a sugar.
- This intermediate has the right number of carbon atoms for shikimic acid and the next stage is a cyclization.

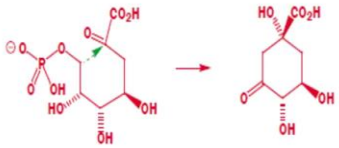


Clayden, 2000

intermediate as shown here.

(Refer Slide Time: 20:01)

- If we redraw the C7 α-keto-acid in the right shape for cyclization we can see what is needed.
- The green arrow shows only which bond needs to be formed

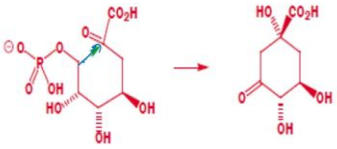


Clayden, 2000

Now if we redraw this C7 alpha-keto-acid in the right shape for cyclization we can see what is needed. So here is the, the bond that we need to

(Refer Slide Time: 20:12)

- If we redraw the C7 α-keto-acid in the right shape for cyclization we can see what is needed.
- The green arrow shows only which bond needs to be formed

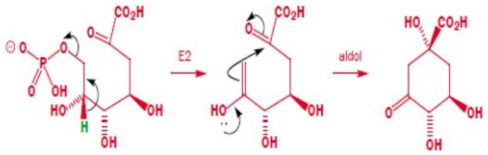


Clayden, 2000

form and this can happen

(Refer Slide Time: 20:15)

- This reaction looks like an aldol reaction too and there is an obvious route to the required enol by elimination of phosphate.
- This would require the removal of a proton (green in the diagram) that is not at all acidic.



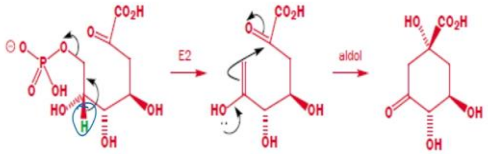
Clayden, 2000

in the following manner. This reaction looks like an aldol reaction too but there is an obvious route to the required enol by the elimination of the phosphate.

This would require removal of a proton which is here

(Refer Slide Time: 20:29)

- This reaction looks like an aldol reaction too and there is an obvious route to the required enol by elimination of phosphate.
- This would require the removal of a proton (green in the diagram) that is not at all acidic.

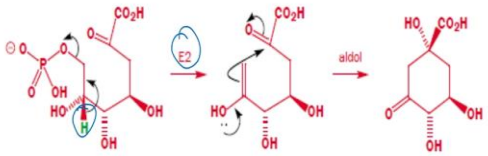


Clayden, 2000

from this molecule but this is not at all acidic, right. So you can imagine that it can go through an E2 process

(Refer Slide Time: 20:37)

- This reaction looks like an aldol reaction too and there is an obvious route to the required enol by elimination of phosphate.
- This would require the removal of a proton (green in the diagram) that is not at all acidic.

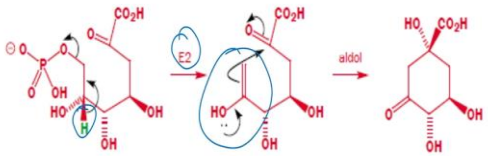


Clayden, 2000

wherein this proton is lost and give you this enol which

(Refer Slide Time: 20:41)

- This reaction looks like an aldol reaction too and there is an obvious route to the required enol by elimination of phosphate.
- This would require the removal of a proton (green in the diagram) that is not at all acidic.

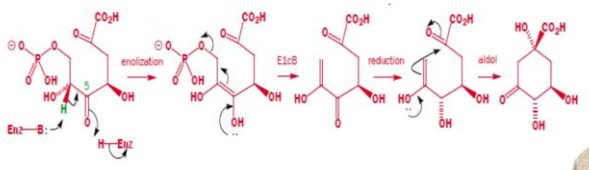


Clayden, 2000

then can react with the ketone. But since this hydrogen is not at all acidic, nature adopts a very interesting route to carry out this reaction. Let us look at that now.

(Refer Slide Time: 20:51)

- The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD^+ is the oxidant).
- Then the green proton is much more acidic, and the elimination becomes an E1cB reaction, similar to the one in the synthesis of PEP.
- The ketone must be reduced back to the alcohol afterwards but Nature can deal with that easily.



Clayden, 2000

So the problem is avoided if the hydroxyl group at C5 is first oxidized to the ketone. So we have already looked at NAD plus

(Refer Slide Time: 20:59)

- The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD^+ is the oxidant).
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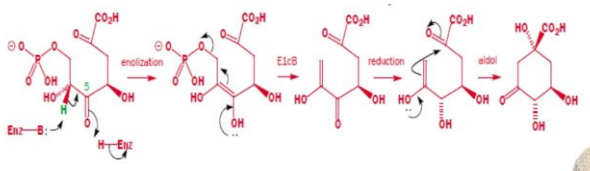

Clayden, 2000

can be the oxidant. So what we are doing here is that this hydrogen

(Refer Slide Time: 21:04)

- The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD^+ is the oxidant).
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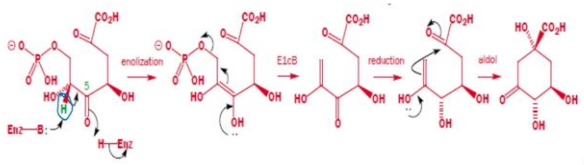
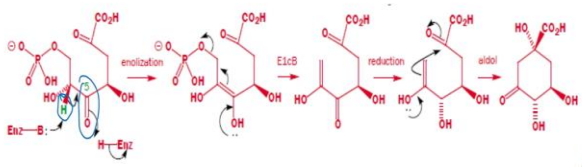


Clayden, 2000

shown here which was previously not acidic

(Refer Slide Time: 21:07)

- The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD^+ is the oxidant).
- Then the green proton is much more acidic, and the elimination becomes an E1cB reaction, similar to the one in the synthesis of PEP.
- The ketone must be reduced back to the alcohol afterwards but Nature can deal with that easily.



Clayden, 2000

is now adjacent to a ketone and now this pushes down the pKa substantially and makes it acidic enough.

Now if it undergoes enolization,

(Refer Slide Time: 21:17)

- The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD^+ is the oxidant).
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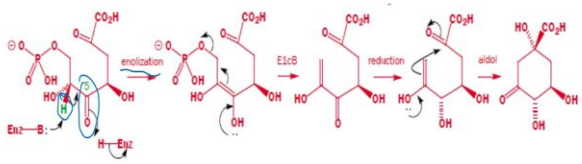

Clayden, 2000

the enolization is going to

(Refer Slide Time: 21:19)

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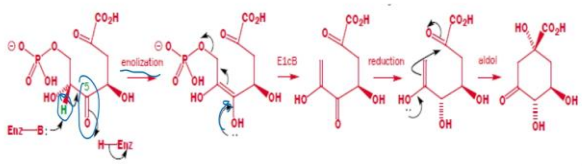
- The ketone must be reduced back to the alcohol afterwards but Nature can deal with that easily.

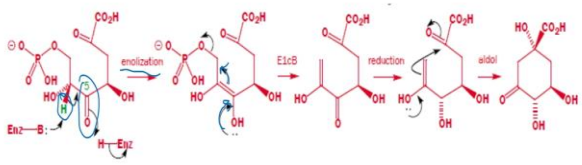


Clayden, 2000

give you

(Refer Slide Time: 21:20)

- The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD^+ is the oxidant).
- Then the green proton is much more acidic, and the elimination becomes an E1cB reaction, similar to the one in the synthesis of PEP.
- The ketone must be reduced back to the alcohol afterwards but Nature can deal with that easily.



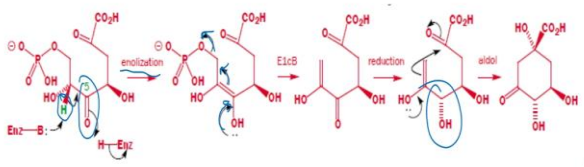
Clayden, 2000

an enol such as this which can undergo E1cB type elimination reaction to kick out phosphate and give you this product.

Subsequently reduction by NADH perhaps was going to give you back the alcohol here

(Refer Slide Time: 21:35)

- The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD^+ is the oxidant).
- Then the green proton is much more acidic, and the elimination becomes an E1cB reaction, similar to the one in the synthesis of PEP.
- The ketone must be reduced back to the alcohol afterwards but Nature can deal with that easily.

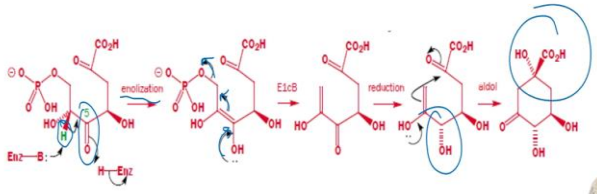


Clayden, 2000

which then undergoes aldol reaction to give you the

(Refer Slide Time: 21:39)

- The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD^+ is the oxidant).
- Then the green proton is much more acidic, and the elimination becomes an E1cB reaction, similar to the one in the synthesis of PEP.
- The ketone must be reduced back to the alcohol afterwards but Nature can deal with that easily.

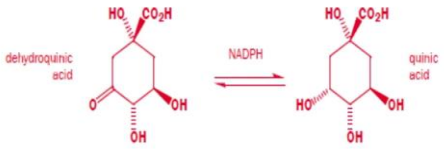


Clayden, 2000

desired product.

(Refer Slide Time: 21:41)

- This product is dehydroquinic acid and is an intermediate on the way to shikimic acid.
- It is also in equilibrium with quinic acid, which is not an intermediate on the pathway but which appears in some natural products like the coffee ester caffeyl quinic acid.



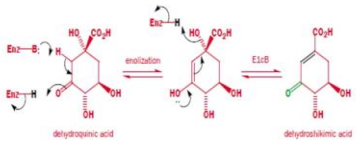
Clayden, 2000

The product is actually, is dehydroquinic acid and is an intermediate on the way to shikimic acid.

It is also in equilibrium with quinic acid which is not an intermediate on the pathway but which appears on some natural products like coffee ester, caffeyl quinic acid.

(Refer Slide Time: 22:00)

- The route to shikimic acid in plants involves, as the final steps, the dehydration of dehydroquinic acid and then reduction of the carbonyl group.
- Doing the reactions this way round means that the dehydration can be E1cB—much preferred under biological conditions.

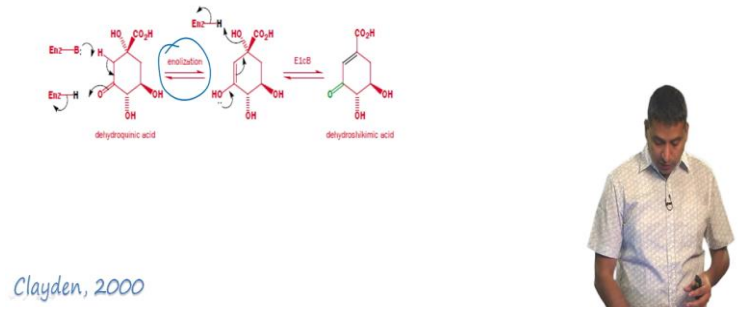


Clayden, 2000

The route to shikimic acid in plants involves as the final steps the dehydration of dehydroquinic acid and then reduction of the carbonyl group. Doing the reaction this way round means that the dehydration can be an E1cB which is much preferred under biological conditions.

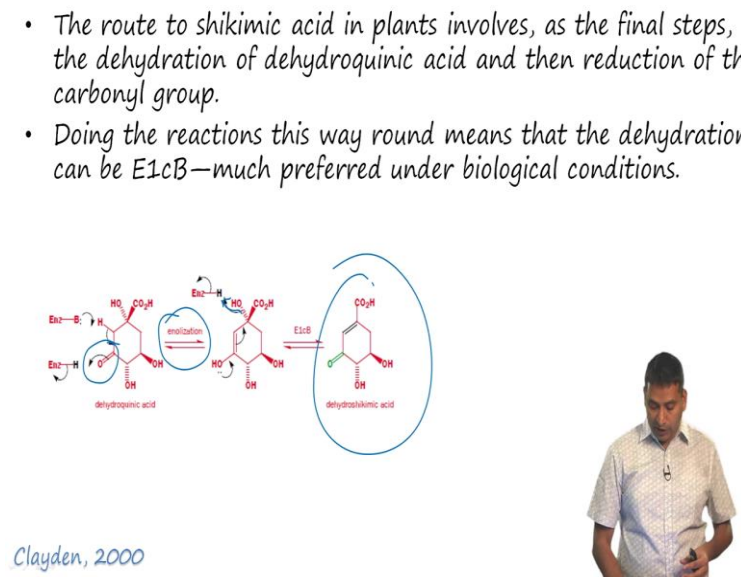
So what we would expect is the enolization

(Refer Slide Time: 22:20)



here of this ketone to give you the corresponding enol which then, if you do an E1cB reaction can eliminate this hydroxide to give you the

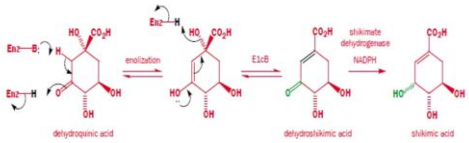
(Refer Slide Time: 22:31)



dehydroshikimic acid.

(Refer Slide Time: 22:33)

- The final reduction uses NADPH as the reagent and is, of course, totally stereoselective with the hydride coming in from the top face of the green ketone as drawn.
- At last we have arrived at the halfway stage and the key intermediate, **shikimic acid**.

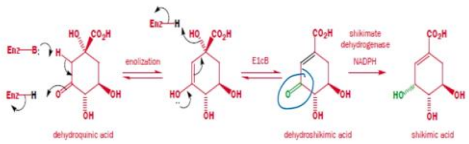


Clayden, 2000

The final reduction gives NADPH as the reagent and is of course totally stereoselective as we have looked at previously with the hydride coming in from the top face of the green ketone as drawn here,

(Refer Slide Time: 22:46)

- The final reduction uses NADPH as the reagent and is, of course, totally stereoselective with the hydride coming in from the top face of the green ketone as drawn.
- At last we have arrived at the halfway stage and the key intermediate, **shikimic acid**.



Clayden, 2000

Ok. So then after this stereospecific, stereoselective reaction you get this alcohol

(Refer Slide Time: 22:53)

- The final reduction uses NADPH as the reagent and is, of course, totally stereoselective with the hydride coming in from the top face of the green ketone as drawn.
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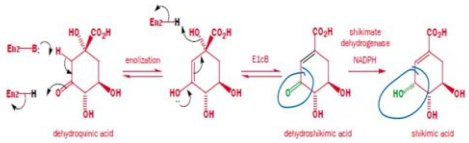

Clayden, 2000

here which is basically shikimic acid.

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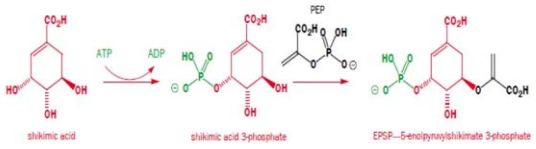
- We are half-way there...

Of course we are here only halfway. We have another half

(Refer Slide Time: 22:59)

- The first step is a chemoselective phosphorylation of one of the three OH groups by ATP—as it happens, the OH group that has just been formed by reduction of a ketone.
- This step prepares that OH group for later elimination.
- Next, a second molecule of PEP appears and adds to the OH group at the other side of the molecule.
- This is PEP in its enol ether role, forming an acetal under acid catalysis.
- The reaction occurs with retention of stereochemistry so we know that the OH group acts as a nucleophile and that the ring–OH bond is not broken.



Clayden, 2000

to carry out. Here the first step is a chemoselective phosphorylation of one of the three hydroxyl groups by ATP. As it happens the hydroxyl group that has just been formed by reduction of a ketone. So the first step here is the phosphorylation over

(Refer Slide Time: 23:17)

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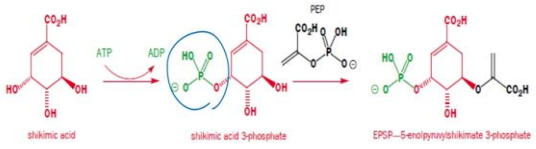

Clayden, 2000

here and this step prepares the hydroxyl group for a later elimination.

Next, a second molecule of phosphoenolpyruvate appears and adds to the hydroxyl group at the other side of the molecule. So here is the other side of the molecule. Here

(Refer Slide Time: 23:33)

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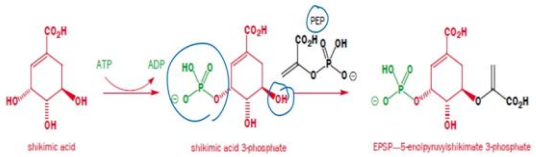

Clayden, 2000

phosphoenolpyruvate comes and adds here and gives you

(Refer Slide Time: 23:36)

- The first step is a chemoselective phosphorylation of one of the three OH groups by ATP—as it happens, the OH group that has just been formed by reduction of a ketone.
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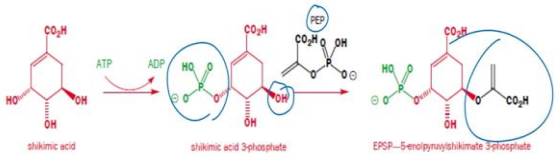


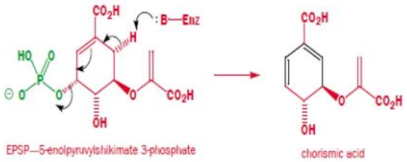
Clayden, 2000

this product.

This is the phosphoenolpyruvate in its enol ether role, Ok and forms an acetal under acidic catalysis. The reaction occurs with retention of stereochemistry. So we know that the hydroxyl group acts as a nucleophile and that the ring hydroxyl group is not broken.

(Refer Slide Time: 23:59)

- Now a 1,4 elimination occurs. This is known to be a *syn* elimination on the enzyme.
- When such reactions occur in the laboratory, they can be *syn* or *anti*.
- The leaving group is the green phosphate added two steps before.

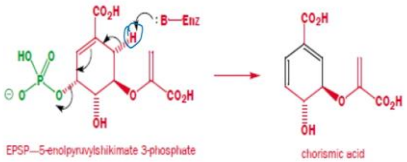


Clayden, 2000

Now a very interesting 1,4 elimination occurs and this is known to be a *syn* elimination on the enzyme. So here this 1,4 elimination occurs in the following manner.

(Refer Slide Time: 24:09)

- Now a 1,4 elimination occurs. This is known to be a *syn* elimination on the enzyme.
- When such reactions occur in the laboratory, they can be *syn* or *anti*.
- The leaving group is the green phosphate added two steps before.



Clayden, 2000

So the enzyme, basic residue of the enzyme comes in, attacks here,

(Refer Slide Time: 24:13)

- Now a 1,4 elimination occurs. This is known to be a syn elimination on the enzyme.
- When such reactions occur in the laboratory, they can be syn or anti.
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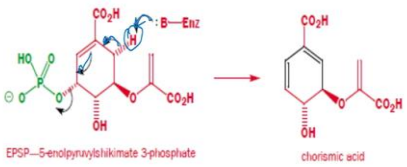


Clayden, 2000

moves this, electron moves here,

(Refer Slide Time: 24:15)

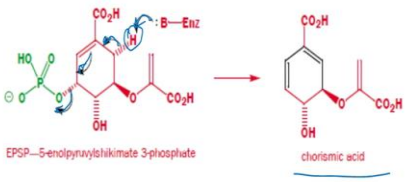
- Now a 1,4 elimination occurs. This is known to be a syn elimination on the enzyme.
- When such reactions occur in the laboratory, they can be syn or anti.
- The leaving group is the green phosphate added two steps before.

Clayden, 2000

this bond moves here and kicks out phosphate. And so this gives us chorismic acid

(Refer Slide Time: 24:22)

- Now a 1,4 elimination occurs. This is known to be a *syn* elimination on the enzyme.
- When such reactions occur in the laboratory, they can be *syn* or *anti*.
- The leaving group is the green phosphate added two steps before.



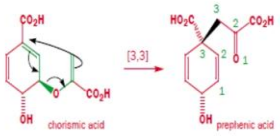
Clayden, 2000

which has a 1,3 diene, right.

Of course in the laboratory when we do this reaction this elimination can be either *syn* or *anti* but since this is happening enzymatically there is a stereochemistry which is very specific stereochemical outcome is expected.

(Refer Slide Time: 24:41)

- The product is chorismic acid and this undergoes the most interesting step of all—a [3,3]-sigmatropic rearrangement.
- Notice that the new (black) σ bond forms on the same face of the ring as the old (green) σ bond: this is, as you should expect, a suprafacial rearrangement.

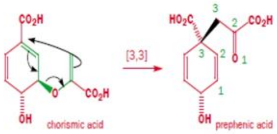


Clayden, 2000

The product here is chorismic acid and this undergoes the most interesting step of all, which is basically a 3,3-sigmatropic rearrangement. So this 3,3-sigmatropic

(Refer Slide Time: 24:51)

- The product is chorismic acid and this undergoes the most interesting step of all—a [3,3]-sigmatropic rearrangement.
- Notice that the new (black) σ bond forms on the same face of the ring as the old (green) σ bond: this is, as you should expect, a suprafacial rearrangement.



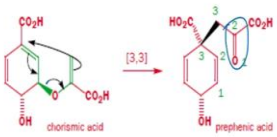
Clayden, 2000

rearrangement is something that some of you may be exposed to in your prior classes and sigmatropic rearrangements are basically neutral reactions which occur in a concerted manner.

We will not have time to go through this mechanism but what happens here is that you form a new carbon carbon bond which then, and as shown here and then you break this carbon carbon double bond and this carbon oxygen bond is broken and you form a new

(Refer Slide Time: 25:22)

- The product is chorismic acid and this undergoes the most interesting step of all—a [3,3]-sigmatropic rearrangement.
- Notice that the new (black) σ bond forms on the same face of the ring as the old (green) σ bond: this is, as you should expect, a suprafacial rearrangement.



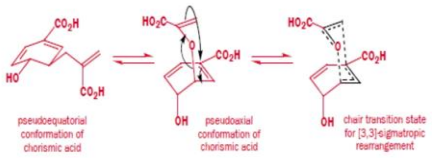
Clayden, 2000

C double bond O, OK.

So this occurs in a 3,3-sigmatropic manner and it is called a suprafacial rearrangement.

(Refer Slide Time: 25:30)

- The most favourable conformation for chorismic acid has the substituents pseudoequatorial but the [3,3]-sigmatropic rearrangement cannot take place in that conformation.
- First, the diaxial conformation must be formed and the chair transition state achieved.
- Then the required orbitals will be correctly aligned.

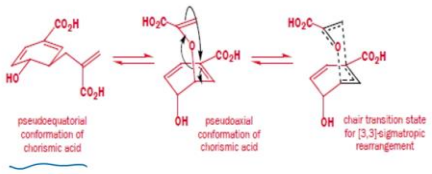


Clayden, 2000

So the most favorable conformation if we draw out the stereochemistry has the substituents in the pseudoequatorial position, so which is shown here,

(Refer Slide Time: 25:40)

- The most favourable conformation for chorismic acid has the substituents pseudoequatorial but the [3,3]-sigmatropic rearrangement cannot take place in that conformation.
- First, the diaxial conformation must be formed and the chair transition state achieved.
- Then the required orbitals will be correctly aligned.



Clayden, 2000

right.

But in this pseudoequatorial position the rearrangement cannot take place because it is not in the right orientation. So it has to first flip and form the diaxial conformation which is shown here,

(Refer Slide Time: 25:55)

- The most favourable conformation for chorismic acid has the substituents pseudoequatorial but the [3,3]-sigmatropic rearrangement cannot take place in that conformation.
- First, the diaxial conformation must be formed and the chair transition state achieved.
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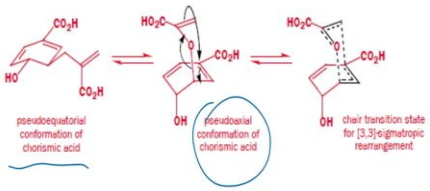
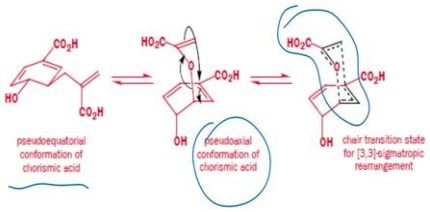


Clayden, 2000

which is known as the pseudoaxial conformation and then we can imagine a chair like transition state that occurs as shown here

(Refer Slide Time: 26:03)

- The most favourable conformation for chorismic acid has the substituents pseudoequatorial but the [3,3]-sigmatropic rearrangement cannot take place in that conformation.
- First, the diaxial conformation must be formed and the chair transition state achieved.
- Then the required orbitals will be correctly aligned.



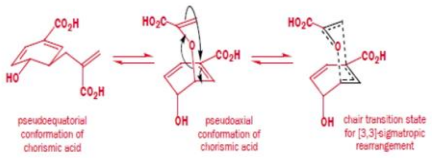
Clayden, 2000

which is going to give the product.

And all the required orbitals are correctly aligned in this conformation and therefore this is favored.

(Refer Slide Time: 26:12)

- These reactions occur well without the enzyme but the enzyme accelerates this reaction by about a 10^6 increase in rate.
- There is no acid or base catalysis and we may suppose that the enzyme binds the transition state better than it binds the starting materials.



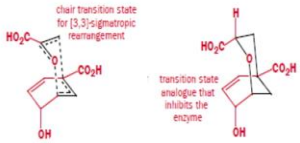
Clayden, 2000

These reactions occur well without an enzyme but the enzyme accelerates this by about a factor of a million increase in rate. So there is no acid or base catalysis but we may suppose that the enzyme binds the transition state better than it binds the starting materials.

So

(Refer Slide Time: 26:31)

- We know this to be the case, because close structural analogues of the six-membered ring transition state also bind to the enzyme and stop it working.
- An example is shown alongside—a compound that resembles the transition state but can't react.

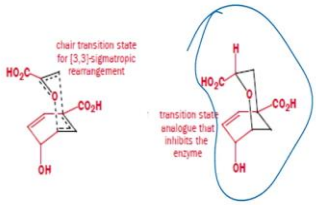


Clayden, 2000

if we were to design a molecule which has a very, which looks similar to the transition state which we have looked at previously as transition state analogue, then this compound can go and inhibit the enzyme. And indeed, when a molecule that was synthesized

(Refer Slide Time: 26:49)

- We know this to be the case, because close structural analogues of the six-membered ring transition state also bind to the enzyme and stop it working.
- An example is shown alongside—a compound that resembles the transition state but can't react.

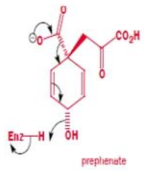


Clayden, 2000

which resembles the transition state as shown here, this molecule can inhibit this enzyme.

(Refer Slide Time: 26:56)

- We have arrived at **prephenic** acid, which as its name suggests is the last compound before aromatic compounds are formed;
- This the end of the shikimic acid pathway.
- The final stages of the formation of phenylalanine and tyrosine start with aromatization.



Clayden, 2000

So in this whole process we have arrived at

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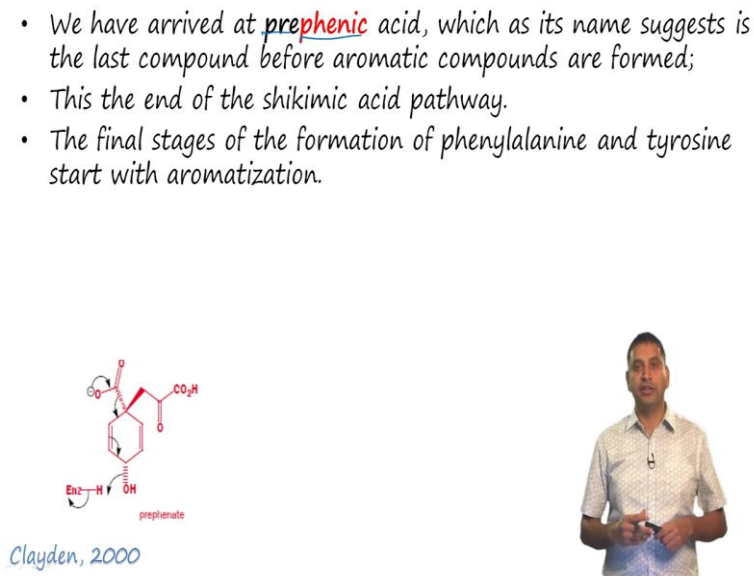
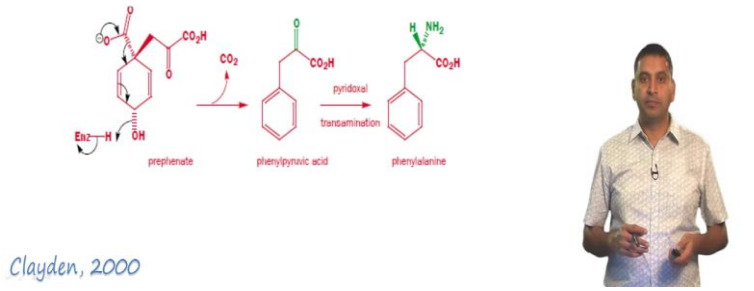


prephenic acid which as its name suggests is the last compound before the aromatic compounds are formed. So this is the end of the shikimic acid pathway and the final stages of formation of phenylanaline and tyrosine start with aromatization.

So aromatization occurs by a decarboxylation followed by pushing of electrons to give you, to kick out hydroxide ion.

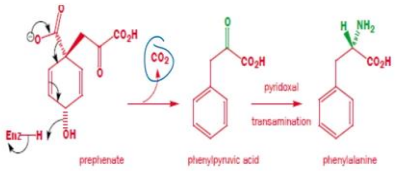
(Refer Slide Time: 27:23)



So the way this would occur is that you can imagine that CO_2 would be lost

(Refer Slide Time: 27:29)

- Prephenic acid is unstable and loses water and CO_2 to form phenylpyruvic acid.
- This α-keto-acid can be converted into the amino acid by the usual transamination with pyridoxal.



Clayden, 2000

by this, from this carboxylate ion and then this pushes electrons in this manner to give you

(Refer Slide Time: 27:37)

- Prephenic acid is unstable and loses water and CO_2 to form phenylpyruvic acid.
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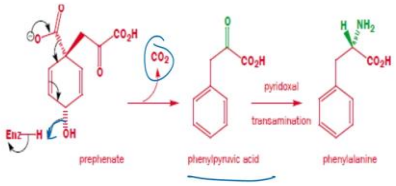
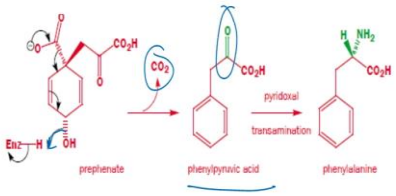


Clayden, 2000

phenyl pyruvic acid and we know that phenyl pyruvic acid which is an alpha-keto-acid

(Refer Slide Time: 27:42)

- Prephenic acid is unstable and loses water and CO_2 to form phenylpyruvic acid.
- This α-keto-acid can be converted into the amino acid by the usual transamination with pyridoxal.



Clayden, 2000

can exist in equilibrium with its corresponding amino acid which is phenylanaline and this transamination is mediated by pyridoxal.

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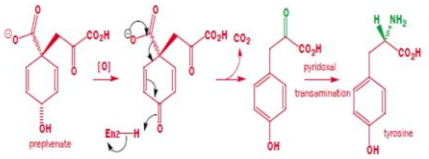
- The route to tyrosine requires a preliminary oxidation and then a decarboxylation with the electrons of the breaking C–C bond ending up in a ketone group.
- Transamination again gives the amino acid.

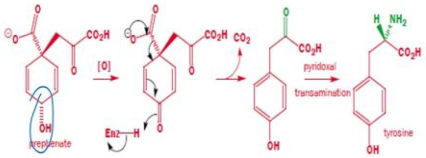


Clayden, 2000

The route to tyrosine requires a preliminary oxidation followed by a decarboxylation. So here this prephenate

(Refer Slide Time: 28:03)

- The route to tyrosine requires a preliminary oxidation and then a decarboxylation with the electrons of the breaking C–C bond ending up in a ketone group.
- Transamination again gives the amino acid.

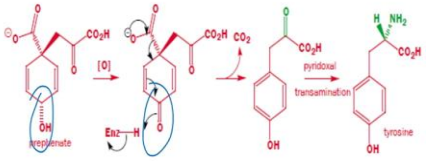


Clayden, 2000

will have to undergo oxidation to

(Refer Slide Time: 28:05)

- The route to tyrosine requires a preliminary oxidation and then a decarboxylation with the electrons of the breaking C–C bond ending up in a ketone group.
- Transamination again gives the amino acid.

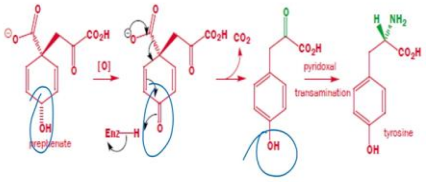


Clayden, 2000

give you this ketone and then subsequent decarboxylation will give you the

(Refer Slide Time: 28:10)

- The route to tyrosine requires a preliminary oxidation and then a decarboxylation with the electrons of the breaking C–C bond ending up in a ketone group.
- Transamination again gives the amino acid.



Clayden, 2000

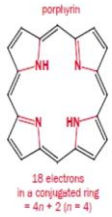
tyrosine residue.

And of course this is, it gives you the, the alpha-keto form which then is going to exist in its equilibrium and equilibrium with the corresponding amino acid which is tyrosine.

(Refer Slide Time: 28:22)

Haemoglobin carries oxygen as an iron(II) complex

- Biological oxidations are very widespread.
- Human metabolism depends on oxidation, and on getting oxygen, which makes up 20% of the atmosphere, into cells.
- The oxygen transporter, from atmosphere to cell, is **haemoglobin**.
- The reactive part of haemoglobin is a **porphyrin**.



Clayden, 2000

The next topic that we are going to look at is how oxygen is carried inside the cell. Haemoglobin carries oxygen as an iron II complex. And this is very important because a number of biological oxidations which we shall look at shortly is mediated by haem containing enzymes.

And human metabolism depends on oxidation and on getting oxygen which makes up about 20 percent of the atmosphere inside cells. The oxygen transporter from atmosphere is haemoglobin and the reactive part of this molecule is the porphyrin ring

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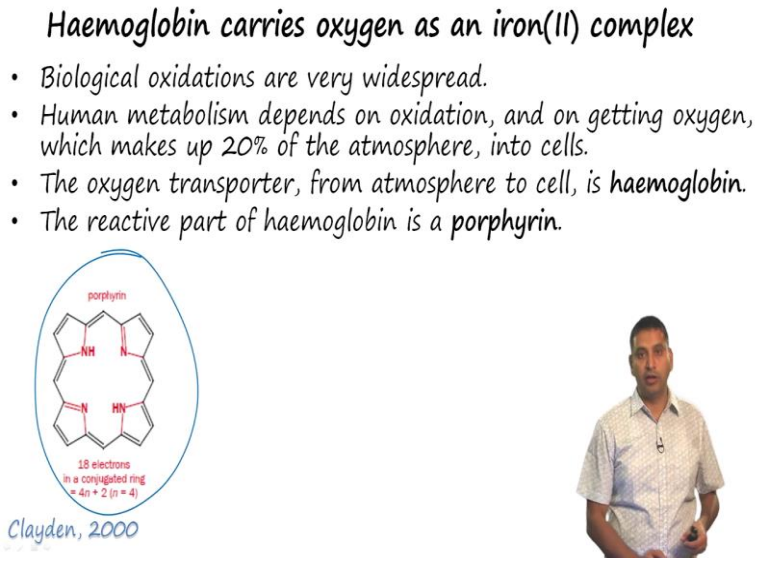
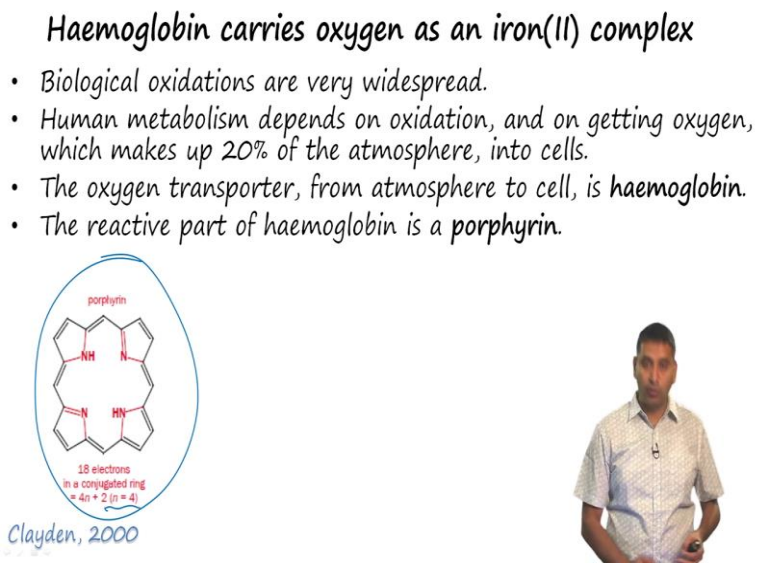


which is shown here.

So porphyrin is actually aromatic because it contains 18 electrons and if you apply 4n plus 2 rule then

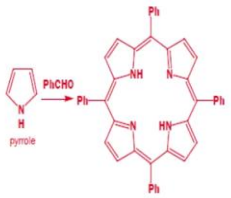
(Refer Slide Time: 29:09)



when n equals 4, you get 4n plus 2 to be 18 and therefore this is an aromatic system.

(Refer Slide Time: 29:14)

- These are aromatic molecules with 18 electrons around a conjugated ring formed from four molecules of a five-membered nitrogen heterocycle.
- Chemically, symmetrical porphyrins are easily made from pyrrole and an aldehyde.



Clayden, 2000

And these are symmetrical porphyrins are easily made from a pyrrole and an aldehyde. So if you react this pyrrole with an

(Refer Slide Time: 29:23)

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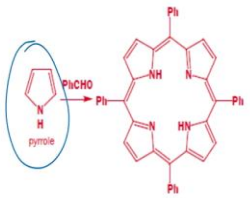
- Chemically, symmetrical porphyrins are easily made from pyrrole and an aldehyde.

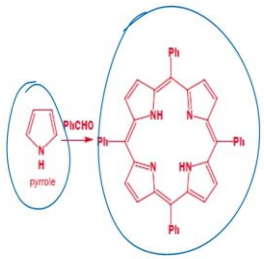


Clayden, 2000

aldehyde you get this kind

(Refer Slide Time: 29:25)

- These are aromatic molecules with 18 electrons around a conjugated ring formed from four molecules of a five-membered nitrogen heterocycle.
- Chemically, symmetrical porphyrins are easily made from pyrrole and an aldehyde.

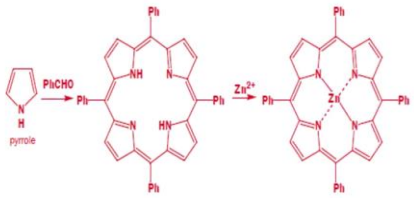


Clayden, 2000

of a porphyrin.

(Refer Slide Time: 29:26)

- The hole in the middle of a porphyrin is just the right size to take a divalent transition metal in the first transition series, and zinc porphyrins, for example, are stable compounds.
- Once the metal is inside a porphyrin, it is very difficult to get out.
- Two of the nitrogen atoms form normal covalent bonds (the ones that were NH in the porphyrin) and the other two donate their lone pairs to make four ligands around the metal.



Clayden, 2000

Then this porphyrin contains a hole in the middle which is just the right size to take a divalent transition metal ion, Ok.

So in the first transition series such as zinc, which is, you know in the form of zinc porphyrin and once which is inside this complex,

(Refer Slide Time: 29:43)

- The hole in the middle of a porphyrin is just the right size to take a divalent transition metal in the first transition series, and zinc porphyrins, for example, are stable compounds.
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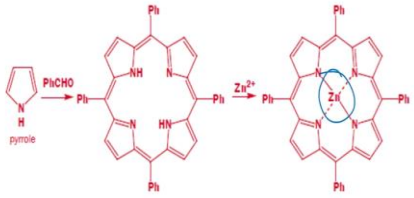


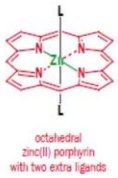
Clayden, 2000

it is extremely stable. It is very difficult to get it out.

So two of the nitrogen atoms form normal covalent bonds and the other two donate their lone pairs to make 4 ligands around the metal.

(Refer Slide Time: 29:57)

- The complexed zinc atom is square planar and still has two vacant sites—above and below the (more or less) flat ring.
- These can be filled with water molecules, ammonia, or other ligands.



octahedral
zinc(II) porphyrin
with two extra ligands

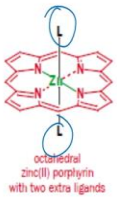
Clayden, 2000

The complex zinc atom is square planar and still has two vacant sites above and below which can coordinate with certain ligands.

And so these ligands can be either ammonia or water

(Refer Slide Time: 30:09)

- The complexed zinc atom is square planar and still has two vacant sites—above and below the (more or less) flat ring.
- These can be filled with water molecules, ammonia, or other ligands.

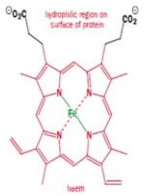


Clayden, 2000

or other ligands.

(Refer Slide Time: 30:12)

- The porphyrin part of haemoglobin is called haem, and it is an iron(II) complex.
- It is unsymmetrically substituted with carboxylic acid chains on one side and vinyl groups on the other..

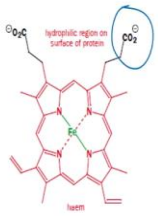


Clayden, 2000

The porphyrin part of haemoglobin is called haem and it is a iron II complex. It is unsymmetrically substituted with a carboxylic acid chain

(Refer Slide Time: 30:21)

- The porphyrin part of haemoglobin is called haem, and it is an iron(II) complex.
- It is unsymmetrically substituted with carboxylic acid chains on one side and vinyl groups on the other..

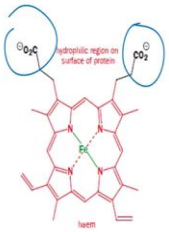


Clayden, 2000

on one side

(Refer Slide Time: 30:22)

- The porphyrin part of haemoglobin is called haem, and it is an iron(II) complex.
- It is unsymmetrically substituted with carboxylic acid chains on one side and vinyl groups on the other..

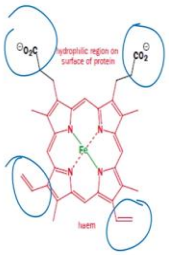


Clayden, 2000

and vinyl groups on the

(Refer Slide Time: 30:25)

- The porphyrin part of haemoglobin is called haem, and it is an iron(II) complex.
- It is unsymmetrically substituted with carboxylic acid chains on one side and vinyl groups on the other..



Clayden, 2000

other side.

(Refer Slide Time: 30:26)

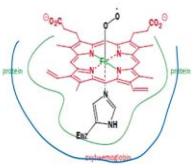
- Haem is bound to proteins to make haemoglobin (in blood) and myoglobin (in muscle). The hydrophilic carboxylate groups stick out into the surrounding medium, while the majority of the molecule is embedded in a hydrophobic cleft in the protein, lined with amino acids such a leucine and valine.
- The octahedral coordination sphere of the iron(II) is completed with a histidine residue from the protein and an oxygen molecule.

Clayden, 2000

Haem is bound to proteins to make haemoglobin in the blood, or it forms myoglobin in the muscle. The hydrophilic carboxylate groups stick out into the surrounding medium where the majority of the molecule is embedded in a hydrophobic cleft in the protein which is lined with amino acids such as leucine and valine, Ok.

(Refer Slide Time: 30:48)

- Haem is bound to proteins to make haemoglobin (in blood) and myoglobin (in muscle). The hydrophilic carboxylate groups stick out into the surrounding medium, while the majority of the molecule is embedded in a hydrophobic cleft in the protein, lined with amino acids such a leucine and valine.
- The octahedral coordination sphere of the iron(II) is completed with a histidine residue from the protein and an oxygen molecule.



Clayden, 2000

The octahedral coordination sphere of iron II is completed with the histidine residue as shown here

(Refer Slide Time: 30:55)

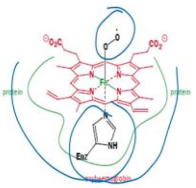
- Haem is bound to proteins to make haemoglobin (in blood) and myoglobin (in muscle). The hydrophilic carboxylate groups stick out into the surrounding medium, while the majority of the molecule is embedded in a hydrophobic cleft in the protein, lined with amino acids such a leucine and valine.
- The octahedral coordination sphere of the iron(II) is completed with a histidine residue from the protein and an oxygen molecule.

Clayden, 2000

and an oxygen molecule which is shown here.

(Refer Slide Time: 30:58)

- Haem is bound to proteins to make haemoglobin (in blood) and myoglobin (in muscle). The hydrophilic carboxylate groups stick out into the surrounding medium, while the majority of the molecule is embedded in a hydrophobic cleft in the protein, lined with amino acids such a leucine and valine.
- The octahedral coordination sphere of the iron(II) is completed with a histidine residue from the protein and an oxygen molecule.

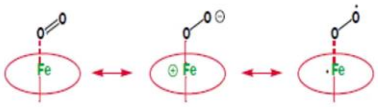


Clayden, 2000

The oxygen

(Refer Slide Time: 31:00)

- The oxygen complex can also be drawn as an Fe(III) complex of an oxyanion

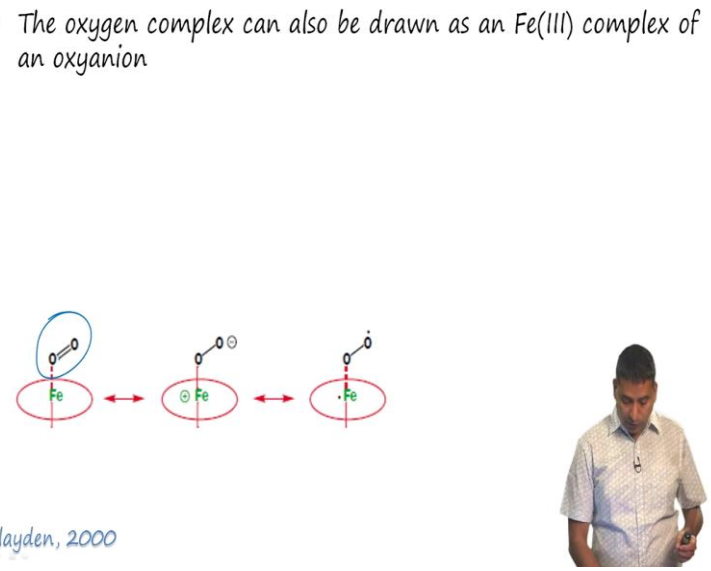


Clayden, 2000

complex can also be drawn as an Fe III complex of the oxyanion.

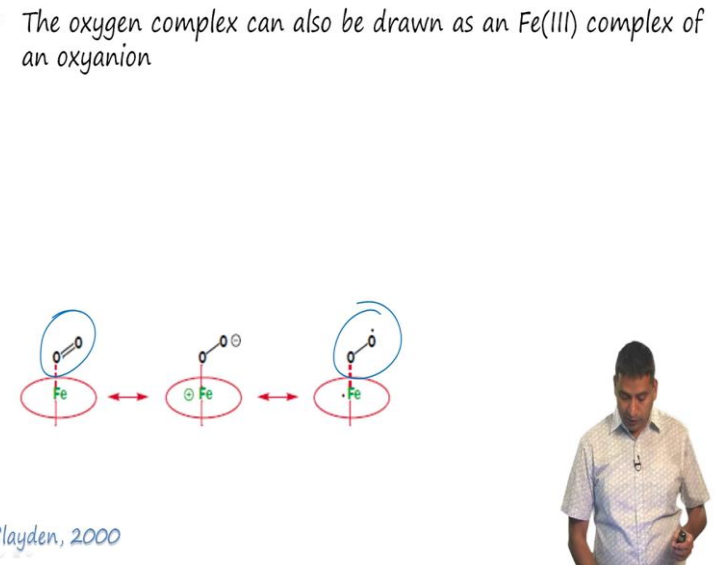
So here

(Refer Slide Time: 31:06)



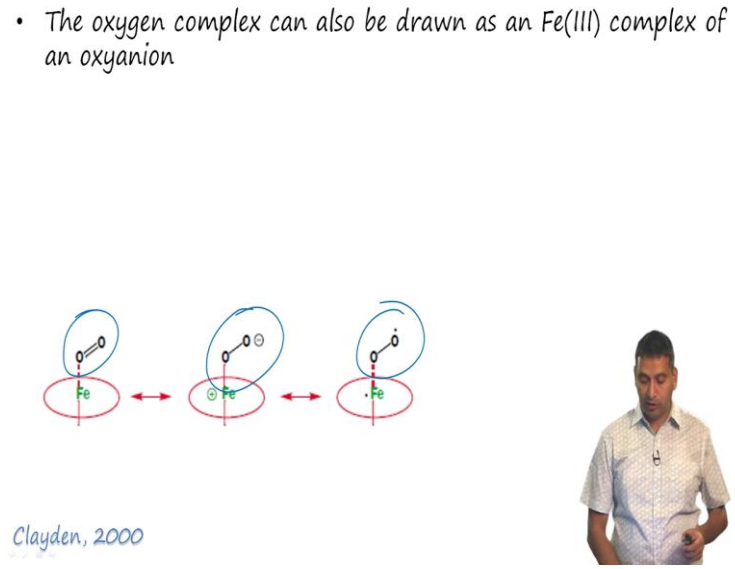
is the oxygen complex, here is the

(Refer Slide Time: 31:08)



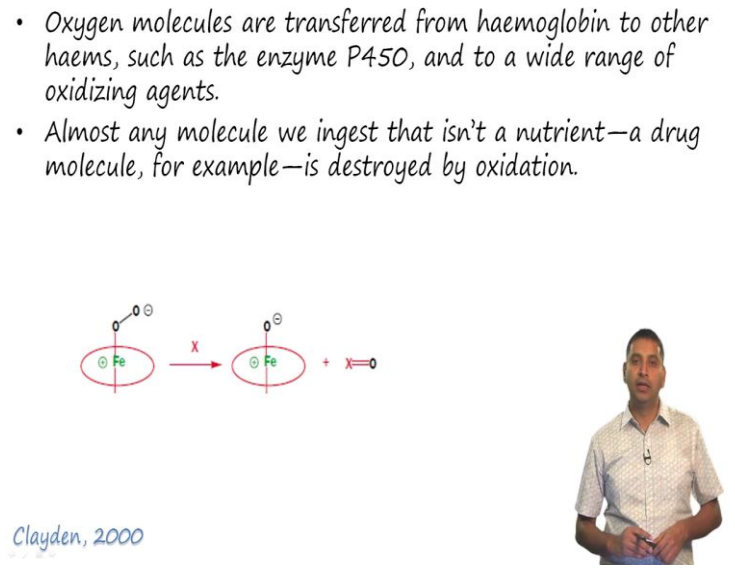
resonance form of it and it can be drawn

(Refer Slide Time: 31:11)



as a oxyanion.

(Refer Slide Time: 31:14)

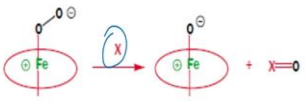


Oxygen molecules are transferred from haemoglobin to other haems such as P 450 which we shall encounter very shortly and to avoid range of other oxidizing agents.

Almost any molecule that we ingest, that is not a nutrient which for example a drug molecule is oxidized. And the way this oxidization occurs is that this X is the

(Refer Slide Time: 31:37)

- Oxygen molecules are transferred from haemoglobin to other haems, such as the enzyme P450, and to a wide range of oxidizing agents.
- Almost any molecule we ingest that isn't a nutrient—a drug molecule, for example—is destroyed by oxidation.

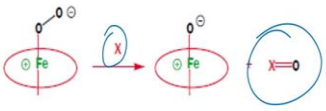


Clayden, 2000

drug molecule. It can

(Refer Slide Time: 31:39)

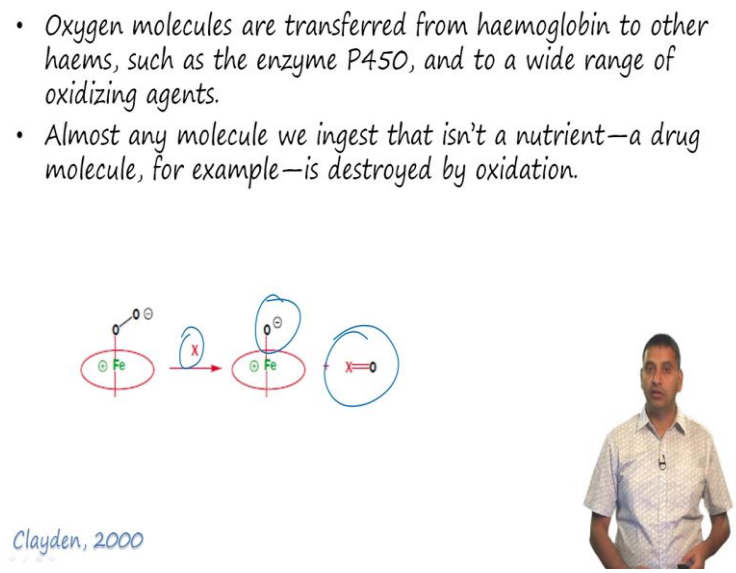
- Oxygen molecules are transferred from haemoglobin to other haems, such as the enzyme P450, and to a wide range of oxidizing agents.
- Almost any molecule we ingest that isn't a nutrient—a drug molecule, for example—is destroyed by oxidation.



Clayden, 2000

get oxidized to give you X double bond O which leaves

(Refer Slide Time: 31:43)



this molecule behind.