Symmetry, Stereochemistry and Applications

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Lecture - 36
Addition Reactions to Alkenes and Alkynes - Part 02

Welcome back to the course entitled Symmetry, Stereochemistry and Applications. In the previous lecture, we have discussed about the addition reactions to double bond. So we will continue our discussion on addition reactions and we will see what happens when we try to do addition reactions on C C triple bond and some other reactions involving C C double bond.

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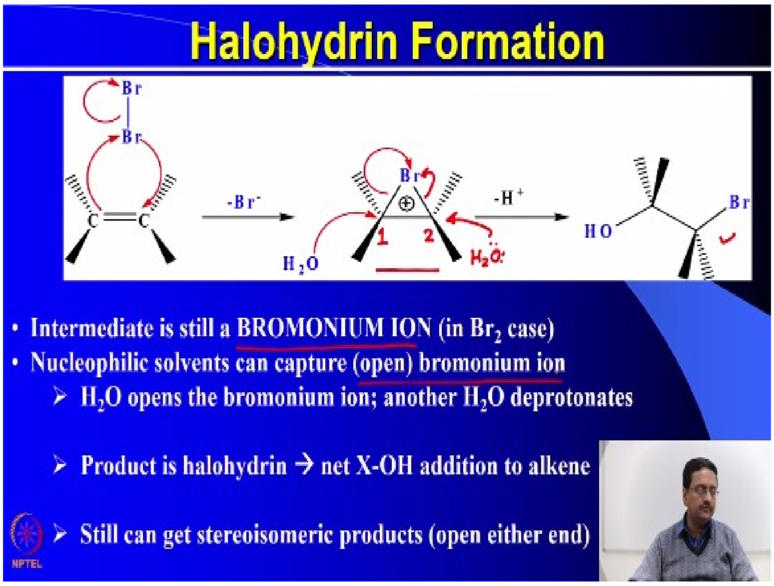

Halohydrin Formation

- Intermediate is still a BROMONIUM ION (in Br_2 case)
- Nucleophilic solvents can capture (open) bromonium ion
  - H_2O opens the bromonium ion; another H_2O deprotonates
  - Product is halohydrin → net X-OH addition to alkene
  - Still can get stereoisomeric products (open either end)

So what we have seen previously is we have seen the addition of halogens, addition of HX. And now here I am trying to discuss about the formation of halohydrin, which happens when you add a halogen molecule along with water to a C C double bond. So as usual, when you add suppose bromine to a C C double bond, so immediately this bromonium ion is formed as a reactive intermediate.

And then in presence of water, which can attack the either the carbon 1 or carbon 2 from either side and open the three membered bromonium ion in either side resulting into a new product. So nucleophilic solvents can capture or open the bromonium ion. So here this water opens the bromonium ion and another water molecule deprotonates the added water molecule and the product is formed.

And this product is called the halohydrin. So if the alkene is unsymmetrical, then you are expected to get a compound which is or which has different isomers when it opens up from the two different sides. So let us see this with one example.

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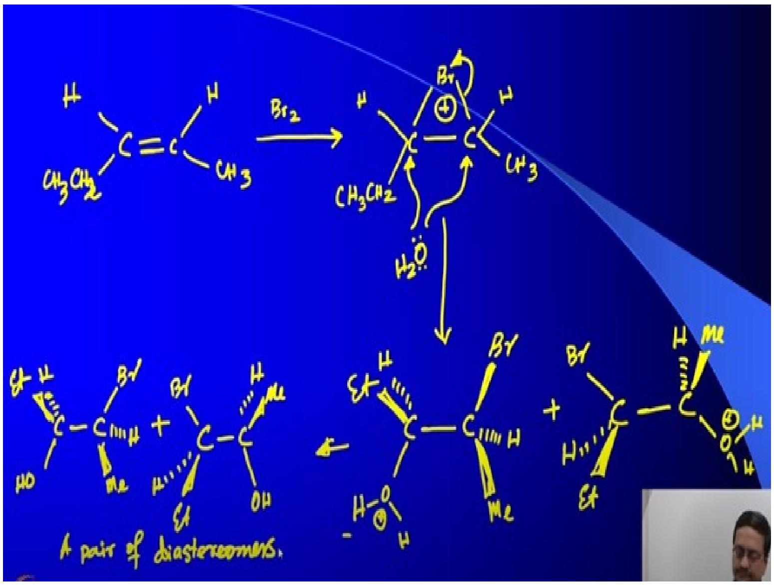

Suppose you had this alkene which is unsymmetrical. So on addition of bromine you will get a bromonium ion which would look like this. Now when we add water molecule to this, when the attack happens from the left hand side carbon, the more substituted carbon here, then what you would get is this one. If the attack happens on the other carbon then you will get the other product which is this one.

And then of course both of them has to be deprotonated to make the neutral compound. So upon deprotonation you will get these two compounds. So what we see is that these two compounds are a pair of diastereomers. Therefore, this type of reactions can yield two different compounds, two different isomers of the same compound and they are having diastereomeric relationship.

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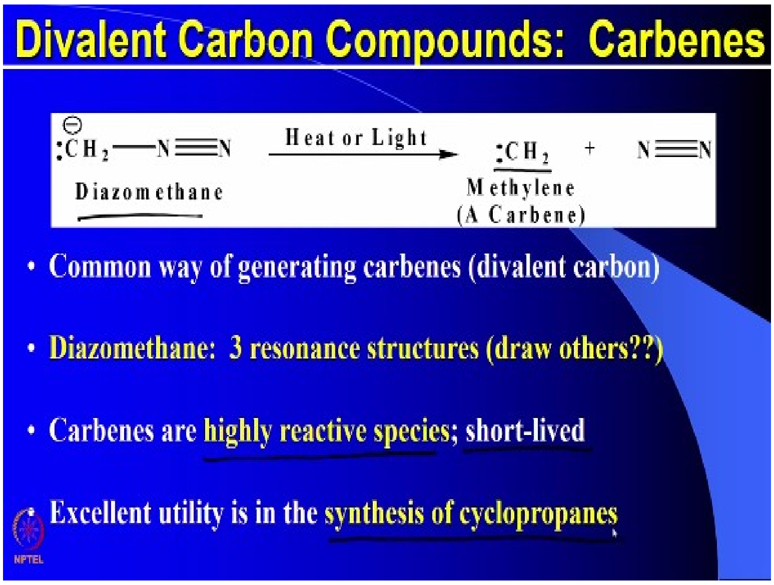

Divalent Carbon Compounds: Carbenes

$$:\overset{\ominus}{C}H_2-N\equiv N \xrightarrow{\text{Heat or Light}} :CH_2 + N\equiv N$$

- Common way of generating carbenes (divalent carbon)
- Diazomethane: 3 resonance structures (draw others??)
- Carbenes are highly reactive species; short-lived
- Excellent utility is in the synthesis of cyclopropanes

Now I would like to introduce you to a new type of molecule or new type of compounds, which are called, new type of molecule, which are called carbenes. And this carbenes are also a species which can be added to C-C double bond to make different types of compounds. So when you take a compound called diazomethane and you apply heat or light to this compound, you generate a species called carbene, a methylene carbene and nitrogen gas is eliminated.

So this is a very common way of generating a carbene. Diazomethane has 3 resonating structure. So you try to draw those yourselves and these carbenes are highly reactive species and short-lived. So these should be generated in situ immediately for the reactions. So this are utilized for making a number of cyclopropane derivatives in organic synthesis.

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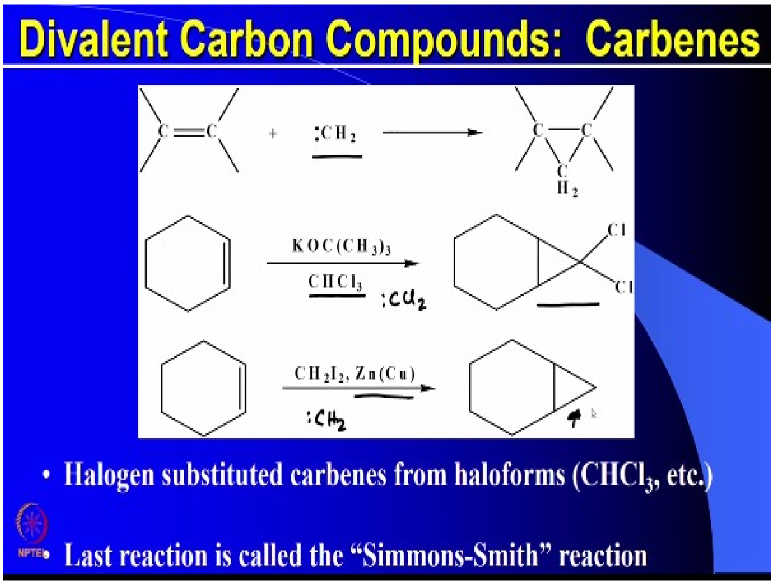

Divalent Carbon Compounds: Carbenes

- Halogen substituted carbenes from haloforms ($CHCl_3$, etc.)
- Last reaction is called the "Simmons-Smith" reaction

Let us see what happens when you add a carbene to a C C double bond. So when you treat a carbene species to a C C double bond, it forms a cyclopropane like this. In case of cyclic alkene, here it is cyclohexene, chloroform reacts with this base to form a dichlorocarbene CCl2 and that CCl2 adds to the double bond to form this three-membered ring in this cyclohexene derivative.

Similarly, CH2I2 in presence of copper zinc as catalyst can also form the methylene carbene and can form a cyclopropane derivative. This last reaction is called the Simmons-Smith reaction. So this is how you can generate a three-membered ring using a carbene on a C C double bond.

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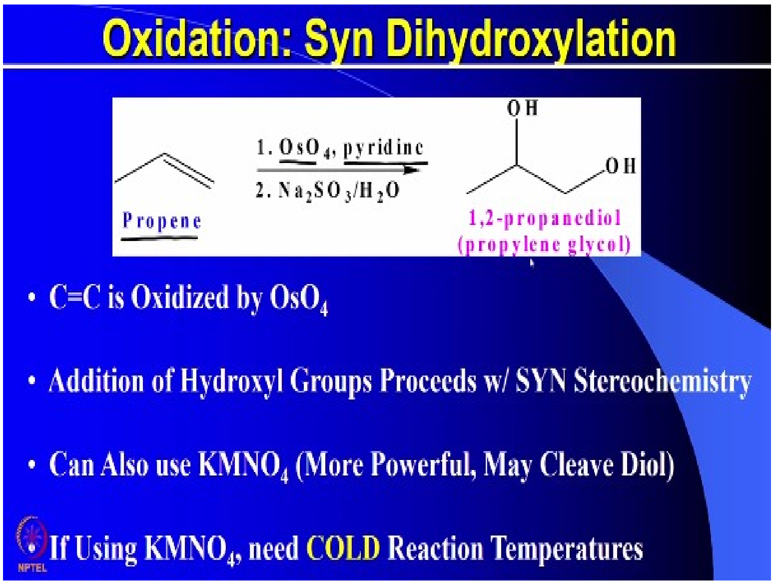

Oxidation: Syn Dihydroxylation

- C=C is Oxidized by OsO_4
- Addition of Hydroxyl Groups Proceeds w/ SYN Stereochemistry
- Can Also use $KMNO_4$ (More Powerful, May Cleave Diol)
- If Using $KMNO_4$, need COLD Reaction Temperatures

Now let us see what happens if you try to oxidize this C C double bonded compounds. That means, oxidation of alkenes. There are various types of oxidizing agents, for example osmium tetroxide, potassium permanganate, potassium dichromate and so on. So when you try to do any oxidation reaction on a C C double bond like propene using osmium tetroxide and pyridine, you would get a diol. So C C double bond is oxidized by osmium tetroxide.

And what happens is addition of hydroxylic groups proceeds with SYN stereochemistry. And it can also be done using potassium permanganate. It is more powerful, so sometimes it may cleave the diol into two parts. So in using potassium permanganate as oxidizing agent one should use a very low temperature or cold reaction condition.

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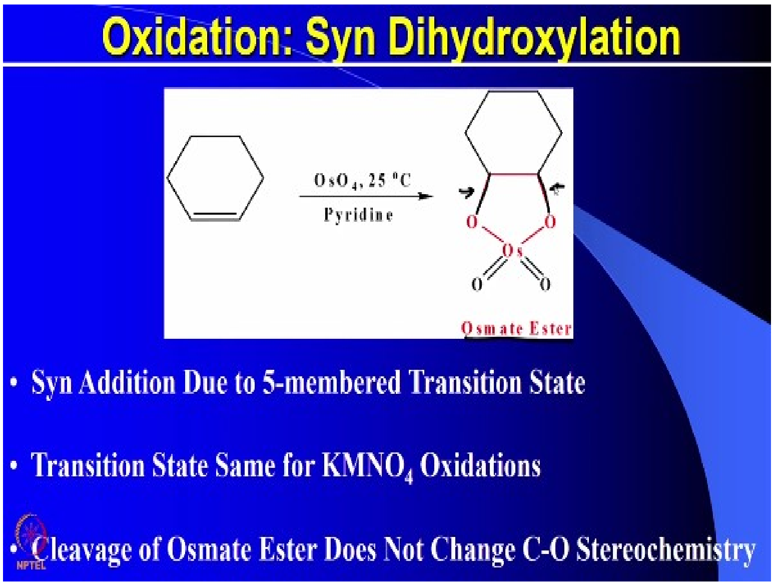

Oxidation: Syn Dihydroxylation

- Syn Addition Due to 5-membered Transition State
- Transition State Same for $KMNO_4$ Oxidations
- Cleavage of Osmate Ester Does Not Change C-O Stereochemistry

So this is the mechanism of this osmium tetroxide oxidation. So when you treat osmium tetroxide with a C C double bond, it initially forms the cyclic osmate ester. So you can see that this C double bond O sorry C single bond O are in the SYN orientation. So it is a SYN addition due to the five-member transition state. This transition state is same or similar for potassium permanganate as well.

And then this cleavage of osmate ester does not change the stereochemistry of those two C-O bonds and hence, it gives you SYN diol or a cis diol.

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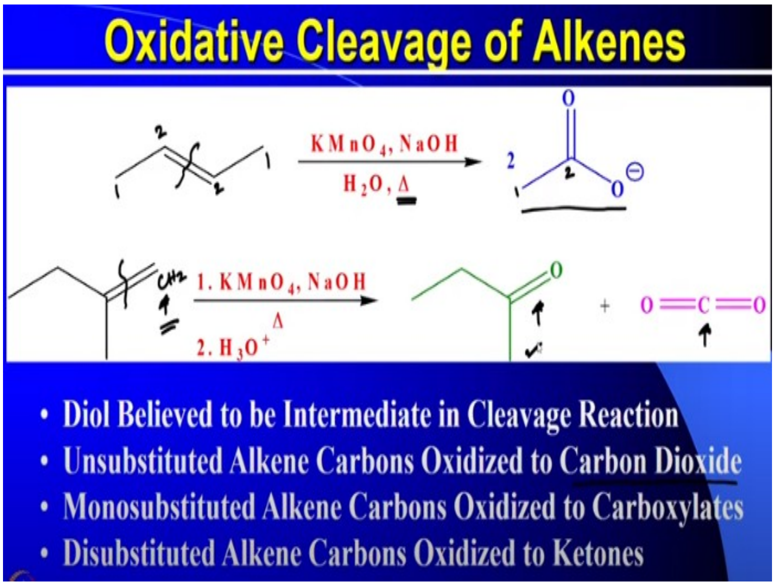

Oxidative Cleavage of Alkenes

- Diol Believed to be Intermediate in Cleavage Reaction
- Unsubstituted Alkene Carbons Oxidized to Carbon Dioxide
- Monosubstituted Alkene Carbons Oxidized to Carboxylates
- Disubstituted Alkene Carbons Oxidized to Ketones

But when you want to cleave an alkene we always use potassium permanganate in alkaline medium with water and we heat it. On heating what happens is the oxidation followed by cleavage of the bond. So it breaks the C C double bond and makes the compound the corresponding carboxylate anion. So this 2-butene you have two carbon atoms here and two carbon atoms on the other side.

So once it breaks it forms the acetate anion. If you do the same reaction on this alkene which has on one side CH2 group, the other side has a larger longer group, so the point where you had a C double bond C is now oxidized to a ketone. And the group which had CH2 group is now oxidized to carbon dioxide. So diol is believed to be intermediate in this clevage reaction.

So initially the diol forms and the cleavage happens. Unsubstituted alkenes, alkyl carbons get oxidized to carbon dioxide just like we see here and monosubstituted alkene carbons get oxidized to carboxylates and disubstituted alkene carbons get oxidized to ketones as we see here. So this few things you need to remember that different type of double bonds get cleaved to give you different types of products.

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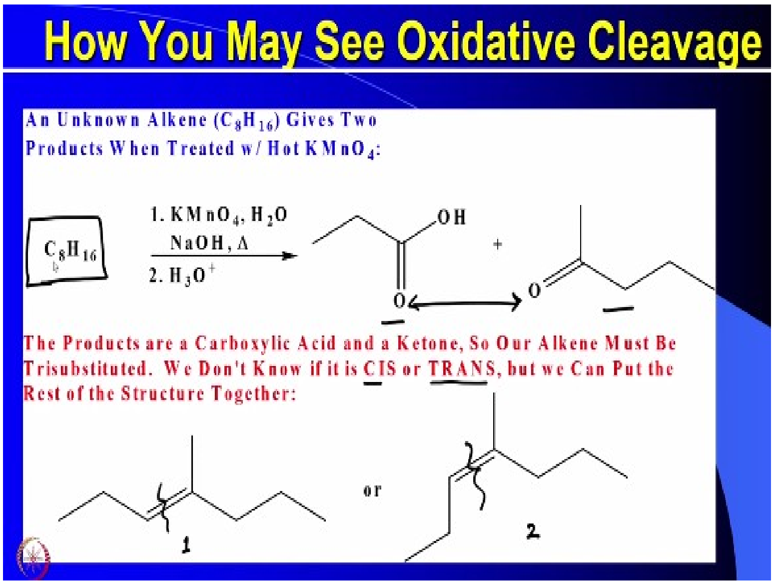

How You May See Oxidative Cleavage

An Unknown Alkene (C_8H_{16}) Gives Two Products When Treated w/ Hot $KMnO_4$:

The Products are a Carboxylic Acid and a Ketone, So Our Alkene Must Be Trisubstituted. We Don't Know if it is CIS or TRANS, but we Can Put the Rest of the Structure Together:

Let us see with one example. An unknown alkene gives two different compounds upon cleavage by potassium permanganate, sodium hydroxide and heat. So when you get these two carboxylic acids or these two carbonyl compounds, one is carboxylic acid and the other one is ketone, what could be the molecule that was the C8H16.

So simply we need to place these two compounds with the oxygens face to face. And we can draw two such isomers. In one case it is a cis or other cases it is trans. And these are the two possibilities that you can see here which may have given us these two compounds. If you cleave this double bond, you would get 1, 2, 3 carbon. So this 1 on 2, 3 carbon and the other side would be ketone. So you would get this ketone.

If you cleave here, then also you would get the same thing and the ketone. So therefore, these two alkenes on cleavage can produce these two carbonyl compounds. Therefore, these two are the possible probabilities of this molecule which is C8H16.

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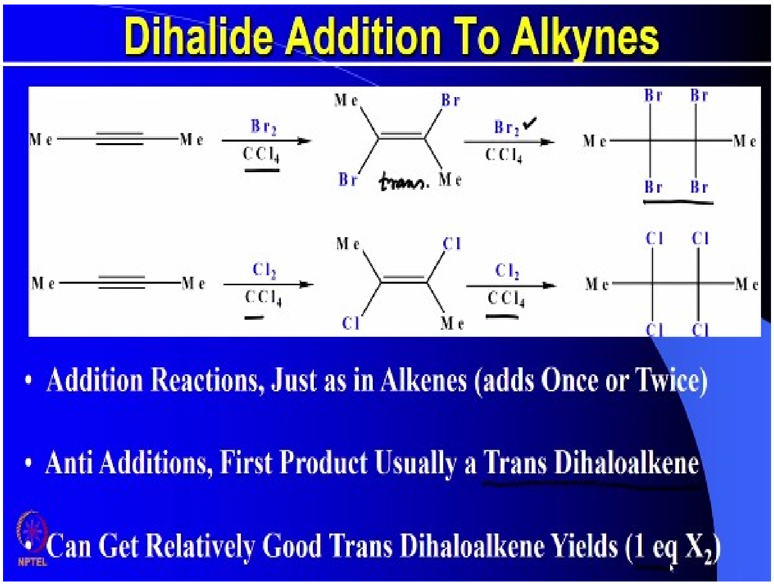

Dihalide Addition To Alkynes

- Addition Reactions, Just as in Alkenes (adds Once or Twice)
- Anti Additions, First Product Usually a Trans Dihaloalkene
- Can Get Relatively Good Trans Dihaloalkene Yields (1 eq X_2)

Let us see what happens when you try to add an halogen to an alkyne. So when we add halogen to an alkyne in a solvent like carbon tetrachloride or dichloromethane, the initial product is a trans compound because it goes through the bromonium ion or halonium ion and then the addition of second molecule of bromine makes it a tetrabromo compound. The same is true for addition of chlorine.

So the addition reactions just like as in alkenes add once or twice, but goes through the halonium ion formation. It is anti-addition. And the first product is usually trans dihaloalkene and can get relatively good trans dihaloalkene yield if you use only one equivalent of X2.

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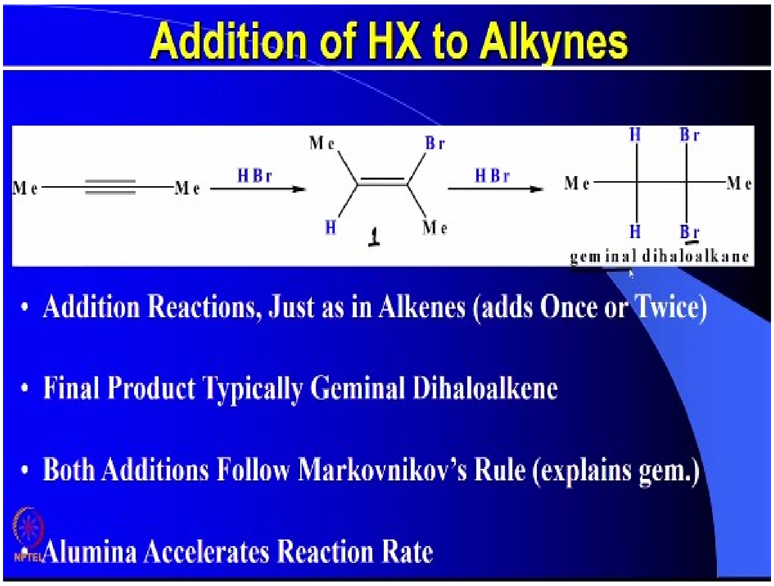

Addition of HX to Alkynes

- Addition Reactions, Just as in Alkenes (adds Once or Twice)
- Final Product Typically Geminal Dihaloalkene
- Both Additions Follow Markovnikov's Rule (explains gem.)
- Alumina Accelerates Reaction Rate

Similarly, when you try to add HX to alkyne it follows the Markovnikov's rule and on addition of first molecule of HBr it produces the first compound one here and then when you add the second molecule of HBr it goes and forms the carbocation which is more stable. Therefore, the gem dihalide or geminal dihalide is the product in this type of reactions. And sometimes this alumina used as a catalyst activates this type of reactions.

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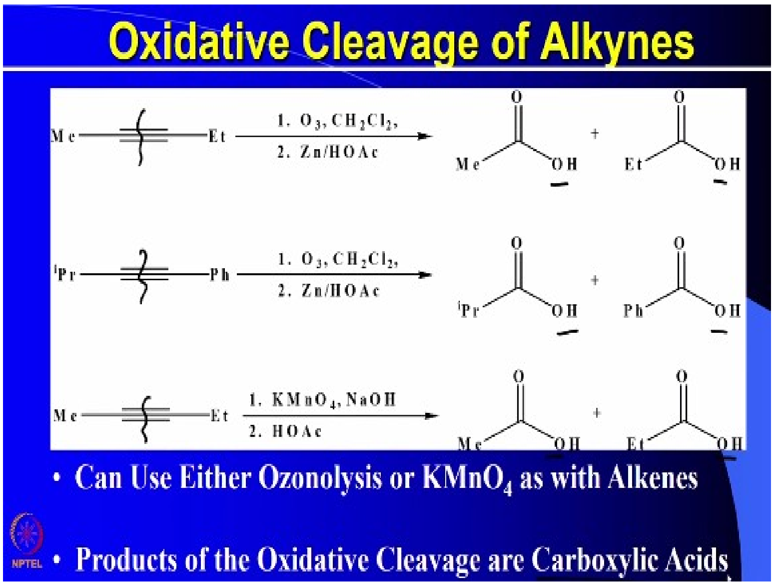

Oxidative Cleavage of Alkynes

- Can Use Either Ozonolysis or $KMnO_4$ as with Alkenes
- Products of the Oxidative Cleavage are Carboxylic Acids

So when you try to treat this alkyne compounds using ozone or potassium permanganate the result is same as that was observed for alkene. So when we treat this alkynes with ozone or potassium permanganate the molecules break from the middle where you have this C triple bond C and the corresponding carbonyl compounds are formed.

You see both in all the cases these are the acids, which have the highest oxidation state of these organic compounds. So always it forms a pair of carboxylic acids on oxidative cleavage reaction.

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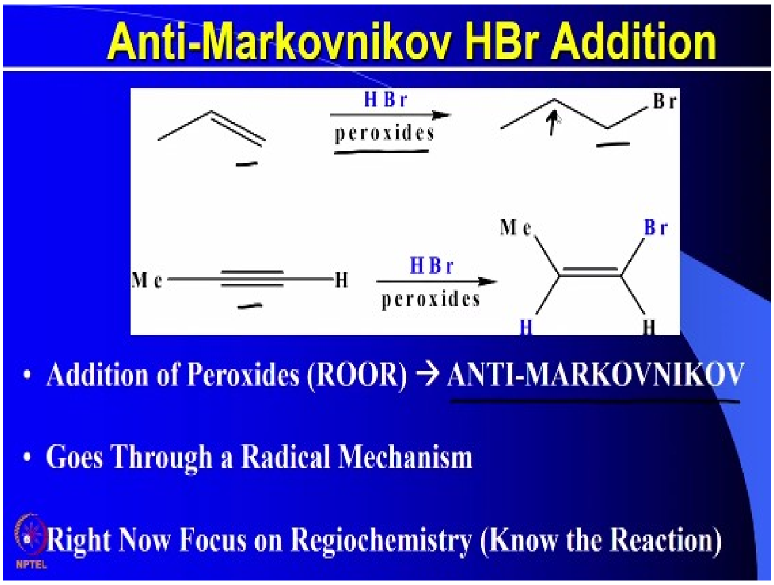

Anti-Markovnikov HBr Addition

- Addition of Peroxides (ROOR) → ANTI-MARKOVNIKOV
- Goes Through a Radical Mechanism
- Right Now Focus on Regiochemistry (Know the Reaction)

When we try to add HBr in presence of peroxide to a double bond or a triple bond, something different happens. This reaction proceeds through a radical mechanism instead of carbocation mechanism and results into a product which is the anti-Markovnikov product.

In case of Markovnikov addition, this bromine should have come to this carbon, but here due to the mechanism difference, as it goes through a radical mechanism the bromine gets added to the terminal carbon atom and we get a product which is termed as anti-Markovnikov product.

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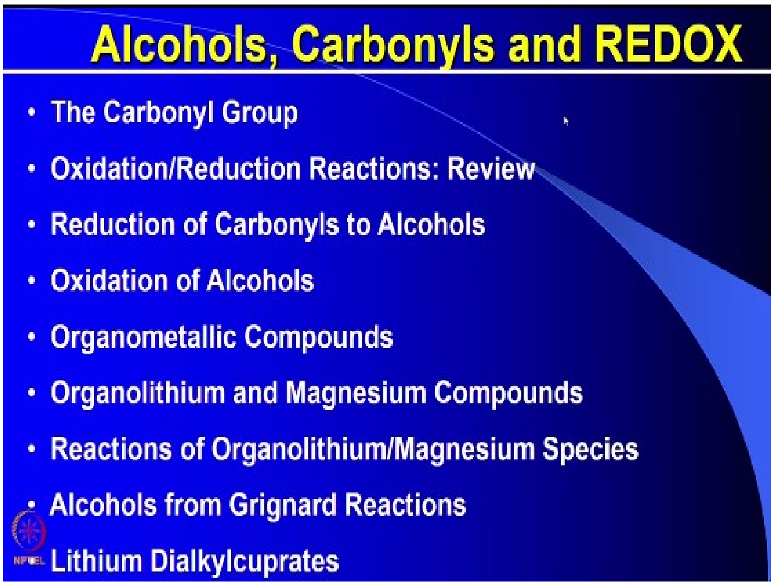

Alcohols, Carbonyls and REDOX

- The Carbonyl Group
- Oxidation/Reduction Reactions: Review
- Reduction of Carbonyls to Alcohols
- Oxidation of Alcohols
- Organometallic Compounds
- Organolithium and Magnesium Compounds
- Reactions of Organolithium/Magnesium Species
- Alcohols from Grignard Reactions
- Lithium Dialkylcuprates

So with this we end the reactions of alkenes and move to the reactions of alcohols, carbonyls and the oxidation/reduction reactions. So here in the next part of this lecture, next 10 to 15 minutes, we will discuss about the carbonyl groups, oxidation/reduction reaction, reduction of carbonyls to alcohols and the remaining will be discussed in the next lecture.

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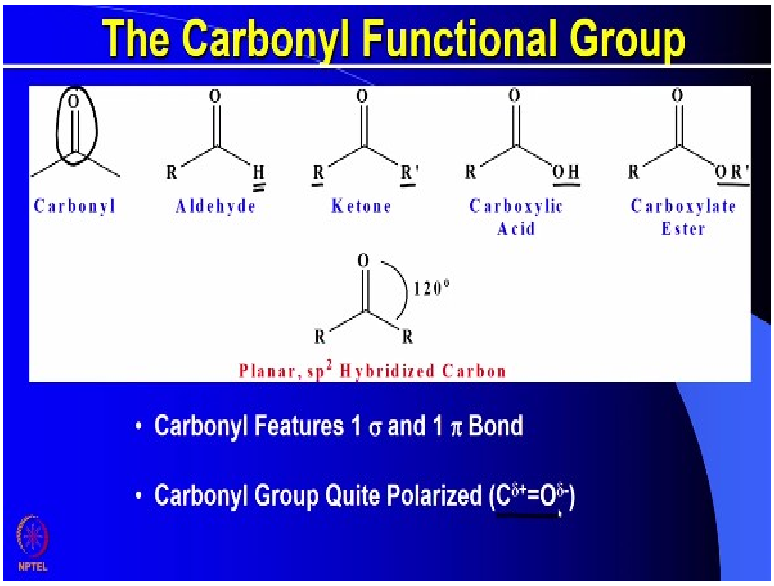

The Carbonyl Functional Group

- Carbonyl Features 1 σ and 1 π Bond
- Carbonyl Group Quite Polarized ($C^{\delta+}=O^{\delta-}$)

By now, you are familiar with various carbonyl compounds, which essentially contains a C double bond O group. When the C double bond O group contains one hydrogen it is called aldehyde. When you have two alkyl groups, it is called ketone. When you have OH it is acid. And when you have OR it is called the ester. So all these carbonyl groups feature one sigma and one pi bond.

And the carbonyl group is always polarized with delta positive charge on carbon and delta negative charge on oxygen.

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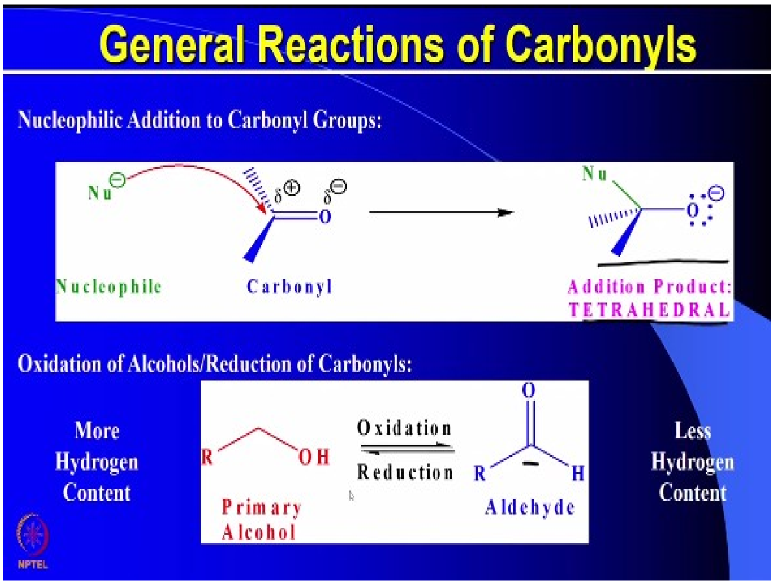

General Reactions of Carbonyls

Nucleophilic Addition to Carbonyl Groups:

Oxidation of Alcohols/Reduction of Carbonyls:

More Hydrogen Content

Less Hydrogen Content

So as a result, it is very susceptible for nucleophilic addition to the carbonyl groups. So a nucleophile attacks the electropositive carbon and forms a tetrahedral product or adduct like this, when you treat a carbonyl compound with a nucleophile. So it is easy to do oxidation and reduction on carbonyl compounds. So if you oxidize an alcohol you get a carbonyl compound. If you reduce an aldehyde you get a primary alcohol.

So we will see how this oxidation and reduction reactions can be controlled using different type organic reagents and inter conversion of alcohol to the ketone, alcohol to ketone, ketone to acid can be done.

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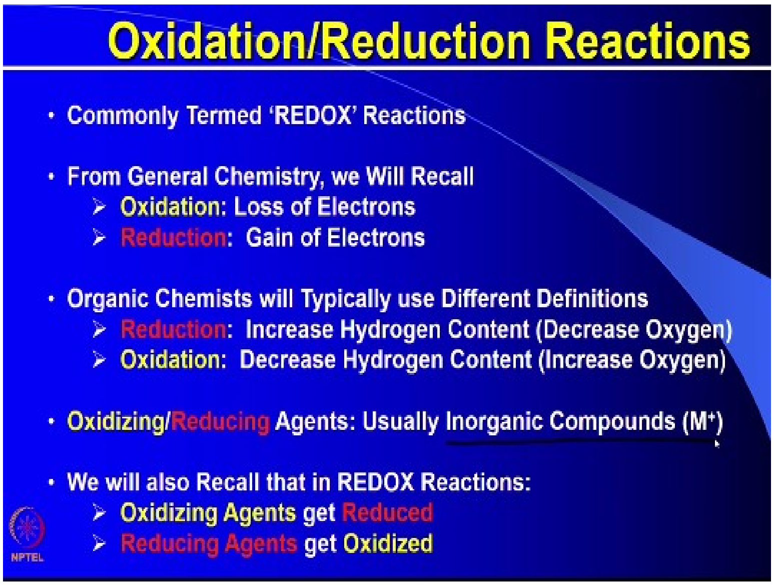

Oxidation/Reduction Reactions

- Commonly Termed 'REDOX' Reactions
- From General Chemistry, we Will Recall
  - Oxidation: Loss of Electrons
  - Reduction: Gain of Electrons
- Organic Chemists will Typically use Different Definitions
  - Reduction: Increase Hydrogen Content (Decrease Oxygen)
  - Oxidation: Decrease Hydrogen Content (Increase Oxygen)
- Oxidizing/Reducing Agents: Usually Inorganic Compounds (M^+)
- We will also Recall that in REDOX Reactions:
  - Oxidizing Agents get Reduced
  - Reducing Agents get Oxidized

This oxidation reduction reactions are commonly termed as REDOX reactions. And from your general chemistry point of view oxidation means loss of electrons and reduction means gain of electrons. And in organic chemistry typically we use slightly different definition. Reduction here means increase of hydrogen content and oxidation means decrease of hydrogen content.

In organic chemistry, we use various reducing and oxidizing agents, which are generally inorganic compounds, generally compounds containing oxidizable metal ions. We will also recall that the REDOX reactions, oxidizing agents get reduced and reducing agents themselves get oxidized.

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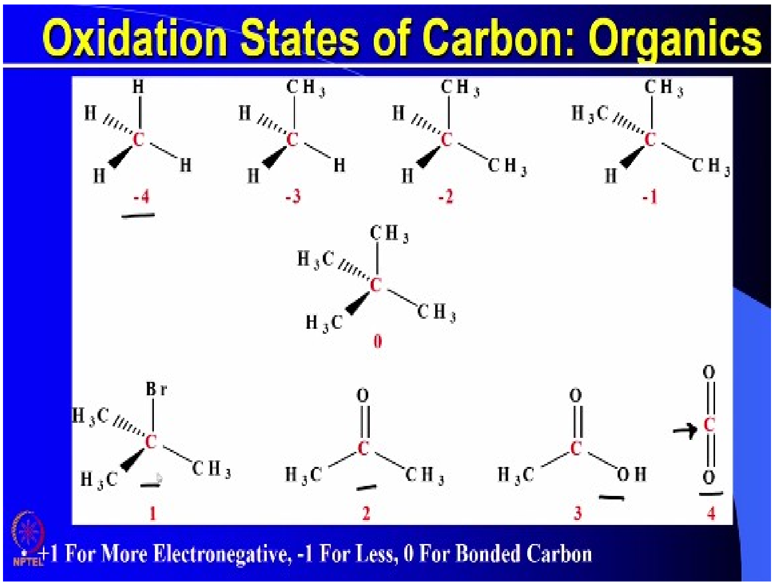

Oxidation States of Carbon: Organics

+1 For More Electronegative, -1 For Less, 0 For Bonded Carbon

Here are various oxidation states of carbon that you are aware of. Starting from an alkane this to a carbon dioxide, carbon can have oxidation state from -4 to +4 in various organic molecules. So the most oxidized state of carbon is carbon dioxide and the remaining others are acid, ketone and bromoalkane and so on.

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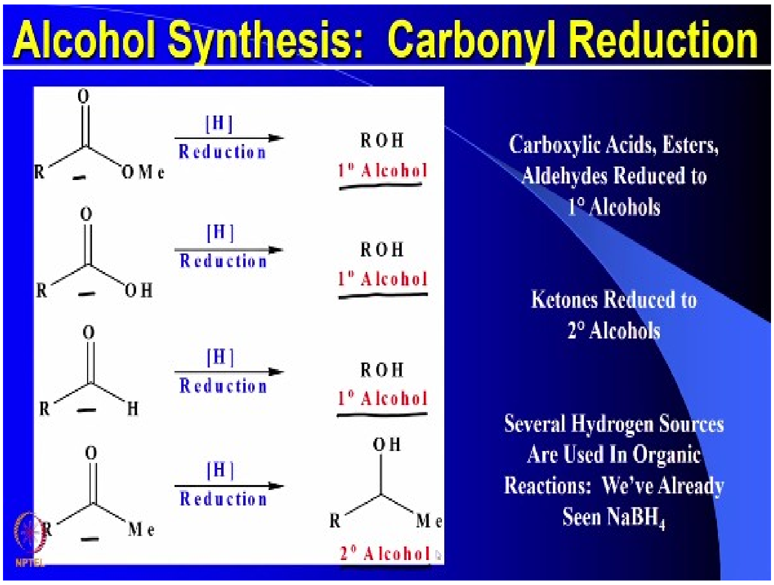

Alcohol Synthesis: Carbonyl Reduction

Carboxylic Acids, Esters, Aldehydes Reduced to 1° Alcohols

Ketones Reduced to 2° Alcohols

Several Hydrogen Sources Are Used In Organic Reactions: We've Already Seen $NaBH_4$

When we try to reduce the ester, we get 1 degree alcohol. When we try to reduce the acid, we end up getting 1 degree alcohol. When we have aldehyde we try to reduce we get 1 degree alcohol, primary alcohol. But then, if we have a ketone, we try to reduce it, we end up getting a secondary or 2 degree alcohol. So for these different reactions, we use different types of reducing agents.

And we will see how those reducing agents should be chosen and how those reducing reagents act on various carbonyl compounds.

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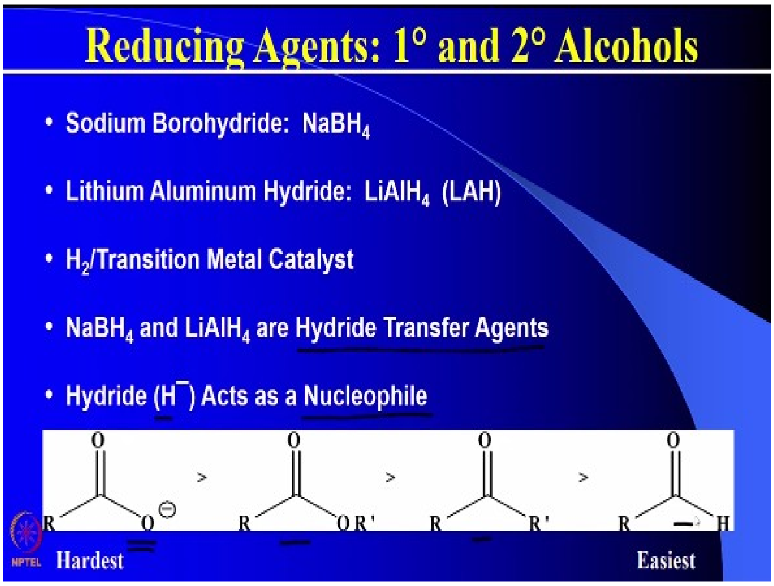

Reducing Agents: 1° and 2° Alcohols

- Sodium Borohydride: $NaBH_4$
- Lithium Aluminum Hydride: $LiAlH_4$ (LAH)
- H_2/Transition Metal Catalyst
- $NaBH_4$ and $LiAlH_4$ are Hydride Transfer Agents
- Hydride (H^-) Acts as a Nucleophile

Mostly used reducing agents are sodium borohydride and lithium aluminum hydride. And then people use hydrogen with transition metal as a catalyst. Not only sodium borohydride and lithium aluminum hydride are used as hydride transfer agents. And this hydride acts as a nucleophile. So then when we try to see that how these reducing agents act on various carbonyl compounds, we see a very well-known trend that the carboxylate anion is hardest to reduce.

Then it is harder to reduce is ester, then ketone and then aldehyde. So aldehyde is most easily reduced. Ketone needs stronger reducing agent and then the ester and carboxylic acid needs much harder reducing agents.

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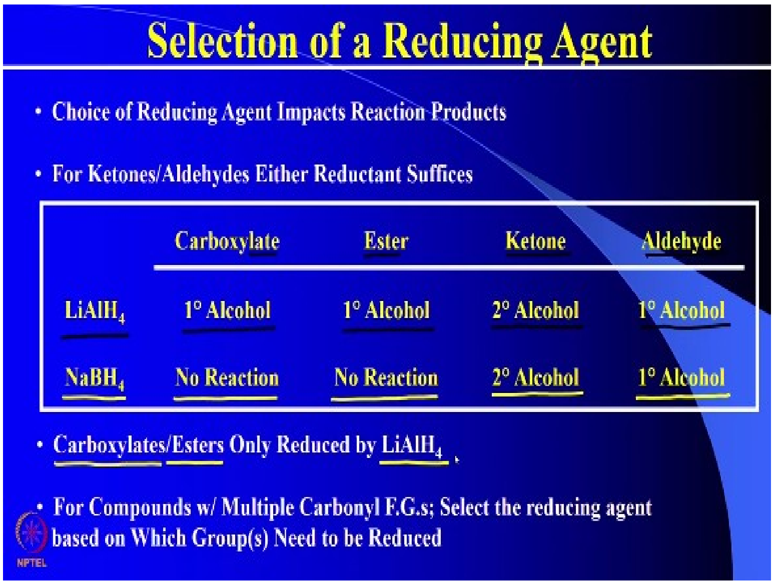

Selection of a Reducing Agent

- Choice of Reducing Agent Impacts Reaction Products
- For Ketones/Aldehydes Either Reductant Suffices

	Carboxylate	Ester	Ketone	Aldehyde
$LiAlH_4$	1° Alcohol	1° Alcohol	2° Alcohol	1° Alcohol
$NaBH_4$	No Reaction	No Reaction	2° Alcohol	1° Alcohol

- Carboxylates/Esters Only Reduced by $LiAlH_4$
- For Compounds w/ Multiple Carbonyl F.G.s; Select the reducing agent based on Which Group(s) Need to be Reduced

So here we will discuss about the choice of reducing agents and what would be the corresponding products of these compounds. So for ketone, aldehyde either reducing agents are sufficient. So if we use lithium aluminum hydride as the reducing agent, then a carboxylate ion or a carboxylic acid is reduced to primary alcohol. Ester is reduced to primary alcohol.

Ketone is reduced to a secondary alcohol. And aldehyde is reduced to a primary alcohol. But then, if we take sodium borohydride as a reducing agent, which is known as a milder reducing agent, it does not reduce carboxylic acid. It does not reduce the ester but it is capable of reducing the ketone to 2 degree alcohol. And it can reduce aldehyde to 1 degree alcohol.

So carboxylic groups or esters are only reduced by lithium aluminum hydrides. So compounds with multiple carbonyl groups, we can select the reducing agent based on which groups need to be reduced.

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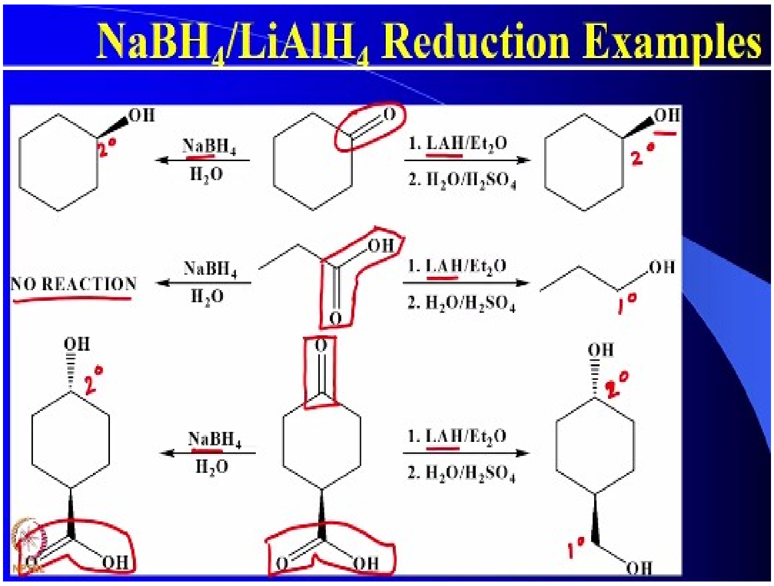

$NaBH_4/LiAlH_4$ Reduction Examples

So in the following slide, we will see some of those examples. So here in the first example at the top, we have a carbonyl group. We have a ketone. No matter what reducing agent we use, we end up getting a 2 degree alcohol. The second compound here we have acid. So if we use lithium aluminum hydride for that acid, we end up getting a 1 degree alcohol. But if we use sodium borohydride, there is no reaction.

This sodium borohydride cannot reduce this acid. Therefore, if in a compound, we had a ketone, and we had a carboxylic acid group, so if we had used a lithium aluminum hydride as a reagent, we would end up getting a 2 degree alcohol here and a 1 degree alcohol at this end. But if we had used sodium borohydride that would only reduce the ketone and form a 2 degree alcohol and this acid remains intact.

So this is how one can choose an appropriate reducing agent to selectively reduce one of the carbonyl groups from the set of carbonyl groups present in a molecule.

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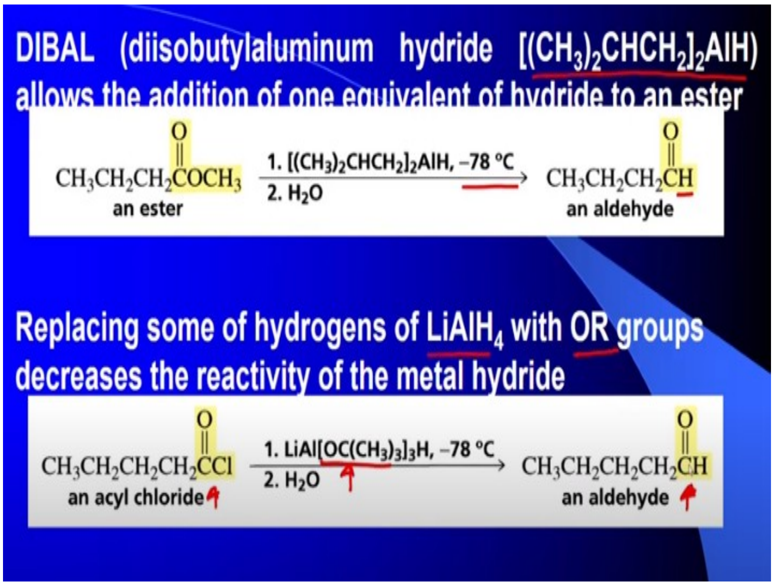

DIBAL (diisobutylaluminum hydride $[(CH_3)_2CHCH_2]_2AlH$) allows the addition of one equivalent of hydride to an ester

$$\underset{\text{an ester}}{CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3} \xrightarrow[2.\ H_2O]{1.\ [(CH_3)_2CHCH_2]_2AlH,\ -78\ ^\circ C} \underset{\text{an aldehyde}}{CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H}$$

Replacing some of hydrogens of $LiAlH_4$ with OR groups decreases the reactivity of the metal hydride

$$\underset{\text{an acyl chloride}}{CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}Cl} \xrightarrow[2.\ H_2O]{1.\ LiAl[OC(CH_3)_3]_3H,\ -78\ ^\circ C} \underset{\text{an aldehyde}}{CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}H}$$

You see here we can use some other hydride transfer reagent like DIBAL, which is called as diisobutylaluminum hydride, and the formula is given here. This also is a hydride transfer reagent. And this reaction is conducted at a very low temperature of -78 degree centigrade. And what we see is that this ester is reduced to an aldehyde in this reaction.

Replacing some of the hydrogen atoms of lithium aluminum hydride with some organic reagent, it reduces the reactivity of the metal hydride. So by doing that, this acid chloride is reduced to aldehyde instead of reducing it to the alcohol which lithium aluminum hydride would have done if we had used it as it is.

So by replacing three hydrides with this alkyl group, we have reduced the reducing capability of this lithium aluminum hydride and stopped the reduction of this compound to 1 degree alcohol.

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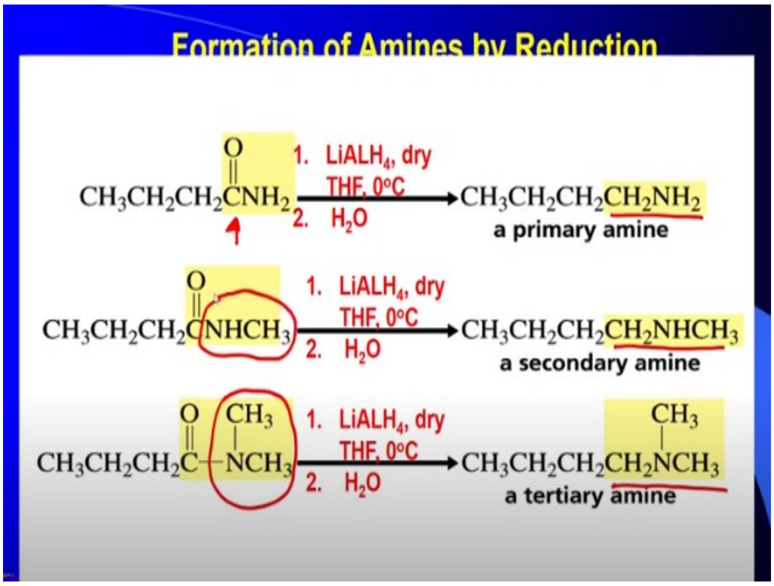

Formation of Amines by Reduction

$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[2.\ H_2O]{1.\ LiALH_4,\ dry\ THF,\ 0^{\circ}C} CH_3CH_2CH_2CH_2NH_2$$

a primary amine

$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}NHCH_3 \xrightarrow[2.\ H_2O]{1.\ LiALH_4,\ dry\ THF,\ 0^{\circ}C} CH_3CH_2CH_2CH_2NHCH_3$$

a secondary amine

$$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{|}{N}}CH_3 \xrightarrow[2.\ H_2O]{1.\ LiALH_4,\ dry\ THF,\ 0^{\circ}C} CH_3CH_2CH_2CH_2\overset{CH_3}{\overset{|}{N}}CH_3$$

a tertiary amine

Similarly, lithium aluminum hydride can be used to reduce the amides. So the amides can be reduced to corresponding amine and it can form 1 degree, 2 degree or 3 degree amine depending on the environment of the amide.

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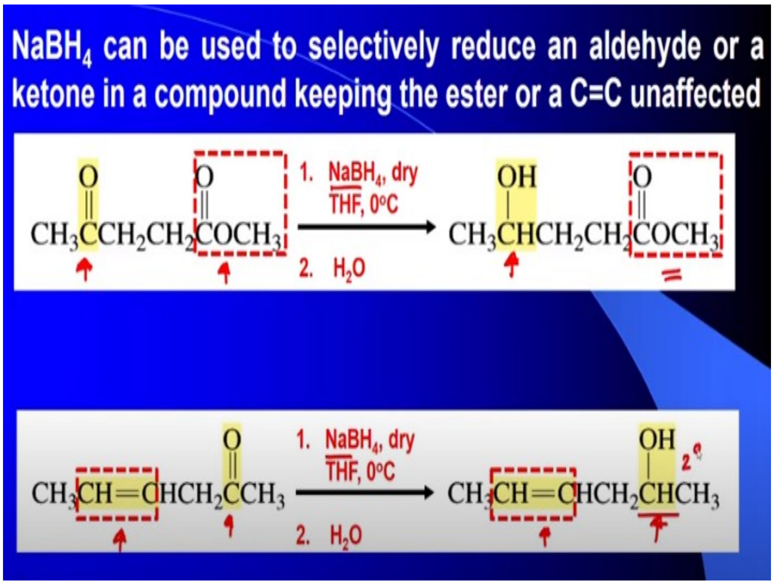

$NaBH_4$ can be used to selectively reduce an aldehyde or a ketone in a compound keeping the ester or a C=C unaffected

$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3 \xrightarrow[2.\ H_2O]{1.\ NaBH_4,\ dry\ THF,\ 0^{\circ}C} CH_3\overset{OH}{\overset{|}{C}}HCH_2CH_2\overset{O}{\overset{\|}{C}}OCH_3$$

$$CH_3CH=CHCH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[2.\ H_2O]{1.\ NaBH_4,\ dry\ THF,\ 0^{\circ}C} CH_3CH=CHCH_2\overset{OH}{\overset{|}{C}}HCH_3$$

2°

This is the last example that we would like to discuss here is that sodium borohydride can be used to selectively reduce an aldehyde or a ketone in a compound keeping the ester or a C C double bond unaffected. Suppose you have a carbonyl group here and you have another ester group there. If we use sodium borohydride it will reduce this ketone to alcohol. But the ester will remain unaltered.

Similarly, if we have a C double bond C in the molecule and a ketone, sodium borohydride will keep this group unaltered. But it will change the ketone to a 2 degree alcohol. So this is how one can use these reagents selectively to reduce one of the carbonyl groups keeping the other susceptible groups unaltered. We will continue from here in the next class.