Concepts of Chemistry for Engineering

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Lecture 74

Substitution Reactions

Hello, everyone, welcome to the module on Organic Reactions. In this module, we shall look at few kinds of organic reactions and how these reactions are used to transform organic molecules from one functional group to the other.

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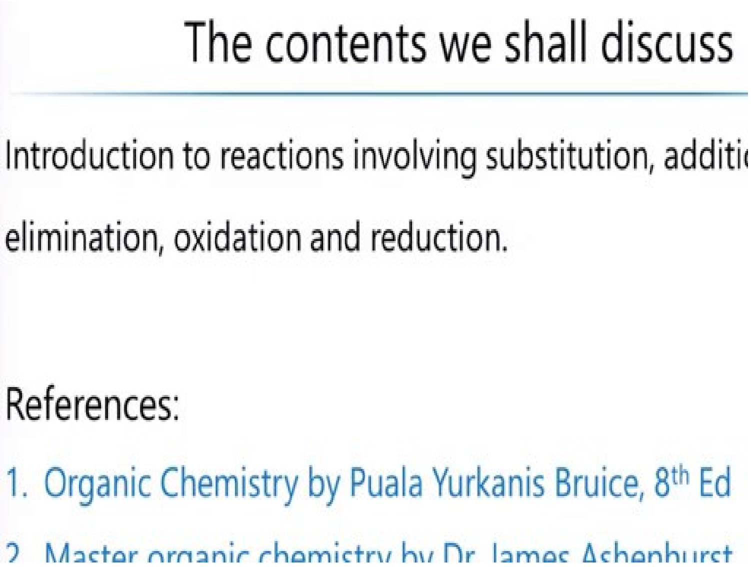

The contents we shall discuss

Introduction to reactions involving substitution, additi
elimination, oxidation and reduction.

References:

1. Organic Chemistry by Puala Yurkanis Bruice, 8th Ed
2. Master organic chemistry by Dr. James Ashenhurst

So, this is the content we are going to discuss for this module that is, we shall begin by looking at an introduction to organic reactions and why one studies them in the first place. Then we shall dwell into a bit on a substitution reactions and the various kinds; both aliphatic as well as the aromatic versions of it. And then we shall look at addition, elimination, oxidation and reduction reactions.

So, the goal of this module is to give you a flavor of organic reactions and how one can do a transformation of one molecule to into another. For this module, I would be using mostly the references as organic chemistry 8th Edition by Paula Yurkanis Bruice and also an excellent online resource which is called as Master Organic Chemistry maintained by Doctor James Ashenhurst. So, for more details, I would urge you to go through either of these.

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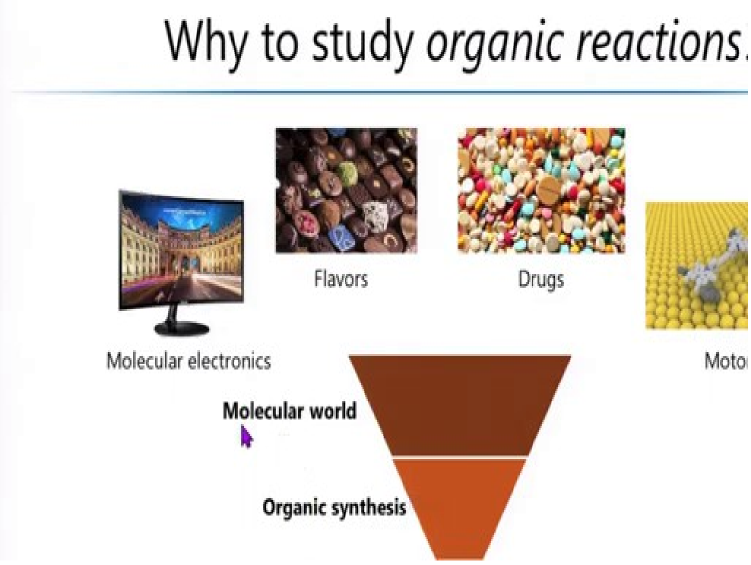

Why to study *organic reactions*

Molecular electronics

Flavors

Drugs

Moto

Molecular world

Organic synthesis

So, let us first begin by asking this question of why one should study an organic reactions. So, you must be wondering, why is this being taught to me? So, to answer this, let us just look around ourselves. And I am sure you will find that many of the things which you use are molecular in nature, such as the electronic devices in your houses or your mobile displays are made up of organic molecules.

And these give them the unique features of curved displays or many other features such as excellent brightness. And I am sure you all love, chocolates and other kinds of flavors. And many of these, let us say the flavors and the fragrances owe their properties to the chemical organic molecules which are presenting them or their active ingredients.

And another important area which we are presently using or which is, which we most of us use at times are these drugs to keep ourselves healthy. And these again are made up of organic molecules and these are very critical for keeping oneself healthy. And finally, there is these new upcoming areas in science or in chemistry, where molecules are being thought of as small motors which run on a car; which run on a road.

Similarly, the individual molecules which is at the length scale of about 1 to 10 angstroms or 10 to the power minus 10 meters can act as a motor similar to our cars which run on the streets, they can act as motors and run on any given surface, we can use such properties to come up with functional devices which can do cool things. So, all of this is what we call it as a molecular world.

And this molecular world hinges very critically on what is called as organic synthesis. So, by this I mean, if I want to use a given molecule in any of these applications or any or other kinds of applications in the first place, one should be able to make them in the desired purity and in the desired confirmation, configuration and all kinds of things. So, that is where organic synthesis plays a very critical and a pivotal role.

So, in order to achieve organic synthesis, or synthesize a given molecule, which could be a drug molecule, or which could be conjugated polymer for an electronic application, we must first understand how molecules, individual molecules and functional groups behave in themselves that gives us a tool to manipulate different kinds of functional groups and ultimately achieve the transformation we are looking at.

And using that we can make the ultimate molecule of interest and use it for various kinds of applications. So, in the sort of perspective, there is been a significant amount of interest in trying to understand the physical principles which govern the reactivity and the selectivity of organic molecules. And that is where organic chemistry plays a very central role in many kinds of applications which we come across.

So, I hope this gives you an at least in sort of overview an idea of why one studies organic reactions or what is the role of organic reactions in day to day life and to control all of this one must be able to understand or to control principles of organic chemistry. And in the next 20 minutes or so, we shall look at some of the aspects of how one goes about controlling the selectivity and reactivity in organic reactions. Already having said this, let us begin by looking at what are the basic kinds of organic reactions which are around and then we shall look into some of them in some detail.

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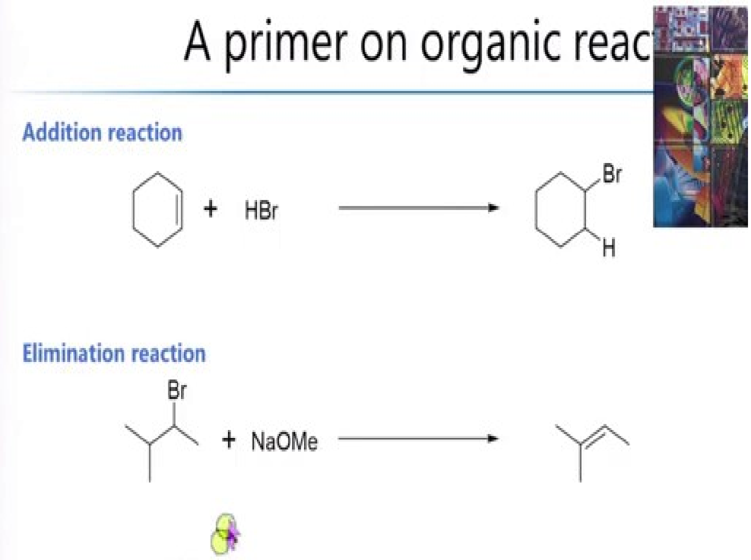

A primer on organic reac

Addition reaction

Elimination reaction

So, there are mainly three classes of organic reactions; or very common ones, the first one is what is called as an addition reaction. And I hope what you can recognize is that we here we have a cyclohexene this is being reacted with the HBr, molecule of HBr. And along you will see that both the hydrogen and the bromine in the HBr now goes and ads across the double bond and that is the reason why one call, this is an addition reaction.

And there are many such reactions in this particular class. And the second class of reaction is what is called as an elimination reaction here you have this alkyl halide which has a bromine substituent, if this is reacted with sodium methoxide and inappropriate solvents and temperatures or reacts with this alkyl halide and what you end up in is loss of the bromine leading to the formation of the double bond.

So, such reactions were halide or other kinds of small living groups are lost are called as elimination reactions. And we shall look at some of them in some detail. And finally, another very sort of intuitive to understand class of reactions is what is called a substitution reaction. Here again I have N-butyl bromide and this is rated with a sodium cyanide and the product is the Bromo is replaced with a Cyano group.

So, this is a simple substitution of one group by another group and this guy these kinds of reactions are what are called a substitution reactions. And there are a number of them, we shall look at them in some detail, I hope you recognize that these classifications are based on simple ways in which the reaction takes place that is a reagent is added across an unsaturated double bond like this or one of the part of a molecule is eliminated, which is why we call it an elimination reaction.

And in another substitution reaction, we see that one of the groups is being substituted by another group. So, these are very simple and sort of intuitive to understand. And in addition to this, there are other various ways of classifying organic reactions, but this is a simpler way to begin and to understand organic reactions. So, having said this, we shall begin by looking at what are called as substitution reactions and then later we shall look at both addition as well as the elimination reactions.

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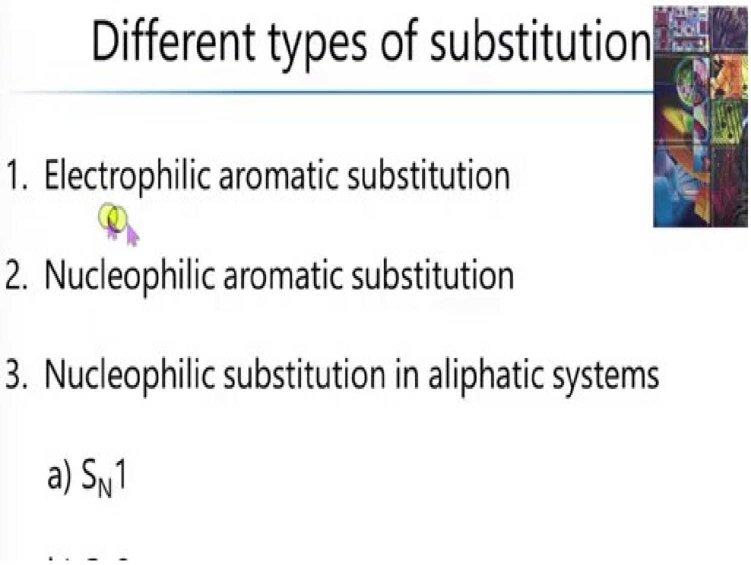

Different types of substitution

1. Electrophilic aromatic substitution
2. Nucleophilic aromatic substitution
3. Nucleophilic substitution in aliphatic systems
    a) S_N1

So, if we talk about substitution reactions, like the one I told you in the previous slide, even among substitution reactions, there are various categories or subclasses. So, let us first see what are these sub classes. The first one is what is called as electrophilic aromatic substitution. So, it might look a mouthful, but please bear with me, I will explain this in detail in a minute or so. So, and there is another class of substitution reactions which is called as a nucleophilic aromatic substitution.

And finally, one can also have a substitution reaction in aliphatic systems, that is systems which are mostly saturated and among this we can have two kinds of substitution reactions. The first one is called as an SN1 and the second one is called as an SN2 kind of reaction. And both of these classification stem from mechanism by which this reaction takes place.

So, before we begin talking about substitution reactions, or in more specifically electrophilic, aromatic substitutions, I hope you are all aware of what are called as electrophiles and nucleophiles. Electrophiles are species which actually love electrons that is they are deficient of electrons are another word they are typically positively charged systems and that is where the word electrophile also comes from electro stands for the electron; philic stands from loving.

So, these are the substituents or these are the kinds of species which allow electrons. Similarly, nucleophilic substitution, the word nucleophile stands for species which love nucleus that is they allow the positive charge. So, these are typically negatively charged species or which have excess electrons around them. Alright, so now let us begin by looking at what is called as electrophilic aromatic substitution reactions.

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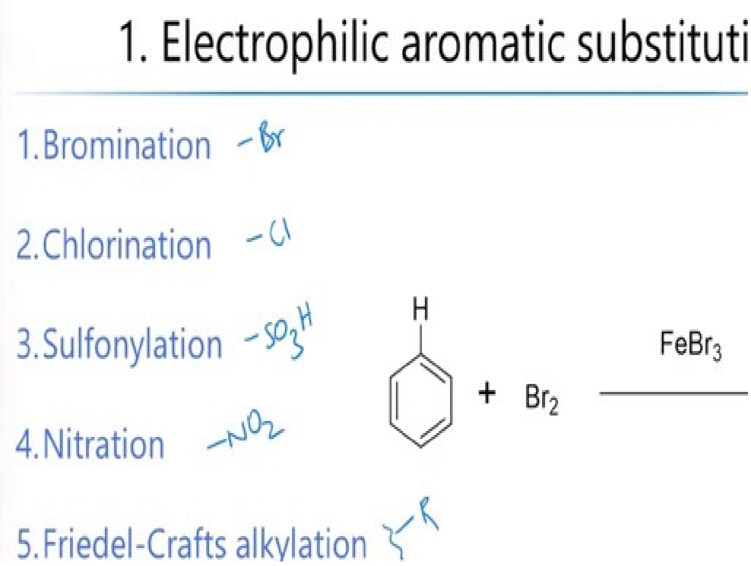

1. Electrophilic aromatic substituti

1. Bromination $-Br$
2. Chlorination $-Cl$
3. Sulfonylation $-SO_3H$
4. Nitration $-NO_2$
5. Friedel-Crafts alkylation R

And in electrophilic aromatic substitutions there are various kinds of reactions one can find in various textbooks. And some of the common ones are listed here that is a bromination, chlorination, sulfonation nitration, and Friedel-crafts alkylation and acylation. So, do not get overwhelmed by the number of reactions you see, because they all follow a very simple mechanistic paradigm. And that is what we are going to try and understand.

So, for example, here I have shown you the bromination of benzene with bromine as well as FeBr3 which is Lewis acid and this leads to the formation of the Bromo benzene. So, I hope you see that this CH bond is being now replaced by CBR bond. So, that is the substitution which we are currently interested in that is a hydrogen on the benzene or any aromatics system is being replaced by in this case bromine or any other kind of an electrophile.

So, this is a typical general kind of reaction wherein automatic system reacts with the electrophilic reagent which is, could be generated by itself or in the presence of a Lewis acid as a catalyst and that would lead to a substitution of one of the hydrogen on the aromatic system by the corresponding electrophile which could be a bromine, chlorine or SO3H or NO2 or any kinds of substituents, that is how we get this name we get these reactions, which is bromination.

If the, if a hydrogen is replaced by bromine, we call it chlorination if a chlorine group is replaces the hydrogen and we call it sulfonation, if an SO3H group replaces and we call it nitration, if the hydrogen is replaced by NO2 by using the HNO3 and H2SO4. And similarly, with the Friedel crafts alkylation you have an alcohol group that is alkanes group which replaces the hydrogen.

And in the case of the acylation, you have an acyle group which is being replaced that is, you have this kind of group, here you have just R, these are the substituents which are going to change from given aromatic system that is the reason why these are called as correspondingly called as electrophilic aromatic substitutes with the following names. So, now let us dive into a bit of the mechanism of this and see how does this reaction even take place.

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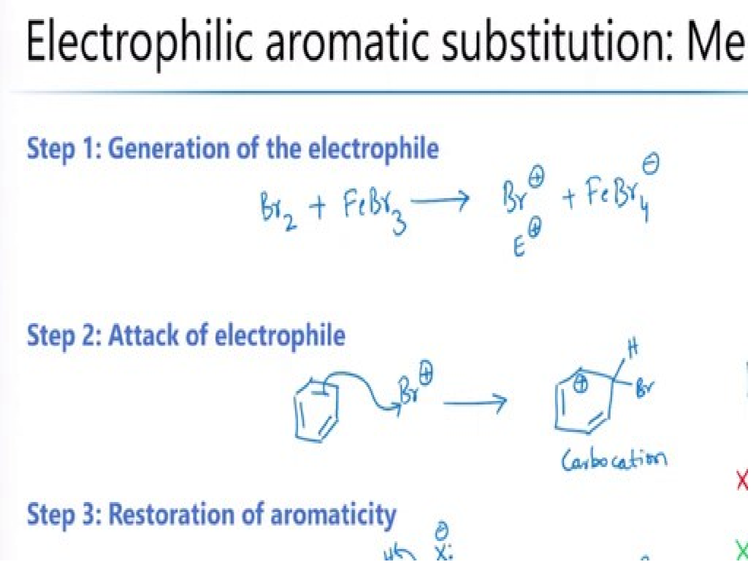

Electrophilic aromatic substitution: Me

Step 1: Generation of the electrophile

Step 2: Attack of electrophile

Step 3: Restoration of aromaticity

So, to do this, there are three steps and the first one is what is called as generation of an electrophile. And I will illustrate this by using the bromination reaction which I showed you on the previous slide. We have a Br2 here this reacts with the Lewis acid that Fe Br3 to give rise to a Br plus and Fe Br 4 minus.

And once this reaction takes place, now you have an electrophile which is this, this is also depicted as E plus, where E stands for the electrophile. And once the electrophile is generated, now this would go and attack the aromatic system. So, the next step is the attack of the electrophile, so let us see how does that take place; so, I am going to take benzene again and we have a Br plus. So, we are going to go attempt this.

So, this would lead to what is called as a Carbo cation. So, the aromaticity in the aromatic system is currently lost and you have the bromine now attached onto the system. So, this is the second step where the electrophile attacks the nucleophilic benzene, and then the next step or the third and the last step would be the restoration of aromaticity or loss of the H minus to regain the aromaticity that is, I am going to redraw the same thing again here.

So, now an x minus put come and take away the hydrogen and that would lead to the formation of the product. So, I hope you see that this the reaction involves 3 steps and the first one is the generation of the electrophile by reaction of the Lewis acid that is in this case Fe Br3 or it could also be l Br3 or other Lewis acids.

The next step generated electrophile attacks the aromatic system of interest that is in this case the benzene and that would lead to the carbo cation which is shown on the screen and this carbon cation further reacts with an x minus where hydrogen is lost and aromaticity is regained. So, the driving force for the last reaction is the restoration of the aromaticity because the system if it regains aromaticity it becomes far more stable.

So, having understood this there is a small couple of more minor points that needs to be addressed that is if I take a, if I have a substituent here on the benzene that is I am trying to do this electrophilic aromatic substitution on not on purely benzene but on substituted benzene which could be (())(17:45) which could be aniline, which could be anisol or any other kind of derivative.

So, in this case, the electrophilic aromatic substitution will depend on the position as well as the rate of the reaction will depend on the substituent on the substrate that is it will depend heavily on what is the x group. So, if the x group is let us say OH OME NH2 and so on and so forth, that is groups which can donate an electron density into the benzene system, they would make it far more facile for the attack of the electrophile and that would lead to a much faster reaction rate.

And in this case, the reaction will be more favored at ortho and the para position. So, you will get products which are predominantly ortho and para. And if you now take a similar substituents, but which is now an electron withdrawing substituents, let us say I have an x and this x is NO2 or any electron withdrawing groups you can think of right, strongly electron withdrawing groups.

So, these would reduce the electron density on the aromatics system of choice as a result attack by the incoming electrophile would be far more slow. Thus one, the rate of the reaction would be slow and two, the products are predominantly favored in what is called as a meta position. So, one can understand why ortho position ortho and para positions are favored for electron donating groups.

And why meta position is favored for electron withdrawing groups by looking at what are called as resonance structures of these benzene substituents. So, I hope one can convince themselves by looking at this. So, having now looked at electrophilic aromatic substitution, both the scope, mechanism and the influence of various substituents that is either electron donating or electron withdrawing groups on the rate as well as the regio selectivity of the product. We shall now go ahead and look at what is called as nucleophilic aromatic substitution reactions.

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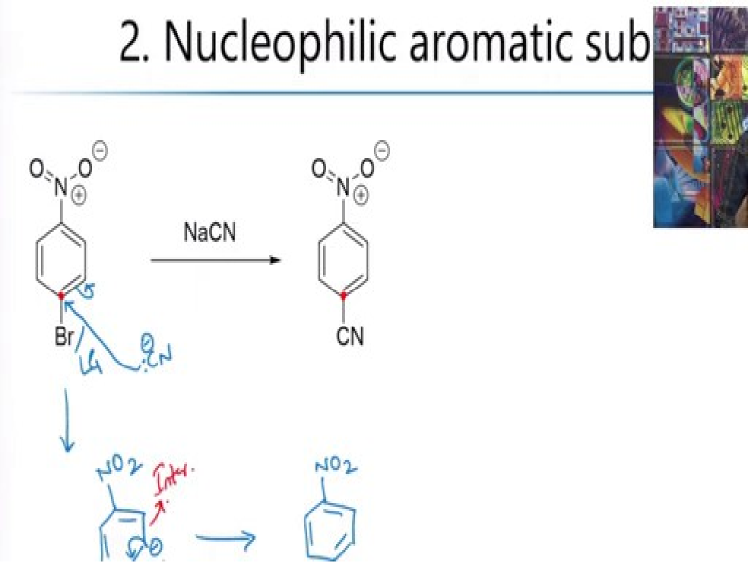

2. Nucleophilic aromatic sub

So, here what a typical reaction of a nucleophilic aromatic substitution is shown on the screen and what you would notice is that you have a Bromo benzene derivative with a nitro group at the para position and if this compound is treated with NaCN, where CN is an electron drip system, so, that would act as a nucleophile.

So, if you could write this again or let me write this here. So, this the CN minus is electron bridge. So, it would act as a nucleophile and in this case what the reaction taking places it goes and attacks on to the carbon which bears halide and then this would get substituted to the next one and as a result you would end up in having the following intermediate, right. So, this is what one would expect to get the intermediate.

So, once this happens, then what typically happens is that this negative charge floats back in and then you have a loss of Br minus and that would lead to your product… that would lead to the desired product. So, an important point to notice that the difference between an electrophilic aromatic substitution and a nucleophilic aromatic substitution is that the nucleophilic aromatic substitution takes place on the carbon which beers the halide or the living group.

So, one can also call this as leaving group algae. And what I want you to notice is the following; that this is the carbon which has the bromine and on the same carbon we have now sino group. So, this is the distinction compared to electrophilic aromatic substitution where the substitution occurred at ortho and para or meta based on the kind of substituents we had on the initial reactant.

So, you must be wondering then what is the role of this nitrile group or why is it not emphasizing or explaining the role of a nitro group. So, the role of the nitro group is very critical in this that is, if you actually look at this intermediate which is formed here, this would be highly resonance stabilized because the NO2 group can pull the electron density towards itself through resonance as a result the intermediate gets stabilized enormously.

Thus, the activation energy going from the reactant to the intermediate is substantially lower. Thus, the reaction proceeds forward and leads to the formation of the product. Imagine if you did not have a nitrile group for example, if you had a electron donating group such as an OME or NH2 or any other kind of electron donating group that would significantly destabilize the intermediate which is which beers a negative charge.

Thus, the rate of the reaction would be very-very slow and in many cases, one may not even obtain the product as well. So, it is very critical to note that typically electrophilic, nucleophilic aromatic substitution take place more facile in a more facile manner when they beer electron withdrawing groups because they tend to stabilize the intermediate.

So, this is the intermediate which would be far more stabilized in the presence of electron withdrawing groups such as an NO2 or any other kind of electron withdrawing groups. I hope this is clear to you all. So now, having looked at electrophilic and nucleophilic aromatic substitutions now, let us go ahead and look at nucleophilic substitution in aliphatic systems.

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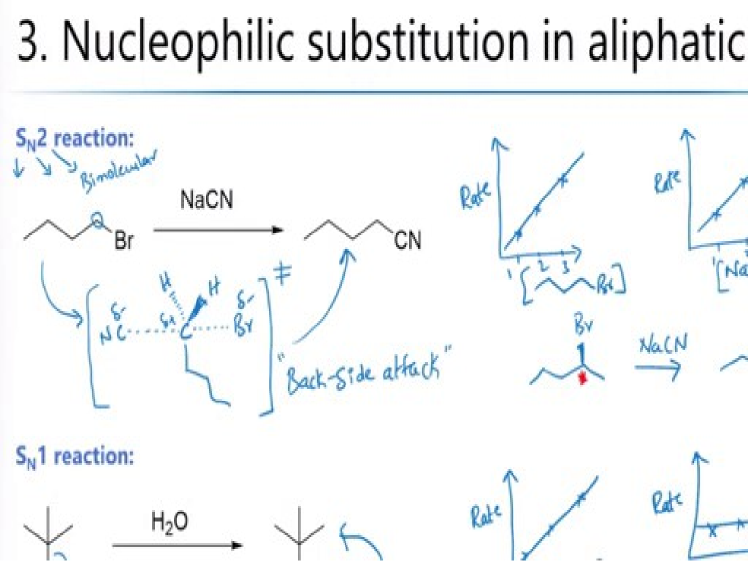

3. Nucleophilic substitution in aliphatic

S_N2 reaction:

S_N1 reaction:

And as I told you previously, there are here two classes, one is called as SN2 and other is called as an SN1 reaction, so will look at each of them in some detail. Here on your screen, you see that the N Bromo butane or one Bromo butane is converted into its corresponding sino product by using sodium cyanide. And I have written this as an SN2 reaction. So, the SN2 stands for Substitution Nucleophilic Bimolecular, 2 stands for Bimolecular here.

So, the S stands for the substitution, N stands for nucleophilic and 2 stands for bimolecular. So, you must be wondering why is he calling it by molecules. So, actually, when these were, when these kinds of reactions were discovered, or when they were understood roughly 70, 60, 70 years ago, what people were doing were to, they did this reaction like conversion of the bromide to the cyanide and then they were interested in looking at what happens if I change the or double the concentration of the reactant, either one or both of the reactant.

And what they observed is that the rate of the reaction increased doubles with the doubling the concentration of each of the reactant. So, what I mean by that is the following; that if I draw rate of this reaction, which is shown on the left hand side versus the concentration of the bromide, you do see a linear increase when you go from 1 to 2 to 3, concentration, it could be milli-molar or any units. And similarly, they also observed that if you double the concentration of the sodium cyanide then one again observed a similar trend that is a linear trend with the doubling of the rate when the concentration was doubled.

So, what is suggested is that maybe the mechanism which is involved in doing this transformation takes place involving both of the molecules that is both the bromide as well as the cyanide. And one of the ways to account for this is the following mechanism that is I have a carbon which is having, so I am depicting this carbon now here. This is what one would encounter as the, what is called as a transition state that is, this reactant goes through this pathway to lead to the product which is shown here.

And if you look at this, in this both the CN minus is involved this will have a delta minus and this will have a delta minus and this will be a delta plus on the carbon. Both the CN as well as the bromide are involved in as well as bromide are involved in the reaction. So, that is the reason why it is called as a bi-molecular because the rate of the reaction depends on both the reactants.

And it is a nucleophilic substitution which is very intuitive because you have a nucleophile CN minus which is attacking on an alkyl halide, in this case a primary halide to give rise to the product. So, what is important to bear in mind is that, this is what is called as a backside attack. You will in chemical jargon, this is called as a backside attack, that is the incoming nucleophile CN minus comes from the back of the backside of the this carbon which is attached to the bromine and attacks and bromide leaves and you form a CN bond here, CCN bond and the CBr bond gets broken down.

And major consequence of this is, in case the carbon which bears the bromide is a stereogenic carbon or it is a tidal carbon center. Then an inversion in the stereochemistry is observed. Just to illustrate that I shall show you an example that is, let us say I have this molecule. And I am going to create again with sodium cyanide.

So, I hope you take note of the fact that the stereochemistry here on this carbon is now opposite compared to reactant and the product. So, this is a consequence of the backside attack in the reaction mechanism. And so, this is a very important tool to actually obtain the stereochemistry, desired chemistry in a given reaction and I am sure you are all aware that stereochemistry plays a very important role in the properties of the molecule.

And now you are seeing a tool or a technique by which you can play around with the stereochemistry in a substitution reaction, okay. And the nature of the solvent and the nature of the nucleophile and to dictate to a large extent the outcome of the reaction and we shall dwell on that in a bit more detail.

So, this is what people typically call us an SN2 or substitution nucleophilic bimolecular that is because both the molecules in this case the bromide and the sodium cyanide are involved in the rate determining step of the reaction and there is another brother or cousin version of this which is called as SM1 reaction, which is again substitution nucleophilic uni-molecular reaction.

And here I have shown you an example of this particular reaction where a tertiary butyl bromide reacts with water to give rise to a tertiary butyl alcohol and here the mechanism is slightly different and the mechanism is as follows. If you take this the first step which takes place is the bromide leaves and you would get a plane a Carbo cation plus a Br minus.

And what people observed is that when they did the similar studies as shown above they did try to look at the rate of this reaction by varying the concentration of the tertiary butyl bromide and they observed a linear relationship whereas, when they tried to look at the rate of the reaction as a function of the water concentration, it is actually independent of the concentration of the water.

So, what this tells us is that the reaction which we are studying depends only on the concentration of the substrate which is the tertiary butyl bromide, but it does not depend on the thing the nucleophile which is present which is the water in this case. So, to account for this uni-molecular reaction which is depends only on the tertiary butyl bromide, the following reaction is proposed.

And the first step is the leaving of the bromide minus and that generates a Carbo cation and this is also the rate determining step of the reaction. And once this happens, then the (())(33:56) H2O attacks. And ultimately one would and you will have a loss of proton and that would lead to a corresponding tertiary butyl alcohol.

And this next step is what is typically called as fast, that is fast compared to the previous step. And this is another typical example where one can convert a bromide to an alcohol or any other kind of substituted product. And I hope this has given you some sort of an idea or a flavor of what are called as substitution reactions. And we shall stop here now and in the next lecture we shall look at what are called as elimination reactions, which actually build upon these principles. Thank you.