Introductory Organic Chemistry
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Lecture - 41
Substitution & Elimination Part 3

Let us discuss nucleophilicity a little bit. What are the factors that make up a good nucleophile? And if we have to answer this question, one of the few things that we look at is what is the ability of this nucleophile to go and attack and perform the nucleophilic reaction. It could be anything S_N1, S_N2; but how good is this nucleophile to perform that reaction, right. So, the first thing that we look at is actually the charge on the nucleophile. So, if we think about it, then the first thing that comes to our mind is charge. Any charged nucleophile is going to be more reactive than the uncharged nucleophile.

So, we can take the example of OH^-, it's going to be a better nucleophile than H_2O, right. So, when you take the conjugate acid of it the conjugate acid is always the worst nucleophile and the base itself is going to be a better nucleophile. So, for example, SH^- is also better nucleophile than H_2S. And this is really easy to explain is that there would be a higher electron density on the nucleophile. So, it is more electron rich and thus it becomes better nucleophile as there is a charge present on that nucleophile.

The other thing that we can always remember is that the conjugate base is always a better nucleophile no matter what. If you take a conjugate base and its acid pair then the conjugate base is always going to be a better nucleophile than the corresponding acid, the second thing that we look at is actually the solvent in which the reaction is done. And for this I want to actually take examples of various solvents.

Now, we categorize solvents based on a lot of things, but the more known category is polar protic solvent and polar aprotic solvent Now, why are we talking only about polar solvents here? Because remember that in the case of S_N1 and S_N2 reactions we want to discuss polar solvents because our reactants are polar, our products are polar. So, because we follow the principle of 'like dissolves like' we need a solvent also that is polar.

So, we are not going to be talking about non-polar solvents. So, S_N1 and S_N2 both of these reactions will require polar solvents. Now, when we talk about polar solvents there are two categories again, one is polar protic solvent. So, polar protic solvents meaning they have a hydrogen that can participate in hydrogen bonding with the nucleophile what really it means is that the hydrogen in the case of water for example, because water is a polar protic solvent, the hydrogen-oxygen bond in water is such that it is polar.

Hydrogen has a partial positive charge, oxygen has a partial negative charge and thus there is a charge distribution in water molecules, right. So, when you take a nucleophile that is negatively charged remember that the partial positively charged hydrogen can be attracted towards this negatively charged nucleophile really stabilizing the nucleophile. So, if you can think about it in polar protic solvents your nucleophiles are going to be less reactive, because they have all of these hydrogen bonds that are making them more stable, that are helping them stabilize that negative charge.

And as a result of which the nucleophile won't be as effective. One of the other reasons that is given is that imagine yourself walking in a crowd. If you have a lot of people surrounding you it is going to be very difficult for you to reach a particular destination, and that's what happens in the case of polar protic solvents when we have nucleophiles in them. Is that the solvent molecules will surround this nucleophile and really will make it less reactive such that its ability to go and attack gets decreased.

Now, really the ability of nucleophiles to participate in hydrogen bonding with the solvent molecule goes down as we go down the periodic table. So, for example, fluoride will form the strongest hydrogen bond whereas, if we go down the periodic table fluoride, chloride, bromide, iodide as we go down the periodic table like that then iodide becomes the weakest hydrogen bond acceptor and as a result of which you can make a conclusion that as we go down the periodic table as the size of the nucleophile increases it can form less and less hydrogen bonds with the solvent.

And that really means that the lone pair on that nucleophile will be considerably more free than in the case of the nucleophile that can form strong hydrogen bonds. So, if we take a polar protic solvent in which hydrogen bonds can be formed one of the strongest nucleophiles is actually iodide as compared to fluoride or chloride.

Because iodide can form less and less hydrogen bonds and can use its negative charge to attack on that carbon. Similarly, a trend if we can come up with, SH^- is going to be a better nucleophile in water than the OH^-. Now, we have seen that OH^- is a much stronger base, but when we are in water medium SH^- becomes a better nucleophile because it forms lesser hydrogen bonds.

So, what are some examples of polar protic solvents? We have water, we have all sorts of alcohols ethanol, methanol; we also have various acids carboxylic acids which can form hydrogen bonds with the nucleophile. Now, when we think of polar aprotic solvents however, so, 'aprotic' meaning it cannot form a hydrogen bond. In the case of polar aprotic solvents since the hydrogen bonding cannot be done, the solvent molecules are not really tightly surrounding the nucleophile in the case of polar aprotic solvents and in which case really the nucleophilicity should correlate with basicity.

So, for example, if we take the same trend that we saw a hydroxide ion is going to be a much better nucleophile than SH^- iron in this case and that is because hydroxide has a much better charge, it is a strong base and as we have seen basicity will parallel nucleophilicity unless we are talking about really strong bases. So, a hydroxide ion is going to behave as a much better base than SH^- when we are in polar aprotic solvent. Now, what are some examples of polar aprotic solvents?

So, acetone is polar aprotic, we have an N,N-dimethylformamide or DMF, we have acetonitrile, we have DMSO, all of these compounds are going to be polar aprotic solvents and in which case the basicity will parallel nucleophilicity. So, that is regarding the solvent and how really solvents affect the nucleophilicity of a compound. Just to give another correlation we saw how in the case of water as a solvent iodide was the best nucleophile. Now, in the case of acetonitrile as a solvent the fluoride ion will be the most unstable or the better base and thus it will react fastest with the electrophiles.

Now, the other thing, the last thing that we want to talk about is the size of the nucleophile and this really has to do with the kind of reaction you want it to perform; but in S_N2 reactions for example, we have seen how the bulkiness of the substrate kind of hinders the reaction such that the nucleophile cannot reach the carbon center. If the nucleophile is really bulky you are going to see a very similar trend. So, tertiary butoxide for example, even though it has a great charge it's so bulky that it very seldomly will do S_N2 type of reactions.

In fact, if it does, it will try to do it only with methyl alkyl halides. Tertiary butoxide on the other hand will be functioning as a better base instead of a better nucleophile. On the other hand if we take methoxide OCH_3^-, it is going to be functioning as one of the really good or well-known nucleophiles. Because it is small enough, it can attack that carbon center by really going and attacking that carbon center.

So, one of the analogies I always give is like in order to do S_N2 type of reactions the nucleophile should be like an arrow or like a harpoon that it needs to attack on that carbon and kick out the leaving group. And so really small nucleophiles do a great job, hydroxide, methoxides are going to be better nucleophiles than let's say tertiary butoxide. So, that is the trend that is seen in nucleophilicity of most compounds and it is important for us to take this trend into account when we are discussing S_N1 and S_N2 reactions.

So, here in I am going to summarize the nucleophiles for you. And in fact, we have given the relative reactivity in a typical S_N2 reaction. So, very good nucleophiles like iodide or SH^-, RS^- have a really high reactivity in an S_N2 reaction. Whereas, hydroxides, bromides, azides, cyanides are categorized as good nucleophiles which react with a little less rate. Kind of fair nucleophiles such as ammonia chlorides can also act as a fair enough nucleophiles.

But the weak nucleophiles are the compounds that lack a negative charge; so for example, water is a weaker nucleophile, ROH or any kind of alcohols are also weak nucleophiles. And for that matter very weak nucleophiles are for example, carboxylic acids they do not do S_N2 type of reactions very effectively. So, when we look at S_N2 reactions it's kind of good to notice the scope that these reactions bring to our table.

For example, just by changing the nucleophile you can easily change the functional group of a particular compound; let's say that we are starting from a generic RX.

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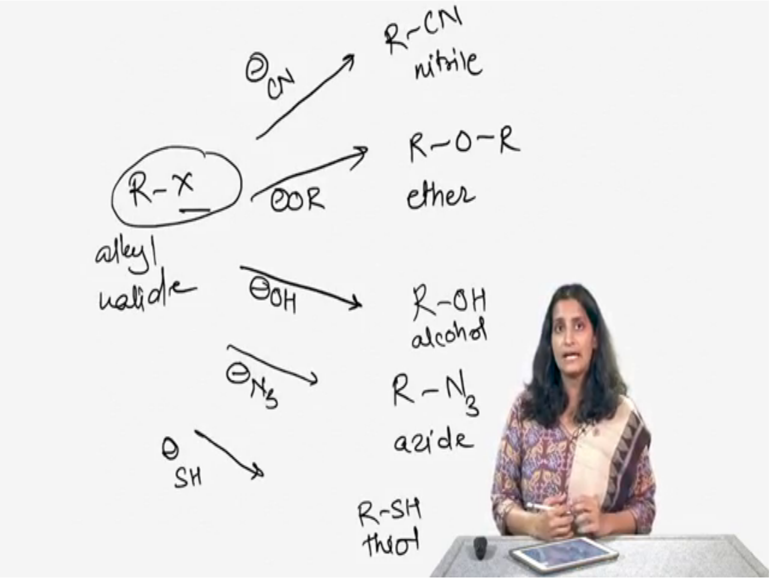

Their X is an alkyl halide, right. So, X is any halogen atom. So, like a good leaving group bromide, iodide things like that and if you react it with a nucleophile like cyanide you can convert this to RCN which is a nitrile functional group, right; if I react it with a nucleophile like OR^- which is like ethoxide, methoxide I can convert this to ROR which is an ether functional group, right.

If I react it with OH^- I can convert it to the corresponding alcohol; if I react it with an azides N_3^-, then I can convert it to the corresponding azide functional group. I can use a good nucleophile like SH^- and convert it to a thiol, right. So, if you see this, I can just do the same S_N2 reaction just change the nucleophile every single time and come up with a new functional group to do this chemistry and that way I can convert an alkyl halide effectively to so many of these functional groups and we just cannot stop at this.

For example if we take ammonia as the nucleophile we can even do a reaction where we convert it to the corresponding amine, right. So, as you can see this particular reaction is very versatile, it can lead to multiple functional groups if you choose your nucleophile correctly.

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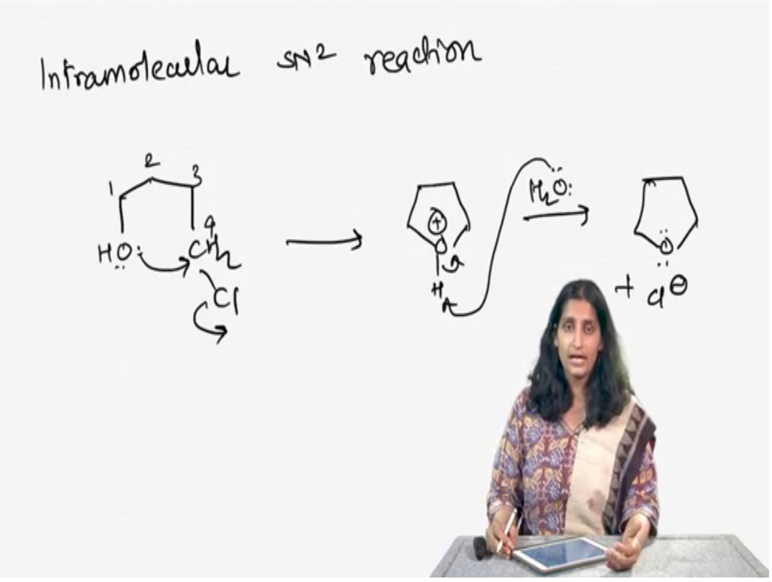

So far we have seen the examples of S_N2 reactions where two different molecules were reacting. But sometimes S_N2 reactions can also happen intramolecularly, meaning the nucleophile and the carbon with the leaving group is present in the same molecule. So, for example, in this one it is possible for the oxygen to attack here and kick off the chloride as a leaving group in turn forming a ring with 5 members in it, right.

And later on this molecule can just lose this proton creating this molecule, but remember such intramolecular S_N2 reactions are also driven by the fact that you are creating a ring which is a 5-membered ring or a 6-membered ring. So, typically you won't see such kind of reactions when you are forming the 3-membered ring or 4-membered ring; although under certain conditions you can create even 3-membered rings using an intramolecular S_N2 kind of a reaction.

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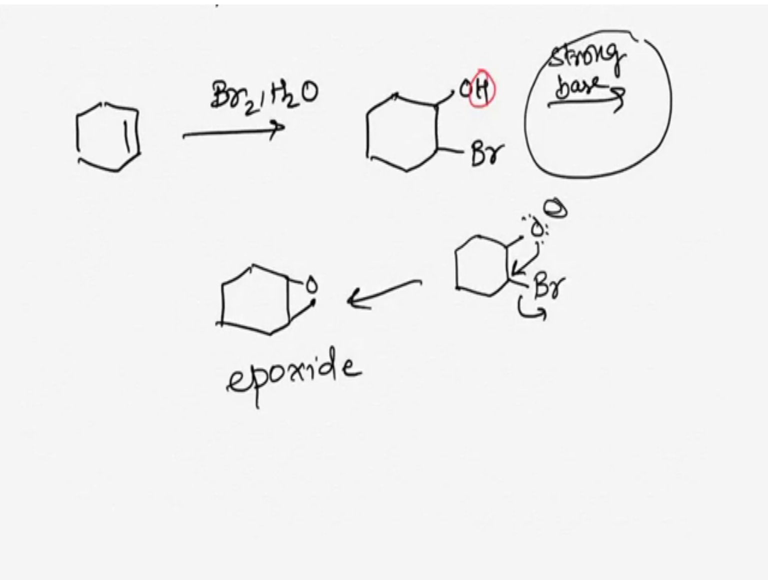

So, for example, let us look at the halohydrin formation reaction. We have seen this reaction in the chapter of alkenes wherein we took an alkene and reacted it in the presence of bromine and water to form a halohydrin, right. Now, when you subject a halohydrin in the presence of a strong base, what ends up happening is the base grabs this particular proton and really creates an oxygen with the negative charge on it. This oxygen can attack this bromine and kick off the bromide really creating an epoxide at the end, okay.

So, this is a new functional group, epoxide functional group that gets created as the halohydrin is subjected to a strong base okay. So, typically we see these S_N2 kind of reactions for the formation of 5 and 6 membered rings, but under certain conditions which is for example, in the case of strong base a halohydrin can give you an epoxide.

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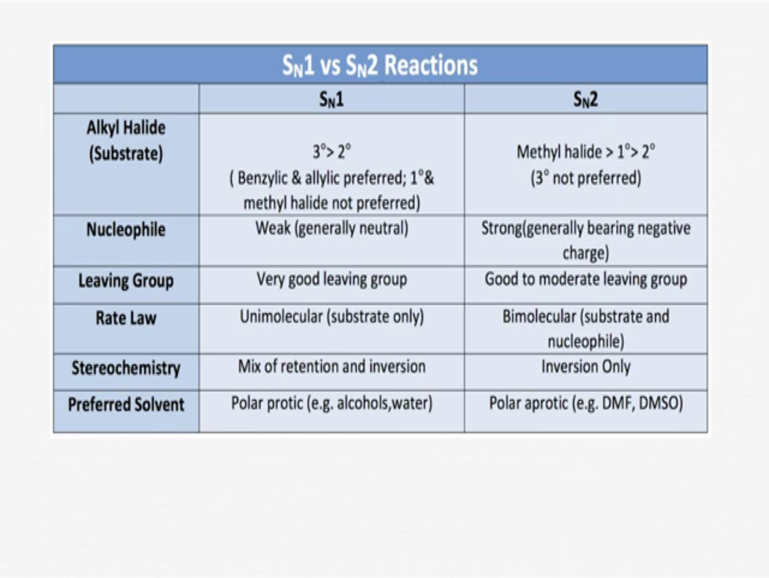

S_N1 vs S_N2 Reactions

	S_N1	S_N2
Alkyl Halide (Substrate)	3°> 2° (Benzylic & allylic preferred; 1°& methyl halide not preferred)	Methyl halide > 1°> 2° (3° not preferred)
Nucleophile	Weak (generally neutral)	Strong(generally bearing negative charge)
Leaving Group	Very good leaving group	Good to moderate leaving group
Rate Law	Unimolecular (substrate only)	Bimolecular (substrate and nucleophile)
Stereochemistry	Mix of retention and inversion	Inversion Only
Preferred Solvent	Polar protic (e.g. alcohols,water)	Polar aprotic (e.g. DMF, DMSO)

So far we have looked at S_N1 reactions and S_N2 reactions and let us kind of summarize what they require. S_N1 reactions are better for alkyl halides that are tertiary or secondary because they create a carbocation. Whereas, S_N2 reactions require the carbon to be either a primary carbon or a methyl carbon they proceed slowly for a secondary carbon, but definitely we do not see S_N2 reactions for tertiary carbon centres.

We have also seen the nucleophiles required for S_N1 reactions versus S_N2 reactions. S_N1 reaction requires weak to moderate nucleophiles whereas, S_N2 reactions require much stronger nucleophiles. The leaving group in the case of S_N1 reaction has to be a very-very good leaving group; in the case of S_N2 reactions also you require decent leaving groups but S_N1 reactions have a higher favourability for a much better leaving group.

The rate equation in the case of S_N1 reaction is a unimolecular rate equation such that the rate of the reaction just depends on the concentration of the substrate. Whereas, in the case of S_N2 reaction the rate depends on the concentration of the substrate as well as the concentration of the nucleophile. So, it’s a bimolecular reaction in the case of S_N2 reactions.

The stereochemistry for an S_N1 reaction if applicable is such that you form both the stereoisomers although inversion is seen more prominently than the retention of the stereochemistry. Whereas for S_N2 reactions we see a hundred percent inversion in the case of stereochemistry, okay. So, we have kind of summarized our S_N1 and S_N2 reactions.

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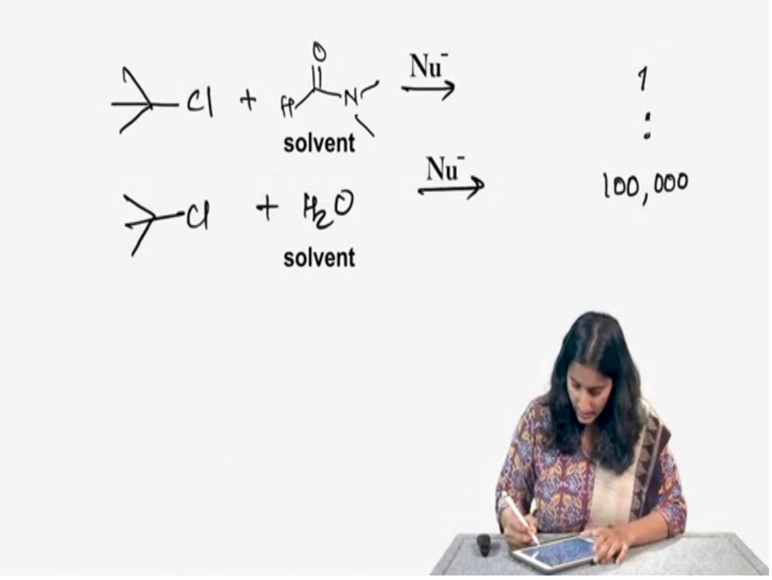

So, Now, let us look at the effect of solvent on S_N1 reaction. If you think about it S_N1 pathway involves formation of a carbocation and formation of the leaving group where it typically leaves with a negative charge, right. So, you are creating charges as the reaction is happening. In fact, the very first step of S_N1 reaction which is the formation of the carbocation is the rate determining step of the reaction.

So, for this reason the rate of S_N1 reaction depends on the ability of the solvent to solvate the carbocation and anion that gets created and also stabilize them. Remember by solvating the carbocation the solvent is really stabilizing that particular carbocation. So, for S_N1 reactions we are going to require polar solvent because polar solvents will be able to better solvate it. Not only that we require a protic solvent to also stabilize the leaving group and in turn also increase the rate of the reaction.

Let’s take this particular reaction where a tertiary butyl chloride is reacted with DMF, versus when the same tertiary butyl chloride is reacted with water, the rate for the previous reaction is such that it is let’s say 1 then the rate for the reaction with water as the solvent is around 100000 times faster, okay. That is because water can really stabilize the carbocation the tertiary butyl carbocation that gets created in the reaction and favour the reaction. We can also explain this based on the energy profile diagram.

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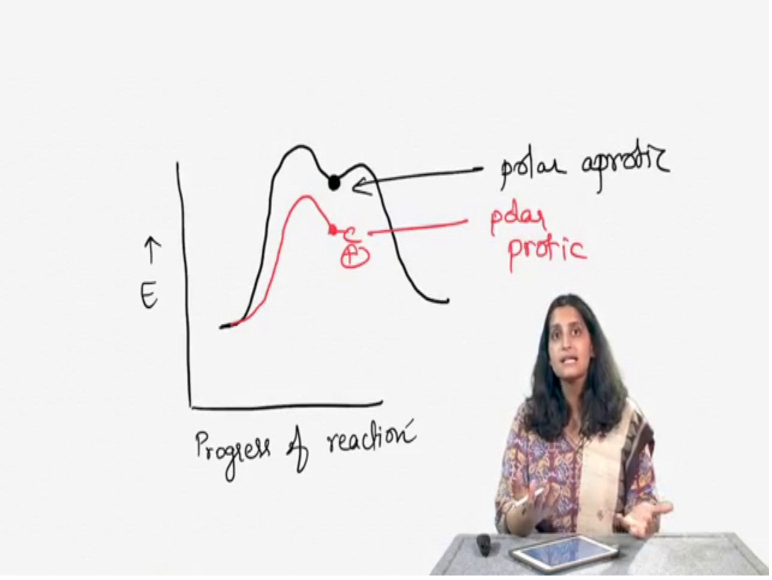

So, we have seen that a typical S_N1 reaction proceeds by a formation of a carbocation and you do create a valley in the energy profile diagram. Now, a properly solvated carbocation, one that is surrounded by solvent molecules such that the higher polarity solvent will better solvate the reactants and the intermediates, will have a lower energy right. So, this will be a carbocation in let's say polar protic solvents. Whereas, the top one will be the carbocation in a polar aprotic solvent.

Because the energy of the carbocation in a polar protic solvent is way lower, the corresponding transition state also becomes lower and thus will be achieved at a much higher rate. So, typically the polar protic solvents lower the barrier for the reaction and thereby accelerate the reaction.

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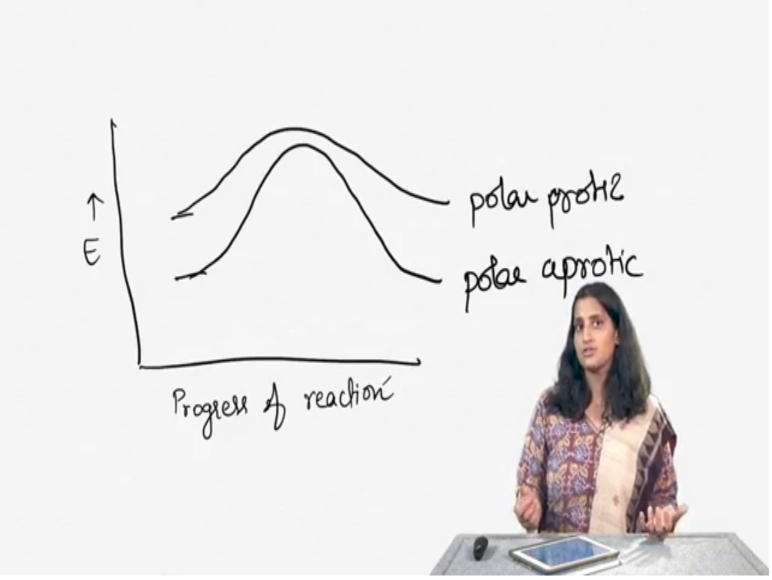

Whereas if you think about S_N2 reactions, right. Now, in the case of S_N2 reactions you require a negatively charged nucleophile. If a nucleophile that is negatively charged and its aim is to go and attack a carbon centre is surrounded by a lot of solvent molecules, remember as we said earlier it cannot move around freely.

So, in the case of S_N2 reaction we want to least solvate the nucleophile such that it still retains its ability to go and attack, but we need to stabilize the transition state and we also need to stabilize the products that are forming. More importantly the starting molecules which are your alkyl halide as well as the nucleophile both really have to be dissolved in the solvent such that they can interact with each other, right. Now, in the case of S_N2 reactions the nucleophile has to be least solvated, right.

So, what we are going to prefer is that we will prefer aprotic solvents, because a negatively charged ion if surrounded by protons or if surrounded by protic solvents, it's going to create hydrogen bonds with that negatively charged ion and it's really going to lose its ability to act as a nucleophile. If the nucleophile really gets solvated then we need a larger energy to remove the nucleophile from this solvated shell and this really lowers the rate of the S_N2 reaction.

So, here in for example, for S_N2 reaction a polar aprotic versus polar protic solvent will really change the rate of the reaction. So, for S_N1 reaction we prefer solvents that are polar protic; for S_N2 reactions we will prefer the solvents that are polar aprotic. So, for example, here in I have the relative reaction rates for S_N2 reactions, when we do the same reaction of let's say ethyl bromide reacting with a nucleophile and the solvent is methanol if the relative rate is 1.

When I do the same reaction in DMF the relative rate is 2800 or if we go higher up for acetonitrile the relative rate is 5000. So, as you can see that the solvent we use can really affect the rate of an S_N1 or S_N2 reaction. So, so far we have looked at S_N1 reactions, we have looked at S_N2 reactions, we have summarized the kind of conditions that are required for the reaction to happen. We have looked at stereochemistry of the reaction, mechanism of the reaction, we have looked at arrow pushing and we have also looked at the various conditions which favour or disfavour the reaction.

In next class we will start talking about Elimination reactions, okay. So, elimination reactions are reactions in which a halide and a hydrogen atom on the neighbouring carbon are removed as a part of the elimination. And typically substitution and elimination reactions go hand in hand in fact, they are competing reactions. So, in the next class we will begin our discussion of elimination reactions.

Thank you.