

Lecture 19B • 11/15/11

Today we finally, officially are going to begin covering the S_N2 and S_N1 reactions. [overview of lecture]

Let's start with those six aspects of a reaction. To do that, let me just redraw a mechanism for the S_N2 reaction. Going to use a primary alkyl halide, but one labeled with deuterium so that I can have a stereocenter. I'll go ahead and use hydroxide as the incoming nucleophile. The product of the reaction, in this case, is going to be an alcohol. As far as the synthetic utility, it's to convert – usually but not exclusively – an alkyl halide to one of a small number of functional groups that, for right now, we're going to say includes alcohols, ethers, and thiols. That brings us to the types of reagents that are used. For an S_N2 reaction, it's usually going to be something basic, and it does have to be a nucleophile. Examples of such reagents are: sodium hydroxide; you could take deprotonated alcohols known as alkoxides – structurally very similar to hydroxide, undergo the same types of reactions. We will see other molecules like cyanide being able to undergo this type of reaction as well. What are the conditions? We need to use, ideally, what is known as a polar, aprotic solvent. Protic means something that has relatively easily dissociatable protons. If you have protons that are easily dissociatable, and then you have basic nucleophiles that you're trying to have react. If you have, let's say in an extreme case, an acid-base reaction between the solvent and the nucleophile, then of course you're not going to have your nucleophile work very well. We want something that's aprotic, does not interact with the nucleophile, and so the nucleophile can more easily attack its target substrate.

The fourth item is mechanism, which I have up above. As far as classifying the mechanism, we would say that it's anionic, and it's concerted, meaning that the two steps shown – the nucleophile coming in to attack and the bond breaking – both occur at the same. It is the fact that you have – almost always with the S_N2 reaction – a negatively charged species that does the attacking, so anionic type of mechanism. What is the stereochemical consequence of this reaction? It is conversion of configuration. Finally, as far as regiochemistry, it is specific. In this is reaction, it is only the site where the leaving group is located where you're going to have substitution occurring, so the regiochemistry is specific at the site of the leaving group.

Let me rewrite the reaction so I can identify some of the different components. First, the alkyl halide – or, more generally, the molecule that's going to be attacked – I refer to that as the substrate. Then the nucleophile: what is a nucleophile? Something that wants a positive charge. The hydroxide in this case, because it's negatively charged, is going to be the nucleophile. Then the leaving group: that is the portion of the molecule that's going to come off during substitution. I want to review the idea that this mechanism occurs with inversion of configuration.

I've drawn the product again here, and we see the sigma bond that is there between the carbon and the bromine. You might remember that a sigma bond is one that lies in between the two nuclei. It's because that sigma bond lies between the two nuclei that you have electrons between two positive charges, that's a favorable interaction, so that's why the bond wants to form. The antibond, on the other hand, has portions of the orbital on either side of the nucleus on the outside of that bond. So a sigma bond, to simplify, looks something like this – electrons distributed between nuclei. A sigma star bond, if I worried about shading, would look like this: electrons towards the outside, with a node in between. Let's take that picture of the antibond and superimpose it on top the carbon-bromine bond. For simplicity, let me drop the distinction between the positive and negative sign of the wavefunction; let's just put the orbital itself. That's the sigma star carbon-bromine bond. Of course, it's empty to start with, because if it were full, you wouldn't even have the carbon-bromine bond. But this is where the electrons of the nucleophile end up. You could look at that and say there's two different ends, couldn't the nucleophile, in theory, attack either of these lobes? In theory, yes, but why does the nucleophile want to attack the substrate in the first place? What's the driving force of this reaction? Why is it that alkyl halides are much more reactive than just plain old alkanes. In plain old alkanes, there's hardly any polarity differences across the molecule at all. That's why, even though it might be uncontrolled, free radical halogenation can be a good reaction because at least you get a product that's reactive. So because of that polarity difference, because of the fact that there's a delta positive at that position where the carbon is, that's why the nucleophile's going to be attracted to that side of the molecule, where the bromine is. The antibond is pointed collinear, but just on the opposite side. The nucleophile, it's going to donate some electrons into this antibonding orbital. Once it does, it causes the carbon-bromine bond to break. It's going to the carbon that's going to be more likely to get attacked because it's more positive, and the nucleophile's negative, so it makes more sense for it to go to that end.

But, that end is pointed directly behind from where the bromine is located. Once the nucleophile attacks, you make a new bond at that position, you kick the bromine off, but therefore you have inverted the stereochemistry of that position. You can imagine that hydroxide comes from behind to fill that antibonding orbital. In S_N2 reactions, the nucleophile attacks by adding into the sigma star bond to the leaving group. Since electrons are added into the antibonding orbital, the bond to the leaving group is going to break. Since that bond is broken, and since the electrons have already attacked that carbon, a new bond is able to form, but in the completely opposite direction of where the leaving group had been. That is inversion of configuration.

I'd like to do something we have not yet done with mechanisms. If you look back up at the mechanism, you see that we have two arrows involved in the same step and we show the product. This is the way that mechanisms are normally shown. But every once in a while, if we want to discuss a reaction, we might want to know what is the structure of the transition state.

[warning the transition states are normally not included in mechanisms]. I want to do it just in this one case because it's another way of discussing this inversion of configuration. What would the reaction coordinate diagram for this reaction look like? Let's say that, if we're going to have a successful S_N2 reaction, it's going to be exothermic. How many humps would we have in the reaction coordinate diagram? One. Why only one? Cause there's only one step to the reaction. Remember that every step has its own transition state. We could draw a reaction coordinate diagram that looks like this: reactants on the left, products on the right, and then, we'll have the transition state. The transition state is closer in energy to the reactants than the products. We had gotten this concept of the Hammond postulate. What does the Hammond postulate say? The structure of the transition state more closely matches whatever is closest to it in energy. In this case, the reactant is closer to it in energy, so the transition state's going to look a little bit more like the reactant.

Let's see if we can draw the structure of the transition state. Let's imagine that we have the molecule oriented so that we have a hydrogen and bromine as I've drawn here, in the plane of the paper. If I do this, then that means one group is going to have to point towards us, one group is going to have to point back away from us. Let's say that we imagine that those two groups are pointed directly in front and directly in back. I would have to write this, though, draw it at a little bit of an angle or we won't be able to see the two groups. Let's say I take the alkyl group, put it in front, and the deuterium and have it in back. We know that hydroxide is going to come from exactly behind where the bromine is located. Bromine's pointed out to the right, then the hydroxide's going to come in from the left, and it's going to push the bromine out. Here's the part where you're normally not going to have to write. The bromine bond is breaking, but hasn't broken yet at the point where it's at the transition state, because the transition state more closely matches the structure of the reactant. The nucleophile's coming in to attack, but it hasn't formed a bond yet, because again we're still looking more like the reactants. At one moment, though, you're effectively going to have a planar structure, where the hydrogen is getting pushed over to the other side of the molecule, as the bromine is being kicked out. In that case, you can think of the hydroxide being directly left trying to make a bond, and the bromine being kicked out to the right. I want to show the hydroxide's coming in as the bromine's coming off. Think of it kinda like an inverting umbrella; you're pushing the hydrogen from one side to the other. The handle, you could say, had been where bromine is, but we're going to invert it. What we get out the other side is now hydroxide is connected instead, but you have pushed that hydrogen all the way to the other side of the molecule, if we're drawing all of this with the alkyl group and the deuterium still in the same position. Again, this is inversion, because what's left is in the opposite direction of what came in.

We could draw this from another perspective where we show the alkyl group being displaced. One way or another, if you imagine a tetrahedron, you've got the three groups of that tetrahedron; all of them, really, are going to be inverting, kinda like an umbrella. If you think of the structure of a tetrahedron, you lay a tetrahedron down and set it down on the table, one group will be pointed down, while the other three are pointed the opposite way. If you're inverting stereochemistry, that means all three of those groups are going to be pointed the opposite way once this is done. I've shown it on paper as only one switching places; what we really need is an animation showing all three of them.

Let's get to these factors of the substrate, nucleophile, and leaving group. Our first factor we're going to talk about is substrate. Let's compare methyl bromide versus ethyl bromide versus isobutyl bromide versus tert-butyl bromide. If we look at the relative rates of reaction, there's a connection between energy difference and the rate that resulted; the faster reactions happen for the more energetically favorable reaction. If we assign the secondary alkyl halide a relative rate of one, then the tertiary is, for all effective purposes, zero; it just doesn't want to react; versus about 40, a round number, for a primary position, a very open primary position, versus about 1200 for a methyl group itself. What [is] the reason for the big difference in reactivity? Steric hinderance. Because the attack of the nucleophile depends on being able to get to that position behind the leaving group, if it can't get there easily, there won't be a reaction. By the time you get to a tertiary alkyl halide, that's enough steric hinderance that it effectively makes the reaction impossible. Since the S_N2 reaction depends on the nucleophile directly attacking the carbon bearing the leaving group, steric hinderance around that position will slow the rate of reaction, or prevent it. In fact, it isn't quite as simple as just whether it's primary, secondary, or tertiary, because you can have a primary reaction site that still won't be reactive. A classic example of that is neopentyl bromide. If you put sodium hydroxide, trying to react it with neopentyl bromide, effectively there's no substitution[, or if there is, it's incredibly slow]. Why should that be? Even though the primary position itself might not be too hindered, you've got all of this stuff next door that's branched enough, taking up enough room that it could prevent substitution. Watch out for trick cases like this. Neopentyl, that's a common gotcha.

There's one other example that I want to show for now. Bromobenzene; benzene is the name of the molecule itself, but benzene, if it becomes a substituent, has a different name for the substituent – phenyl. Why do you imagine that phenyl halides do not undergo S_N2 reactions? Benzene does have unusual activity because it's what is known as aromatic, but that isn't influencing this particular reaction. Think about what the approach of the nucleophile would be – it would have to come through the molecule; the antibonding orbital would be pointing right in the middle of benzene, so you'd have to come through the benzene molecule to attack, which you can't do. Nu is a general symbol sometimes used for nucleophile; I'm showing it's just not possible. Phenyl halides do not under S_N2 because of too much steric hinderance.

Next I want to talk about nucleophiles. Let's talk about the difference between something being nucleophilic and something being basic. Nucleophilicity, we had determined that that's how strongly does a compound seek positive charge.

One of the most common ways that nucleophiles are classified is by charge. Let's see that we're just comparing hydroxide versus water; they're just acid conjugates of each other. Which one would be the much better nucleophile in an S_N2 reaction? Hydroxide. Why? Because it has a negative charge. If you were having a nucleophilic reaction, it's seeking out positive charge, what more actively seeks out positive charge: neutral water, or negatively charged hydroxide? It's going to be negatively-charged hydroxide, but it's not automatically because hydroxide's basic. Hydroxide's much more nucleophilic because it has a negative charge on it. Basicity [is] the ability to pull off a hydrogen from a molecule. [ignoring Lewis definition; Brønsted-Lowry] Basicity [is defined as] now able is a compound to remove H^+ . Just to talk about an example, basic nucleophile, we could generalize this structure; the OR^- group, R just being a plain old alkyl group, so this is a deprotonate alcohol. The general term for these molecules is alkoxide, which is a contraction of alkyl oxide.

Nucleophilic means likes to attack positive charge; basic means it likes to pull off H^+ . What's an example of these being different? Let's look at the case of OH^- versus SH^- . To compare the two, let me put up that, for water, the pK_a is 15.74; for hydrogen sulfide, it's right at seven. Do not confuse that with being neutral: pK_a of 7 is just an equilibrium constant; it has nothing directly to do with pH being 7. But if I give you these two pieces of information, which of the two molecules is more basic: hydroxide, or SH^- ? Hydroxide, because the higher the pK_a , the lower the K_a , the less strong of an acid it is. Water, being the weak acid, if you force it to deprotonate, therefore becomes the stronger conjugate base. Hydroxide is the stronger base. But, if you threw a primary alkyl halide at a solution that has both hydroxide and SH^- in it, by far the major product would be the one with sulfur in it – even though hydroxide's more basic, it doesn't matter because that sulfur is actually the stronger nucleophile. What's the difference between oxygen and sulfur? They're different sizes; sulfur's below oxygen on the periodic table; sulfur is therefore a squishier ion than oxygen. Not a very technical term; the more technical term would be polarizable – polar means to have plus and minus, polarizable means it's able to become plus and minus, able for some of that electron density to be moved around a bit. Oxygen's a tighter, smaller ion, holds its electrons more tightly, therefore doesn't let them start interacting with another orbital as easily in a chemical reaction. Sulfur, being the bigger, squishier ion, it may not have as concentrated a negative charge, but therefore, that electron density can begin the process of forming a bond more easily, cause that electron density could be more easily displaced – sulfur is more polarizable. Because of polarizability, when this attack of the nucleophile begins, sulfur, with it's bigger, squishier ion, begins the process of donating electrons into the antibonding orbital much more easily – so much more easily that that's why it's a much better nucleophile than oxygen is.

Fluorine is a poorer nucleophile than hydroxide is. It's less basic than hydroxide. Hydroxide, that's really basic, but still more able to attack and give back electron density than the less basic and even more tightly packed fluorine. Back to this sulfur example. Let's define polarizability: polarizability means able to become polarized, which in this case, you could describe it as the following: larger ions are squishier, meaning that electron density can be more easily displaced. Since sulfur is more polarizable than oxygen, the process of forming a bond occurs more easily. Since more easily effectively has an energetic connotation with it, that there's this smaller barrier to that process beginning, that also's going to mean a faster rate. Since sulfur is more polarizable than oxygen, the process of forming a bond occurs more easily, and therefore more quickly for sulfur versus oxygen. That means sulfur is more nucleophilic than oxygen – if we're comparing similar molecules.

I mentioned that there's a side reaction that could occur. This is why we need to worry about something being nucleophilic versus something being basic. The side reaction is the following: let's say that you had a tertiary alkyl halide, and let's say that we did through a basic nucleophile like hydroxide at it. Let's take it to one more extreme: let's say that the nucleophile itself has a lot of steric hinderance around it. Even if the alkyl halide might be able to be attacked, now I've got a nucleophile that itself would have difficulty getting in to attack that position. Notice that I've written a hydrogen out here; hydrogen is much further away from all of this steric hindered site that we have around the bromine. What if this little itty bitty hydrogen could be pulled off by the nucleophile. That pair of electrons that had been there could collapse and it be the thing that kicks off the leaving group. That's exactly what can happen. This is therefore called an elimination reaction: specifically, this is the $E2$ reaction, because two molecules are involved at the same time in the one reaction step.

Coming back to nucleophiles versus bases, S_N2 reactions require strong nucleophiles – you need something to force that leaving group off. These nucleophiles are often, but not always, basic. Here's the important point: extremely basic nucleophiles – especially sterically hindered ones – can undergo elimination instead of substitution.

Let me introduce the third aspect of the reaction – leaving group. Let me write up two different examples of reactions. Let's say that we have some unspecified strong nucleophile that tries to come in and do the following attacks: trying to push off a hydroxide, versus pushing off a bromide. Which of these two reactions do you think is going happen: the first one, the second one, both, or neither? The second one. Why? Because bromine's a good leaving group – when you kick it off, all you make is bromide minus; we're not necessarily going to be in aqueous solution, but Br^- is something that easily could tolerate being an anion. If you kick off hydroxide, hydroxide's awfully basic; it doesn't really want to disconnect from the molecule in the first place. In fact, it won't do so. In general, good leaving groups are conjugate bases of strong acids.

- 1) synthetic utility: alkyl halide → alcohol, ether, thiol
- 2) reagents: basic nucleophile; ex: NaOH, NaOCH₃, NaCN
- 3) conditions: polar aprotic solvent
- 4) mechanism: anion, concerted
- 5) stereochemistry : inversion of configuration
- 6) regiochemistry : specific (@ site of leaving group)

In S_N2 rxn, the nucleophile attacks by adding into the sigma star bond of the leaving group. Since electrons are added into the antibonding orbital, the bond with the leaving group breaks. This allows a new bond with the nucleophile to form, but in the exact opposite direction of the leaving group → inversion of configuration

Factors that affect an S_N2 rxn

1) Substrates – Since the S_N2 rxn depends on the nucleophile directly attacking the carbon bearing the leaving group, since steric hinderance around that position will slow the rate of reaction (or prevent it).

phenyl = benzene substituent; phenyl halides do not undergo S_N2 because of too much steric hinderance (attack would have to occur through the ring).

2) Nucleophile – Nucleophilicity – how strongly does a compound seek + charge

Ex: H₂O vs OH⁻; hydroxide is much more nucleophilic because it has a - charge on it

Basicity – how able is a compound to remove H⁺

RO⁻ alkoxide (alkyl + oxide)

polarizability – able to become polarized – larger ions are “squishier”, meaning that electron density can more easily be displaced. Since sulfur is more polarizable than oxygen, the process of forming a bond occurs more easily – and therefore more quickly – for sulfur versus oxygen → sulfur is a better nucleophile than oxygen (in similar molecules)

S_N2 rxns require strong nucleophiles, which are often, but not always, basic. *Extremely basic nucleophiles, especially sterically hindered ones, can undergo elimination instead of substitution.

3) leaving group – good leaving groups are the conjugate bases of strong acids.

Structures (remaining structures identical to lecture 19A)

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