Symmetry, Stereochemistry and Applications
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Lecture - 30
Nucleophilic Reactions

Welcome back to the course entitled Symmetry, Stereochemistry and Applications. In the first six weeks of this course, we have discussed about nomenclature, various aspects of stereochemistry. We have tried to understand stereochemical aspects of small organic molecules. And now we will move to the next part of this course where we will try to apply our knowledge of stereochemistry in understanding different reaction mechanisms. So that is the application part of this course.

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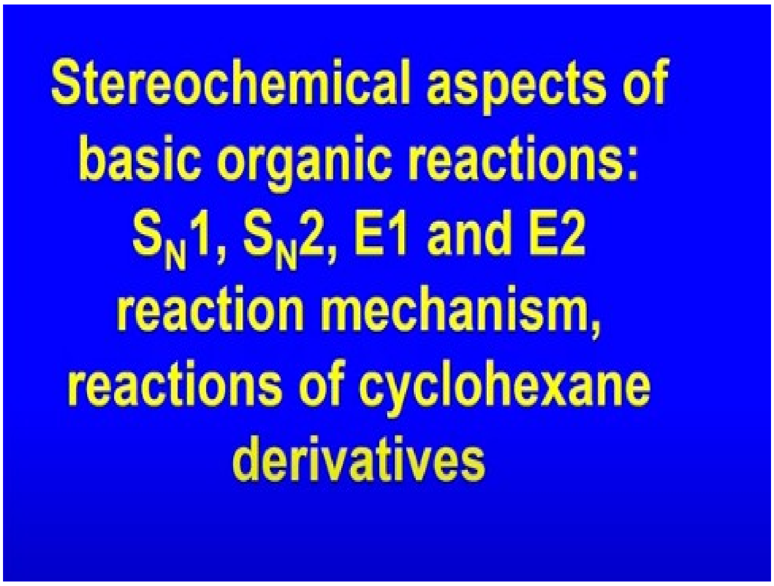

Stereochemical aspects of basic organic reactions: S_N1, S_N2, E1 and E2 reaction mechanism, reactions of cyclohexane derivatives

So in this course, we will start by discussing the stereochemical aspects of some basic organic reactions. So we would like to start by talking about S_N1, S_N2, E1 and E2 reaction mechanisms, reactions of cyclohexane derivatives etc.

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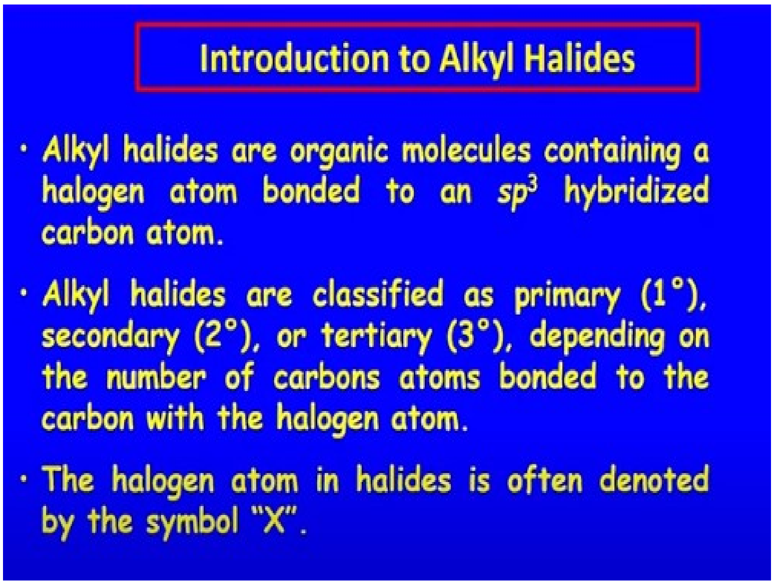

Introduction to Alkyl Halides

- Alkyl halides are organic molecules containing a halogen atom bonded to an sp^3 hybridized carbon atom.
- Alkyl halides are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of carbons atoms bonded to the carbon with the halogen atom.
- The halogen atom in halides is often denoted by the symbol "X".

So when we try to understand different types of reaction mechanisms, always we are interested to know about the substrates and the reactants which are involved in a given reaction. So these substitution reactions which are essentially called S_N1 or S_N2 reactions, what do they mean, we will talk about it in a few minutes. Those reactions involve compounds called alkyl or arly or acetyl, acyl halides.

So we need to know what are those alkyl halides. Alkyl halides are organic molecules containing a halogen atom bonded to an sp3 hybridized carbon atom. It can be also sp2, we will talk about it later. Alkyl halides are classified as primary, which is written as 1 degree, secondary or 2 degree or tertiary which is written as 3 degree depending on the number of carbon atoms bonded to the carbon with the halogen atom. And generally the halogen atom in this halide is denoted by the symbol X.

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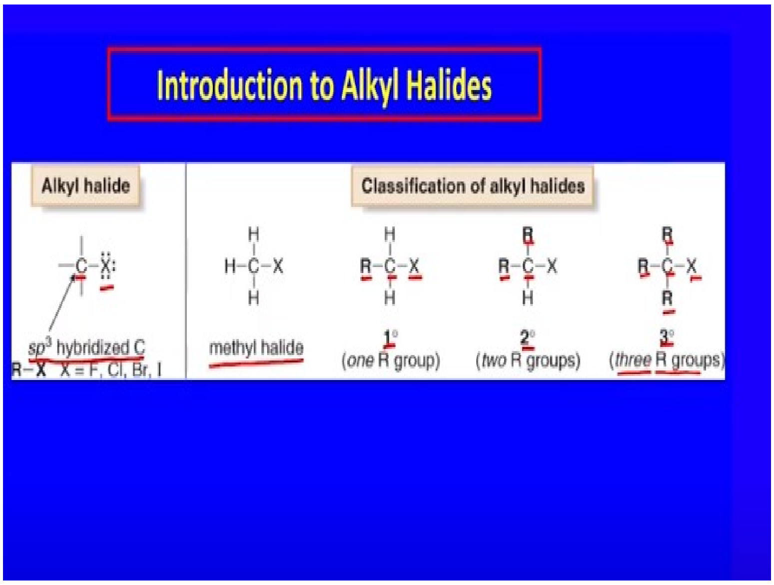

Introduction to Alkyl Halides

Alkyl halide

sp^3 hybridized C

R–X X = F, Cl, Br, I

Classification of alkyl halides

methyl halide

1° (*one* R group)

2° (*two* R groups)

3° (*three* R groups)

So here is the example of alkyl halides. So an alkyl halide will have a halogen atom connected to a carbon which is sp3 hybridized carbon. That means it is a tetrahedral carbon atom. And the simplest alkyl halide that one can think of is methyl halide. That is by replacing one hydrogen of methane by halogen, you get methyl halide. So then, when you have one alkyl group connected to the carbon which contains the halogen, we call it as 1 degree halide or a primary halide.

When there are two alkyl groups connected, we call that as a 2 degree halide. And when there are three alkyl groups connected to that sp3 carbon, we call these halide as a 3 degree halide. We will see that these different alkyl halides 1 degree, 2 degree and 3 degree have different types of reactions when we talk about substitution reaction.

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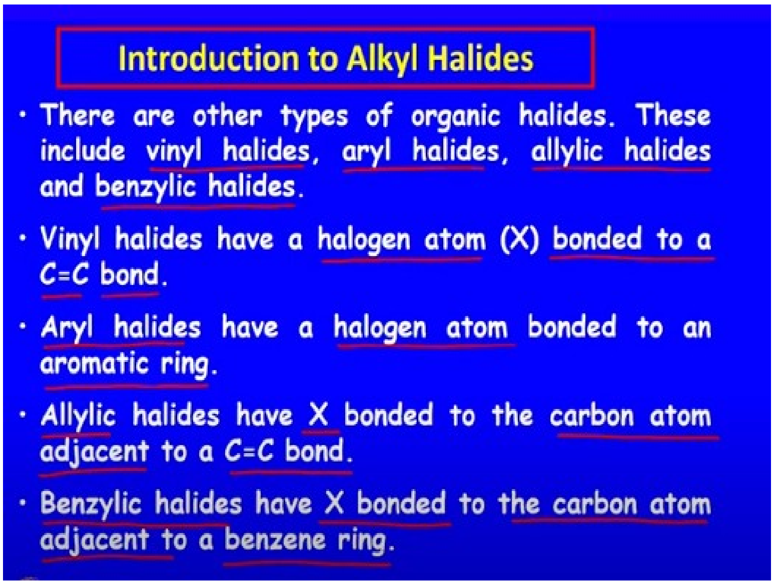

Introduction to Alkyl Halides

- There are other types of organic halides. These include vinyl halides, aryl halides, allylic halides and benzylic halides.
- Vinyl halides have a halogen atom (X) bonded to a C=C bond.
- Aryl halides have a halogen atom bonded to an aromatic ring.
- Allylic halides have X bonded to the carbon atom adjacent to a C=C bond.
- Benzylic halides have X bonded to the carbon atom adjacent to a benzene ring.

Other than these alkyl halides there are other types of organic halides. These include vinyl halide, aryl halide, allylic halide, and benzylic halides. So what are these different types of halides? Vinyl halides have the halogen atom bonded to a C=C double bonded carbon, that means bonded to an sp2 hybridized carbon. Aryl halides have the halogen atom bonded to an aromatic ring.

So if it is PhX, we call it as aryl halide. The third type is allylic halide, where the halogen is bonded to the carbon atom adjacent to a C=C double bond. So immediately next carbon atom if it contains an halogen, we call it as allylic halide. And similarly benzylic halides have the halogen bonded to the carbon atom adjacent to the benzene ring. So let us see what are the chemical natures or chemical structures of these four different halides.

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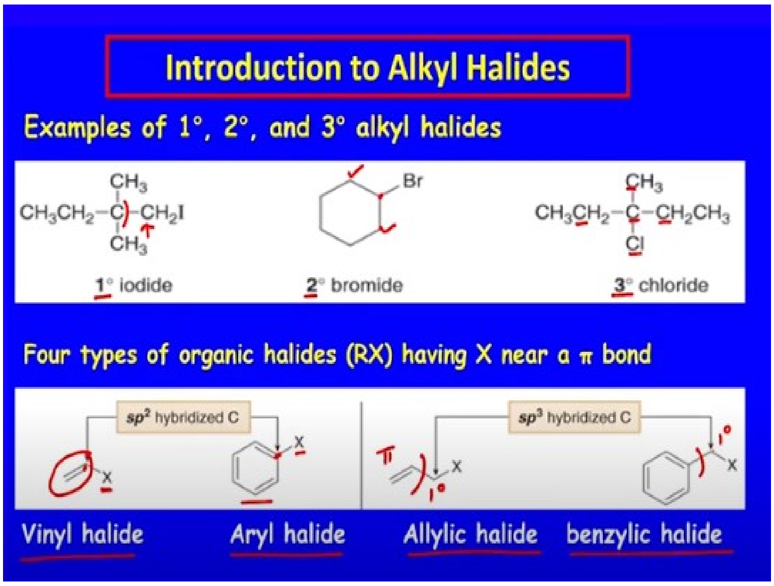

Introduction to Alkyl Halides

Examples of 1°, 2°, and 3° alkyl halides

1° iodide

2° bromide

3° chloride

Four types of organic halides (RX) having X near a π bond

sp² hybridized C

sp³ hybridized C

Vinyl halide

Aryl halide

Allylic halide

benzylic halide

We have already seen that the 1 degree, 2 degree and 3 degree halides can have one carbon atom attached to this carbon where the halogen is bonded. So that is this one. In this case, this carbon has two carbon atoms connected. So this is a 2 degree halide. And here, this carbon with which the halogen is bonded, has three carbon atoms bonded to it. So this is a 3 degree alkyl halide.

Then the other four types which we discussed in the previous slide are the following. The vinyl halide where the X atom is directly connected to a C=C double bonded carbon. Aryl halide when the halogen is directly connected to a phenyl ring or an aromatic ring. Remember that both the cases the carbon we are talking about is sp2 hybridized carbon. The other two halides are allylic halide and benzylic halide.

Allylic halide is essentially a 1 degree halide, but connected to a group which contains a pi bond. Similarly benzylic halide is essentially an 1 degree halide, but is connected to a phenyl ring. So these are four different types of alkyl or allyl halides, which we will encounter during this course for different types of reactions.

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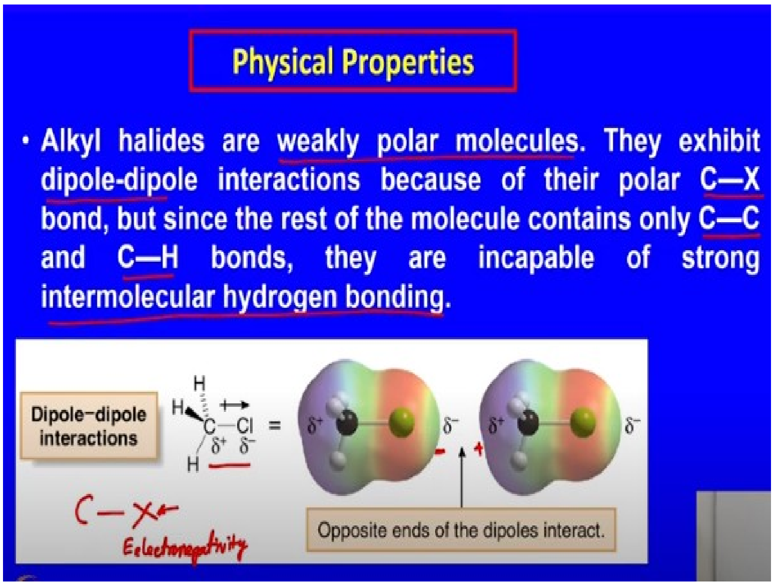

Physical Properties

- Alkyl halides are weakly polar molecules. They exhibit dipole-dipole interactions because of their polar C—X bond, but since the rest of the molecule contains only C—C and C—H bonds, they are incapable of strong intermolecular hydrogen bonding.

So we need to know a little bit about the physical properties of these alkyl or allyl halides. Alkyl halides are weakly polar molecules because the carbon-halogen bond gets polarized. They exhibit dipole-dipole interaction because of the polar nature of the corresponding C-X bond. As you know, the halogens have higher electronegativity compared to carbon. So the C-X bond is always polar.

But since the rest of the molecule only contains C-C and C-H bonds, this alkyl halides the group that we are discussing about the C-X, this group although this has a very high electronegativity where we expect that this halogen to be accepting strong hydrogen bonds, but unfortunately it does not. So this intermolecular hydrogen bonding is poor in case of these alkyl halides.

If you look at the polarity of that bond, what we see is a separation of delta positive and delta negative charge on that bond and the electrostatic potential that is shown here indicates a slightly negative lobe on the side and a slightly positive lobe on that side. So that these molecules have a certain dipole moment.

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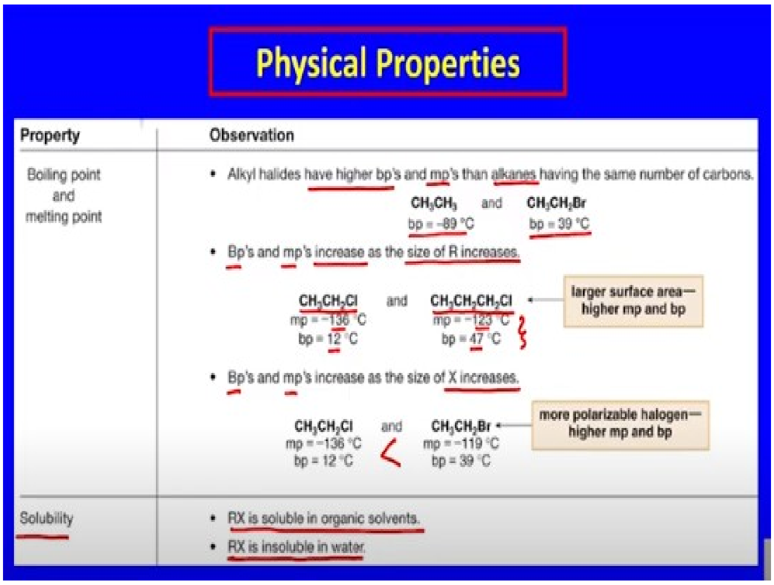

Physical Properties

Property	Observation
Boiling point and melting point	• Alkyl halides have higher bp's and mp's than alkanes having the same number of carbons. CH_3CH_3 and CH_3CH_2Br bp = −89 °C bp = 39 °C • Bp's and mp's increase as the size of R increases. CH_3CH_2Cl and $CH_3CH_2CH_2Cl$ ← larger surface area—higher mp and bp mp = −136 °C mp = −123 °C bp = 12 °C bp = 47 °C • Bp's and mp's increase as the size of X increases. CH_3CH_2Cl and CH_3CH_2Br ← more polarizable halogen—higher mp and bp mp = −136 °C $<$ mp = −119 °C bp = 12 °C bp = 39 °C
Solubility	• RX is soluble in organic solvents. • RX is insoluble in water.

When we look at their real physical properties, we talk about their melting and boiling point. We see that alkyl halides have higher boiling points and melting points than the corresponding alkane from which they are derived. So ethane has a boiling point of -89 degree centigrade, while bromoethane or ethyl bromide has a boiling point of +39 degree centigrade.

Boiling point and melting point increases as the size of R increases. So when we talk about ethyl chloride and propyl chloride, the propyl chloride has a higher molecular weight. Therefore, it has slightly higher melting point and higher boiling point as well. Boiling point and melting point increases as the size of halogen increases. That means ethyl chloride has a lower boiling and melting point compared to ethyl bromide, right?

So these are certain physical properties which one can use to identify these alkyl halides. When we talk about the solubility of these alkyl halides, these are in general soluble in organic solvents and they are not soluble in water. Why are they not soluble in water? Because they are incapable of forming hydrogen bond with water and hence they cannot be dissolved in water.

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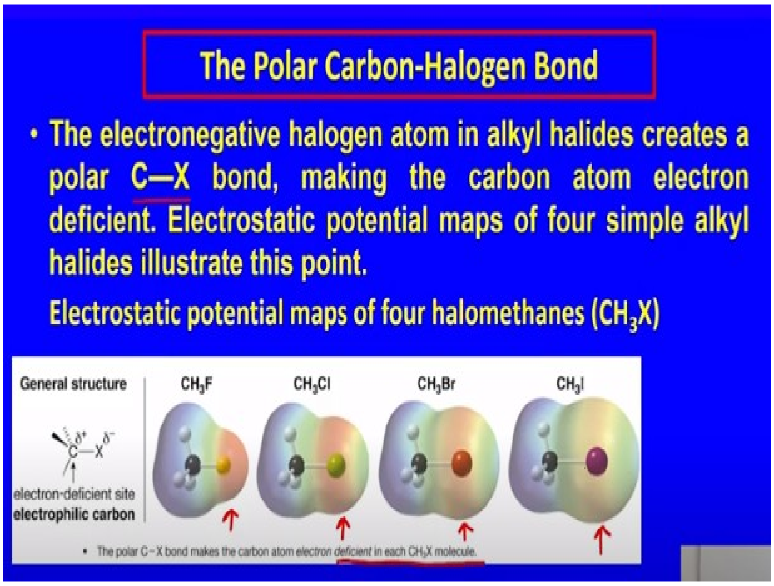

The Polar Carbon-Halogen Bond

- The electronegative halogen atom in alkyl halides creates a polar C—X bond, making the carbon atom electron deficient. Electrostatic potential maps of four simple alkyl halides illustrate this point.

Electrostatic potential maps of four halomethanes (CH_3X)

- The polar C−X bond makes the carbon atom electron deficient in each CH_3X molecule.

So this polarity of carbon-hydrogen bond is a matter of extensive research which many of us are involved in. So the electronegative halogen atom in alkyl halide creates a polar C-X bond which we have already seen making the carbon atom electron deficient. Therefore, electrostatic potential maps of this four alkyl halides are shown here.

What we see is that the polar C-X bond makes the carbon atom electron deficient in each of these molecule. And this size of the halogen when it increases, the electron density, diffused electron density becomes more diffused in case of larger halogens.

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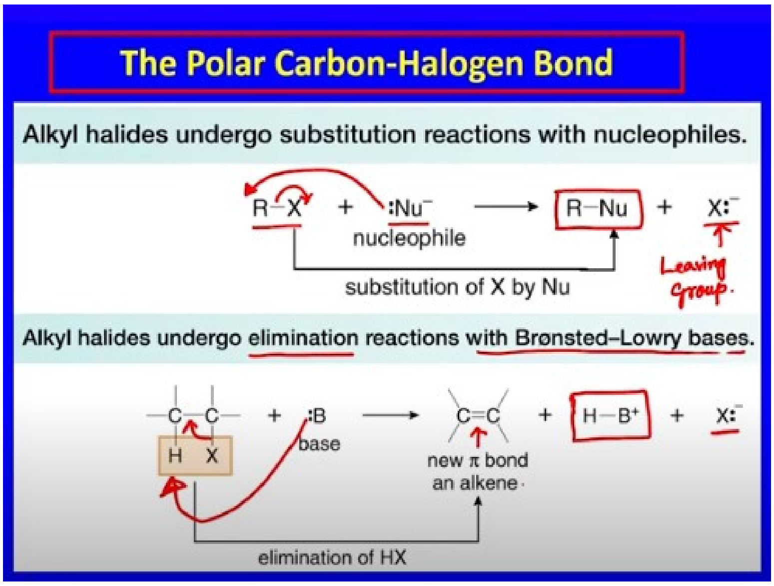

The Polar Carbon-Halogen Bond

Alkyl halides undergo substitution reactions with nucleophiles.

$$R-X + :Nu^- \longrightarrow \boxed{R-Nu} + X:^-$$

Alkyl halides undergo elimination reactions with Brønsted–Lowry bases.

$$-\overset{|}{\underset{H}{C}}-\overset{|}{\underset{X}{C}}- + :B \longrightarrow C=C + \boxed{H-B^+} + X:^-$$

So when we try to react these alkyl halides with nucleophiles, that means a species which may contain a charge or may contain a pair of electron, lone pair of electron.

So then when we react alkyl halide with a nucleophile what happens is that this nucleophile attacks the electron deficient carbon center and throws away the halogen and forms a new molecule, which is called R-Nu and it eliminates the halide.

So this halide that is eliminated is called the leaving group. Depending on the nature of this leaving group, the feasibility of this reaction is determined. Similarly, this alkyl halides can undergo elimination reaction with Bronsted and Lowry bases. So if you have a compound which contains an halogen and the adjacent carbon contains a hydrogen atom, then it is possible that the base takes up this proton and the halogen is eliminated.

You get a complex of the conjugate acid of the base and the halogen is eliminated, a new pi bond is formed here. So by elimination of this H X from here, you get a double bond created in a molecule. So at some point we will understand, we will try to learn how this reaction happens and what are the possible reaction mechanisms of this particular reaction.

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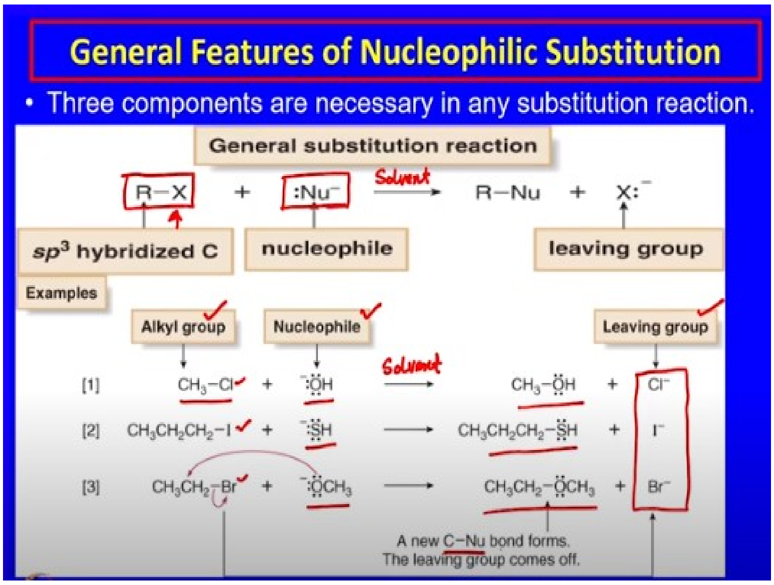

General Features of Nucleophilic Substitution

- Three components are necessary in any substitution reaction.

General substitution reaction

$$\boxed{R-X} + \boxed{:Nu^-} \xrightarrow{\text{Solvent}} R-Nu + X:^-$$

[1] $CH_3-Cl + {}^-:\ddot{O}H \xrightarrow{\text{Solvent}} CH_3-\ddot{O}H + Cl^-$

[2] $CH_3CH_2CH_2-I + {}^-:\ddot{S}H \longrightarrow CH_3CH_2CH_2-\ddot{S}H + I^-$

[3] $CH_3CH_2-Br + {}^-:\ddot{O}CH_3 \longrightarrow CH_3CH_2-\ddot{O}CH_3 + Br^-$

A new C−Nu bond forms.
The leaving group comes off.

So when we try to talk about any substitution reaction, general features of nucleophilic substitution reaction, there are three components that are necessary in any substitution reaction. The first thing that you need is an alkyl halide. You need a nucleophile and that alkyl halide should have a very good leaving group and you would require something called solvent.

So what you need is to have the alkyl group, the nucleophile, the leaving group and a solvent for the given reaction. As you know that these molecules are not in general soluble in water, which I have to use different solvents which will dissolve the alkyl halide. So here are some examples where alkyl halides are treated with OH-, SH- and OME- with different halogens, chloride, iodide and bromide and the halogen ions, halide ions are eliminated.

Those are called the leaving groups and the nucleophile gets attached to form different organic compounds. So everywhere, we see that a Nu-C and nucleophile bond has formed.

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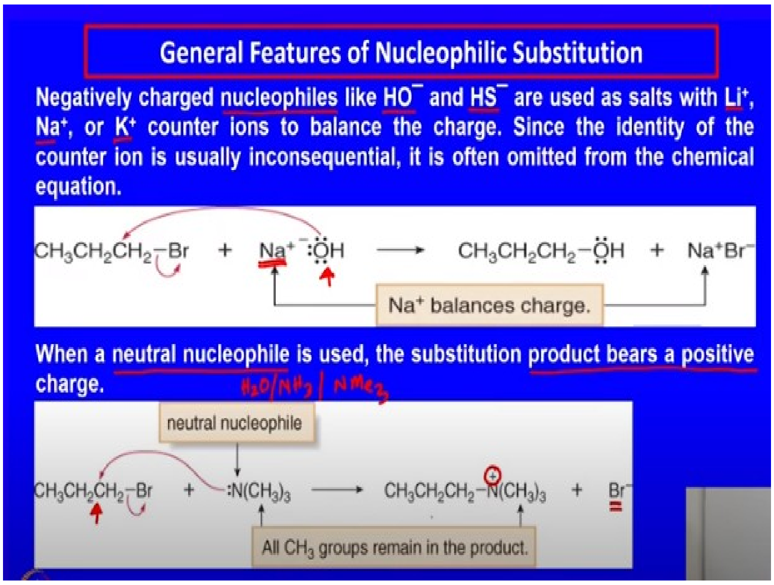

General Features of Nucleophilic Substitution

Negatively charged nucleophiles like HO^- and HS^- are used as salts with Li^+, Na^+, or K^+ counter ions to balance the charge. Since the identity of the counter ion is usually inconsequential, it is often omitted from the chemical equation.

$CH_3CH_2CH_2-Br + Na^+ \, {}^-{:}\ddot{O}H \longrightarrow CH_3CH_2CH_2-\ddot{O}H + Na^+Br^-$

Na⁺ balances charge.

When a neutral nucleophile is used, the substitution product bears a positive charge.

H_2O/NH_3 | NMe_3

neutral nucleophile

$CH_3CH_2CH_2-Br + {:}N(CH_3)_3 \longrightarrow CH_3CH_2CH_2-\overset{+}{N}(CH_3)_3 + Br^-$

All CH_3 groups remain in the product.

So when we try to understand the general features of nucleophilic substitution reaction, we see with that we are using nucleophiles like OH-, SH-. These are used as salts with the alkali metal ions like sodium, lithium, sodium and potassium as counter ions to balance the charge. Since the identity of the counter ion is not really important in this reaction, it is often omitted from the chemical equation.

So we do not in general write Na+, we only write the OH-. It does not matter whether it is sodium, potassium or lithium, it is only used in the chemical reaction to balance the charges. When we see a neutral nucleophile like water, ammonia, etc., or any derivative of an ammonia NMe_3 and so on, the substitution product bares a positive charge.

So when you have an amine, here it is trimethylamine, this reacts at this carbon center which is nucleophilic center and the C-Br bond is broken and it releases Br-. So the actual product bears a positive charge on this and it exist as a cation anion pair.

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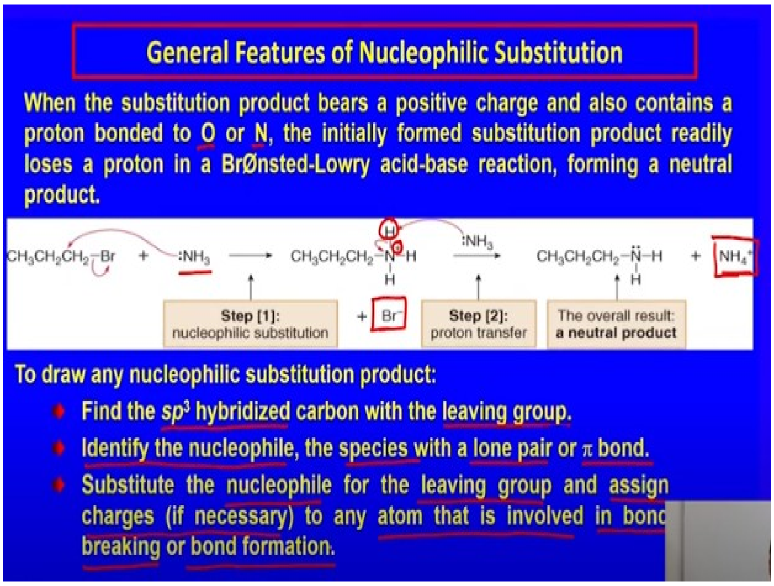

General Features of Nucleophilic Substitution

When the substitution product bears a positive charge and also contains a proton bonded to O or N, the initially formed substitution product readily loses a proton in a BrØnsted-Lowry acid-base reaction, forming a neutral product.

To draw any nucleophilic substitution product:

- Find the sp^3 hybridized carbon with the leaving group.
- Identify the nucleophile, the species with a lone pair or π bond.
- Substitute the nucleophile for the leaving group and assign charges (if necessary) to any atom that is involved in bond breaking or bond formation.

When the substitution product bears a positive charge and also contains a proton bonded to oxygen or nitrogen, the initially formed substitution product readily loses a proton in a Bronsted-Lowry acid base reaction forming a neutral product. So for example, here if we use ammonia in this reaction, the product that forms contains N+ and it contains N-H bonds.

So if there are additional NH3 or the ammonia molecule in the solution, then it will take up the proton from this positively charged species and make a neutral organic compound and release ammonium ion in solution. So in a stepwise process, bromine will be eliminated as Br- and the charged species will become uncharged species by removal of one H+ and making it NH4+.

So in the solution you will have ammonium bromide as a final product. To draw any nucleophilic substitution product, what we need to do is we need to find the sp3 hybridized carbon with a good leaving group. We need to identify a suitable nucleophile, a species which has a lone pair or a pi bond, can have a charge or may not have a charge.

Substitute the nucleophile for the leaving group and assign appropriate charges if necessary to any atom that is involved in the bond breaking and bond formation mechanism. And then neutralize the charge if possible by elimination of one proton.

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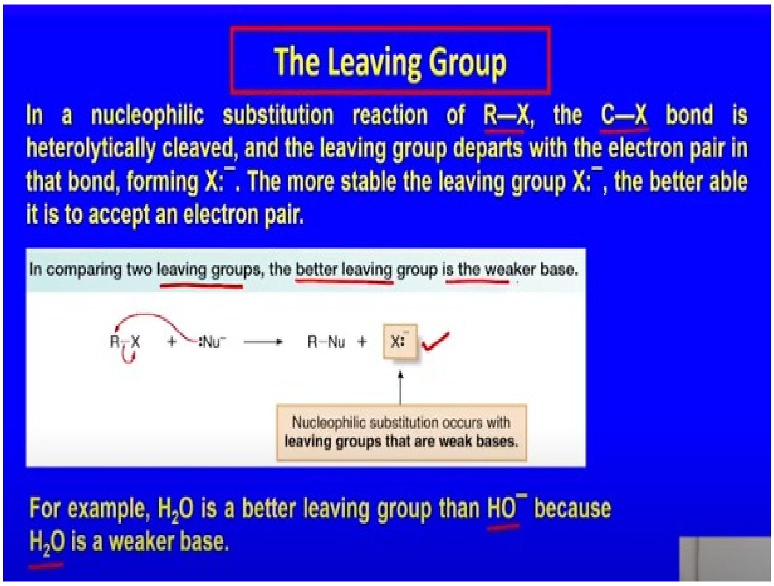

The Leaving Group

In a nucleophilic substitution reaction of R—X, the C—X bond is heterolytically cleaved, and the leaving group departs with the electron pair in that bond, forming $X:^-$. The more stable the leaving group $X:^-$, the better able it is to accept an electron pair.

In comparing two leaving groups, the better leaving group is the weaker base.

$$R{-}X + :Nu^- \longrightarrow R{-}Nu + \boxed{X:^-}$$

Nucleophilic substitution occurs with leaving groups that are weak bases.

For example, H_2O is a better leaving group than HO^- because H_2O is a weaker base.

Now let us talk about the leaving group. In a nucleophilic substitution reaction with R-X, the carbon halogen bond is heterolytically cleaved. That means, the electron pair of the bond is released or left with the leaving group making the leaving group as a negatively charged ion. And the leaving group departs with the electron pair of that bond forming X-ion.

The more stable the leaving group that is X-, the better it is able to accept the electron pair. So it is the capability of this group how easily it can accept the pair of electron it then gets released from the molecule. For example, water is a better leaving group than OH- because water is a weaker base compared to OH-. So in comparing two leaving groups, the better leaving group is a weaker base.

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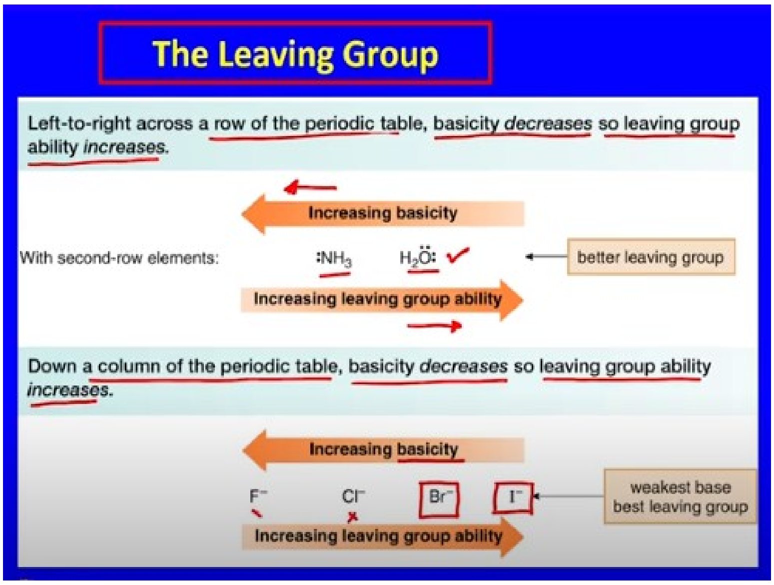

The Leaving Group

Left-to-right across a row of the periodic table, basicity *decreases* so leaving group ability *increases*.

Increasing basicity

With second-row elements: $:NH_3$ $H_2\ddot{O}:$ ← better leaving group

Increasing leaving group ability

Down a column of the periodic table, basicity *decreases* so leaving group ability *increases*.

Increasing basicity

F^- Cl^- Br^- I^- ← weakest base best leaving group

Increasing leaving group ability

So when we try to understand this leaving group property or leaving group capability, we look at the periodic table. From left to right across a row in a periodic table basicity decreases. So the leaving group ability increases. So if we are talking about comparing between water and ammonia, ammonia is more basic than water.

Therefore, the leaving group, as a leaving group water is a better leaving group compared to ammonia. So the basicity increases from right to left and the leaving group ability is increasing from left to right. Again, when we are comparing among the halogens, down the column of a periodic table basicity decreases, so the leaving group ability increases.

So from iodide to fluoride, the basicity increases while the leaving group capability is better for iodide. So you will see that in many of the reactions when we try to do it in our laboratory, we try to take halides which are either bromide or iodide. And we generally do not take chloride or fluoride as they are not very good leaving group.

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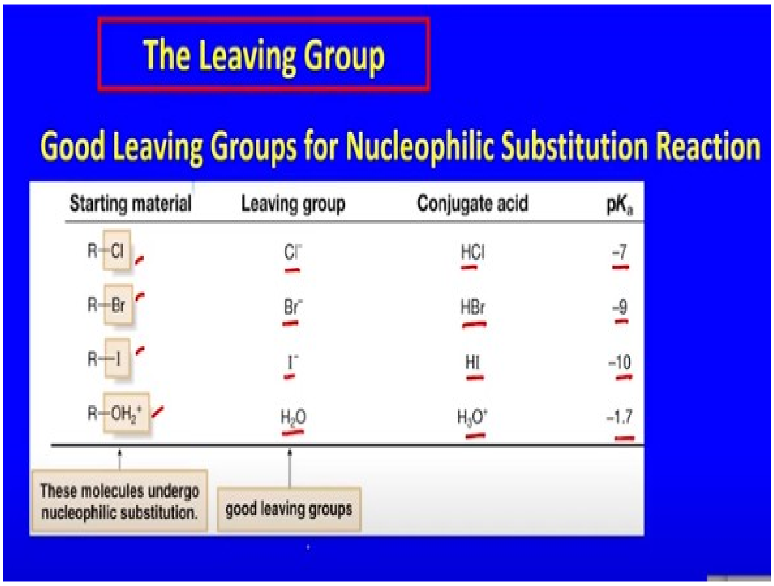

The Leaving Group

Good Leaving Groups for Nucleophilic Substitution Reaction

Starting material	Leaving group	Conjugate acid	pK_a
R—Cl	Cl^-	HCl	−7
R—Br	Br^-	HBr	−9
R—I	I^-	HI	−10
$R—OH_2^+$	H_2O	H_3O^+	−1.7

These molecules undergo nucleophilic substitution.

good leaving groups

So good leaving group for nucleophilic substitutions are listed here; chloro, bromo, iodo, water and it reads as chloride, bromide iodide and H2O and the corresponding conjugate acids are these and their pK a values identified them as a very strong acid. So these molecules undergo nucleophilic substitution very easily. And these are examples of some very good leaving groups.

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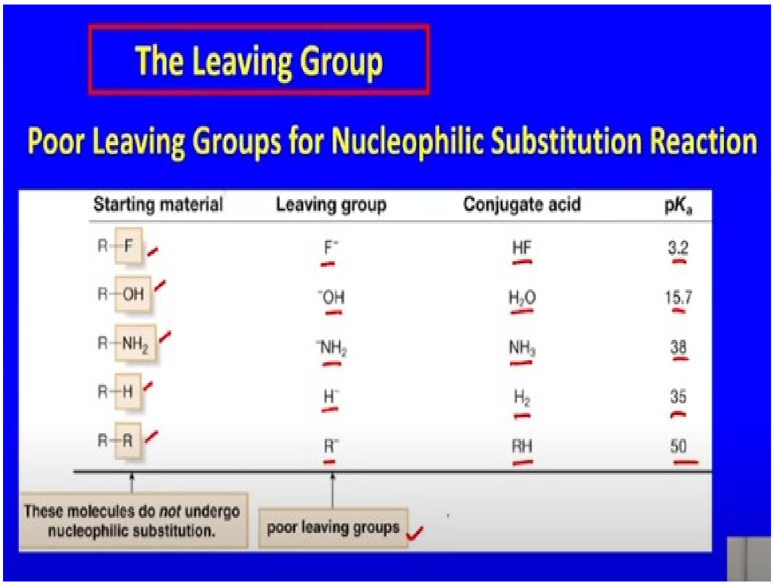

The Leaving Group

Poor Leaving Groups for Nucleophilic Substitution Reaction

Starting material	Leaving group	Conjugate acid	pK_a
R—F	F^-	HF	3.2
R—OH	^-OH	H_2O	15.7
$R—NH_2$	$^-NH_2$	NH_3	38
R—H	H^-	H_2	35
R—R	R^-	RH	50

These molecules do *not* undergo nucleophilic substitution.

poor leaving groups

On the other hand, there are many poor leaving groups which we should be aware of. If we have alkyl fluoride, alcohol, amine, simple RH or an alkane, if you try to do this nucleophilic reactions, the leaving groups should be of this type; fluoride, OH- NH2-, H-, R- etc. The corresponding conjugate acid of these groups have very high pKa values. Therefore, they are very weak acids and these groups are poor leaving groups. I hope you are able to follow.

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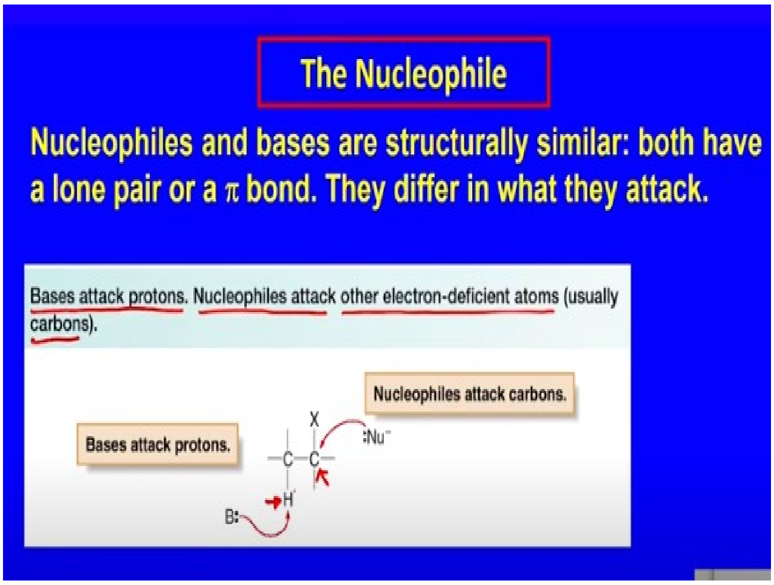

The Nucleophile

Nucleophiles and bases are structurally similar: both have a lone pair or a π bond. They differ in what they attack.

Bases attack protons. Nucleophiles attack other electron-deficient atoms (usually carbons).

Nucleophiles attack carbons.

Bases attack protons.

So what happens when nucleophiles and bases are structurally similar? Both of them have lone pair or a pi bond. But they differ in what they attack. That means, there is a certain subtle difference between a base and a nucleophile. If you have a base, that base generally attacks a proton, while a nucleophile attacks other electron deficient atoms usually the carbon atoms.

So if you do a reaction with a compound, which has the halogen and a hydrogen like this, and you throw a nucleophile to this reaction, nucleophile will attack to this electron deficient carbon atom, while the base will attack the adjacent carbon atom's hydrogen to abstract that proton and form a BH+ molecule.

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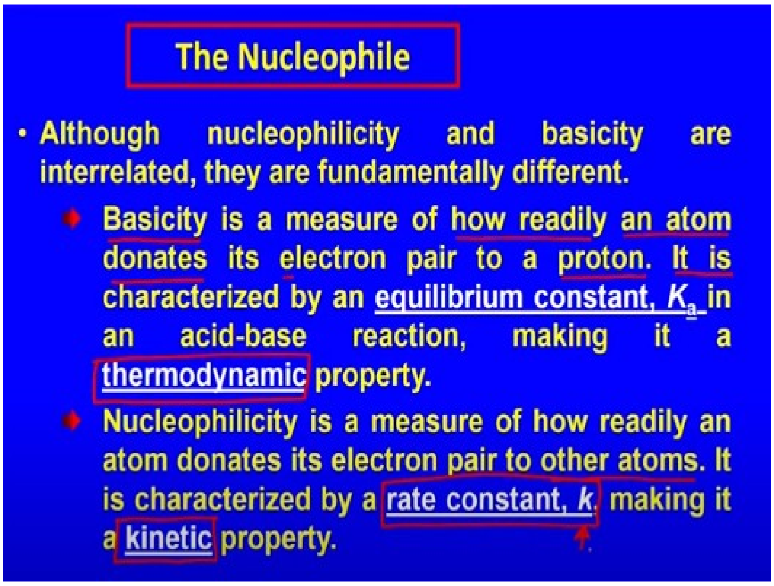

The Nucleophile

- Although nucleophilicity and basicity are interrelated, they are fundamentally different.
  - Basicity is a measure of how readily an atom donates its electron pair to a proton. It is characterized by an equilibrium constant, K_a in an acid-base reaction, making it a thermodynamic property.
  - Nucleophilicity is a measure of how readily an atom donates its electron pair to other atoms. It is characterized by a rate constant, k, making it a kinetic property.

So what is a nucleophile? A nucleophile is something which has a lone pair of electron and it has a capability to attack a nucleophilic center. Although nucleophilicity and basicity are interrelated, they are fundamentally different. Basicity is a measure of how readily an atom donates its electron pair to a proton.

So it is characterized by the equilibrium constant Ka in an acid base type of reaction, making it a thermodynamic property, while nucleophilicity is a measure of how readily an atom donates its electron pair to other atoms. It is characterized by rate constant k and it is a kinetic property. You see the difference here this K is capital K with a and this k is small k.

That one is equilibrium constant and this is a rate constant, which you may have studied in your physical chemistry course.

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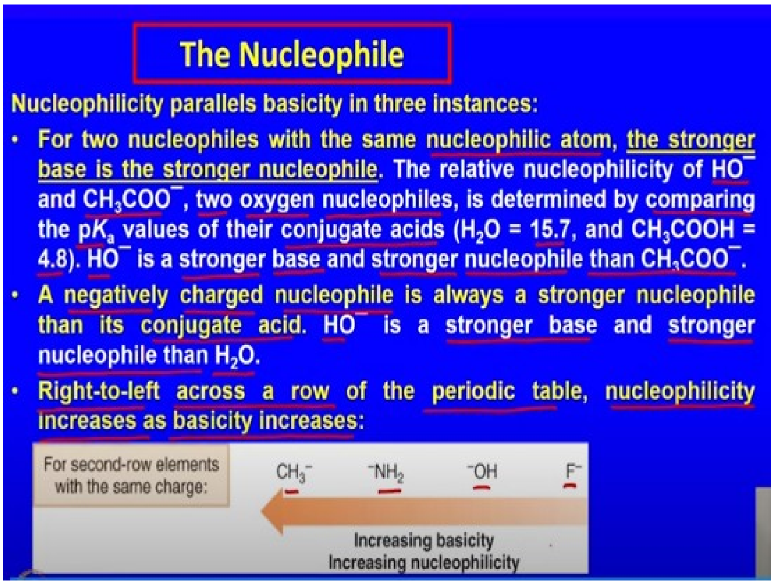

The Nucleophile

Nucleophilicity parallels basicity in three instances:

- For two nucleophiles with the same nucleophilic atom, the stronger base is the stronger nucleophile. The relative nucleophilicity of HO^- and CH_3COO^-, two oxygen nucleophiles, is determined by comparing the pK_a values of their conjugate acids (H_2O = 15.7, and CH_3COOH = 4.8). HO^- is a stronger base and stronger nucleophile than CH_3COO^-.
- A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid. HO^- is a stronger base and stronger nucleophile than H_2O.
- Right-to-left across a row of the periodic table, nucleophilicity increases as basicity increases:

For second-row elements with the same charge:

CH_3^- $^-NH_2$ ^-OH F^-

Increasing basicity
Increasing nucleophilicity

Nucleophilicity parallels basicity in three instances. For two nucleophiles with the same nucleophilic atom, that means the atom is same, the stronger base is the stronger nucleophile. So when we compare the relative nucleophilicity of OH- and acetate, in both the cases we have oxygen atom as a nucleophile. It is determined by comparing the pKa values of their conjugate acids.

So water has pKa of 15.7 while acetic acid has pKa of 4.8. Therefore, OH- is a stronger base and a stronger nucleophile as well compared to the acetate group. A negatively charged nucleophile is always a stronger nucleophile than its conjugate acid, which means OH- is a stronger base and a stronger nucleophile compared to water.

And then third point is in the periodic table right to left across a row of a periodic table, nucleophilicity increases as basicity increases. So from right to left, when the basicity is increasing from fluoride to OH- to NH2- to methyl minus, when the basicity increases, the nucleophilicity of these groups also increases.

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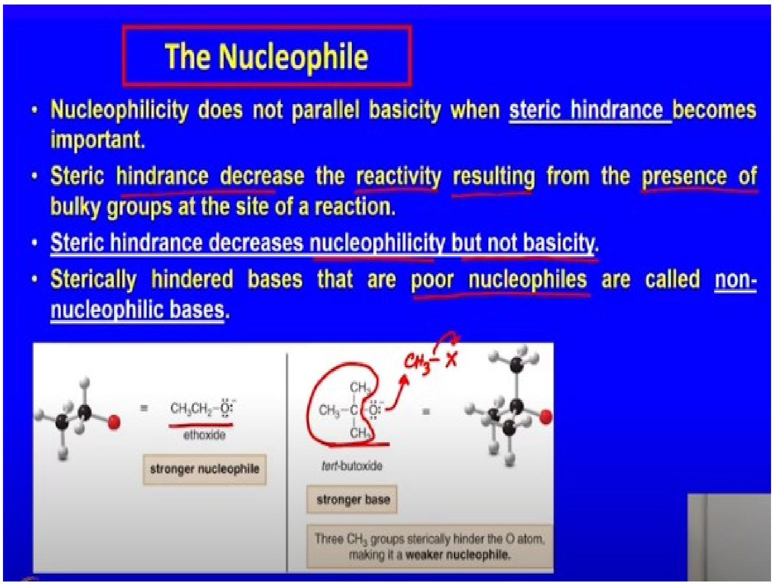

The Nucleophile

- Nucleophilicity does not parallel basicity when steric hindrance becomes important.
- Steric hindrance decrease the reactivity resulting from the presence of bulky groups at the site of a reaction.
- Steric hindrance decreases nucleophilicity but not basicity.
- Sterically hindered bases that are poor nucleophiles are called non-nucleophilic bases.

Three CH_3 groups sterically hinder the O atom, making it a **weaker nucleophile**.

Nucleophilicity does not parallel basicity when steric hindrance becomes important. That means, when there are bulky groups, then there is a difference in this basicity and nucleophilicity of different negatively charged species. Steric hindrance decreases the reactivity resulting from the presence of bulky groups at the site of reaction. So steric hindrance decreases nucleophilicity but not basicity.

Because if a site is sterically hindered, then the nucleophile which has a negative charge does not get chance to get connected to the carbon atom which is already sterically hindered. Therefore, its nucleophilicity decreases, but the basicity is the nature of it to abstract proton. So its basicity is not hampered due to the steric hindrance.

So we can state that sterically hindered bases, which are pure nucleophiles, they are called non-nucleophilic bases. Hope you are able to follow this course, follow this what I am trying to say. Here in the example we have the ethoxide and tertiary butoxide. Here the tertiary butoxide has a sterically hindered site which is this one.

And if you try to react this with any alkyl halide, where you may have a CH3-X, it will have difficulty to attack at that center to give away the substitution product. Whereas the ethoxide which does not have any steric hindrance will be stronger nucleophile compared to tert-butoxide and both are strong bases. So we will continue from here in the next class.